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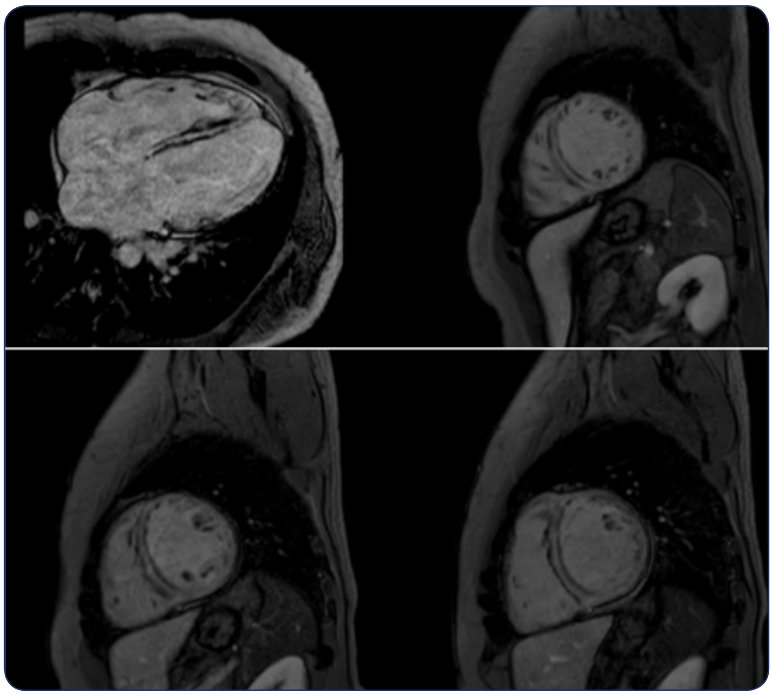

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Overweight, the Cardiovascular Risk of the Century

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Over time, the scientific community has accurately identified the main cardiovascular risk factors. There is no doubt about their importance, the weight of each one in determining the increase in morbidity and mortality due to this cause.[1]

On the other hand, the temporal growth of circulatory system pathologies as the main cause of death and leave from work was gigantic. An untold social, economic and affective harm.

Scientific development has enabled the emergence of instruments and drugs to address major modifiable risk factors.

Ironically though, is that, in general, from the point of view of disease control, we make more progress in secondary prevention than in primary prevention.[1]

In secondary prevention, combating some of the greatest risk factors has greater appeal. Treatment of hypertension, dyslipidemia and even diabetes has evolved a lot. Platelet antiaggregation and anticoagulation as a means of preventing further events have also gone a long way. In this case, despite the problems related to lack of access or adherence to treatment, we have cleared the ground and keep on moving.[1]

Regarding lifestyle habits, there are multiple answers even in this situation. Smoking cessation is well accepted and, due to the actions taken on all levels in our country, the results are very encouraging. However, there is greater resistance to changing sedentary behaviors, despite the dissemination of knowledge about its importance. Psychosocial stress is another factor that needs further studies and more effective actions.[1]

However, there is a major public health challenge against which we have been sustaining setbacks year after year.

The challenge of the century: overweight

Published studies have shown that, worldwide, over the past 50 years, the population has increased in weight. A 2014 publication reported that between 1980 and 2013 individuals had an increase in body mass index above 25 kg/m^2, which classifies them as overweight, from 28.8% to 36.9% among men and 29.8% to 38.0% among women. Worse than that, children and adolescents also had weight gain both in developed countries where, in 2013, 23.8% of boys and 22.6% of girls were overweight or obese, and in developing countries, where 12.9% of boys and 13.4% of girls were also overweight.[2]

In 2016, another publication that evaluated the period from 1975 to 2014 also showed that obesity increased from 3.2% to 10.8% among men and from 6.4% to 14.9% among women. These studies estimate that if this trend continues, in 2025, the prevalence of obesity around the world will be greater than 18% among men and 21% among women.[3]

This said, we clearly have a worldwide overweight pandemic, made worse by the fact that there has not been, so far, any description of any developed program that has succeeded in stopping this harsh reality.

This is an important cardiovascular risk that went unnoticed initially, which is taking alarming proportions and gaining momentum.

It should be noted that, in 2015, overweight drove more than 100 million people away from their jobs and was responsible for about 4 million deaths worldwide.[4]

In Brazil it is no different: the epidemic is severe and progresses noticeably. From 2006 to 2016, in a survey using VIGITEL data, which somewhat underestimates information, the prevalence of overweight increased from 48.1% to 57.5% among men and from 37.8% to 48.2% among women, and obesity increased from 11.7% to 18.1% among men and from 12.1% to 18.8% among women.[5]

Another major longitudinal study – ELSA-Brasil – showed in a 2015 publication, in a population aged 35 to 74, a prevalence of 40.2% of overweight individuals and 22.9% of obese individuals.[6] It is scary, but there is more.

These surveys report data from capital cities and/or large urban centers and, when we seek information about small towns, we find the same reality.

For example, a 13-year longitudinal study in a small town in the Midwest of Brazil, in a population of people older than 18, found an increase in overweight/obesity, which was already high in 2002, from 49.1% to 69.8% in 2015. As atypical as it may seem and even more challenging, overweight in the period increased from 34.6% to 38.4%, while obesity increased from 14.5% to a scary rate of 31.4%. Note that the same individuals were investigated at two different times. Considering stratification by gender, there was a decrease in the number of normal weight individuals and an increase in obesity in that time frame.[7] (Figure 1)

It is also worth noting that in Brazil, even in children, from very young kids to teenagers, there are impressive percentages of overweight and obesity.

A study with children aged 2 to 5 in midwestern Brazil found 11.2% of overweight.[8] Another sample of 3169 slightly

Keywords

Cardiovascular Diseases; Risk Factors; Prevention & Control; Overweight; Indicators of Morbidity and Mortality; Feeding Behavior/trends; Obesity.

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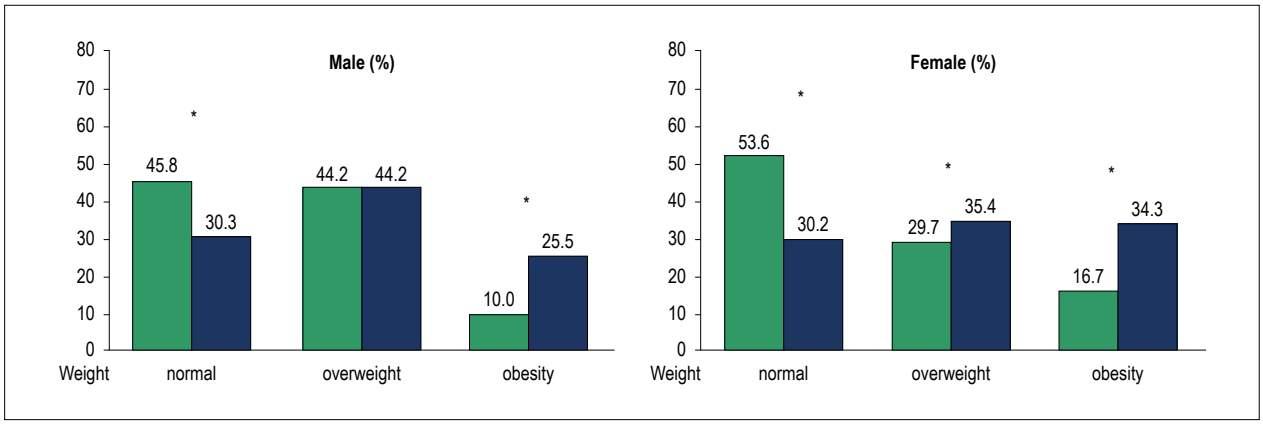

Figure 1 – *Nutritional status based on body mass index (n = 685). Firminópolis, Brazil (2002–2015). *Significant p = 0.05.*

older school children (7 to 14 years old), also in the Midwest region, found 16% of overweight children and 4.9% of obese children, revealing the same trend since childhood.[9]

Finally, wrapping up the cycle, in the evaluation of school adolescents (12 to 17 years old), two population-based studies, one representing a city and another representing the whole country – the studies CORADO and ERICA – found overweight percentages of 23.3% and 17.1%, respectively.[10,11]

There is no other way of looking at it: it is an epidemic, it ravages the world, it grows rapidly and is not effectively tackled.

The scientific community has not realized the seriousness of this issue, it still works from a "treatment" perspective and is very shy when it comes to primary prevention, as it was clearly outlined in recent documents from the European Society of Hypertension and the European Association for the Study of obesity.[12,13]

We already have strong indications that incentives or even restrictive measures with taxation of certain products that may be considered harmful are cost-effective and may potentially lead us to a safer spot.[14,15]

It is really a time for taking action, for us to stop being doctors of illness and acting from the perspective of real healthcare professionals. We should all make more of an effort. And that includes each individual from society and especially from the government.

Tackling overweight should be a government policy in pursuit of an effective action nationwide, otherwise we will move towards an even darker future in terms of cardiovascular disease.

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Global Longitudinal Strain Predicts Poor Functional Capacity in Patients with Systolic Heart Failure

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Abstract

Background: Left ventricular global longitudinal strain value (GLS) can predict functional capacity in patients with preserved left ventricular ejection fraction (LVEF) heart failure (HF) and to assess prognosis in reduced LVEF HF.

Objetive: Correlate GLS with parameters of Cardiopulmonary Exercise Test (CPET) and to assess if they could predict systolic HF patients that are more appropriated to be referred to heart transplantation according to CPET criteria.

Methods: Systolic HF patients with LVEF < 45%, NYHA functional class II and III, underwent prospectively CPET and echocardiography with strain analysis. LVEF and GLS were correlated with the following CPET variables: maxVO_2, VE/VCO_2 slope, heart rate reduction during the first minute of recovery (HRR) and time needed to reduce maxVO_2 in 50% after physical exercise ($T_{1/2}VO_2$). ROC curve analysis of GLS to predict VO_2 < 14 mL/kg/min and VE/VCO_2 slope > 35 (heart transplantation's criteria) was performed.

Results: Twenty six patients were selected (age, 47 ± 12 years, 58% men, mean LVEF = 28 ± 8%). LVEF correlated only with maxVO_2 and $T_{1/2}VO_2$. GLS correlated to all CPET variables (maxVO_2: r = 0.671, p = 0.001; VE/VCO_2 slope: r = –0.513, p = 0.007; HRR: r = 0.466, p = 0.016, and $T_{1/2}VO_2$: r = –0.696, p = 0.001). GLS area under the ROC curve to predict heart transplantation's criteria was 0.88 (sensitivity 75%, specificity 83%) for a cut-off value of –5.7%, p = 0.03.

Conclusion: GLS was significantly associated with all functional CPET parameters. It could classify HF patients according to the functional capacity and may stratify which patients have a poor prognosis and therefore to deserve more differentiated treatment, such as heart transplantation. (Arq Bras Cardiol. 2019; 113(2):188-194)

Keywords: Heart Failure;Longitudinal Strain; Torsion,Mechanical; Torsion Abnormality; Ventricular Dysfunction, Left; Echocardiography, Doppler/methods.

Introduction

The cardiopulmonary exercise test (CPET) is the gold standard method for assessing functional capacity in patients with heart failure (HF). It is able to measure during exercise, maximum myocardial oxygen consumption (maxVO_2), CO_2 production, ratio minute ventilation/carbon dioxide production VE/VCO_2 slope, VO_2 recovery kinetics after physical exertion ($T_{1/2}VO_2$), stratify cardiovascular risk and predict mortality and hospitalization by these parameters, for example, VO_2 values < 14 mL/kg/min and VE/VCO_2 slope >35 that are criteria for heart transplantation.[1-4] Furthermore, CPET evaluates the presence of dysautonomia, by measuring the reduction in heart rate within the first minute after exercise (HRR),[5,6] which is directly related to cardiovascular outcome.[7-9]

However, in patients with systolic HF, the reduction of myocardial contractility, measured mainly by echocardiography through the left ventricular ejection fraction (LVEF), is the main parameter used to classify the myocardial damage degree,[10] although its value is little associated with the clinical symptoms and functional capacity of these patients.[1,10] The strain analysis is a newer echocardiography tool and has demonstrated more effective in assessing global derangement of the left ventricle (LV) than the LVEF measurement.[10]

Recent studies show that the left ventricular global longitudinal strain value (GLS) can predict functional capacity in patients with HF and preserved LVEF,[11] and assess prognosis in HF with reduced LVEF when compared with life expectancy scores.[12] Additionally, this technique evaluates the degree of myocardial deformation and it seems to predict the degree of regional and global LV fibrosis.[13] However, there are no studies comparing the GLS with CPET parameters

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in patients with systolic HF. The aim of this study was to correlate GLS value with functional parameters of CPET and to assess if GLS could predict systolic HF patients that were more appropriated to be referred to heart transplantation according to CPET criteria.

Methods

This is an observational, prospective cross-sectional study, guided by the recommendations of the STROBE Statement.[14] This study was approved by the Ethics and Research Committee of our Institution under number 1507992.

The study population consisted of adults (21-65 years), both sexes, diagnosed with HF in functional class II and III by the New York Heart Association (NYHA), sedentary, with systolic dysfunction (LVEF <45%) assessed by transthoracic echocardiography performed until one month before they had been referred for cardiopulmonary program and recruited for this study. Data were collected between January, 2015 and March, 2016.

Exclusion criteria were: deformity in the face to prevent the coupling of the CPET mask, orthopedic and neurological diseases that could preclude the execution of CPET, psychological problems restricting them to respond to the questionnaire, functional class IV HF or hospitalization due to cardiac decompensation in the last three months, unstable angina, myocardial infarction or cardiac surgery up to three months before the study; forced expiratory volume on the first one second/forced vital capacity <70% of predicted characterizing obstructive respiratory disorder.

To ensure standardization, a single examiner performed the exams. None of them had access to the patients' other evaluations results. The researchers responsible for data collection were not responsible for carrying out the examinations, thus ensuring the blinding of the study.

Cardiopulmonary exercise test

All patients in the study underwent CPET by the method ramp on a treadmill (*Centurium 300*, Micromed, Brazil) through ErgoPC Elite® software associated with the electrocardiogram (Micromed, Brazil) with 12 channels. Respiratory variables were evaluated by a gas analyzer (Cortex - Metalyzer II, Germany) and obtained in conditions of standard temperature, pressure and dry (STPD), breath-by-breath, with the patient breathing in a face mask without leaks during exercise. During the test, functional capacity, maxVO_2 measured in METs, the maximum VE/VCO_2, VE/VCO_2 slope, $T_{1/2}VO_2$ and HRR were evaluated.

Echocardiography

All echocardiograms were performed according to ASE.[14] Patients underwent the two-dimensional echocardiography, using an ultrasound system Vivid I (GE Medical Systems, Horten, Norway) with a multifrequency transducer from 2.5 to 5 MHz.

After the echocardiogram, a strain analysis technique was performed using an echocardiogram analysis software (EchoPAC, GE Medical Systems, Horten, Norway, version 10.0). The images in the longitudinal sections were analyzed (4 chambers, 3 chambers and 2 chambers).[15] A region of interest was applied automatically by the software and, if necessary, was adjusted manually. The strain analysis software performed the analysis. Patients were excluded when more than two segments were considered to have insufficient quality for monitoring by the analysis system.[16]

Statistical analysis

To calculate the sample, G*Power 3 software was used,[17] in which we chose the post hoc option with $\alpha = 0.05$ and two-tailed hypothesis. Thus, the two most important ergospirometric variables were chosen for the study population: maxVO_2 and VE/VCO_2 slope. We found an effect size of 0.81 ($R^2 = 0.67$) for the maxVO_2 and 0.71 ($R^2 = 0.51$) for the VE/VCO_2 slope. We observed for both variables a power of 99% with a total sample of 25 patients.

Patients were later divided into two groups according to values of maxVO_2 and VE/VCO_2 slope found to CPET: Group 1 - maxVO_2> 14mL/kg/min and/or VE/VCO_2 slope < 35; and Group 2 - maxVO_2 < 14mL/kg/ min and VE/VCO_2 slope > 35 (IIa class indication criteria for heart transplantation).[16]

The data was presented by absolute and percentage frequencies for categorical variables; by the mean and standard deviation for parametric quantitative variables; and by median and interquartile range for non-parametric variables. Shapiro-Wilk test was applied to verify if the quantitative data were normals. For comparison of parametric variables, we used the Student t-test for independent samples and for non-parametric variables the Mann-Whitney test. To compare categorical variables, we used the chi-square non-parametric test.

In the second step, the correlation between the values of the GLS strain index with ergospirometric variables was performed by using the Pearson coefficient for parametric and Spearman variables for non-parametric variables. The Receiver Operating Characteristic (ROC) curve was performed to evaluate the GLS's ability to predict maxVO_2 < 14 mL/kg/min and VE/VCO_2 slope > 35.

P value inferior to 0.05 was considered statistically significant. Data were entered in an EXCEL spreadsheet and statistical software used for statistical calculations was the SPSS (Statistical Package for Social Sciences) version 23.

Results

During the study period, 39 patients with HF were referred to the cardiopulmonary rehabilitation program. Of these, 10 were not included because of a LVEF higher than 45%, one patient for presenting inadequate acoustic window for subsequent analysis of the GLS and two patients due to arrhythmia. Therefore, 26 patients (mean age, 47±12 years, 58% men) participated in this study, Table 1.

Regarding the CPET results the average maxVO_2 was 19.09 ± 9,52 mL/kg/min and the VE/VCO_2 slope was 39.43 ± 9.91. The mean HRR and $T_{1/2}VO_2$ were respectively, 19.65 ± 17.42 bpm and 168.61 ± 43.90s. By echocardiography, the mean LVEF was 28.0 ± 8.6% and mean GLS index was -7.5 ± 3.92 % for all studied patients, Table 1.

Table 1 – Characteristics of the study population

Variable	(n = 26)
Age (years), mean ± DP	47.31 ± 12.71
Gender: n (%)	
Men	15 (57.7)
Women	11 (42.3)
BMI (Kg/m²): Mean ± DP	29.31 ± 5.38
Comorbidities: n (%)	
SAH	20 (77)
DM	15 (61)
HF Etiology: n (%)	
Ischemic	6 (23)
Hypertensive	10 (39)
Myocarditis	4 (15)
Chagas' Disease	1 (4)
Idiopathic	5 (19)
Medication: n (%)	
ACEI/ARB	23 (88)
Beta blocker	26 (100)
Diuretics K-sparing	22 (84)
LVEF (%) (mean ± DP)	28,0 ± 8.62
Strain (%) (mean ± DP)	-7.5 ± 3.92
$maxVO_2$ (mean ± DP)	19.09 ± 9.52
VE/VCO_2 slope (mean ± DP)	39.43 ± 9.91
HRR (bpm) (mean ± DP)	19.65 ± 17.42
$T_{1/2}VO_2$ (s) (mean ± DP)	168.61 ± 43.90

BMI: body mass index; SAH: systemic arterial hypertension; DM: diabetes mellitus; ACEI/ARB: converting the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF: left ventricular ejection fraction; $maxVO_2$: maximal oxygen consumption; VE/VCO_2 slope: slope of the VE/VCO_2 curve; HRR: heart rate recovery; $T_{1/2}VO_2$: time to VO_2 halving recovery.

Correlation of CPET variables with LVEF and GLS measurements

When comparing the CPET with LVEF data (Table 2), a positive correlation was observed only with $maxVO_2$ ($r = 0.585$, $p = 0.02$) and negative with $T_{1/2}VO_2$ ($r = –0.530$; $p = 0.005$). For the other variables, LVEF showed no correlation, Table 2.

The GLS showed significant correlation with all analysed CPET variables. This parameter was positively correlated with $maxVO_2$ and HRR and inversely with VE/VCO_2 slope and $T_{1/2}VO_2$, Table 2 and Figure 1.

Regarding VO_2 group > 14 mL/kg/min and/or VE/VCO_2 slope < 35 and VO_2 group < 14 mL/kg/min and VE/VCO_2 slope > 35, there were no differences in clinical variables, comorbidities and medications used. However, echocardiographic variables showed differences, as shown in Table 3.

The area under the ROC curve (Figure 2) for the GLS index value as a predictor of poor functional capacity and worse prognosis was 0.88 (95% CI = 0.75 to 1.00), with a sensitivity of 75%, specificity of 83%, positive predictive value of 67%, and negative predictive value of 88%, for a cut-off GLS value of -5.7%, $p = 0.03$.

Discussion

In this study, in patients with systolic HF referred for a cardiopulmonary rehabilitation program, the GLS was significantly associated with all functional CPET parameters. It seems to be more accurate than LVEF in classifying patients with HF according to the functional capacity and thus may stratify which patients have a poor prognosis and therefore to deserve more differentiated treatment, such as heart transplantation.

Previous studies have demonstrated that LVEF has no correlation with functional capacity.[1,10] However, there is limited data on the association between exercise tolerance and the results of analysis by cardiac strain. This study showed that LVEF was associated with $maxVO_2$ and $T_{1/2}VO_2$, however, showed no correlation with the other CPET variables. Whereas peak VO_2 values and VE/VCO_2 slope are parameters which help in end-stage HF decision making[4,16] and that in this study, the GLS value was correlated with all these variables, we could suggest that the GLS may have a prognostic significance in this group of patients. In addition, GLS correlation with $maxVO_2$ and $T_{1/2}VO_2$ was better than LVEF, thus demonstrating that the GLS is a more accurate tool.

Hasselberg et al.,[11] in their study that evaluated HF patients, either with normal or reduced LVEF, were able to show the importance of GLS as a predictor of exercise capacity in patients with preserved LVEF HF.[11] However, these authors have failed to demonstrate this relationship in patients with reduced LVEF. In the present study, we observed this correlation between GLS and functional capacity. This may have occurred since our study evaluated patients in more advanced stages of cardiac dysfunction. The average GLS in our study was worse than the Hasselbach study.[11]

The $T_{1/2}VO_2$ has also proven an important tool for predicting outcomes. The longer the VO_2 recovery time of HF patients after physical exercise, the worse the cardiovascular prognosis.[18-21] Our study demonstrated that the GLS was able to determine patients that have delayed recovery of VO_2. The lower the value of GLS, the greater the time required for the post-physical effort VO_2 to be reduced to half, suggesting the hypothesis that the GLS could estimate the prognosis of the patient.

Another evidence that supports the prognostic importance of GLS was dysautonomia analysis. It is known that there is a relationship between HRR in the first minute after physical exercise with mortality. The cardiovascular prognosis appears to be independent of symptoms, the type of recovery protocol, LVEF, and severity of coronary lesions in coronary angiography.[7-9,21,22] This study showed a direct relationship between the GLS value and HRR in the first minute after effort, with a less accentuated drop in heart rate in patients who had a lower GLS value.

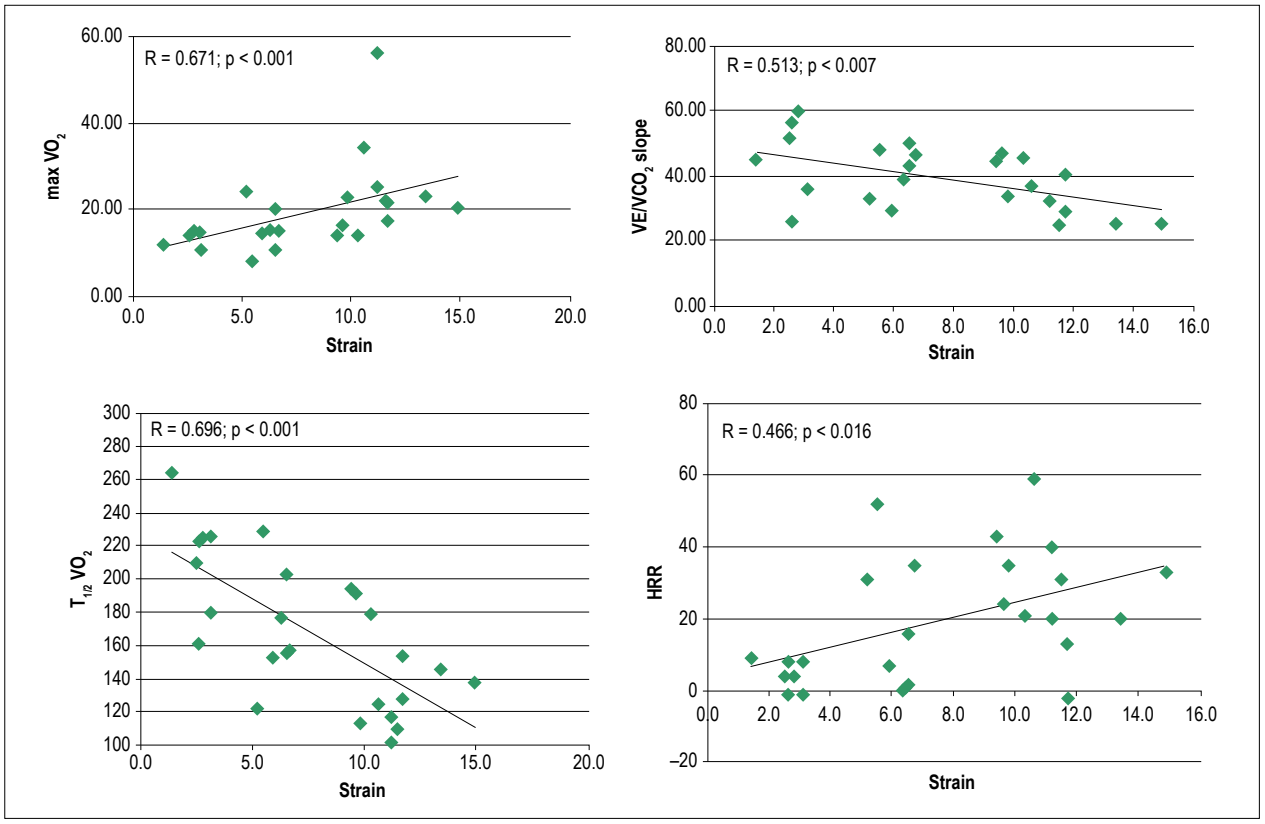

Figure 1 – *Global longitudinal strain index (GLS) scatter plots compared to maxVO_2, VE/VCO_2 slope, HRR, and $T_{1/2}VO_2$. maxVO_2: maximal oxygen consumption; VE/VCO_2 slope: slope of the VE/VCO_2 curve; HRR: heart rate recovery; $T_{1/2}VO_2$: time to VO_2 halving recovery.*

Table 2 – Correlation of numerical variables of Cardiopulmonary Exercise Test with left ventricular ejection fraction (LVEF) and global longitudinal strain index (GLS)

Variables	LVEF (p value)	GLS (p value)
HRR-bpm	0.288 (0.154)(1)	0.466 (0.016)*(1)
maxVO_2	0.585 (0.002)*(2)	0.671 (< 0.001)*(2)
VE/VCO_2 slope	–0.330 (0.100)(1)	–0.513 (0.007)*(1)
$T_{1/2}VO_2$	–0.530 (0.005)*(1)	–0.696 (< 0.001)*(1)

*HRR: heart rate recovery; $T_{1/2}VO_2$: time to VO_2 halving recovery; VE/VCO_2 slope: slope of the VE/VCO_2 curve; maxVO_2: maximal oxygen consumption. *p < 0,05; (1) – Pearson coefficient; (2) – Spearman coefficient.*

Cameli et al.,[13] evaluated patients with severe HF, with cardiac transplant indication, and, by histopathology of the heart after heart transplantation, found that no echocardiographic parameter, performed before heart transplant, was able to correlate with the presence of fibrosis except the GLS value. Therefore, a lower GLS value indicates that there is presence of more cardiac fibrosis, and consequently, there is less deformation and myocardium thickening, and relaxation and contractility is more defective. These changes entail low functional capacity and are responsible for worse prognosis.[13] However, in that study, functional capacity was not assessed through an objective test, such as CPET.

Rangel et al.[12] evaluated patients with LVEF less than 45% and demonstrated that the GLS value correlates with more advanced stages of the disease and is an independent predictor of life expectancy.[12] That is, in patients with severe HF and similar LVEF, GLS was able to show which patients would present an unfavourable outcome. Our study showed that in patients with reduced LVEF, the lowest GLS value was correlated with CPET parameters that assess exercise tolerance and prognosis disease.

When rating the GLS cut-off in predicting poor prognosis, Rangel et al.[12] used the Seattle HF model to assess the long-term survival, and it was shown that the best GLS cut-off point

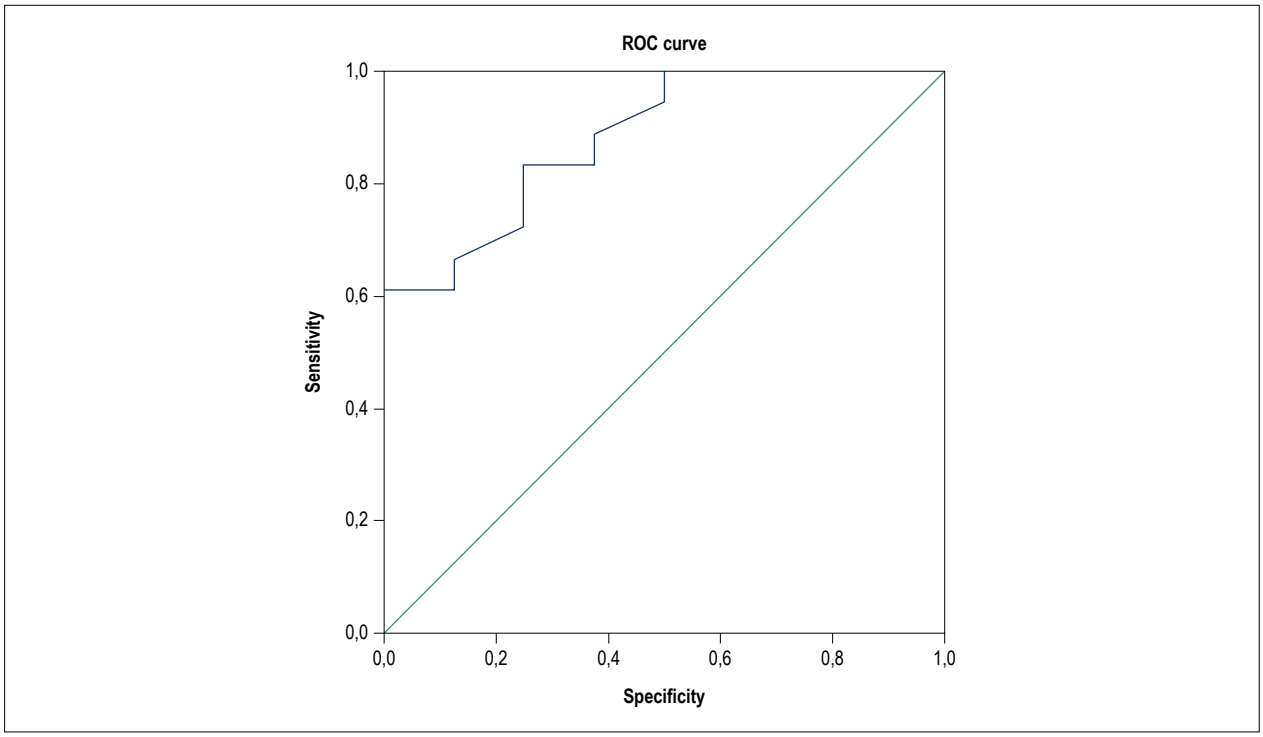

Figure 2 – *ROC curve for evaluating the ability of the global longitudinal strain index (GLS) in predicting VO_2 < 14 mL/kg/min and VE/VCO_2 slope > 35. Sensitivity of 75% and specificity of 83% for a GLS cut-off of –5.7%, p = 0.03.*

was -9.5%. Our study correlated the GLS value with CPET parameters and suggested a cut-off point of -5.7% for GLS value, with sensitivity of 75% and specificity of 83% in predicting CPET heart transplantation's criteria.

Study limitations

Considering the small number of patients included in this study, our findings that the GLS showed a strong correlation with the CPET data and have been able to identify the patients who had ergospirometric criteria of worse prognosis, need to be proven through a study with a larger number of patients and of long-term monitoring, and thus determine the real power of GLS in the prognostic assessment and therapeutic setting in systolic HF.

Conclusion

In systolic HF patients, the GLS showed significant association with the main parameters of CPET and was able to classify patients with low functional capacity. Thus, GLS may be a more accurate parameter than LVEF in stratifying systolic HF patients. Moreover, it may play a role in helping to evaluate patients in the end stage of HF.

Author contributions

Conception and design of the research: Brandão SCS, Brandão DC, Leite J, Martins SM, Andrade AD; Acquisition of data: Maia RJC, Brandão DC, Leite J, Pinheiro F, Araújo BTS, Aguiar MIR, Martins SM; Analysis and interpretation of the data: Brandão SCS, Brandão DC, Leite J, Parente GB, Pinheiro F, Araújo BTS, Aguiar MIR, Andrade AD; Statistical analysis: Brandão SCS, Parente GB; Writing of the manuscript: Maia RJC, Brandão SCS, Leite J; Critical revision of the manuscript for intellectual content: Brandão SCS, Brandão DC, Andrade AD.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Rafael José Coelho Maia, from Universidade Federal de Pernambuco.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Pernambuco under the protocol number 38572614.1.000.5208. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 3 – Comparison between Group 1 - VO_2 max > 14 mL/kg/min and/or VE/VCO_2 slope < 35 and Group 2 - maxVO_2 < 14 mL/kg/ min and VE/VCO_2 slope > 35

Variables	VO_2 > 14 mL/kg/min and/or VE/VCO_2 slope < 35 (n = 18)	VO_2 < 14 mL/kg/min and VE/VCO_2 slope > 35 (n = 8)	p value
Age (years): Mean ± DP	45.7 ± 13.7	51.0 ± 10.0	0.334(1)
Gender: n (%)			
Men	11 (61.1)	4 (50.0)	0.683(2)
Women	7 (38.9)	4 (50.0)	
BMI (Kg/m²): Mean ± DP	29.4 ± 6.1	29.0 ± 3.7	0.849(3)
Comorbidities: n (%)			
SAH	13 (72.2)	7 (87.5)	0.628(2)
DM	10 (55.6)	6 (75.0)	0.420(2)
HF Etiology: n (%)			
Ischemic	5 (27.8)	1 (12.5)	0.628(2)
Hypertensive	7 (38.9)	3 (37.5)	1.000(2)
Myocarditis	3 (16.7)	1 (12.5)	1.000(2)
Chagas' disease	1 (5.6)	0 (0.0)	1.000(2)
Idiopatic	2 (11.1)	3 (37.5)	0.281(2)
Medication: n(%)			
ACEI/ARB	16 (88.9)	7 (87.5)	1.000(2)
Beta blocker	18 (100.0)	8 (100.0)	1.000(2)
Diuretics K-sparing	15 (83.3)	7 (87.5)	1.000(2)
LVEF (%) (mean ± DP)	30.6 ± 8.5	22.4 ± 6.0	0.021(1)
Strain (%) (mean ± DP)	8.6 ± 3.8	5.2 ± 3.3	0.037(3)
maxVO_2 (mean ± DP)	22.1 ± 10.0	12.4 ± 3.3	0.014(3)
VE/VCO_2 slope (mean ± DP)	35.8 ± 9.3	47.5 ± 5.8	0.003(1)
HRR (bpm) (mean ± DP)	20.2 ± 17.2	18.4 ± 19.0	0.004(3)
$T_{1/2}VO_2$ (s) (mean ± DP)	147.5 ± 32.1	216.1 ± 25.7	< 0.001(1)

BMI: body mass index; SAH: hypertension; DM: diabetes mellitus; ACEI/ARB: converting the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF: left ventricular ejection fraction; maxVO_2: maximal oxygen consumption; VE/VCO_2 slope: slope of the VE/VCO_2 curve; HRR: heart rate recovery; $T_{1/2}VO_2$: time to VO_2 halving recovery. (1) – Student t test; (2) – Mann-Whitney test; (3) – chi-square test.

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Global Longitudinal Strain or Measurement of Ejection Fraction: Which Method is Better in Stratifying Patients with Heart Failure?

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Short Editorial related to the article: Global Longitudinal Strain Predicts Poor Functional Capacity in Patients with Systolic Heart Failure

Heart failure (HF) is a complex syndrome that has a poor prognosis and a stigma of high mortality.[1] The current prevalence estimated in the United States is six million cases, with a predicted incidence of another two million patients until 2030.[2] Brazil, specifically, had more than 26 thousand deaths by HF in 2012 and approximately 230 thousand hospitalizations attributed to this disease.[3]

The main HF symptoms include progressive dyspnea, fatigue, exercise intolerance, and signs of volume overload, reducing the functional capacity and quality of life of patients and greatly increasing the risk of morbidity and mortality.[4] In this regard, a peak oxygen consumption ($maxVO_2$), on average, approximately 50% lower is not uncommon in HF patients when compared to healthy individuals paired by variables such as age and gender.[5] The cardiopulmonary exercise testing (CPET) is a method widely used and trusted in this scenario, with a consistent role in risk stratification of HF patients and various variables obtained with consolidated prognostic value. $MaxVO_2$ is an important marker of one-year mortality, surpassing ejection fraction and pulmonary capillary wedge pressure, used as Class I to define candidates for heart transplantation.[6] Other prognostic markers obtained from CPET that proved to be important in this population include the measurement of ventilatory efficiency through the VE/VCO_2 slope, regular ventilation, oxygen uptake efficiency slope (OUES), heart rate recovery (HRR) in the first minute, chronotropic competence, and partial pressure of carbon dioxide at rest ($PetCO_2$).[7,8]

HF patients are usually classified according to their left ventricular ejection fraction (LVEF); however, the prognostic value of LVEF can be controversial.[9] Following this reasoning, although the LVEF measurement is a validated method that has been widely used for decades, the assessment of myocardial deformation with the Global Longitudinal Strain (GLS) has shown greater effectiveness in analyzing the overall breakdown of the left ventricle when compared to the LVEF measurement. GLS can provide an additional value for prognostic HF stratification, regardless of the LVEF values, and serve as an auxiliary instrument for therapeutic decision making in specific clinical situations in this population, such as: cardiac defibrillator and resynchronization device implantation, indication of ventricular assist devices, and follow-up of patients with cardiotoxicity due to chemotherapeutic agents.[10]

Recently, Park et al.[11] assessed the prognostic value of GLS in more than 4 thousand individuals with acute HF, divided into preserved (≥50%), mid-range (40-49%), and reduced LVEF (<40%). The primary outcome analyzed was all-cause mortality, evaluated over five years. Patients with reduced and preserved LVEF presented lower and higher GLS, respectively. GLS, but not LVEF, was an independent predictor of mortality in the whole group of patients. The three groups presented no significant difference in mortality; however, individuals with reduced LVEF had slightly higher mortality compared to those with mid-range or preserved LVEF (41%, 38%, and 39%, respectively).[11] Corroborating these findings, Sengelov et al.[12] showed in an echocardiographic analysis of more than one thousand subjects that GLS was the main predictor of mortality in HF and reduced LVEF patients. Even after adjustment for several variables, such as age, gender, cholesterol, blood pressure, heart rate, ischemic cardiomyopathy, and conventional echocardiographic parameters, no other echocardiographic parameter remained an independent predictor. Therefore, despite the need for further randomized trials to confirm the applicability of the method in clinical practice, the evidence points to the superiority of GLS in predicting the mortality of HF patients – higher than even LVEF.

In this issue of the Journal of Brazilian Society of Cardiology, Maia et al.[13] conducted a cross-sectional study to verify the correlation between GLS findings and CPET parameters in a sample comprising 26 HF patients of both genders, sedentary, with New York Heart Association (NYHA) functional class II and III, reduced LVEF, and mean age of 47 years. The patients showed a mean strain of -7.5 ± 3.92, $maxVO_2$ of 19.09 ± 9.52 mL.kg.min, VE/VCO_2 slope of 39.43 ± 9.91, HRR of 19.65 ± 17.42, and $T_{1/2}VO_2$ (s) of 168.61 ± 43.90. They found a statistically significant correlation between GLS and all CPET variables analyzed: HRR, $maxVO_2$, VE/VCO_2 slope, and $T_{1/2}VO_2$ (s).

Regarding HRR in the first minute post-exercise, patients with slower heart rate reduction showed a strong correlation with lower GLS values. When compared to data collected from CPET, LVEF presented a significant correlation only with $maxVO_2$ (direct) and $T_{1/2}VO_2$ (s) (inverse). On the other hand, GLS was able to predict all variables analyzed by CPET. In short, the study aimed to show the correlation of functional capacity and other CPET variables with GLS, both with established prognostic roles, and that GLS might be more accurate when classifying the severity of HF patients compared to LVEF, providing important knowledge and possible future applications in this scenario.

Keywords

Heart Failure; Systolic; Myocardial Contraction; Myocardial Stunning; Stroke Volume: Strain; Echocardiography/methods.

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Nevertheless, the study by Maia et al.[13] has important issues that should be addressed. The low sample size is a significant limitation of the study, making it impossible to extrapolate the data and use them routinely in clinical practice. Also, the study was not designed and did not have the power to demonstrate the prognostic impact of the findings. On the other hand, the data corroborate previous findings of the literature, indicating that the smaller the GLS value found, the poorer the functional capacity of the individual tends to be; these data are relevant, as they predict a worse prognosis. These outcomes help open new doors and perspectives for further studies in this field, which could confirm important messages conveyed in the literature and strengthened by Brazilian authors.

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High Level of Lipoprotein(a) as Predictor for Recurrent Heart Failure in Patients with Chronic Heart Failure: a Cohort Study

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Abstract

Background: Elevated plasma levels of Lipoprotein(a) [Lp(a)] are recognized as a significant risk factor for atherosclerotic vascular disease. However, there are limited data regarding association between Lp(a) and recurrent heart failure (HF) in patients with chronic HF caused by coronary heart disease (CHD).

Objective: Elevated levels of Lp(a) might have a prognostic impact on recurrent HF in patients with chronic HF caused by CHD.

Methods: A total of 309 patients with chronic HF caused by CHD were consecutively enrolled in this study. The patients were divided into 2 groups according to whether Lp(a) levels were above or below the median level for the entire cohort (20.6 mg/dL): the high Lp(a) group (n = 155) and the low Lp(a) group (n = 154). A 2-sided $p < 0.05$ was statistically considered significant.

Results: During the median follow-up period of 186 days, 31 cases out of a total of 309 patients (10.03%) could not be reached during follow-up. A Kaplan–Meier analysis demonstrated that patients with higher Lp(a) levels had a higher incidence of recurrent HF than those with lower Lp(a) levels (log-rank < 0.0001). A multivariate Cox regression analysis revealed that Lp(a) levels were independently correlated with the incidence of recurrent HF after adjustment of potential confounders (hazard ratio: 2.720, 95 % confidence interval: 1.730-4.277, $p < 0.0001$).

Conclusions: In Chinese patients with chronic HF caused by CHD, elevated levels of Lp(a) are independently associated with recurrent HF. (Arq Bras Cardiol. 2019; 113(2):197-204)

Keywords: Lipoproteins; Apolipoproteins; Heart Failure; Coronary Artery Disease; Hypertension; Diabetes Mellitus; Echocardiography/methods; Cohort Studies.

Introduction

Heart failure (HF) is a global, severe public health issue.[1] According to previous reports, the prevalence of HF is stable, at approximately 1% to 2% of the general population, but this number sharply increases to 20% in those aged over 80 years.[2] Among most developed and developing countries, the increasing number of HF patients has already become a significant epidemic and a major cause of hospitalizations, morbidity, and mortality despite advances in the treatment of HF.[3-6]

Elevated plasma levels of Lipoprotein(a) [Lp(a)] are recognized as a significant risk factor for atherosclerotic cardiac and cerebrovascular disease.[7-11] Lp(a) consists of one molecule of a low density lipoprotein (LDL)-like particle, containing apolipoprotein B-100 (apoB) and one molecule of a large highly polymorphic glycoprotein, named apolipoprotein(a) (apoA), which are connected by a single disulfide bond.[12] Studies have shown that Lp(a) contributes to cardiovascular disease (CVD) risk through multiple mechanisms, such as proatherogenic, proinflammatory, and potentially antifibrinolytic mechanisms.[13-15]

In the current studies, high levels of Lp(a) have been shown to be an independent risk factor for myocardial infarction,[8] stroke,[7] aortic stenosis,[16] and, as now shown, HF.[17] However, no studies have illustrated the significant association between Lp(a) levels and recurrent HF in participants with chronic HF caused by coronary heart disease (CHD). Therefore, our study sought to evaluate the association between plasma levels of Lp(a) and recurrent HF in patients with chronic HF caused by CHD.

Methods

Research design and population

In total, 309 hospitalized patients who were diagnosed with chronic HF due to CHD in the First Affiliated Hospital of Jinan University Guangzhou, China, were consecutively

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enrolled over a continuous period between January 2014 and December 2016. Chronic HF was diagnosed by two cardiologists based on 2016 European Society of Cardiology guidelines.[18] Patients were enrolled based on the following criteria: 1) The etiology of chronic HF is CHD; 2) patients with HF in New York Heart Association functional class II to IV. Patients were excluded according to the following criteria: 1) chronic HF secondary to other heart diseases, such as valvular heart disease, obstructive hypertrophic cardiomyopathy, and myocarditis and pericardial disease; 2) complicated with infectious diseases, autoimmune diseases, malignant tumors, severe liver and end-stage kidney disease with dialysis and systemic disease such as hyperthyroidism; 3) removal of patients who lack clinical data; 4) administration of medications that affect Lp(a) levels (nicotinic acid including niceritrol, tocopherol nicotinate, and nicomol).

Data at the first admission were collected for patients with multiple hospitalizations. Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg on repeated measurements, or the use of antihypertensive medication. Diabetes mellitus (DM) was defined according to the World Health Organization criteria.[19] We assessed the estimated glomerular filtration rate (eGFR) according to the Chinese Modification of Diet in Renal Diseases equation based on serum creatinine, age, and gender.[20] This study was approved by the ethics committee of the First Affiliated Hospital of Jinan University and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants involved in the study.

Laboratory measurements

The venous blood samples were usually obtained on the 2nd morning of admission after an 8-hour fasting. Serum Lp(a) levels were measured by latex agglutination immunoassays and apolipoproteins were determined by fixed-rate immunonephelometric assay using a HITACHI 7600 chemistry autoanalyzer (Hitachi High-Technologies Corporation, Tokyo, Japan).

Echocardiography

Transthoracic echocardiographic examination was performed on each enrolled patient by an experienced ultrasonographist using a Philips IE33 (Philips Healthcare, the Netherlands) cardiac ultrasound system machine within 24 to 48 hours after admission and within 24 hours after the primary PCI. Left ventricular ejection fraction (LVEF) was estimated with the modified Simpson method.

Clinical outcome and follow-up

The primary outcome evaluated in the present study was recurrent HF. The patients included in this study were followed for 1, 3, 6, 9, and 12 months after discharge with 1) access to medical records, outpatient electronic workstations, and medical insurance system; 2) telephone or face-to-face visits. For follow-up failures, we contacted the patients' family or neighbors, or even their workplaces.

Statistical analysis

First, continuous variables with normal distribution were expressed as mean (standard deviation [SD]); non-normal variables were reported as median (interquartile range [IQR]). Categorical variables were described as numbers and/or percentages. Means of 2 continuous normally distributed variables were compared by independent samples Student's *t* test. Mann-Whitney U test was employed to compare means of 2 groups of variables not normally distributed. The frequencies of categorical variables were compared using Pearson χ^2 test.

Second, patients were divided into 2 groups according to whether Lp(a) levels were above or below the median level for the entire cohort (20.6 mg/dL): the high Lp(a) group (n = 155) and the low Lp(a) group (n = 154). The event-free rate for recurrent HF was plotted using Kaplan−Meier method with the log-rank test.

Third, we analyzed the association of plasma Lp(a) levels as a continuous variable and as categorical variables with recurrent HF. Cox proportional hazards models were used to evaluate these associations, both with and without adjustment for confounding variables. In the adjusted regression model I, number of stents, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, and NYHA class were included. Model II was further adjusted for the same variables as Model I plus the following risk factors: gender, DM, atrial fibrillation (AF), hypertension, LAD lesion, prior PCI, two lesions, diuretics, ACEI/ARBs, digoxin, beta-blockers, anti-diabetic drugs, heart rate, total cholesterol (TC), potassium, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides, hemoglobin, LVEF, age, body mass index (BMI), and eGFR.

The MedCalc software, version 15.2.2, was used to calculate the clinical outcomes with relative risk and 95% confidence interval (CI). The Cox proportional hazards models analyses was performed using the EmpowerStats statistical software (http://www.empowerstats.com, X&Y Solutions, Inc. Boston, MA) and the statistical package R (http://www.R-project.org). A 2-sided $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 309 patients with chronic HF caused by CHD were enrolled in this study. 31 patients (10.03%) could not be reached during follow-up. The mean age of the patients was 68.6 ± 11.6 years, and 174 (56.3%) were males. The medians (IQR) of two groups of Lp(a) levels were 12.0 (7.6-16.6) mg/dL and 35.3 (25.4-52.0) mg/dL, respectively ($p < 0.001$).

Baseline characteristics and laboratory results, past medical history, and medications at discharge are shown in Table 1. There were differences in NYHA class, LVEF, NT-proBNP and Lp(a) levels, prior MI, prior PCI, multiple lesions, and number of stents between 2 groups. Meanwhile, there were no differences regarding medication at discharge, age, male gender, current smoker, BMI, heart rate, eGFR, conventional lipid profile, DM, AF, hypertension, and prior CABG.

Table 1 – Baseline characteristics of the study population

Variables	All patients (n = 309)	Low-Lp (a) Group (n = 154)	High-Lp (a) Group (n = 155)	p value
Age (years)	68.6 ± 11.6	68.5 ± 11.7	68.8 ± 11.6	0.833
Male gender (%)	174 (56.3)	79 (51.3)	95 (61.3)	0.077
Current smokers (%)	72 (23.3)	31 (20.1)	41 (26.5)	0.189
Alcohol intake (%)	15 (4.9)	6 (3.9)	9 (5.8)	0.435
Heart rate (beats/min)	81.6 ± 18.5	81.7 ± 18.0	81.5 ± 19.1	0.920
BMI (kg/m^2)	21.9 ± 4.5	22.4 ± 4.5	21.5 ± 4.5	0.087
SBP (mmHg)	142.5 ± 28.1	146.0 ± 29.3	139.0 ± 26.4	0.801
NYHA class (%)				**< 0.001**
II	154 (49.8)	103 (66.9)	51 (32.9)	
III	102 (33.0)	32 (20.8)	70 (45.2)	
IV	53 (17.2)	19 (12.3)	34 (21.9)	
Potassium (mmol/L)	3.9 ± 0.4	3.9 ± 0.4	4.0 ± 0.4	0.754
Sodium (mmol/L)	141.1 ± 4.2	141.2 ± 3.9	141.0 ± 4.4	0.633
Hemoglobin (g/dL)	131.0 ± 17.8	130.6 ± 16.3	131.2 ± 19.2	0.760
NT-proBNP (pg/ml)	3109.0 (1500.0-6313.0)	1534.5 (1075.0-2523.5)	5977.0 (3222.0-8835.0)	< 0.001
LN-NT-proBNP (pg/ml*)	8.0 ± 0.8	7.4 ± 0.7	8.6 ± 0.6	< 0.001
LVEF (%)	48.3 ± 4.2	49.2 ± 3.8	47.4 ± 4.4	< 0.001
eGFR (mL/min/1.73 m^2)	85.3 ± 29.8	88.4 ± 28.1	82.1 ± 31.1	0.063
TC (mg/dL)	156.7 (129.7-190.4)	161.0 (135.3-187.9)	156.0 (127.3-191.9)	0.974
Lp(a) (mg/dL)	20.6 (12.0-35.3)	12.0 (7.6-16.6)	35.3 (25.4-52.0)	< 0.001
HDL-C (mg/dL)	42.6 (36.4-50.3)	42.8 (36.1-50.3)	42.6 (37.0-49.5)	0.762
LDL-C (mg/dL)	90.3 (72.6-118.1)	92.1 (74.9-111.2)	88.4 (64.3-121.8)	0.609
TG (mg/dL)	117.8 (82.3-167.3)	125.7 (81.5-189.5)	112.5 (83.7-155.4)	0.133
LAD lesion(%)	278 (90.0)	137 (89.0)	141 (91.0)	0.557
Two lesions(%)	91 (29.4)	41 (26.6)	50 (32.3)	0.277
Multiple lesions(%)	89 (28.8)	34 (22.1)	55 (35.5)	0.009
Number of stents (%)				**< 0.001**
0	141 (45.6)	87 (56.5)	54 (34.8)	
1	96 (31.0)	47 (30.5)	49 (31.6)	
2	50 (16.2)	11 (7.1)	39 (25.2)	
3	14 (4.5)	5 (3.2)	9 (5.8)	
4	8 (2.6)	4 (2.6)	4 (2.6)	
History of				
DM(%)	130 (42.1)	57 (37.0)	73 (47.1)	0.073
AF(%)	32 (10.4)	18 (11.7)	14 (9.0)	0.444
Hypertension (%)	251 (81.2)	131 (85.1)	120 (77.4)	0.085
Prior MI(%)	91 (29.4)	33 (21.4)	58 (37.4)	0.002
Prior CABG(%)	2 (0.6)	2 (1.3)	0 (0.0)	0.475
Prior PCI(%)	164 (53.1)	66 (42.9)	98 (63.2)	<0.001
Medications at discharge				
Diuretics (%)	183 (59.2)	88 (57.1)	95 (61.3)	0.458
Digoxin (%)	12 (3.9)	5 (3.2)	7 (4.5)	0.564
ACEI/ARBs (%)	285 (92.2)	140 (90.9)	145 (93.5)	0.386

Continuation

Beta-blockers (%)	276 (89.3)	133 (86.4)	143 (92.3)	0.093
Aldosterone antagonists (%)	171 (55.3)	83 (53.9)	88 (56.8)	0.611
antiplatelet drugs(%)	296 (95.8)	146 (94.8)	150 (96.8)	0.389
Statins (%)	303 (98.1)	150 (97.4)	153 (98.7)	0.405
Anti-diabetic drugs(%)	125 (40.5)	55 (35.7)	70 (45.2)	0.091

*AF: atrial fibrillation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LAD: lesion left anterior descending artery lesion; NYHA class: New York Heart Association class; NT-proBNP: N-terminal pro-B type natriuretic peptide; Prior MI: prior myocardial infarction; Prior CABG: prior coronary artery bypass grafting; Prior PCI: prior percutaneous coronary intervention; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides. *LN-NT-proBNP was the natural logarithm of NT-proBNP. Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]) or n (%).*

Clinical outcomes

The median follow-up period was 186 days, with a maximum of 365 days. Clinical outcomes between groups are summarized in Table 2. The recurrent HF was significantly different between the 2 groups, but cardiac death, acute coronary syndrome, and ischemic stroke were not. The presence of elevated Lp(a) levels was associated with a greater rate of the recurrent HF (51.3% vs 78.1%, $p < 0.0001$).

Kaplan-Meier survival analysis

Kaplan-Meier survival analysis demonstrated that patients in the high Lp(a) group had a significantly higher incidence rate of the recurrent HF compared with those in the low Lp(a) group (log-rank $p < 0.0001$) (Figure 1).

Hazard ratio (95% confidence interval) for recurrent HF events

Considering Lp(a) < 20.6 as the reference group, Lp(a) ≥ 20.6 had higher risks for recurrent HF, with HR of 3.071 (95% CI, 2.283-4.130, $p<0.0001$). When adjusted for clinical parameters such as number of stents, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, NYHA class, the HR of Lp(a) ≥ 20.6 was 2.244 (95% CI, 1.493-3.371, $p = 0.0001$). The HR from adjusted II was further increased after further adjustment for other known confounding variables. Compared with the reference, the HR of Lp(a) ≥ 20.6 was 2.720 (95% CI, 1.730-4.277, $p = 0.0001$). In addition, analyses with the plasma Lp(a) levels as a continuous variable were conducted for the overall population, which showed these associations remained statistically significant after adjustment in Adjust I and Adjust II (Table 3).

Discussion

To our knowledge, this is the first study to analyze the association between baseline Lp(a) levels and recurrent HF in patients with chronic HF due to CHD. We found that a higher Lp(a) level is an independent predictor of the occurrence of recurrent HF in patients with chronic HF caused by CHD.

Previous several studies have demonstrated the association between Lp(a) levels and cardiac and cerebrovascular events. High levels of Lp(a) are associated with increased risk of myocardial infarction in a prospective general population study with 16 years of follow-up.[8] One study revealed that Lp(a) levels at admission were independently correlated with the occurrence of MACCE in patients with STEMI.[21] Another study suggested that an elevated Lp(a) level was significantly associated with long-term mortality following coronary angiography or percutaneous coronary intervention.[22] Although many studies have shown that LP(a) is an independent risk factor for adverse cardiac and cerebrovascular outcomes, limited data are available on the association between baseline Lp(a) levels and recurrent HF. In our study, we showed that baseline levels of Lp(a) ≥ 20.6 mg/dL was associated with significantly increased risk of recurrent HF with an HR of 2.720 (95% CI, 1.730-4.277; $p < 0.0001$) in patients with chronic HF due to CHD during the one-year follow-up, even after adjustment for major covariables. This observed association is consistent with the findings from a large-scale prospective study in a Danish overall population that consisted of 98,097 participants aged 48–67 y at baseline, followed for up to 21 years (mean of 7). The population attributable risk of HF was 9% for elevated Lp(a) levels.[17]

Currently, there are a few possible reasons for HF. Two possible mechanisms might explain this association between Lp(a) and HF occurrence:1) The increased HF risk due to elevated Lp(a) levels was partially mediated by myocardial infarction and/or aortic valve stenosis,[17,23] which can also be observed in our study. However, most part cannot be explained through both sides. 2) Given its proatherogenic properties, increased arterial stiffness, including vascular noncompliance in the aorta, was strongly associated with increased risk of HF.[24] Because echocardiography data were not collected, we could not assess the associations of Lp(a) levels, aortic stenosis, arterial stiffness and HF in our study. Compared with previous studies, our study included patients with a history of chronic HF. In addition, patients have poor left ventricular systolic function. The abovementioned fact is the possible cause of HF recurrence.

Additionally, the median value of Lp(a) is also different among different ethnicities, such as non-Hispanic Caucasians (median, 12 mg/dL [IQR, 5-32 mg/dL]), and Japanese individuals (median, 13 mg/dL [IQR, 5-26 mg/dL]).[25] In our study, Lp(a) was higher than in other populations (median, 20.6 mg/dL [IQR, 12.0-35.5 mg/dL]). Apo (a) contains 10 KIV repeated

Table 2 – Clinical outcomes

Variables	Low-Lp (a) Group (n = 154)	High-Lp (a) Group (n = 155)	RR	95% CI	p value
Recurrent HF	79 (51.3)	121 (78.1)	1.52	1.28-1.81	< 0.0001
Ischemic stroke	1 (0.6)	3 (1.9)	2.98	0.31-28.34	0.3419
ACS	1 (0.6)	5 (3.2)	4.97	0.59-42.03	0.1412
NSTEMI	0 (0)	2 (1.3)	4.97	0.24-102.65	0.2995
STEMI	1 (0.6)	3 (1.9)	2.98	0.31-28.34	0.3419
Cardiac death	0 (0)	2 (1.3)	4.97	0.24-102.65	0.2995

ACS: acute coronary syndrome; CI: confidence interval; HF: heart failure; NSTEMI: non-ST-segment elevation myocardial infarction; RR: relative risk; STEMI: ST-segment elevation myocardial infarction. Data are presented as n (%).

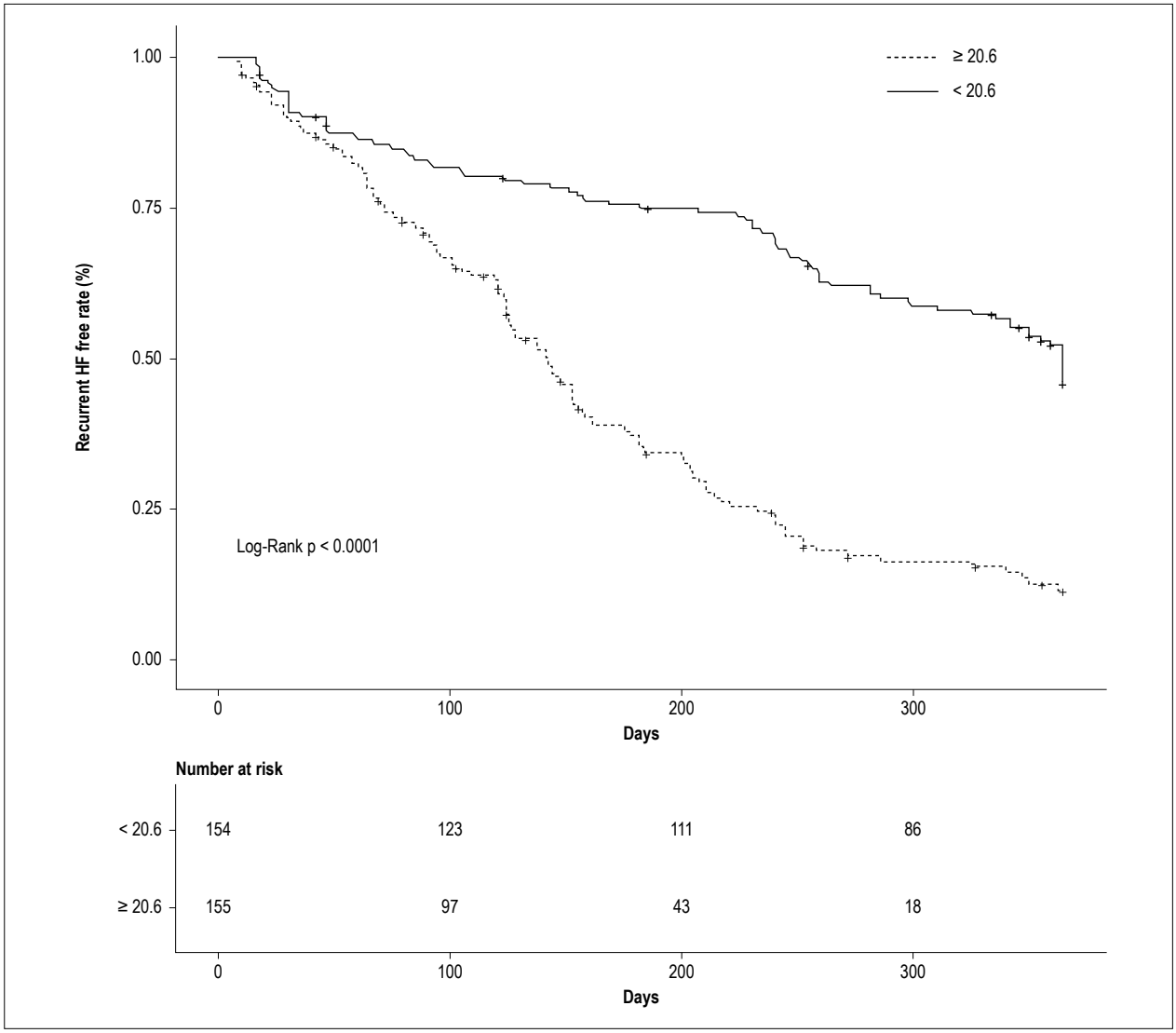

Figure 1 – *Kaplan-Meier curve for recurrent HF free rate according to Lp(a) levels. HF: heart failure.*

subtypes comprised of a single copy of KIV1, multiple copies of KIV2, a single copy of KIV3 ~ 10.[12] Lp(a) levels are genetically determined by the variation of the copy number of kringle IV type 2 (KIV-2) repeats on the *LPA* gene and various single nucleotide polymorphisms.[25] The number of repeats was inversely associated with Lp(a) levels.[25] In addition, Frischmann et al.[26] observed that increased plasma LP(a) levels were associated with renal dysfunction. In our study, the

Table 3 – Associations between baseline Lp(a) with recurrent heart failure

Exposure	Non-adjusted HR (95%CI)	p value	Adjust I HR (95%CI)	p value	Adjust II HR (95%CI)	p value
LP(a)	1.022 (1.016-1.028)	< 0.0001	1.014 (1.006-1.023)	0.0008	1.018 (1.009-1.027)	0.0001
LP(a)						
< 20.6	1.0		1.0		1.0	
≥ 20.6	3.071 (2.283-4.130)	< 0.0001	2.244 (1.493-3.371)	0.0001	2.720 (1.730-4.277)	< 0.0001

AF: atrial fibrillation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LDL-C: low-density lipoprotein cholesterol; LAD: lesion left anterior descending artery lesion; Lp(a): lipoprotein(a); NYHA class: New York Heart Association class; NT-proBNP: N-terminal pro-B type natriuretic peptide; Prior PCI: prior percutaneous coronary intervention; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides. Non-adjusted model adjust for: none. Adjust I model adjust for: number of stent, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, NYHA class.

included subjects had lower glomerular filtration rate, which led to reduced clearance of Lp(a), and higher plasma levels than in other previously studied Chinese populations.

In our study, the rates of statin use were up to 97.4% and 98.7% in patients with low-Lp(a) group and high-Lp(a) group, respectively, and most patients adhered to statin therapy during follow-up, but statins were originally intended to lower LDL-C levels. Moreover, previous studies have shown that statin therapy did not easily alter Lp(a) levels.[27,28] About the Lp(a) reduction treatment, early treatment with nicotinic acid, with the increase in nicotinic acid treatment dose, also correspondingly resulted in lower serum levels of Lp(a), and a maximum reduction in Lp(a) levels of up to 30-40%.[29] Because of the significant side effects such as facial blushing and liver toxicity, it is no longer widely used.[30] Recently, new Lp(a)-lowering treatments have emerged. The novel lipid-lowering drug Mipomersen is a synthetic inhibitor of apoB that indirectly reduces the synthesis of Lp(a) by reducing the synthesis of apo B, which can significantly reduce Lp(a) levels in patients with CHD.[31] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce the level of LP(a) by inhibiting the degradation of low-density lipoprotein receptors (LDLR).[32] In the present study, none of the subjects used the abovementioned drugs. For patients with chronic HF due to CHD, further multicenter prospective randomized controlled trials are needed to verify whether lowering the levels of serum Lp(a) can reduce the risk of cardiovascular and cerebrovascular events.

Conclusion

In conclusion, in Chinese patients with chronic HF caused by CHD, our study demonstrates that elevated levels of Lp(a) significantly predict recurrent HF.

Limitations

Our study has several limitations. First, it was a retrospective, observational and single-center study with selection bias. Therefore, whether the associations between LPA, B and HF are actually established, further multicenter prospective randomized controlled trials are needed to verify them in the future. Second, although we adjusted several known confounding variables in the multivariable Cox proportional hazards models, other unknown factors might have played roles in recurrent HF. Third, the detection of events may have been incomplete due to follow-up failures. 31 cases out of a total of 309 patients (10.03%) could not be reached during follow-up. Fourth, our study did not differ between HF with preserved and reduced ejection fraction when assessing the association between Lp(a) and recurrent HF in patients with chronic HF who have CHD.

Author contributions

Conception and design of the research: Yan J, Pan Y, Xiao J; Acquisition of data: Yan J, Pan Y; Analysis and interpretation of the data: Yan J, Pan Y, Xiao J, Zhong M, Long H; Statistical analysis: Yan J, Pan Y, Xiao J, Ma W, Li L, Zhong M, Long H, Kong F; Writing of the manuscript: Yan J, Pan Y, Shao W; Critical revision of the manuscript for intellectual content: Yan J, Pan Y, Ma W, Li L, Kong F, Shao W.

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 The First Affiliated Hospital of Jinan University under the protocol number 017. 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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Biomarkers in Heart Failure

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Short Editorial related to the artticle: High Level of Lipoprotein(a) as Predictor for Recurrent Heart Failure in Patients with Chronic Heart Failure: a Cohort Study

The World Health Organization defines biomarker as any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence or outcome of a disease.[1] Biomarkers can serve multiple purposes: diagnostic, disease staging, prognostic and prediction and monitoring of responses to an intervention.[1]

A useful biomarker should allow repeated and accurate measurements with a rapid turnaround time at a reasonable cost, should provide information that is not already available from careful clinical assessment and its performance should be superior to other available tests, and should assist decision making and enhance clinical care.[2]

Several biomarkers have been studied in the context of acute and chronic heart failure (HF). In 2016 the American Heart Association issued a statement on the Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure.[3] After an extensive review, they stated that a number of biomarkers associated with HF are well recognized, and measuring their concentrations in circulation can be a convenient and noninvasive approach to provide important information about disease severity and help in the detection, diagnosis, prognosis, and management of HF. These include natriuretic peptides, soluble suppressor of tumorigenicity 2 (ST-2), highly sensitive troponin, galectin-3, mid regional pro adrenomedullin (MR-proADM), cystatin-C, interleukin-6 and procalcitonin. There is a need to further evaluate existing and novel markers for guiding therapy.

The 2018 Brazilian Guidelines on Chronic and Acute Heart Failure recommends the use of natriuretic peptides with diagnostic and prognostic purposes.[3] According to these guidelines other biomarkers such as troponins T and I, galectin-3 and ST-2 may add prognostic information in HF patients.[4]

More recently Swedish investigators reported that elevated plasma levels of NT-proBNP, MR-proADM, copeptin, and cystatin C were associated with higher mortality after discharge in a cohort of 286 patients hospitalized for newly diagnosed or exacerbated HF.[5] Nonetheless, NT-proBNP was the only biomarker to predict the risk of re-hospitalization due to cardiac causes.

Lipoprotein(a) (Lp(a)) is a biomarker associated with increased risk of atherosclerotic disease. In 2016 Kamstrup and Nordestgaard demonstrated a clear stepwise association of elevated Lp(a) levels with increased risk of HF in a study with more than 98,000 danish participants.[5] In addition, they provided genetic evidence that this association was mediated at least partly via coronary heart disease (CAD) and aortic valve stenosis.

This issue of *Arquivos Brasileiros de Cardiologia* presents the paper of Jianlong et al.[6] examining the prognostic value of Lp(a) in Chinese patients admitted for decompensated HF of ischemic origin. An Lp(a) greater than 20,6 mg/dL was associated with 3 fold increase in readmission for HF. Patients with higher Lp(a) levels also had higher NT-proBNP levels, higher NYHA class, lower left ventricle ejection fraction, more CAD. The results were adjusted for theses covariates with a slight decrease in the hazard ratio.

Lp(a) may be a prominent new biomarker in patients with HF of ischemic origin. More studies in different populations are needed to validate these results.

Keywords

Biomarkers; Lipoproteins; Heart Failure; Hypertension; Diabetes Mellitus.

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Presystolic Wave is Associated with Subclinical Left Ventricular Dysfunction Assessed by Myocardial Performance Index in Type 2 Diabetes Mellitus

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Abstract

Background: **Myocardial performance index (MPI), demonstrates both systolic and diastolic functions of the left ventricle. Presystolic wave (PSW) is frequently detected on Doppler examination of the left ventricular outflow tract and possible mechanism of PSW is impaired LV compliance and left ventricular stiffness.**

Objective: **To investigate the relationship between PSW and MPI in type 2 diabetic patients.**

Method: **A total of 129 type 2 diabetic patients were included in this study. Patients were divided into two groups according to the presence of PSW on Doppler echocardiography. There were 90 patients (38 male, mean age 57.77 ± 10.91 years) in the PSW-positive group and 39 patients (13 male; mean age: 55.31 ± 11.29 years) in the PSW-negative group. The p values of < 0.05 were considered statistically significant.**

Results: **MPI was higher in PSW- positive group (0.63 ± 0.17vs 0.52 ± 0.13, p < 0.001). In addition, subclinical left ventricle dysfunction (LVD) was higher in the PSW- positive group (p = 0.029). Univariate analysis showed that the presence of PSW associated with abnormal MPI (p = 0.031). Pearson correlation analysis showed that PSW velocity correlated with MPI (r: 0.286, p = 0.006).**

Conclusion: **Presence of the PSW on Doppler examination was associated with subclinical LV dysfunction in patients with DM type 2. This easy-to-perform echocardiographic parameter may be related to subclinical LVD among patients with type 2 DM. (Arq Bras Cardiol. 2019; 113(2):207-215)**

Keywords: **Heart/physiopathology; Diabetes Mellitus Type 2; Ventricular Dysfunction,Left; Heart Failure; Risk Factors.**

Introduction

Diabetic cardiomyopathy is a common, albeit frequently missed, clinical entity affecting even asymptomatic patients with type 2 diabetes mellitus (DM).[1] These patients suffer excessive left ventricular (LV) enlargement, which starts as a normal functional consequence but later progresses to subclinical LV dysfunction (LVD).[2,3] Patients with type 2 DM actually suffer subclinical LVD at variable rates between 25% and 60%.[4-6] The earliest stages of diabetic cardiomyopathy are reportedly characterized by both subclinical LV systolic dysfunction (LVSD) and subclinical LV diastolic dysfunction (LVDD).[7-9] Importantly, the latest studies have indicated a continuum in the progress of subclinical LVD despite fine glycemic control over a period of 5 years.[10] This phenomenon may be indicative of a heightened risk of new-onset heart failure in even well-controlled type 2 DM.[11]

First defined by Tei et al.,[12] myocardial performance index (MPI) is a surrogate marker of both ventricular systolic and diastolic functions. Its utility has been investigated in a variety of cardiac conditions including myocardial infarction, hypertension (HT), diabetes, and heart failure, and an increased MPI is reportedly an ominous prognostic sign and independent predictor for morbidity and mortality.[13,14] A presystolic wave (PSW) is commonly found when the LV outflow tract (LVOT) is examined with the Doppler examination.[15] PSW may theoretically be associated with poor LV compliance and increased LV stiffness.[16,17] Given the hypothetical link between PSW and subclinical LVD in type 2 DM, we theorized that PSW may be associated with subclinical LVD in patients with type 2 DM.

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Methods

Study population

Patients with Type 2 DM who were referred to the Cardiology and Endocrinology clinic of the Trabzon Kanuni Education and Research Hospital were enrolled by the study. A total of 129 patients were included in this study consecutively. Patients were divided into two groups according to the presence of PSW on Doppler echocardiography. There were 90 patients (38 male, mean age 57.77 ± 10.91 years) in the PSW- positive group and 39 patients (13 male; mean age: 55.31 ± 11.29 years) in the PSW-negative group. Demographic characteristics, biochemical parameters, and echocardiographic characteristics of the patients were compared between the groups. The following subjects were excluded: those with a history of hypertrophic obstructive cardiomyopathy, angina pectoris, recent myocardial infarction, coronary artery bypass surgery, peripheral arterial disease, cardiac failure, moderate to severe valvular heart disease, valvular operation, history of stroke and transient ischemic attack, atrial fibrillation, chronic renal failure, chronic liver diseases, hematological disorders, malignancy, thromboembolic disorders, congenital heart disease, congestive heart failure, and acute bacterial endocarditis. The study was approved by the local ethics committee, and all patients provided informed consent.

Cardiovascular risk factor assessment

History of arterial HT, DM, hyperlipidemia (HL), and smoking, as well as a family history of coronary artery disease (CAD), were recorded for all patients. Type 2 DM was diagnosed on the basis of a history of treated DM and/or had a fasting blood glucose level equal to or greater than 126 mg/dl. HL was considered to exist when fasting total cholesterol level was ≥ 200 mg/dl, fasting low-density lipoprotein level ≥ 160 mg/dl, fasting triglyceride (TG) level ≥ 200 mg/dl, or using medication for HL. HT was said to be present in the case of a history of treated or untreated HT or when a mean systolic blood pressure of ≥ 140 mmHg and/or a mean diastolic blood pressure of ≥ 90 mmHg were obtained by averaging two blood pressure readings taken from each arm. The family history of CAD included a history of CAD or sudden cardiac death in first-degree male relative younger than 55 years or a first-degree female relative younger than 65 years.

Echocardiography

All subjects underwent a transthoracic echocardiographic examination using the Philips Epic 7 system (Philips Epic 7 Ultrasound AS) unit with a 2.5 MHz FPA probe. The conventional M-mode, B-mode, and Doppler parameters were done in compliance with the American Society of Echocardiography guidelines.[18] All echocardiographic examinations were performed by an experienced echocardiographer who was unaware of the patients' clinical and demographic data. Quantification of LV end-diastolic and end-systolic diameters and posterior and septal wall thicknesses were carried out. The Devereux equation was used to derive LV mass (LVM): $LVM = 0.8 \times [1.04 (LVEDD + IVST + PWT)^3 – (LVEDD^3)] + 0.6$, where LVEDD denotes LV end-diastolic diameter, IVST denotes intraventricular septal wall thickness, and PWT denotes posterior wall thickness. The LVM index was calculated by the formula: LVM/body surface area. Body surface area (BSA) was calculated using the 'BSA (m^2) = 0.007184 x Height (cm)$^{0.725}$ x Weight (kg)$^{0.425}$ ' formula. LV hypertrophy was considered positive if LVM index was above 115 g/m^2 for men and above 95 g/m^2 for women.[19] LVOT's portion just proximal to the aortic valve was interrogated with pulsed wave Doppler in the apical five-chamber window in order to check the presence of a PSW just before the LVOT flow. PSW peak velocity was quantified whenever a quantifiable PSW signal was present Figure 1. Tissue Doppler evaluation of the left ventricle was performed from the apical four-chamber view with a frame rate of greater than 80/s. All quantifications were performed on frozen images obtained from three to five cardiac cycles. Mitral annular velocities were quantified with the sample volume being placed at the junction of the mitral valve annulus and the septal myocardial wall. Time elapsed between the end of A' wave and the beginning of the E' wave and between the beginning of and the end of the S wave was defined as (a) and ejection time (ET), respectively, in tissue Doppler recordings done from the apical four-chamber. MPI was calculated using the 'MPI = (IVCT + IVRT)/ET = [(a) − (ET)]/(ET)' formula[20,21] (Figure 2). There existed intraobserver and interobserver variability of 3% to 5% for conventional Doppler and TDI-derived variables (PSW velocity, Em, Am, and MPI). 0.5 and over MPI level was defined as subclinical LVD.

Statistical analyses

The minimum number of subjects required in each group was determined to be 32 in order to find a significant difference between the two groups. Type I Error = 0.05, Test Power 0.80. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 19 (SPSS Inc. Chicago, IL, USA) software package. The continuous variables were reported as mean±SD or median (interquartile range) while the categorical variables were reported as frequency and percentage. Kolmogorov Smirnov test was used to test the distribution of the quantitative variables. Independent samples t-test was used to make inter-group comparisons for normally distributed quantitative data and Mann Whitney-U test for non-normally distributed data between. Qualitative variables were compared were with the Chi-square test. Univariate analysis was performed to assess the relations between the abnormal MPI and clinical and echocardiographic variables. Pearson correlation analysis was carried out to investigate the association between PSW peak velocity and mitral A and septal A' velocities. Spearman correlation analysis was carried out to investigate the association between PSW peak velocity and Em to Am ratio and septal E' to A' ratio. The confidence interval was set at 95 % and statistical significance was set at $p < 0.05$.

Results

Clinical and demographic characteristics of the patients are shown in Table 1. Age, sex, HT, current smoking, dyslipidemia, and family history for CAD were similar in the PSW-positive and negative groups. There was no difference between the

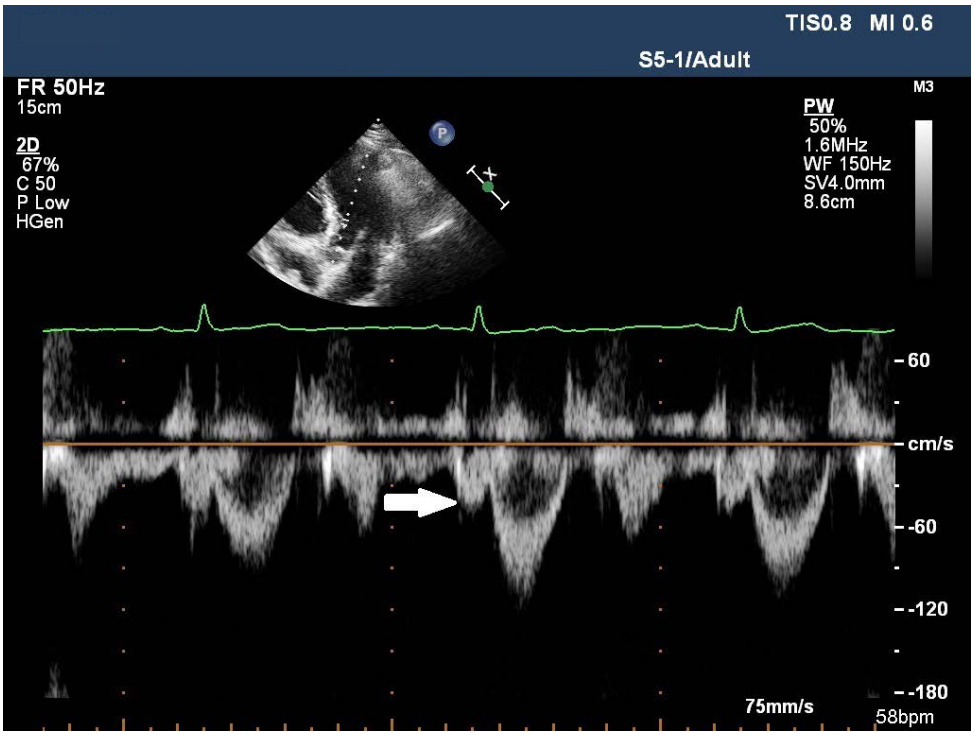

Figure 1 – *Arrow shows the PSW. PSW, presystolic wave.*

groups in terms of left ventricular mass (LVM), left ventricular mass index (LVMI), body mass index (BMI), BSA and duration of DM. There were no patients with LVH in both groups.

Biochemical parameters of the study population are shown in Table 1. Serum fasting glucose, serum creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, TG, and hemoglobin A1C were not different between both groups. There was no difference between the glomerular filtration rate of both groups. There was no difference between white blood cells, hemoglobin, platelet, mean platelet volume and red distribution width between the two groups.

The echocardiographic characteristics of the PSW-positive and negative groups are shown in Table 2. Left ventricular ejection fraction, left atrial diameter, interventricular septal diameter, S velocity, mitral E deceleration time were similar in the PSW-positive and negative groups. Left ventricular end diastolic diameter (LVEDd) and posterior wall diameter was similiar in both groups.

Doppler echocardiographic variables are shown in Table 2. Em, and septal E' wave velocities were greater in the PSW-negative group but Am and septal A' wave velocities were greater in the PSW-positive group. Em to Am ratio and septal E' to A' ratio were greater in the PSW-negative group. MPI was greater in the PSW-positive group (0.52 ± 0.13 vs 0.63 ± 0.17, $p < 0.001$) (Figure 3). Univariate analysis showed that the presence of PSW associated with abnormal MPI ($p = 0.031$) (Table 3). In addition, subclinical left ventricle dysfunction was more prevalent in the PSW-positive group ($p = 0.029$).

The Pearson correlation analysis showed that PSW velocity was significantly correlated with mitral A wave (r: 0.402, $p < 0.001$) and septal A' (r: 0.493, $p < 0.001$) velocities. PSW velocity was correlated with MPI (r: 0.286, $p = 0.006$) (Figure 4). The Spearman correlation analysis demonstrated that PSW velocity was significantly negatively correlated with Em to Am ratio (r: –0,527, $p < 0.001$) and septal E' to A' ratio (r: -0.572, $p < 0.001$).

Discussion

We demonstrated an overall prevalence of PSW of 69% among type 2 DM with preserved LV ejection fraction. As compared to those without, patients with PSW had a significantly higher prevalence of subclinical LVD. Furthermore, PSW had a correlation with subclinical LVD among these patients.

A PSW is formed late in diastole commonly encountered on Doppler examination of the LVOT, which has been linked to LVDD.[16] Mittal et al.[16] showed a direct correlation between PSW velocity and transmitral A wave velocity; significant inverse correlation with the Em to Am ratio; and no correlation with age and LVM.[16] Joshi et al.[22] reported a significant correlation between PSW velocity with mitral A-wave velocity and septal A' velocity.[21] Among hypertensive patients, Akyuz et al.[23] showed that PSW velocity was directly correlated with lateral A' wave velocity and inversely with the Em to Am ratio.[23] We detected a significant direct correlation between PSW velocity and mitral A-wave velocity, septal A' wave velocity but there was a significant inverse relation with the mitral E to A ratio and septal E' to A' ratio. Akyuz et al.[23] demonstrated a significant correlation between PSW velocity and age, LVM among hypertensive patients.[23]

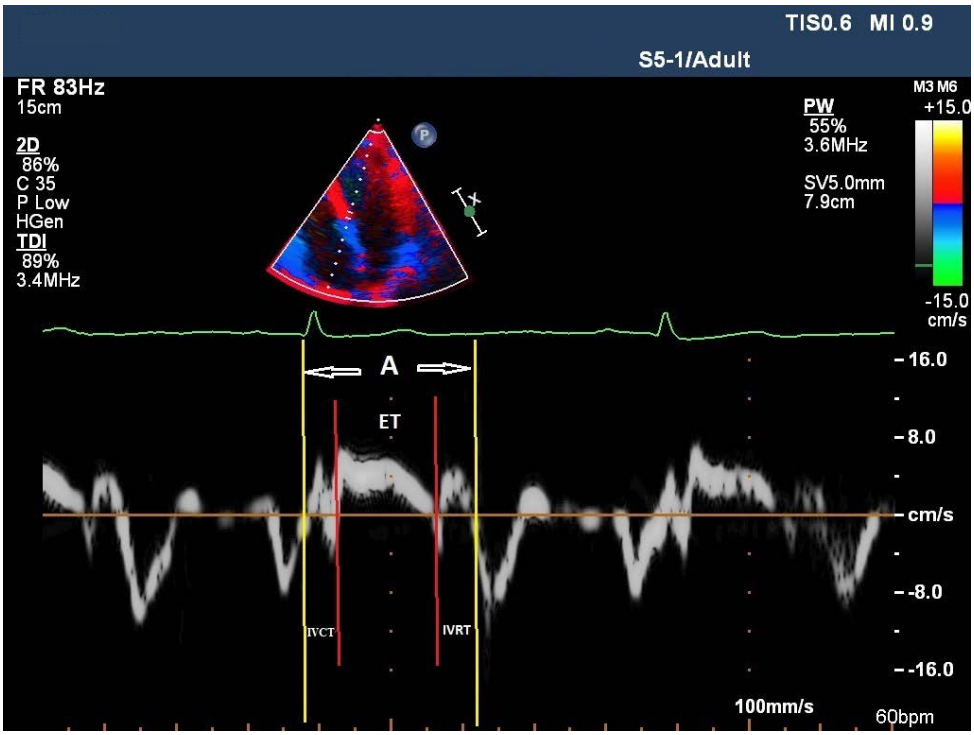

Figure 2 – *Myocardial performance index calculation. ET: ejection time; IVCT: isovolumetric contraction time; IVRT: isovolumetric relaxation time; A - time spent between closure and reopening of tricuspid valve. MPI = (IVCT+IVRT)/ET = ((A)-(ET))/(ET). MPI: myocardial performance index.*

Similar to Akyuz et al.,[23] we showed a correlation between PSW velocity and age. Unlike they, however, we failed to show any correlation between PSW velocity and LVM.

As of 2015, DM affects a total of 30.3 million Americans or 9.4% of the US population. Of these individuals, 7.2 million had clinically silent DM. Moreover, 1.5 million Americans yearly are added to the diabetic population in the US.[24] Diabetes is characterized by an increased risk of cardiovascular complications, mainly in the form of CAD, as the main source of morbidity and mortality among affected persons.[25] Simone et al.[26] recently reported that the risk of heart failure is heightened among type 2 diabetics and that this effect still occurs even persons do not sustain myocardial infarction or suffer HT.[26] Hence, the term diabetic cardiomyopathy has been recommended by medical communities, referring to the dysfunctional ventricle in the absence of CAD and HT.[27] Hyperglycemia is the source of advanced glycosylation end products (AGE). The latter are proteins with longer half-lives that have altered functional properties after being exposed to sugars and becoming glycated.[28]

When in excess, AGE formation may alter myocardial proteins structure and lead to stiff myocardium. The latter is a direct consequence of AGEs forming crosslinks between collagen molecules, which limits their degradation and leads to their accumulation in myocardial tissue, with resulting myocardial stiffness and reduced myocardial relaxation.[29] Diabetics suffer altered myocardial function largely due to hypertrophied ventricles, metabolic abnormalities, extracellular matrix remodelling, fibrosis, vascular changes, insulin resistance, oxidative stress and apoptosis.[30,31] Hyperglycemia may also promote myocyte apoptosis necrosis,[32] resulting in net myocardial cell loss,[33] reduced ventricular contractility, and systolic dysfunction. In combination, these phenomena cause reduced LV systolic and diastolic function among diabetics.

We used MPI to detect subclinical LVD. MPI is a noninvasive tool reflecting both systolic and diastolic ventricular functions, which is easy-to-perform.[34] Its use may predict future LV impairment and development of clinical heart failure long before they become clinically apparent.[35] It has been conclusively reported that MPI independent of blood pressure, heart rate, valvular regurgitation, ventricular geometry, preload, and afterload in patients who are lying flat.[36,37]

It is important for the clinician to determine subclinical LVD before apparent LVD occurs. For this purpose, we used MPI to identify subclinical LVD in type 2 DM. We demonstrated that MPI was significantly greater in PSW positive type 2 DM patients. This means that subclinical LVD is higher in the PSW positive group in type 2 DM. In addition, we found a correlation with PSW velocity and MPI in type 2 DM in this study. According to our study results, the presence of PSW on Doppler echocardiography and increased PSW velocity may be related to subclinical LVD in type 2 DM patients.

We did not aim to investigate the causal relationship between PSW and subclinical LVD in our study, but this relationship can be explained by several theories.

Table 1 – Demographic and biochemical characteristics of PSW positive and negative patients with type 2 DM

Variables	PSW - negative (n = 39)	PSW- positive (n = 90)	p
Age (years)	55.31 ± 11.29	57.77 ± 10.91	0.190
Sex, male, n	13	38	0.343
Hypertension, n	16	47	0.257
Current smokers, n	3	10	0,541
Family CAD, n	3	17	0.102
Dyslipidemia, n	7	13	0.632
BMI (kg/m^2)	30.42 ± 4.97	31.29 ± 5.80	0.423
BSA (m^2)	1.86 ± 0.18	1.87 ± 0.15	0.847
DM year	7 (1-10)	7 (4-12)	0.190
LVM, gr	124.17 ± 19.95	123.51 ± 32.86	0.908
LVMI, gr/m^2	67.37 ± 10.15	66.04 ± 16.40	0.647
Biochemical parameters			
Glucose, mgr/dl	173.43 ± 60.14	179.38 ± 64.60	0.760
Serum creatinine, mg/dL	0.69 ± 0.18	0.78 ± 0.17	0.108
GFR,%	103.14 ± 17.71	91.10 ± 21.85	0.065
Triglyceride, mgr/dl	145.91 ± 90.44	127.67 ± 68.20	0.481
LDL-c, mgr/dl	120.72 ± 44.32	126.85 ± 30.68	0.607
HDL-c, mgr/dl	49.70 ± 11.86	47.73 ± 10.97	0.627
HbA1c, %	8.15 ± 1.74	8.26 ± 1.83	0.844
HbA1c mmol	65.57 ± 19.03	66.87± 19.97	0.842
WBC, x10^9/L	7.77 ± 2.12	7.47 ± 1.78	0.614
PLT, x10^9/L	240.85 ± 63.80	244.41 ± 77.61	0.881
Hb, gr/dL	13.44 ± 1.49	13.57 ± 1.59	0.789
RDW, fL	13.6 (12.9-14.9)	13.5 (13.05-14.20)	0.863
MPV, fL	9.31 ± 1.00	8.80 ± 0.94	0.104

BMI: body mass index; BSA: body surface area; CAD: coronary artery disease; DM: diabetes mellitus; LVM: left ventricle mass; LVMI: left ventricle mass index; GFR: glomerular filtration rate; LDL-c: low-density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; WBC: white blood cell; Hb: hemoglobin; RDW: red distribution weight; MPV: mean platelet volume; PLT: platelet.

The increased formation of AGEs secondary to hyperglycemia may alter structural proteins and lead to increased myocardial stiffness and impaired LV relaxation.[29] A possible mechanism of PSW is impaired LV compliance and increased LV stiffness.[16,17] Impaired left ventricle compliance and increased stiffness may cause the occurrence of PSW in diabetic patients. In addition, PSW is associated with LVDD.[16] Development of LVDD may be one of the reasons for the occurrence of PSW in diabetic patients. As a result, PSW can be expected to occur in diabetic patients with subclinical LVD.

Conclusion

Presystolic wave on echocardiography was associated with subclinical LVD in patients with DM type 2. PSW is a simple and easily detectable echocardiographic parameter seen in late diastole and may associated with subclinical left ventricle dysfunction in type 2 DM.

Limitations of the study

Myocardial structural changes were not tested using imaging modalities. Type 2 diabetic patients alone were included in our study, limiting the use of our findings for the general population. Our findings may have been altered by antidiabetic drugs used by our patients. As our study is a cross-sectional study, its findings do fall short in making a causal relationship between MPI and PSW.

Author contributions

Conception and design of the research: Kul S, Dursun I, Ayhan S, Sayin MR, Üçüncü Ö, Bülbül NE, Akyüz AR; Acquisition of data: Kul S, Ayhan S, Üçüncü Ö, Bülbül NE, Akyüz AR; Analysis and interpretation of the data: Kul S, Akyüz AR; Statistical analysis: Kul S, Dursun I, Sayin MR, Ateş AH; Writing of the manuscript: Kul S; Critical revision of the manuscript for intellectual content: Kul S, Dursun I, Ayhan S, Sayin MR, Üçüncü Ö, Bülbül NE, Ateş AH, Akyüz AR.

Table 2 – Echocardioographic variables of PSW positive and negative patients with type 2 DM

Variables	PSW negative (n = 39)	PSW positive (n = 90)	p
LVEF, %	65 (60-65)	65 (65-65)	0.858
LVEDd, cm	4.33 ± 0.36	4.26 ± 0.39	0.338
LVESd, cm	2.61 ± 0.37	2.57 ± 0.40	0.584
LAD, cm	3.22 ± 0.40	3.27 ± 0.39	0.531
IVSd, cm	0.89 ± 0.10	0.92 ± 0.16	0.265
PWd, cm	0.86 ± 0.86	0.89 ± 0.13	0.177
S velocity, cm/sn	6.29 ± 1.23	6.39 ± 1.41	0.731
E' velocity, cm/sn	9.18 ± 2.40	7.47 ± 2.35	< 0.001
A' velocity, cm/sn	8.50 ± 1.87	10.18 ± 2.21	< 0.001
Em velocity, cm/sn	94.95 ± 17.23	80.20 ± 18.81	< 0.001
Am velocity, cm/sn	82.23 ± 14,00	91.69 ± 20.50	0.010
MEdt, msn	169.35 ± 37.39	160,32 ± 34.69	0.209
MPI	0.52 ± 0.13	0.63 ± 0.17	< 0.001
Subclinic LV dysfunction	23	70	0.029
Em to Am ratio	1.14 (1.07-1.35)	0.81 (0.72 -1.13)	< 0.001
E' to A' ratio	1.18 (0.81-1.39)	0.70 (0.56-0.85)	< 0.001

LVEF: left ventricle ejection fraction; IVSd: interventricular septal diameter; PWd: posterior wall diameter; LVEDd: left ventricle end-diastolic diameter; LVESd: left ventricle end-systolic diameter; LAD: left atral diameter; MPI: myocardial performance index; MEdt: mitral E wave deceleration time; LV: left ventricle.

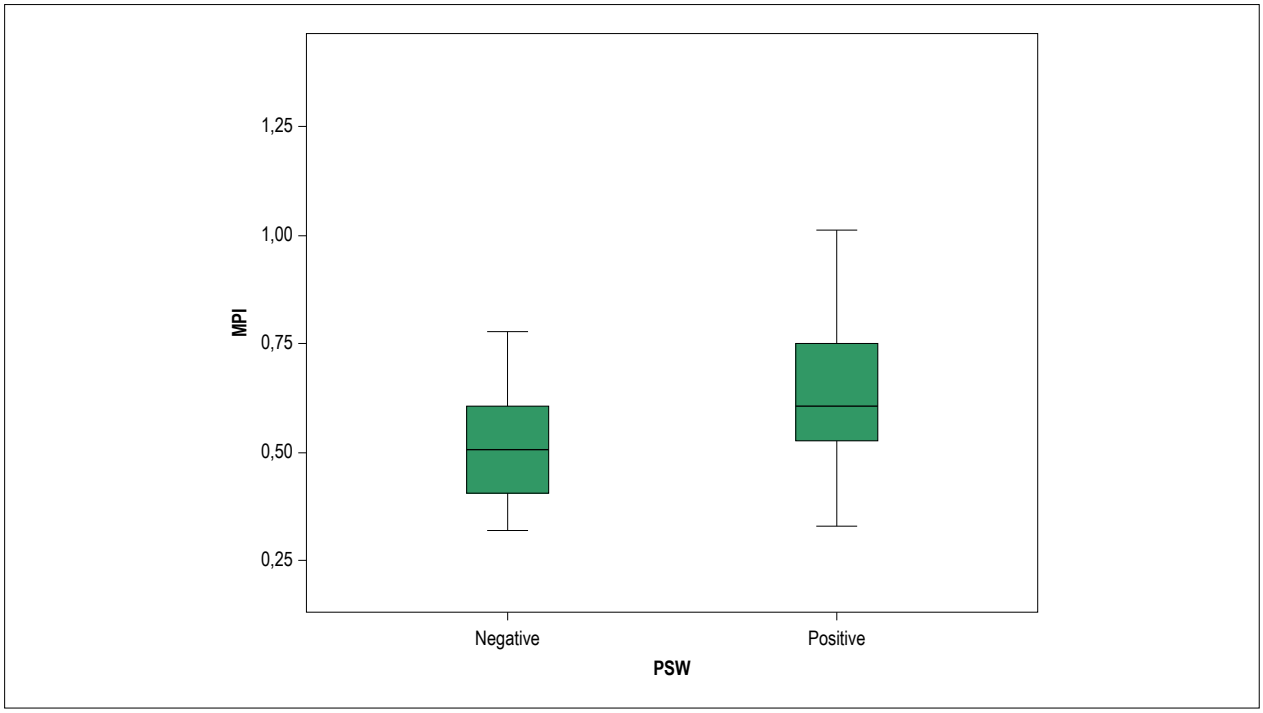

Figure 3 – *MPI level of PSW-positive and PSW-negative subjects. MPI: myocardial performance index; PSW: presystolic wave.*

Table 3 – Univariate analysis for abnormal MPI.

Variables	Odds ratios (% 95 CI)	p
Duration of DM	1.026 (0.967 - 1.089)	0.402
Age	1.014 (0.978 - 1.050)	0.445
Gender	0.818 (0.369 - 1.813)	0.621
Hypertension	2.057 (0.931 - 1.074)	0.075
Presence of PSW	2.435(1.084 - 5.466)	0.031
Hyperlipidemia	0.525 (0.195 - 1.417)	0.203
Current Smoking	1.153 (0.331 - 4.009)	0.823
Family history of CAD	4.135 (0.908 - 18.836)	0.067
BMI	1.012 (0.942 - 1.088)	0.741
Glucose	1.006 (0.995 - 1.017)	0.270
LDL-c	0.987 (0.965 - 1.009)	0.241
Trygliceride	0.999 (0.990 - 1.008)	0.812

MPI: myocardial performance index; DM: diabetes mellitus; PSW: presystolic wave; CAD: coronary artery disease; LDL-c: low-density lipoprotein cholesterol; BMI: body mass index.

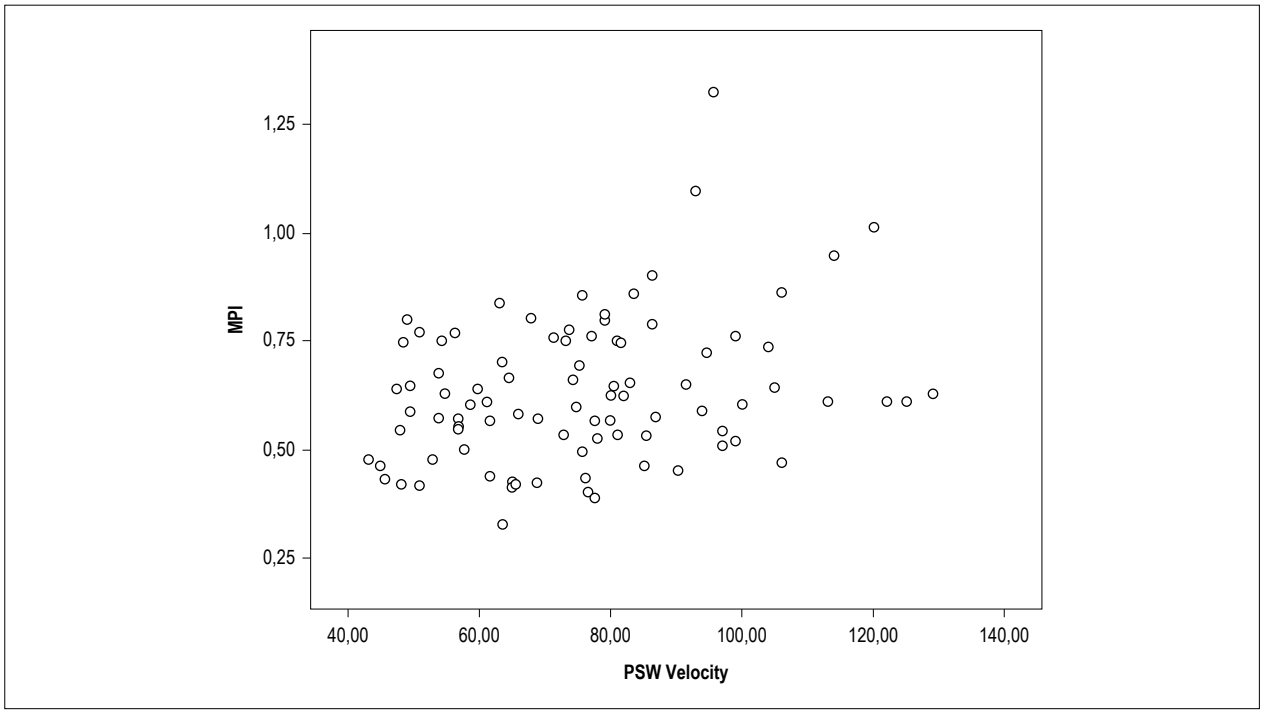

Figure 4 – *Correlation analysis between PSW velocity and MPI. PSW: presystolic wave; MPI: myocardial performance index.*

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 Trabzon Kanuni Education and Research Hospital under the protocol number 2017-64. 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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New Method Improves the Evaluation of Subclinical Left Ventricular Dysfunction in Type 2 Diabetes Mellitus

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Short Editorial related to the article: Presystolic Wave is Associated with Subclinical Left Ventricular Dysfunction Assessed by Myocardial Performance Index in Type 2 Diabetes Mellitus

Tei et al.[1] firstly described the myocardial performance index (MPI), which is showing both systolic and diastolic functions of the left ventricle. As a prognostic marker increased MPI has been shown to be an independent predictor of mortality and morbidity in various diseases such as myocardial infarction, hypertension, diabetes, and heart failure.[2,3] Askin et al.[4] showed that left ventricular (LV) diastolic and systolic functions were negatively affected in prediabetic patients. In addition, MPI can also be used in the assessment of abnormal cardiac function parameters in prediabetic patients. Furthermore, the most prominent feature of our method is that it can be obtained in a short period of time with easily available equipment. It is important to identify subclinical left ventricular diastolic dysfunction (LVDD) for clinical prevention before significant LVDD occurs. For this purpose, MPI is used to identify subclinical LVD in type 2 diabetes mellitus (DM).

Keywords

Antioxidants/pharmacology; Apoptosis/drug effects; Diabetes Mellitus; Reactive Oxygen Species; Myocardial; Systole; Dyastole; Heart Failure.

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Presystolic wave (PSW) measurement is obtained via doppler examination of LV outflow tract (LVOT).[5,6] Kul et al.[7] found that the PSW is associated with subclinical LVDD in patients with type 2 diabetes. PSW is an easily measurable echocardiographic parameter obtained in late diastole and can predict subclinical left ventricular dysfunction in patients with type 2 diabetes. Possible causes of PSW formation are impaired LV compliance and increased LV stiffness, which are also leading causes of PSW in diabetic patients among others. Furthermore, the relationship between PSW and LVDD has been proven.[5]

Stahrenberg et al.[8] reported that LV diastolic dysfunction is associated with glucose metabolism in a broad spectrum from impaired glucose tolerance to overt diabetes. Simone et al.[9] have recently reported that the risk of heart failure was increased markedly with type 2 diabetes, which was independent of myocardial infarction and hypertension (HT). Therefore; in the medical literature, the term "diabetic cardiomyopathy" has been proposed to be used in cases of ventricular dysfunction in the absence of coronary artery disease and HT.[10]

Hyperglycemia may result in the build-up of myocardial proteins via excessive accumulation of increased glycosylated products (AGE) and this may cause rigid myocardium. Accumulation of AGEs results in reduced myocardial relaxation by disrupting cross-links between collagen molecules. Hyperglycemia may also cause myocyte apoptosis, accelerated myocardial cell loss, decreased ventricular contraction, and systolic dysfunction. In conclusion, these phenomena cause decreased LV systolic and diastolic functions in diabetic patients.[11,12]

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Inter-Individual Responses to Citrulline Malate Oral Supplementation on Post-Exercise Hypotension in Hypertensives: A 24-Hour Analysis

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Abstract

Background: Studies have persuasively demonstrated that citrulline has a key role in the arginine-nitric oxide system, increasing nitric oxide bioavailability, an important mediator of peripheral vasodilation.

Objective: To analyze the inter-individual post-exercise hypotension responsiveness following acute citrulline supplementation in hypertensives.

Methods: Forty hypertensives were randomly assigned to one of the four experimental groups (control-placebo, control-citrulline, exercise-placebo, and exercise-citrulline). They ingested placebo or citrulline malate [CM] (6 grams). During the exercise session, individuals performed 40 minutes of walking/running on a treadmill at 60-70% of HR reserve. For the control session, the individuals remained seated at rest for 40 minutes. Office blood pressure (BP) was taken every 10 minutes until completing 60 minutes after the experimental session. The ambulatory BP device was programmed to take the readings every 20 minutes (awake time) and every 30 minutes (sleep time) over the course of 24 hours of monitoring. Statistical significance was defined as $p < 0.05$.

Results: Unlike the other experimental groups, there were no "non-responders" in the exercise/citrulline (EC) for "awake" (systolic and diastolic BP) and "24 hours" (diastolic BP). The effect sizes were more consistent in the EC for systolic and diastolic ambulatorial BP response. The effects were "large" (> 0.8) for "awake", "asleep", and "24 hours" only in the EC for diastolic BP.

Conclusion: CM supplementation can increase the post-exercise hypotensive effects in hypertensives. In addition, the prevalence of non-responders is lower when associated with aerobic exercise and CM supplementation. (Arq Bras Cardiol. 2019; 113(2):218-228)

Keywords: Exercise; Hypertension; Blood Pressure Monitoring Ambulatory; Citruline; Amino Acids; Nitric Oxide; Dietary Supplements.

Introduction

Post-exercise hypotension (PEH) is defined as a sustained reduction in blood pressure (BP) after a single bout of exercise.[1] This transient reduction can last up to 22h after completion of an exercise session.[2] For this reason, PEH is now considered to be an important physiological phenomenon,[1] which can play a major role in BP management. It is important to emphasize that PEH is a physiological phenomenon characterized by a reduction in BP following exercise compared with pre-exercise or control session values, with may be sustained for some hours.[3] Therefore, for the PEH to be clinically significant, an important magnitude and maintenance of this reduction for some hours are necessary. Furthermore, previous studies have reported that the magnitude of PEH following a single bout of exercise was correlated with chronic changes in rest BP after a period of exercise training.[4-8]

However, despite this possible relationship, some individuals present PEH (i.e., "responders") while others do not (i.e., "non-responders"). Past studies have identified "responders" and "non-responders" in non-hypertensive.[4,8-10] and hypertensive populations.[5,6,11] This means that, in the same intervention group, some individuals may demonstrate PEH whereas others show no changes or even an increased BP response to exercise training. Indeed, results from PEH studies are generally limited to presenting the mean BP reduction responses of the training group, ignoring inter-individual variations which can lead to misinterpretation, as positive effects from a given exercise training protocol may not be fully applied for each person individually.[12]

On the other hand, studies have persuasively demonstrated that citrulline (a non-essential amino acid) has a key role in the arginine-nitric oxide system, increasing nitric oxide (NO) bioavailability,[13] an important mediator of peripheral vasodilation. Thus, it is possible that PEH could be more pronounced after citrulline supplementation, especially in hypertensives, since the BP responses would be different as PEH can be caused by different mechanisms between normotensive

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and hypertensive individuals. Previous studies have shown that hypertensive individuals present cardiac output reduction,[2,14] while normotensive individuals present a reduction in total peripheral resistance.[14-16] For this reason, a non-pharmacological vasodilatation strategy can help hypertensive patients to activate another PEH mechanism together with a cardiac output decrease resulting in additional PEH effects.

Other experiments have observed that the plasma and salivary NO were associated with PEH after resistance[17] and aerobic exercises[17-20] in subjects with chronic diseases. Additionally, citrulline supplementation has shown promise with pre-clinical (animal) evidence for atherogenic-endothelial protection and preliminary evidence is also available for citrulline-induced benefits to muscle and metabolic health (via vascular and non-vascular pathways) in susceptible/older populations.[21]

For these reasons, this study aimed to analyze the inter-individual PEH responsiveness following an acute citrulline supplementation in hypertensives. Our hypotheses were: i) there would be an inter-individual variability in BP responsiveness following a single bout of aerobic exercise and ii) citrulline oral supplementation could contribute to reducing the rate of non-responders.

Methods

Participants

After sample size calculation (see statistical analysis session), 40 hypertensive, sedentary individuals participated in the study. All volunteers (both sexes) were adults without osteoarticular disabilities and had medical authorization to practice physical exercise. Participants were recruited from an exercise program project linked to the university that offered stretching and functional exercise sessions to the external community. The study followed the Declaration of Helsinki and the Institutional Ethics Committee approved all experimental procedures and protocols (78697617.4.0000.0108). Each participant was fully informed of all potential risks and experimental procedures, after which, informed written consent was obtained. Table 1 shows the basic characteristics of the participants.

Study design

A double-blind, placebo-controlled, parallel-groups clinical trial was performed (Figure 1). The participants were randomly allocated (using a random number table - https://www.random.org/) into four different experimental groups (exercise/citrulline [EC]; exercise/placebo [EP]; control/citrulline [CC]; control/placebo [CP]). The participants ingested a sachet, which contained citrulline malate (CM) (6 grams) or placebo (6 grams of corn starch) dissolved in water.

The substances were ingested 120 minutes before the experimental or control session. Anthropometric measures were taken before the rest period. The exercise session consisted of a 5 min warm up (50% of 65% HR [heart rate] reserve) and 40 minutes of running/walking at 60-70% HR reserve on a treadmill. This was followed by a progressive cooldown (5 minutes). The exercise intensity was also evaluated based on the Borg[22] Rating of Perceived Exertion (RPE 6-20 score). The RPE was collected every 5 minutes over the course of 40 minutes during the running/walking exercise period. The exercise intensity was reduced if the participant reported RPE ≥ 15, independently of HR. In the control session, the participants remained seated in a quiet room for 40 min.

After the exercise/control sessions, the BP was measured every 10 minutes over the course of 60 minutes (laboratory phase). Next, the participants were allowed 15 minutes to take a shower and change their clothes before the ambulatory BP device was attached on their arm. The ambulatory BP was recorded over 24 hours. The participants were asked to return to the laboratory the next day to remove the device.

Table 1 – Characteristics of participants and antihypertensive medications

	Control-Placebo		Control-Citrulline		Exercise-Placebo		Exercise-Citrulline		F	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (years)	62.3	18.7	60.6	16.8	52	15.2	58.6	8.6	0.864	0.469
Weight (kg)	77.2	16.5	76.5	9.0	79.6	17.2	72.5	13.1	0.419	0.740
Height (m)	1.66	0.11	1.59	0,08	1.61	0.08	1.58	0.09	1.309	0.286
BMI	27.9	4.2	30.6	4.6	30.8	6.5	29.1	5.8	0.625	0.603
WC (cm)	98.2	9.9	101.4	9.1	98.5	14.9	99.1	11.1	0.159	0.923
	N	%	N	%	N	%	N	%		
BB	3	30	5	50	5	50	3	30		
ACEI	5	50	3	30	4	40	6	60		
DIUR	0	0	1	10	0	0	1	10		
BB+ACEI	2	20	1	10	0	0	0	0		
ACEI+DIUR	0	0	0	0	0	0	0	0		
BB+ACEI+DIUR	0	0	0	0	1	10	0	0		

SD: standard deviation; BMI: body mass index; WC: waist circumference; BB: beta-blockers; ACEI: angiotensin-converting-enzyme inhibitor; DIUR: diuretics.

The study protocol was registered in ClinicalTrials.gov (NCT03378596).

Anthropometry

The weight was measured by a digital anthropometric scale (Urano, OS 180A, Canoas, Brazil), with an accuracy of 0.1 kg and height was measured by a stadiometer with an accuracy of 0.1 cm, in accordance with the procedures described by Gordon et al.[23] The body mass index was defined as the body mass (kg) divided by the square of the body height.

Office blood pressure (laboratorial phase)

The office BP measurements were taken with an oscillometric device (Omron MX3 Plus, Bannockburn, USA) previously validated for clinical measures in adults.[24] Firstly, the participants remained seated (rest period) in a calm, quiet, and thermoneutral (22°-24°C) environment for 20 min. BP was measured three times during the rest period (at 10 min, 15 min, and 20 min). The rest BP value was considered as the average of these three measurements. Immediately following the sessions (exercise or control), BP was measured in a quiet environment for 60minutes. The BP measurements were taken according to the American Heart Association recommendations.[25]

Ambulatorial blood pressure measures (ambulatorial phase)

The ambulatorial BP measurements were taken with an oscillometric device (Dyna-MAPA – São Paulo, Brazil) attached on the left arm, always by the same investigator, in accordance with procedures described by the American Heart Association.[25] The participants received instructions to keep their arm extended during the measures. The device was calibrated by direct comparison with a mercury sphygmomanometer, by a trained technical person, in agreement with recommendations.[25]

The monitor was set to register the systolic and diastolic BP and HR every 20 minutes during "daytime" (08:00 am to 11:00 pm) and every 30 minutes during "night-time" (11:00 pm to 08:00 am) to reduce sleep disturbances. The device screen was electronically blinded to avoid feedback. All participants were instructed to register and report their sleep time in a diary on the following day.

The data were recorded in the device memory and then sent to a computer using specific software (Aplicação Dyna Mapa – Version 5.0.382.12) for analysis. The average of the valid readings was above 90% for all participants.

Statistical analysis

Assuming a standard deviation (SD) of 5 mmHg[26] for the systolic BP, an alpha of 5% and a desired statistical power of 80% for detecting a minimum difference of 7 mmHg,[26] 7 subjects were required in each group. The Shapiro-Wilk test was employed to examine the normality of the data distribution. The data are presented in the text as mean and SD. Levene's homogeneity test was applied before the ANOVA one-way. Turkey (if homogeneity was accepted) or Games-Howell (if homogeneity was not accepted) multiple comparisons were employed to examine differences between pairs of trials. Effect size from the paired t-test was calculated (d = mean/SD). The results of the periods (60 minutes, awake, asleep, and 24 hours) were obtained through the average of the respective periods. Statistical significance was defined as $p < 0.05$.

To assess the inter-individual BP responsiveness, we first assessed the reproducibility of pre-exercise BP between "-10" and "0" minutes of rest BP measures (see Figure 1). For this analysis, the intraclass correlation coefficient (ICC, model 2,k), coefficient of variation (CV) and standard error measurements (SEM) were considered. The CV between pre-exercise BP measurements was calculated as follows: $CV = 100x(2x(SD_d/\sqrt{2})/(X_1+X_2)$. SD_d represents the SD of the differences between the 2 measurements, and X_1 and X_2 represent the 2 measurement means, respectively. $SEM = SDx\sqrt{(1-ICC)}$, with SD representing the SD of the first pre-exercise BP measure. The SEM was used as a measure of variability, but primarily for the minimal detectable change (MDC) calculation. MDC, which is the minimal change necessary to provide confidence that the results are not a random variation or measurement error, was calculated as follows: MDC=z-score (95% CI) $xSEMx\sqrt{2}$. All above-mentioned procedures were adopted according to Haley and Fragala-Pinkham[27] and Darter et al.[28] The participants were considered as "responder" if their BP reached a value equal to or greater than the MDC.

The statistical analysis was generated using the SPSS, version 20, system for windows.

Results

The exercise intensity was reduced for three participants (15 [EC], 18 and 19 [EP]) because they reported RPE ≥ 15. The exercise intensity based on HR reserve varied between 51-59% during the time (9 ± 3 minutes) that they could not keep 60-70% HR reserve.

The results of the variables related to the MDC calculation were: 0.915 (ICC), 5.08 (CV), 5.25 (SEM) and 2.37 (MDC) for systolic BP, and 0.846 (ICC), 5.64 (CV), 3.74 (SEM) and 1.69 (MDC) for diastolic BP.

Table 2 presents the absolute and relative BP changes in the different experimental groups. A significant reduction in systolic BP was identified for the EC when compared with the CP in the first 60 minutes (relative changes) after the experimental session. The same lowering effects were observed over the course of 24 hours (absolute changes) and for the "awake" and "24 hour" periods, considering relative changes (Δ% Awake and Δ% 24 hours) compared to the CP. No significant differences were found for the CC and EP.

Table 3 presents the effect sizes from the paired t-test (rest vs 60 min, awake, asleep, and 24 hours) for each experimental group. Considering systolic BP, the CP showed a significant effect for the asleep and 24 hours, the EP showed a significant effect for the awake and asleep, and the EC showed a significant effect for all periods (60 min, awake, asleep, and 24 hours). Additionally, considering diastolic BP, the CP presented a significant effect for the asleep, the CC presented a significant effect for the 60 min, asleep, and 24 hours, the EP presented a significant effect for the awake and asleep, and the EC presented a significant effect for the awake, asleep, and 24 hours.

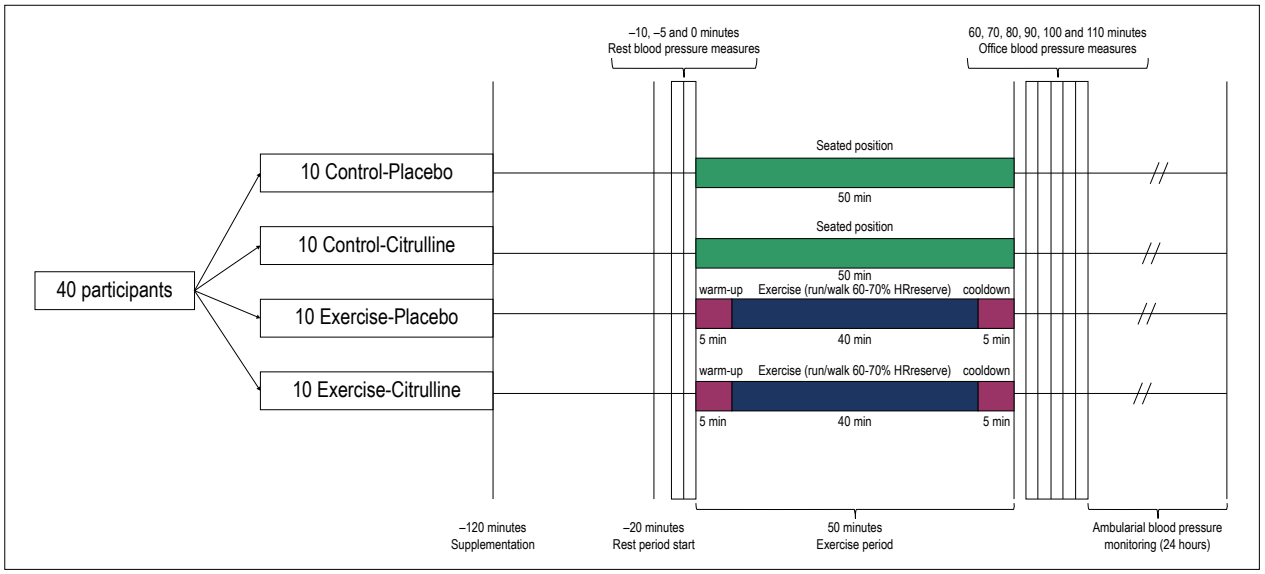

Figure 1 – *Study design.*

Table 2 – Absolute (rest, 60 min, awake, asleep, and 24 hours) and relative (Δ% 60 min, Δ% Awake, Δ% Asleep, Δ% 24 hours) blood pressure changes

	Control-Placebo		Control-Citrulline		Exercise-Placebo		Exercise-Citrulline		F	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
SBP										
Rest (mmHg)	140	19	132	15	136	12	142	20	0.714	0.550
60 min (mmHg)	138	19	137	14	130	9	127	15	1.240	0.310
Awake (mmHg)	127	11	128	8	124	11	126	8	0.334	0.801
Asleep (mmHg)	125	16	120	14	126	10	126	15	0.465	0.709
24 hours (mmHg)	128	11	125	9	127	10	125	13	0.216	0.884
Δ% 60 min	–2.3	3.4	5.4	9.4	–6.3	11.4	–15.0**	8.1	9.737	< 0.001
Δ% Awake	–9.7	12.5	–4.2	12.3	–9.1	15.2	–21.0	16.7	2.469	0.078
Δ% Asleep	–15.8	14.0	–9.8	16.2	–9.5	19.5	–17.0	14.1	0.588	0.627
Δ% 24 hours	–11.5	12.4	–6.0	12.6	–9.2	16.3	–20.1	16.8	1.935	0.141
DBP										
Rest (mmHg)	82	5	80	9	86	11	85	10	0.889	0.456
60 min (mmHg)	83	9	84	8	86	10	85	10	0.237	0.870
Awake (mmHg)	80	8	75	8	79	7	71	9	2.847	0.051
Asleep (mmHg)	75	11	70	8	76	10	71	10	1.083	0.369
24 hours (mmHg)	82	8	73	7	79	8	71*	9	3.999	0.015
Δ% 60 min	0.4	5.9	4.1	4.8	1.0	7.2	0.1	7.4	0.796	0.504
Δ% Awake	–1.5	5.2	–4.7	7.3	–6.8	8.1	–13.9†	6.2	5.917	0.002
Δ% Asleep	–6.6	9.1	–10.0	8.0	–9.2	11.1	–13.2	7.3	0.923	0.439
Δ% 24 hours	–3.3	6.1	–6.8	6.9	–7.6	8.4	–14.5*	6.4	4.505	0.009

*SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; Δ%: +/- percent change from "rest" value. *: p < 0.05 vs control-placebo (Tukey post-hoc); **: p < 0.05 vs control-placebo and control-citrulline (Games-Howell post-hoc); †: p < 0.05 vs. control-placebo and control-citrulline (Tukey post-hoc).*

Table 3 – Effect size from Paired t test (versus rest [d = mean/SD])

	Control-Placebo		Control-Citrulline		Exercise-Placebo		Exercise-Citrulline	
	ES	p	ES	p	ES	p	ES	p
SBP								
60 min	0.61	0.084	-0.56	0.109	0.53	0.127	1.81	< 0.001
Awake	0.69	0.055	0.26	0.428	1.00	0.011	0.74	0.042
Asleep	0.73	0.044	0.65	0.068	0.83	0.027	0.78	0.034
24 hours	0.92	0.017	0.48	0.156	0.57	0.102	0.88	0.020
DBP								
60 min	–0.12	0.717	–0.91	0.018	–0.12	0.707	–0.01	0.968
Awake	0.32	0.333	0.71	0.051	0.81	0.030	2.06	< 0.001
Asleep	0.84	0.027	1.21	0.004	0.90	0.019	2.16	< 0.001
24 hours	0.04	0.905	0.97	0.014	0.65	0.071	2.27	< 0.001

SD: standard deviation; ES: effect-size; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The percentages of responders and non-responders in the different experimental groups for different time periods (60 min, awake, asleep, and 24 hours) are shown in table 4. The percentages of the systolic BP responders varied from 20% (CC) to 90% (EC) for 60 min; 60% (CC and EP) to 100% (EC) for awake; 60% (CC and EP) to 90% (EC) for asleep; and 60% (CC and EP) to 90% (EC) for 24 hours.

The percentages of the diastolic BP responders varied from 10% (CC) to 40% (CP) for 60 min; 50% (CP) to 100% (EC) for awake; 70% (CP) to 100% (CC and EC) for asleep; and 60% (CP) to 100% (EC) for 24 hours.

Absolute systolic and diastolic BP individual changes for each experimental group in the 60 min, awake, asleep, and 24 hours are presented in Figures 1 (systolic) and 2 (diastolic). All participants in the EC demonstrated a reduction in systolic BP in the 60 min, awake, and 24 hours. For the asleep period, only one EC participant (number 23) did not present a reduction in systolic BP (Figure 2).

All participants in the EC presented a reduction in diastolic BP in the awake, asleep, and 24 hours (Figure 3).

Discussion

The main findings of this study were: (i) there was considerable inter-individual responsiveness variability in systolic and diastolic BP responses following all experimental protocols, (ii) despite the inter-individual responsiveness variability, there was PEH only when associated with CM supplementation. To the best of our knowledge, this is the first report on inter-individual analysis of PEH following a single bout of aerobic exercise preceded by CM supplementation in hypertensive subjects.

Unlike the other experimental groups, there were no "non-responders" in the EC for "awake" (systolic and diastolic BP) and "24 hours" (diastolic BP). These results are interesting since "non-responders" have generally been identified both in non-hypertensive[9,10] and hypertensive[5,6] populations. It is important to clarify that in an intervention group, some individuals may demonstrate improvement in a given outcome (responder) whereas others show no changes or even an adverse response to exercise training (non-responders or adverse responders).[9] In fact, the heterogeneity of responses to exercise training is a current concern in exercise investigations[29] since even homogeneous samples may demonstrate a wide range of heterogeneous responses.[12] In addition, results of PEH are generally limited to presenting the average reductions in the experimental group, ignoring inter-individual variations[12] which can lead to misinterpretation since not all individuals respond favorably.

It is important to consider that the results reported by central tendency measures can vary depending on the analysis. In medical studies, it is common to take measurements before and after medical interventions. How to measure the changes from baseline is a common question posed by researchers. For example, in the present study, when absolute values were used for inter-group comparisons (Table 2), no statistical differences were found for systolic BP. On the other hand, using the percentage difference (delta), a significant reduction was found in the EC for "60 min" post-exercise. Another inconsistency can be seen in diastolic BP analysis. When absolute values were used for inter-group comparisons, a significant difference was found in the EC for "24 hours" post-exercise. On the other hand, using the percentage difference, significant reductions were found in the EC for "awake" and "24 hours" post-exercise. In specific situations, some studies (e.g., Vickers)[30] suggested avoiding using percentage changes. Despite these inconsistencies, clinicians may prefer to choose the method that will most obviously demonstrate the health-improvement. Some researchers may choose the method that can be best understood by the majority of people interested in the research.

However, one of the most common questions driving the evaluation of intervention programs is "how does this effect compare with the effects of other interventions?". Therefore, previous studies have encouraged the use of "effect size" in quantitative studies.[31] Researchers are often stimulated

Table 4 – Percentage of responders and non-responders and inter-individual percentage changes (min; max) on Control-Placebo, Control-Citrulline, Exercise-Placebo and Exercise-Citrulline groups

	Control-Placebo		Control-Citrulline		Exercise-Placebo		Exercise-Citrulline	
	N	Min:Max (%)	N	Min:Max (%)	N	Min:Max (%)	N	Min:Max (%)
SBP								
60 min								
Responders	5	(-2;-7)	2	(-2;-4)	7	(-2;-17)	9	(-2;-18)
Non-responders	5	(-1;2)	8	(-1;17)	3	(0;10)	1	(-1;-1)
Awake								
Responders	8	(-2;-18)	6	(-4;-16)	6	(-9;-24)	10	(-3;-33)
Non-responders	2	(0;9)	4	(5;16)	4	(2;13)	0	-
Asleep								
Responders	8	(-5;-21)	6	(-2;-33)	6	(-8;-32)	9	(-3;-28)
Non-responders	2	(4;7)	4	(-1;9)	4	(0;13)	1	(1;1)
24 hours								
Responders	8	(-5;-18)	6	(-2;-20)	6	(-6;-26)	9	(-2;-31)
Non-responders	2	(0;9)	4	(-1;14)	4	(1;11)	1	(-1;-1)
DBP								
60 min								
Responders	4	(-3;-13)	1	(-7;-7)	3	(-3;-10)	3	(-3;-13)
Non-responders	6	(0;12)	9	(1;14)	7	(-1;18)	7	(-2;22)
Awake								
Responders	5	(-3;-13)	7	(-2;-19)	6	(-3;-21)	10	(-8;-27)
Non-responders	5	(-1;10)	3	(0;10)	4	(-1;1)	0	-
Asleep								
Responders	7	(-6;-30)	10	(-1;-31)	8	(-3;-28)	10	(-6;-28)
Non-responders	3	(2;5)	0	-	2	(6;6)	0	-
24 hours								
Responders	6	(-3;-15)	8	(-1;-20)	8	(-3;-22)	10	(-7;-25)
Non-responders	4	(-2;6)	2	(5;5)	2	(-2;2)	0	-

SBP: systolic blood pressure; DBP: diastolic blood pressure.

to report effect sizes for three reasons. First, to present the magnitude of the reported effects in a standardized metric; second, effect sizes allow researchers to draw meta-analytic conclusions by comparing standardized effect sizes across studies, and third, effect sizes from previous studies can be used when planning a new study, providing an indication of the average sample size needed.[32] In the present study, we found that the effect sizes (from the paired t-test [versus rest]) were more consistent in the EC for systolic and diastolic ambulatorial BP response, however, it is important to highlight that for diastolic BP the effects were "large" (> 0.8) for "awake", "asleep", and "24 hours" in the EC.

Despite some inconsistencies in the "effect size" outcomes for systolic and diastolic BP in the other experimental groups, the percentage of "responders" and "non-responders" and inter-individual percentage changes in the different groups (Table 4) could aid understanding. There were no "non-responders" in the EC for systolic and diastolic BP responses for "awake" (systolic and diastolic), "asleep" and "24 hours" (diastolic). These responses are important, considering that the BP response following a single bout of exercise has been considered as a simple predictive clinical tool that can help to identify and manage "high responder" and "low responder" subjects to exercise training.[33]

Concerning the physiological mechanisms that might be involved in this response, we hypothesized that the vascular resistance reduction due to increased NO concentration could potentiate the PEH. Previous studies reported that oral citrulline supplementation raises plasma arginine concentration and augments NO production by the citrulline-NO cycle.[34,35] It is exactly because of this vasodilation resulting from greater NO release that citrulline oral supplementation might potentiate the PEH response, especially in hypertensive individuals. It is important to highlight that hypertensive individuals present

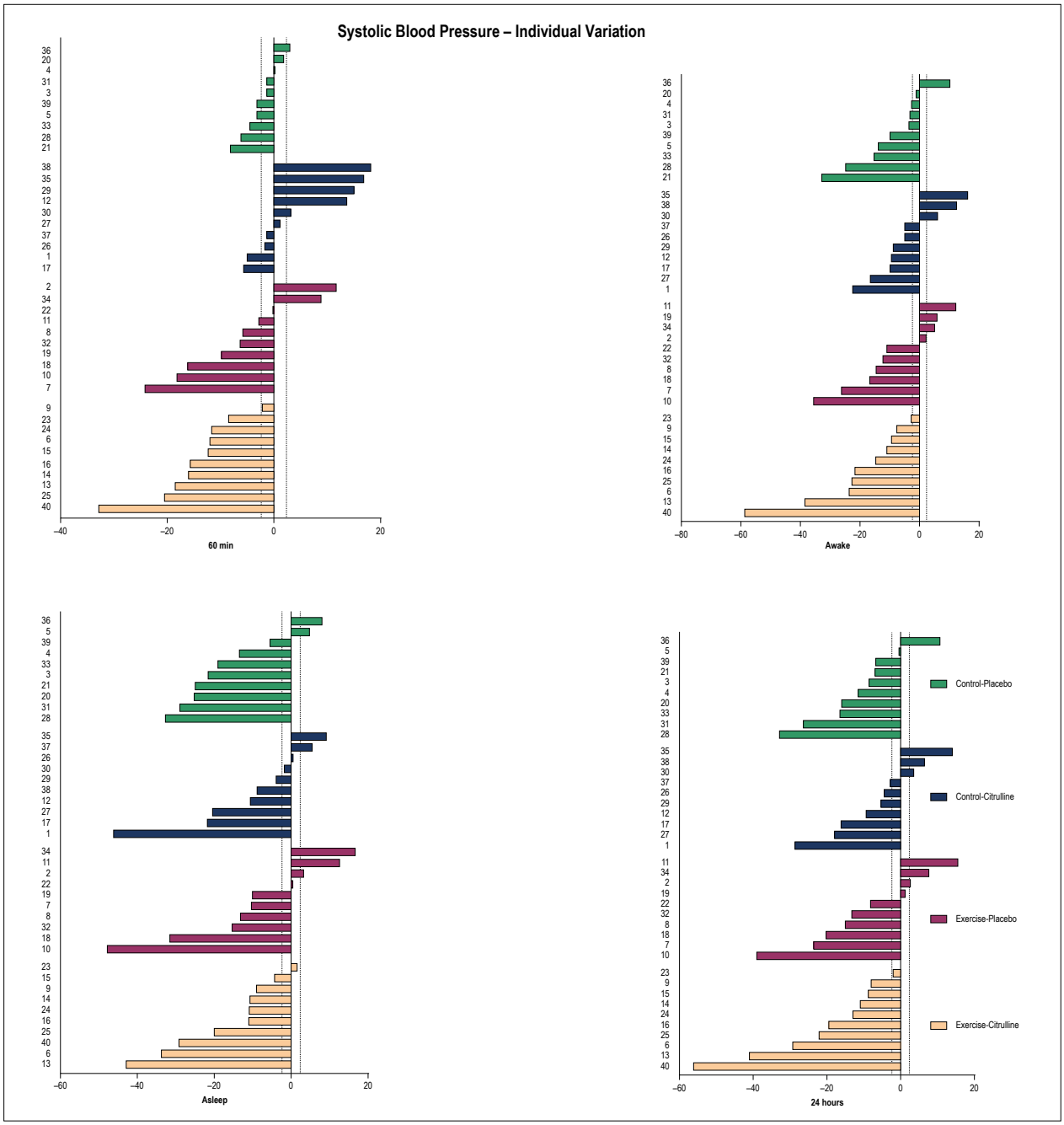

Figure 2 – *Individual changes – Systolic blood pressure. Dashed line: MDC (minimal detectable change).*

deficiency in peripheral vasodilation modulators, such as a compensation mechanism so autonomous nervous system can work to reduce cardiac output.[2,14] For this reason, we expect that citrulline oral supplementation could contribute to improving the peripheral vasodilation mechanisms in hypertensive individuals, resulting in a greater magnitude and/or duration of PEH. Unfortunately, in the present study we did not evaluate important NO biomarkers such as nitrite and nitrate.

Independent of the mechanisms that are involved in this response, the present study demonstrated that the exercise plus citrulline (intermediate of NO metabolism) caused a greater hypotensive effect and this effect can last up to 24 hours. This finding suggests that NO might be involved in this response[36] and it might be over stimulated by exercise plus citrulline compared to one of them in isolation.

Concerning the CP and CC results, we expected that acute citrulline supplementation, independent of exercise, could contribute to improving hypotension effect, resulting in a lower prevalence of non-responders in comparison to CP. Contradicting our hypothesis, the results indicate that acute

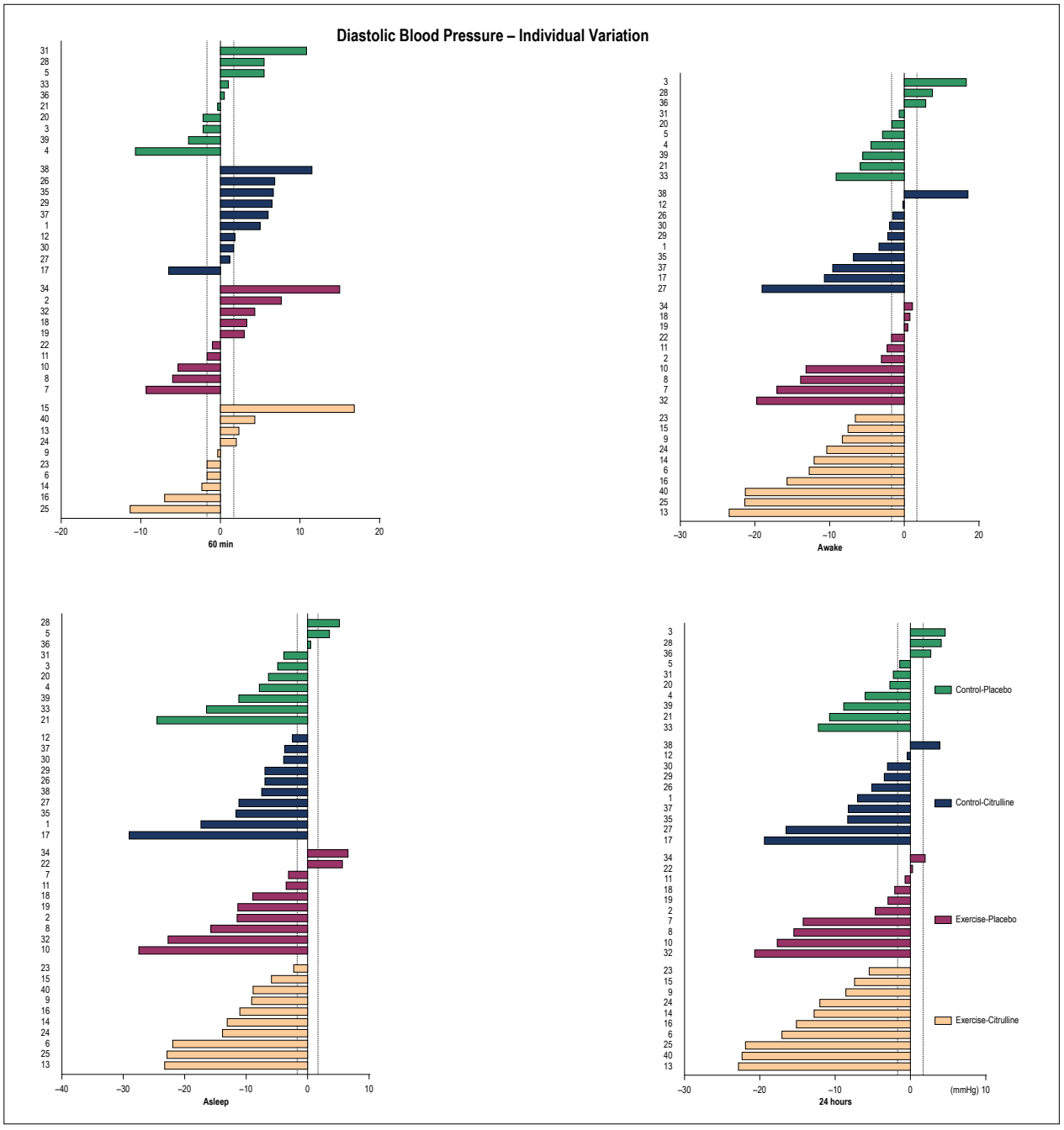

Figure 3 – *Individual changes – Diastolic blood pressure. Dashed line: MDC (minimal detectable change).*

citrulline supplementation was not related to lower prevalence of non-responders. Previous studies have demonstrated that the acute ingestion of citrulline increased NO synthesis, but endothelium-mediated vasodilation was not improved in older adults with heart failure.[37] Recent studies have evaluated endothelial function after some days of citrulline supplementation. Bailey et al.,[38] found increases in nitrite levels (21%) after 7 days of citrulline supplementation in healthy young men. Likewise, oral citrulline supplementation (6 g/day) for 7 days increased plasma nitrate levels by 37% in middle-aged men with increased arterial stiffness.[39] Evidence suggests that resting BP level may influence the hypotensive effect of citrulline supplementation. For instance, previous study found decreases in BP (7/3 mmHg) after 8 weeks of citrulline supplementation (6 g/day) in prehypertensive and hypertensive obese postmenopausal women.[40] Therefore, we suppose that citrulline supplementation (without exercise) can induce vasodilation only after some weeks.

Despite the interesting findings of this study, it is important to consider that there is no consensus to distinguish "responders" from "non-responders" due to the lack of agreement on whether to define "response" as a clinically relevant change or a clearly measurable change.[41] Additionally, BP measurements incorporate some degree of error (instrumentation noise + biological noise), and changes can often occur due to factors independent of the intervention (biological variability).[42] For this reason, the authors decided not to apply a theoretical construct (based on SD, confidence intervals, or smallest worthwhile change) to determine the extent to which changes were the direct result of the intervention or effectively "random" external causes. On the other hand, it is important to highlight that independent of the theoretical measurement error degree adopted, the EC group presented more "responsive" individuals in all hypothetical situations.

Some limitations of this study should be considered. The results from the few available studies differ considerably, making comparisons somewhat difficult. Although drug therapies were not changed during the study, patients were using different types of medication, and this factor might have affected the results. Moreover, it is recommended that future studies include NO availability measurements, such as nitrite and nitrate. These measurements associated with the evaluation of important mechanisms such as peripheral vascular resistance and cardiac output might help us to understand the citrulline action combined with exercise in hypertensives.

Conclusion

These results suggest that acute CM supplementation can increase the post-exercise hypotensive effects in hypertensives. In addition, the prevalence of non-responders is lower when associating aerobic exercise and CM supplementation.

Clinical messages

- There was considerable inter-individual responsiveness variability in systolic and diastolic BP responses following all experimental protocols.
- Despite the inter-individual responsiveness variability, there was a PEH potentiation by the CM supplementation.

Author contributions

Conception and design of the research, Statistical analysis and Obtaining financing: Casonatto J; Acquisition of data: Enokida DM, Grandolfi K; Analysis and interpretation of the data: Casonatto J, Enokida DM, Grandolfi K; Writing of the manuscript: Casonatto J, Enokida DM; Critical revision of the manuscript for intellectual content: Grandolfi K.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Daniel Massaharu Enokida, from Universidade Norte do Paraná.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Norte do Paraná under the protocol CAAE: 78697617.4.0000.0108 – Appraisal number: 2.593.090. 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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Group Means and Inter-Individual Analysis in Post-exercise Hypotension: Effects of Citrulline Malate Oral Supplementation

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Short Editorial related to the article: Inter-Individual Responses to Citrulline Malate Oral Supplementation on Post-Exercise Hypotension in Hypertensives: A 24-Hour Analysis

Hypertension is pointed out as one of the most aggressive risk factor for cardiovascular morbidity and mortality, since it is directly associated with nearly 8 million obits per year related to cardiovascular diseases such as cardiac arrest or stroke.[1] Hypertensives with low levels of physical activity present higher risk of cardiovascular morbidity and mortality even when receiving anti-hypertensive medication.[2] The regular practice of exercise, mainly aerobic exercises, is highly recommended due to its hypotensive effect.[3] Actually, a single session of exercise is already able to promote a sustained reduction of blood pressure, this phenomenon is called post-exercise hypotension (PEH).[4-6]

Kenney and Seals[6] were the first to term the most accepted version of PEH as a phenomenon – It is the decrease of systolic and/or diastolic blood pressure after an acute session of exercise to below a control value followed by no clinical hypotensive symptom. PEH has been faced as a clinically relevant tool, mainly due to its known magnitude and for lasting many hours.[5] In this context, a meta-analysis including 65 studies recently showed reductions of blood pressure averaging from 6/4 mmHg for systolic/diastolic after aerobic exercise session,[7] while hour-to-hour analysis reported a decrease for 16 hours.[8]

Despite established, PEH presents a large variation in magnitude and duration across the literature, which suggest that many factors of influence and different mechanisms are involved in promoting PEH.[4] Along this line, Casonatto et al.[9] suggested that citrulline malate oral supplementation might favor a greater PEH in middle-age treated hypertensives. For this, the authors supplemented the subjects with citrulline malate in a randomized double-blinded study controlled by placebo. The supplementation of citrulline malate increases arginine plasma levels, which favors the augment of nitric oxide through the cycle of citrulline-nitric oxide.[10] Thus, the authors suggest that greater levels of nitric oxide were responsible for a greater decrease in systemic vascular resistance and subsequently PEH. However, in healthy subjects, Halliwill et al.[11] did not observe any influence on blood pressure, calf and forearm vascular resistance post-exercise after inhibiting systemic nitric oxide synthase. It is also important to highlight that citrulline malate did not promote hypotensive effect stand-alone, which suggests a greater effect only when it is associated to exercise. Such results bring an open field for future studies to investigate how citrulline malate and aerobic exercise can together promote a greater PEH and the mechanisms behind it.

Although reproducibility is good for PEH,[12] subjects present not uniform blood pressure responses post-exercise. Such pattern has encouraged researchers to explore individual analysis as an additional approach to show their data and not only the statistical difference for group means.[13,14] The authors of the study discussed in this Short Editorial also highlighted inter-individual analysis in which they categorized "responders" (i.e. who the blood pressure decrease post-exercise) and "non-responders" (i.e. who the blood pressure did not change or was increased post-exercise). This type of analysis allows even though is observed no mean differences, most of the subjects might present clinically relevant blood pressure decrease post-exercise, which occurred for some variables in the discussed study. However, it is not still totally settled which is the best approach to interpret inter-individual data, and researchers should be careful about assumptions and conclusions when introduce this analysis.

The best strategy is still to be matched to define a "responder" and a "non-responder", and the debate remains whether it needs to be based on changes clinically relevant or representing a measure defined by a mathematical approach. Concerning the magnitude of PEH to determine a clinically relevant change for PEH is also not still determined; a quite acceptable option might be employing the error of blood pressure measurement to be overcame by exercise reducing blood pressure below these values.[15] Nonetheless, few well-designed studies have adequately investigated the reproducibility of PEH to characterize a universal error measurement. Then, to calculate the error in each study would be the best approach, taking blood pressure measurements at rest in two different days considering the subjects and the same evaluator involved in the study.

Thus, the results presented by Casonatto et al.[9] suggest a possible associated effect of citrulline malate oral supplementation in promoting greater PEH in hypertensives, and which mechanisms are involved in this response should be explored in the future. Another unsolved question was raised in this study; might oral supplementation with citrulline malate associated to aerobic exercise be a promising tool to promote other cardiovascular benefits, such as vascular function, in both, acute and chronic studies?

Regarding analysis to report data, studies investigating group mean data demonstrated the clinical implications for PEH, but inter-individual analysis may be a step forward in the comprehension of this phenomenon. Then, to identify whether and what are the clinical meanings for "responders" and "non-responders".

Keywords

Cardiovascular Diseases; Blood Pressure; Hypertension; Mortality & Morbidity; Exercise; Post-Exercise Hypotension; Citrulline.

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Test-Retest Reliability of Non-Invasive Cardiac Output Measurement during Exercise in Healthy Volunteers in Daily Clinical Routine

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Abstract

Background: Thoracic bioreactance (TB), a noninvasive method for the measurement of cardiac output (CO), shows good test-retest reliability in healthy adults examined under research and resting conditions.

Objective: In this study, we evaluate the test-retest reliability of CO and cardiac power (CPO) output assessment during exercise assessed by TB in healthy adults under routine clinical conditions.

Methods: 25 test persons performed a symptom-limited graded cycling test in an outpatient office on two different days separated by one week. Cardiorespiratory (power output, VO_{2peak}) and hemodynamic parameters (heart rate, stroke volume, CO, mean arterial pressure, CPO) were measured at rest and continuously under exercise using a spiroergometric system and bioreactance cardiograph (NICOM, Cheetah Medical).

Results: After 8 participants were excluded due to measurement errors (outliers), there was no systematic bias in all parameters under all conditions (effect size: 0.2-0.6). We found that all noninvasively measured CO showed acceptable test-retest-reliability (intraclass correlation coefficient: 0.59-0.98; typical error: 0.3-1.8). Moreover, peak CPO showed better reliability (intraclass correlation coefficient: 0.80-0.85; effect size: 0.9-1.1) then the TB CO, thanks only to the superior reliability of MAP (intraclass correlation coefficient: 0.59-0.98; effect size: 0.3-1.8).

Conclusion: Our findings preclude the clinical use of TB in healthy subject population when outliers are not identified. (Arq Bras Cardiol. 2019; 113(2):231-239)

Keywords: Cardiac Output; Cardiography, Impedance/methods; Exercise; Exercise Test/methods; Echocardiography/methods; Reproducibility of Results; Adult.

Introduction

Cardiac output (CO) is an important physiological surrogate parameter, reflecting the hemodynamic demands of the organism. CO measuring has a wide application spectrum[1] and can provide information on hemodynamic status in patients[2] as well as athletes.[3] In chronic heart failure, CO is decreased and patients suffer from exercise intolerance.[4,5] In contrast, the athlete´s heart shows structural and functional adaptations due to training[6] resulting in a higher CO.[7] Interestingly altered cardiac structure and function do not predict exercise intolerance[8,9] or CO response[3] in both cases. Thus, cardiopulmonary exercise testing is necessary and peak oxygen consumption (VO_{2peak}) is measured to determine exercise capacity.[10,11] But, estimation of VO_2 is influenced by several non-cardiac factors,[4,12] and can, therefore, be misleading.[9,13,14] Furthermore, CO cannot be accurately predicted from cardiopulmonary exercise testing.[4,15]

However, to evaluate hemodynamic status, catheter-based measuring (i.e., Fick method, thermodilution method) is considered as the clinical standard.[16,17] Since such invasive methods are associated with high risk, their applicability is restricted.[18,19] Therefore, noninvasive measuring methods (i.e., transoesophageal echocardiography, lithium dilution CO, pulse contour CO, partial CO_2 rebreathing, thoracic electrical bioimpedance) were developed.[17] Of the noninvasive measuring methods, especially the thoracic electrical bioimpedance was frequently used in clinical studies and evaluated for its reliability.[20] However, thoracic bioreactance (TB) is a further promising technology to noninvasively monitor CO.[21] TB is based on the measurement of blood flow-related phase shifts of transthoracic electric signals to monitor noninvasively and continuously CO. Therefore theoretically, TB is superior to other methods[22,23] and has been used in several clinical settings.[21,23-25] But, before TB can be adopted for clinical and performance decision making, test´s quality criteria, as the test-retest reliability, must be fulfilled.

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Jones et al.[26] tested the test-retest reliability in a healthy study population. 22 healthy adults performed twice a symptom-limited exercise test. Standard cardiorespiratory data were measured via spiroergometry and the hemodynamic response was monitored via TB using the NICOM® system. The authors state that TB allows good test-retest reliability for hemodynamic measurement at rest as well as under submaximal and maximal exertion. This particular study was the first to confirm that TB might be a feasible test method. Noteworthy, the study was performed under tightly controlled research conditions. Overall, three visits were necessary to determine individual cardiorespiratory capability and to perform both exercise tests. Furthermore, to exclude confounders, certain inclusion criteria had to be fulfilled (e.g., non-smokers, empty stomach for > 2 h, no vigorous exercise 24 h before testing, no alcohol or caffeine consumption). Such scientific testing conditions are often difficult to guarantee in daily clinical routine. Thus, it remains unclear, if TB is an appropriate examination procedure not only in a research setting but also in daily clinical routine.

Contrary to CO based on heart rate (HR) and stroke volume (SV), cardiac power output (CPO) indicates the overall function of the heart.[27] CPO is the product of the CO and mean arterial pressure (MAP) and therefore is a measure of cardiac pumping.[28] Peak cardiac power output (CPO_{peak}), the CPO achieved during maximal stress, is a major determinant of exercise intolerance and performance in cardiac patients and healthy persons, respectively.[29,30]

Worth mentioning, CPO measuring can improve medical management[31,32] and risk stratification[33-35] in cardiac patients. In chronic heart failure, CPO is a powerful and independent predictor of survival outcome.[35] CPO also reflects cardiovascular adaptions and training status in athletes.[6] In fact, compared to non-athletes,[36] CPO is higher in athletes.[3,37] Thus, CPO might be an additive performance diagnostic parameter, which could help to guide training modalities.[37,38] Like other established measures of exercise capacity, CPO cannot be predicted from resting cardiac parameters.[3]

Under this background, the aims of the present study were: 1) to evaluate the test-retest reliability of TB in healthy adults during the daily clinical routine, and 2) to assess the relationships between CPO and resting measures of cardiac structure and function as well as traditional cardiopulmonary exercise parameters. Here, we applied a progressive statistic approach to provide thresholds above which effects might be meaningful and to present CO and CPO values that may be used as reference values in future studies.

Methods

Participants

In the study, 25 test persons were included into the study. All participants had no history of cardiovascular or pulmonary diseases, no cardioactive medication, a blood pressure of ≤ 140/90 mmHg, a body mass index < 25, a normal electrocardiogram, and a normal echocardiogram at the time of inclusion.

Study design

This study is a prospective non-interventional diagnostic single-center study. Participants were recruited in a cardiologic and internal medicine facility. The study was approved by the ethics committee of the University Witten/Herdecke and written informed consent was obtained. A standard echocardiogram was performed to exclude structural heart diseases and to investigate the relationships between established echocardiographic parameters and cardiopulmonary and hemodynamic values. Heart size, wall thickness, systolic, and diastolic function were all in physiological limits. All participants underwent two cardiopulmonary exercise tests separated by on week. During testing, TB using the NICOM™ device was applied.

Transthoracic echocardiography

Echocardiography was performed to assess cardiac structure and function using a standard ultrasound system (Vivid 7, General Electric, Milwaukee, Wisconsin). A complete transthoracic study was performed, including 2D, M-mode, spectral, and color Doppler techniques according to current recommendations and guidelines.[39,40] Standard parameters were: interventricular septal wall thickness in diastole, left ventricle end-diastolic diameter, left ventricular posterior wall thickness in diastole, and fractional shortening. Left ventricular ejection fraction was measured by means of modified biplane Simpson´s method. Doppler tissue imaging was performed at the junction of the septal and lateral mitral annulus in apical 4-chamber view to determine peak mitral annular velocity during early filling (E`) and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (V).

Cardiopulmonary exercise testing

A symptom-limited incremental exercise test was performed in a seated position on a cycling ergometer (ec-3000, customed GmbH, Germany). The tests were performed by trained personal. After 5 min of rest, participants started at 0 W and the workload increased every 2 min by 25 W (standard WHO protocol). HR, blood pressure on the right arm using a sphygmomanometer, and a 12-lead electrocardiogram were obtained at rest and each stage as well as for 3 min post-exercise. The respiratory gas analysis was performed using a spiroergometry system (Cortex Metalyzer® 3B, Leipzig, Germany, software Metasoft studio 5.1.2 SR1). Ventilatory oxygen consumption and standard gas exchange data were measured breath-by-breath and averaged over 30 s. The following standard parameters were measured: Time to exhaustion, maximum workload, ventilatory anaerobic threshold (VAT) and peak oxygen uptake (VO_{2peak}). The anaerobic threshold was determined using the V-slope method.[41] The submaximal load was determined as the second last completed incremental. VO_{2peak} was defined as the highest VO_2 observed during testing.

Thoracic bioreactance

TB (NICOM®, Cheetah Medical, Portland, Oregon, USA) was added for noninvasive hemodynamic monitoring during rest and exercise. The examination was performed according to the manufacturer's protocol, as described previously.[2,21,42]

Table 1 shows the parameters that were calculated by the Cheetah NICOM® system. The NICOM® system uses four sensors applied to the right and left sides of the chest. Each sensor consists of an outer transmitting electrode and an inner receiving electrode. The outer electrodes transmit a low amplitude alternating electrical current with a frequency of 75 kHz to the thoracic cavity. The electrical properties of the thorax cyclically change due to the pulsatile volume of blood ejected from the heart. The pulsatile blood flow in the large thoracic arteries causes time delays (phase shifts) between the applied alternating electrical current and the thoracic voltage measured by the inner electrodes. Based on the measured phase shift the maximum aortic flow (dX/dtmax) and the ventricular ejection time (time from aortic valve opening to aortic valve closure, VET) were measured. Finally, the SV was obtained as SV = DX/DT × VET. Thereon, the CO, and finally the CPO, was derived.[43] The SV data were measured beat-by-beat and averaged over 60 s.

Statistical analysis

In a first step, participants were excluded from statistical analyses due to measurement errors (outliers), which were defined as ≥mean ± twofold pooled standard deviation.[44]

The test-retest reliability of cardiopulmonary and hemodynamic parameters was analyzed by (1) the difference in means to detect systematic bias, (2) intraclass correlation coefficients (ICC) to examine the relative reliability, and (3) typical error (TE) of measurements to quantify the absolute reliability.[45] To examine the difference in means, a progressive statistical approach using magnitude-based inferences for practical significance were computed.[46] Compared to traditional null-hypothesis testing, that is influenced by the sample size, magnitude-based inferences ground an analysis, how big the observed effect is, and if the effect is lower, similar, or higher than the smallest worthwhile difference (SWD).[46] Therefore, means and 90% confidence intervals (CIs) was computed first. Then, the disposition of the mean differences in relation to the SDWs were investigated. While the SDW for the maximal workload was calculated from the pooled standard deviation multiplied by 0.2, the SWD for all other physiological variables were calculated from the pooled standard deviations multiplied by 0.6, because it is well known that physiological variables showed a clearly higher spontaneous variability than biomechanical measures.[47] Finally, the likelihoods for test 2 showing "true" higher, similar, or lower values than test 1 were determined and qualitatively described using the following probabilistic scale: <1%, *most unlikely*; 1 to <5%, *very unlikely*; 5 to <25%, *unlikely*; 25 to <75%, *possibly*; 75 to <95%, *likely*; 95 to <99%, *very likely*, and ≥99%, *most likely*. If the likelihoods for having both higher and lower values were ≥5%, the differences were described as *unclear*. Otherwise, the differences were interpreted according to the observed likelihoods. To clarify the meaningfulness of the differences, standardized differences labeled as effect sizes (ESs) were calculated and interpreted accordingly: 0.2 to <0.6, *small*; 0.6 to <1.2, *moderate*; 1.2 to <2.0, *large*; 2.0 to <4.0, *very large*; and ≥4.0, *extreme large*. To express the relative reliability, ICCS and 90% CIs were computed. The coefficients were described as follows: <0.20, *very low*; 0.20 to <0.50, *low*; 0.50 to <0.75, *moderate*; 0.75 to <0.90, *high*; 0.90 to <0.99, *very high*; and ≥0.99, *extremely high*. To quantify the absolute reliability, TEs and 90% CIs were calculated. The meaningfulness of the TEs was expressed via standardization for which the aforementioned scale for standardized differences was applied.[47]

The relationships between the CPO and measures of cardiac structure and function as well as traditional cardiopulmonary exercise parameters were investigated using Pearson correlation coefficients (r) that were interpreted accordingly: <0.1, *trivial*; 0.1 to <0.3, *small*, 0.3 to <0.5, *moderate*; 0.5 to <0.7, *large*; 0.7 to <0.9, *very large*; 0.9 to 1.0, *almost perfect*.[47] Lastly, common variances from coefficients of determinations (R^2) were computed. Thereby, a cutting-off value of 50% was defined to clarify, if two variables are dependent or independent from each other.[48]

Results

25 participants completed both exercise tests. 17 participants (10 male, 7 female) were finally included. 8 participants were excluded due to measurement errors (outliers). Anthropometric, echocardiographic, and spiroergometric data of the participants are presented in Table 2.

Reliability

Data concerning systematic bias are presented in Table 3. It shows the differences in means between test 1 and test 2 for all hemodynamic and cardiopulmonary parameters measured at rest and during submaximal and peak exercise conditions. For all parameters, there were *unclear* to *very likely trivial* differences with *small* to *moderate* ESs (ES: 0.2-0.6).

Table 1 – Parameters calculated by the Cheetah NICOM® system

Parameter	Equation	measuring unit
Stroke Volume (SV)	CO/HR x 1000	ml/beat
Stroke Volume Index	SV/BSA	ml/m²/beat
Cardiac Output (CO)	HR x SV/1000	l/min
Cardiac Index (CI)	CO/BSA	l/min/m²
Mean arterial pressure (MAP)	(SBP + (2 x DBP))/3	mmHg
Total Peripheral Resistance	80 x (MAP)/CO	dynes x sec/cm⁵
Total Peripheral Resistance Index	80 x (MAP)/CI	dynes x sec/cm⁵/m²

HR: heart rate; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2 – Anthropometric, echocardiographic, and maximal exercise characteristics of the participants (male: n = 10; female: n = 7)

Variable	Mean ± 90% CI
Age (years)	46 ± 1
BMI (kg/m^2)	23.9 ± 0.9
IVSd (mm)	9.6 ± 0.5
LVed (mm)	46.9 ± 1.8
PLWd (mm)	9.9 ± 0.5
FS (%)	26.9 ± 2.0
EF (%)	66.0 ± 2.2
E´ (cm/s)	9.9 ± 1.1
E/E´	8.5 ± 1.3
Tlim (min:s)	19:42 ± 4:39
Pmax (W)	187 ± 23
VO_{2peak} (ml/min/kg)	33 ± 4
VAT (%VO_{2peak})	60.7 ± 4.0

CI: confidence interval; BMI: body mass index; IVSd: interventricular septal diastole; LVed: left ventricle end-diastolic diameter; PLWd: left ventricular posterior wall thickness; FS: fractional shortening; EF: ejection fraction; E`: peak mitral annular velocity during early filling; E/E`: ratio between early mitral inflow velocity and mitral annular early diastolic velocity; Tlim: time to exhaustion; Pmax: maximum workload; $VO_{2peak:}$ peak oxygen uptake; VAT: ventilatory anaerobic threshold.

Table 4 summarizes the relative and absolute reliability expressed by ICCs and TEs, respectively, for all measured parameters. The ICCS ranged from *moderate* (ICC: 0.59) to *very high* (ICC: 0.98), whereas the TEs ranged from *small* (ES: 0.3) to *large* (ES: 1.8). CPO demonstrated superior relative and absolute reliability under all measurement conditions (ICC: 0.80-0.85; ES: 0.9-1.1) than its underlying parameters (ICC: 0.59-0.98; ES: 0.3-1.8).

Relationships

Figure 1 shows the relationships between echocardiographic measures of cardiac structure and function, traditional cardiopulmonary exercise parameters, and peak CPO. The peak CPO correlated *moderately* with VO_{2peak} (Figure 1A: r = 0.68; R^2 = 0.47) and VAT (Figure 1B: r = 0.55; R^2 = 0.31), but only *small* with left ventricular wall thickness (Figure 1E: r = 0.33; R^2= 0.11), left ventricular end-diastolic diameter (Figure 1F: r = 0.38; R^2 = 0.14), and systolic (Figure 1C: r = –0.32; R^2 = 0.11) as well as *trivial* with diastolic function (Figure 1D: r = 0.20; R^2 = 0.04).

Discussion

Our main findings were: (1) there were no systematic bias for all measured parameters during all conditions, (2) all noninvasively measured hemodynamic parameters showed

Table 3 – Changes in means of the resting, submaximal and maximal hemodynamic and cardiorespiratory characteristics

Variable	Test 1 Mean ± 90% CI	Test 2 Mean ± 90% CI	Bias Mean ± 90% CI	SWD	Likelihood (%) for Bias beeing higher/trivial/lower than SWD	ES ± 90% CI
Rest						
CPO (W)	1.2 ± 0.1	1.2 ± 0.1	0.0 ± 0.1	0.1	11.3/77.4/11.3 (unclear)	0.2 ± 0.3 (small)
CO (l/min)	5.61 ± 0.30	6.04 ± 0.31	+0.43 ± 0.19	0.47	43.6/56.4/0.0 (possibly trivial)	0.6 ± 0.3 (moderate)
SV (ml)	83 ± 6	87 ± 7	+4 ± 3	10	13.2/86.2/0.6 (likely trivial)	0.3 ± 0.2 (small)
HR (1/min)	71 ± 4	74 ± 5	+3 ± 2	7	15.1/84.4/0.5 (likely trivial)	0.3 ± 0.2 (small)
MAP (mmHg)	96 ± 4	92 ± 4	-4 ± 3	6	8.5/53/38.5 (unclear)	0.2 ± 0.2 (small)
Submaximal						
CPO (W)	3.6 ± 0.5	3.4 ± 0.4	-0.2 ± 0.3	0.7	9.1/89.9/1.0 (likely trivial)	0.2 ± 0.3 (small)
CO (l/min)	13.95 ± 1.23	13.66 ± 1.04	-0.29 ± 1.07	1.77	1.6/92.5/5.9 (likely trivial)	0.1 ± 0.5 (small)
SV (ml)	100 ± 7	100 ± 8	-1 ± 6	12	2.9/94.2/2.9 (likely trivial)	0.1 ± 0.4 (small)
HR (1/min)	133 ± 10	131 ± 10	-3 ± 2	15	2.4/91.1/6.5 (likely trivial)	0.1 ± 0.1 (small)
MAP (mmHg)	115 ± 6	112 ± 6	-3 ± 1	9	0.8/90.7/8.5 (likely trivial)	0.2 ± 0.1 (small)
Maximal						
CPO (W)	4.4 ± 0.5	4.2 ± 0.5	-0.2 ± 0.3	0.7	11.3/87.0/1.7 (likely trivial)	0.2 ± 0.3 (small)
CO (l/min)	16.09 ± 1.31	15.51 ± 1.28	-0.58 ± 1.01	2.01	1.0/89.9/9.1 (likely trivial)	0.2 ± 0.4 (small)
SV (ml)	98 ± 9	95 ± 10	-3 ± 7	14	1.7/90.1/8.2 (likely trivial)	0.2 ± 0.4 (small)
HR (1/min)	164 ± 7	161 ± 7	-3 ± 3	11	1.0/89.9/9.1 (likely trivial)	0.2 ± 0.2 (small)
MAP (mmHg)	123 ± 6	122 ± 6	-1 ± 4	9	1.8/94.2/4.0 (likely trivial)	0.1 ± 0.3 (small)
P (W)	187 ± 23	190 ± 25	+3 ± 6	38	3.2/95.0/1.8 (very likely trivial)	0.1 ± 0.1 (small)
VO_2 (l/min)	2.40 ± 0.27	2.39 ± 0.29	-0.01 ± 0.07	0.43	3.1/93.2/3.7 (likely trivial)	0.0 ± 0.1 (small)

CI: confidence interval; SWD: smallest worthwhile differences; ES: effect size; CPO: cardiac power output; CO: cardiac output; SV: stroke volume; HR: heart rate; MAP: mean aterial pressure; P: workload; $VO_{2:}$ oxygen uptake.

Table 4 – Relative (ICC) and absolute reliability (TE) of the resting, submaximal, and maximal cardiorespiratory and hemodynamic characteristics

Variable	Relative Reliability	Absolute Reliability (SI)	
	ICC ± 90% CI	TE ± 90% CI	ES ± 90% CI
Rest			
CPO (W)	0.80 ± 0.16 (high)	0.1 ± 0.0	1.1 ± 0.3 (moderate)
CO (l/min)	0.83 ± 0.14 (high)	0.33 ± 0.11	1.0 ± 0.3 (moderate)
SV (ml)	0.92 ± 0.07 (very high)	5 ± 1	0.6 ± 0.2 (moderate)
HR (1/min)	0.91 ± 0.08 (very high)	4 ± 1	0.7 ± 0.2 (moderate)
MAP (mmHg)	0.91 ± 0.08 (very high)	6 ± 2	0.7 ± 0.2 (moderate)
Submaximal			
CPO (W)	0.85 ± 0.13 (high)	0.5 ± 0.1	0.9 ± 0.3 (moderate)
CO (l/min)	0.59 ± 0.28 (moderate)	1.89 ± 0.60	1.8 ± 0.6 (large)
SV (ml)	0.75 ± 0.19 (high)	10 ± 3	1.2 ± 0.4(large)
HR (1/min)	0.97 ± 0.03 (very high)	4 ± 1	0.4 ± 0.1 (small)
MAP (mmHg)	0.98 ± 0.02 (very high)	2 ± 1	0.3 ± 0.1(small)
Maximal			
CPO (W)	0.82 ± 0.15 (high)	0.5 ± 0.2	1.0 ± 0.3 (moderate)
CO (l/min)	0.73 ± 0.20 (moderate)	1.78 ± 0.57	1.3 ± 0.4 (large)
SV (ml)	0.75 ± 0.19 (high)	12 ± 4	1.2 ± 0.4 (large)
HR (1/min)	0.91 ± 0.08 (very high)	6 ± 2	0.7 ± 0.2 (moderate)
MAP (mmHg)	0.82 ± 0.15 (high)	6 ± 2	1.0 ± 0.3 (moderate)
P (W)	0.97 ± 0.03 (very high)	11.2 ± 3.6	0.4 ± 0.1 (small)
VO_2 (l/min)	0.97 ± 0.03 (very high)	0.13 ± 0.04	0.4 ± 0.1 (small)

ICC: intraclass correlation coefficient; CI: confidence interval; TE: typical error; ES: effect size; CV: coefficient of variation; CPO: cardiac power output; CO: cardiac output; SV: stroke volume; HR: heart rate; MAP: mean arterial pressure; P: workload; VO_2 oxygen uptake.

small to large test-retest-reliability, whereas the CPO_{peak} demonstrated a superior reliability than its underlying parameters, and (3) CPO was independent of measures of cardiac structure and function as well as traditional cardiopulmonary exercise parameters.

Our first finding was that there was no systematic bias during all examination conditions. These outcomes are in line with further studies, investigating hemodynamic and cardiopulmonary exercise parameters.[26,49] Overall, in our study, systematic bias due to learning, subject motivation, and fatiguing effects as well as errors in calibration procedures can be excluded.[45,50] This assumption supports our research design.

The second major finding was that all noninvasively measured hemodynamic parameters showed an acceptable test-retest reliability during rest, submaximal, and maximal exertion. Jones et al.[26] first showed a good test-retest reliability of TB in a healthy population at rest as well as during submaximal and maximal exertion. However, acceptable test-retest reliability was impacted by the fact that we have previously excluded a significant number of outliers (n = 8) due to measurement errors. It is further noteworthy that the reliability of our TB measurements was to some degree inferior compared to a previous study in which the reliability of a comparable technology (beat by beat signal morphology impedance cardiography) to evaluate the hemodynamic response was assessed.[20] One possible explanation for the differences may be that we investigated the reliability under less standardized conditions, another one could be related to significant technological differences.

Overall, when outliers are excluded, TB can be considered as an appropriate technology to not only assess hemodynamic status in a research setting but also in everyday practice.

The central task of the heart is to produce a sufficient CO and maintain an adequate MAP. Therefore, cardiac performance can be best explained by CPO, because it takes both the flow- and pressure-generating capacities of the heart into account.[29]

In chronic heart failure, the application of hemodynamic measuring to standard cardiopulmonary exercise testing may help to explain the underlying mechanism of exercise intolerance with impact on clinical decision making,[31] therapy planning, and performance[32] as well as risk stratification.[51] Chomsky et al.[31] showed that CO respond to exercise is a strong predictor of mortality in cardiac transplantation candidates. In addition, Lang et al.[35] demonstrated CPO as the most powerful and independent predictor of survival chronic heart failure outcome in patients with chronic heart failure and that may enhance the prognostic power of traditional cardiopulmonary exercise testing.

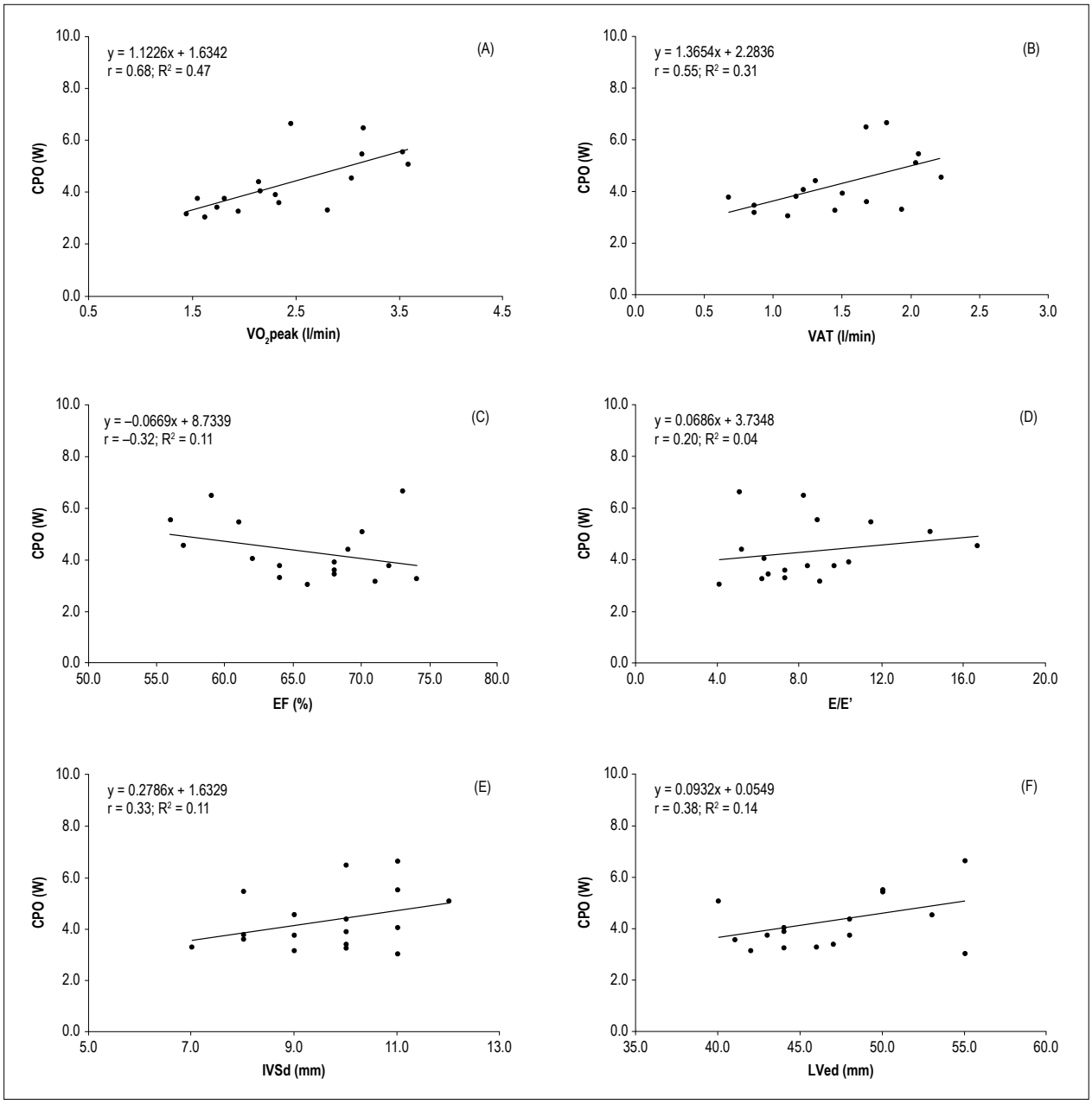

Figure 1 – *Relationships between the CPO and established cardiorespiratory and echocardiographic characteristics. CPO: cardiac power output; VO_{2peak}: peak oxygen uptake; VAT: ventilatory anaerobic threshold; EF: ejection fraction; E/E': ratio between early mitral inflow velocity and mitral annular early diastolic velocity; r: Pearson correlation coefficient; R^2: coefficient of determination.*

In sports medicine, monitoring of the training status is essential to guide the training process. Training leads to significant structural and functional changes of the cardiovascular system.[6] In a randomized cross-over study, Marshall et al.[38] assessed the effect of moderate exercise training on cardiac performance in non-athletic adults. Due to training, the CPO_{peak} increased by 16%, whereas the CPO at rest remained unchanged. In highly trained endurance athletes, Schlader et al.[37] found double CPO_{peak} values compared to non-athletes. These results have been confirmed by Klasnja et al.[3] in football and basketball players.

In our study, the CPO_{peak} showed superior reliability than the underlying physiological single parameters. However, it should be noted that the reliability of the CPO was potentially influenced by the reliability of the MAP (which was higher) rather than that of the SV and CO (which were lower). Thus, CPO measuring by TB seems to be feasible due to its surrogate character. It is, however, important to mention that we have averaged all our beat-by-beat measured TB data, including the CPO, over 60 s, which might have also artificially improved our statistical outcomes. The reason for our data processing method was that we aimed to investigate

the global cardiac performance. Such a data processing proceed is of course inadequately, when aiming to assess transient cardiac abnormalities during exercise like ischemia. Since the beat-by-beat reliability of our TB based measures remains unknown, we recommend other impedance-based technologies, which offer a reliable beat-by-beat analysis of hemodynamic parameters during exercise.[20]

The third major finding was that CPO was found to be independent of cardiac structure and function at rest as well as to traditional cardiopulmonary exercise parameters. Klasnja et al.[3] previously demonstrated a weak correlation between CPO_{peak} and resting parameters of left ventricular morphology and function.[3] We also did not find a strong relation between CPO_{peak} and echocardiographic findings at rest. Our findings show once again that resting parameters cannot be used to estimate maximal cardiovascular performance.

For the first time driven by our progressive statistics,[47] we report the SWDs for all investigated TB parameters. From a practical point of view, the provided thresholds can be used as a framework to judge in healthy adults, whether observed differences in the analyzed parameters should be interpreted or not in a daily medical routine. Further, it is promising to use these thresholds as cutting-off values for minimal required effects detected by longitudinal or cross-sectional studies using the here investigated TB measures in the future. For example, in healthy adults, the calculated SWD of the CPO was 0.7 W, meaning that longitudinal or cross-sectional differences should only be interpreted, when this cut-off value is exceeded.

The major limitation of our study is the high dropout rate (n=8). However, to detect outliers, we objectively defined them as those values, which were greater than the pooled standard deviation. Based on this approach and our recruited healthy adults, it can be assumed that the detected outliers had not a physiological cause. Contrary, it is more likely that the identified outliers had rather an underlying technical reason. Therefore, further improvements in TB, for example, regarding the application and quality of electrodes are required. Consequently, technical errors must be executed by proprietary algorithms, before valid decisions are possible. When taken these aspects together, our findings indicate that TB can only be considered as a reliable technology for measuring hemodynamic parameters after outliers have been excluded.

Conclusion

In conclusion, at this stage, our results preclude the clinical use of TB in healthy subject population when outliers are not identified even if a previous study seem to show its possible application in a strictly controlled research setting.

Author contributions

Conception and design of the research: Coll MT, Dinh W; Acquisition of data: Coll MT, Kiefer C, Dinh W; Analysis and interpretation of the data: Hoppe MW, Dinh W; Statistical analysis: Hoppe MW; Obtaining financing: Krahn T, Mondritzki T, Dinh W; Writing of the manuscript: Coll MT, Hoppe MW, Boehme P, Dinh W; Critical revision of the manuscript for intellectual content: Coll MT, Boehme P, Krahn T, Kiefer C, Kramer F, Mondritzki T, Pirez P.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Witten/Herdecke under the protocol number 131/2914. 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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Continuous Non-Invasive Cardiac Output: Myth or Reality

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Short Editorial related to the article: Test-Retest Reliability of Non-Invasive Cardiac Output Measurement during Exercise in Healthy Volunteers in Daily Clinical Routine

Cardiac output (CO) is an important cardiovascular system function parameter. Changes in cardiac function are commonly observed as a response to physical training and pharmacological interventions.[1] Unfortunately, the methods for assessing CO are invasive, leading to well-known complications and considered inconvenient in daily practice.[2] For this reason, the search for new noninvasive methods that can accurately detect CO at rest, at physical exertion or as a response to a clinical intervention has become desirable in academic and non-academic circles. The ideal method for measuring CO at rest and during exercise should be noninvasive, safe, reproducible and inexpensive.[3]

The Cardiopulmonary Exercise Testing (CPT) is recommended in the evaluation of cardiorespiratory fitness and exercise tolerance in athletes, the general population and in patients.[4] Briefly, CO and systolic volume can be estimated during CPT through measured VO_2.[5] In 2001, Williams et al.[6] were the first ones to integrate CPT with non-invasive measures of CO using rebreathing (RB) of carbon dioxide, but the technique was quickly abandoned due to its difficulty and inaccuracy. Another non-invasive method is thoracic electrical bioimpedance (TEB), first described in 1966 by Kubicek et al.,[7] which measures thoracic resistance as a result of changes in blood velocity during the cardiac cycle and uses an algorithm to calculate the CO.

Another promising technique is based on thoracic bioreactance (TB) (NICOM™, Cheetah Medical Inc., Wilmington, DE), which analyzes the variations in beat-to-beat tension after a high-frequency transthoracic current is applied. This device records the electric current phase in the thorax. The systolic volume is directly proportional to the phase displacement.[8] Despite some controversial studies, this technique seemed to be more reliable.[8-10] It is worth mentioning that the CO measurement is simple to perform and does not require patient cooperation, both at rest and at the exercise peak. It should be noted that some conditions, such as significant pleural effusion, have a negative impact on the accuracy of this method.[11]

In a meta-analysis, the percentage errors for CO monitoring devices were 42% for TEB and TB, 40% for RB of carbon dioxide and 62% for the methods of pulse wave analysis.[12]

Keywords

Cardiac Ouput; Electric; Impedance; Pharmacological; Interventions; Breathing Exercise

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The most recent meta-analysis that evaluated adult and pediatric patients in different clinical situations (mostly in the hospital setting), it was demonstrated that TEB accuracy showed high heterogeneity between the studies and that the mean percentage error grouped in all the subgroups was above the acceptable 30%. Therefore, TEB could not replace thermodilution and transthoracic echocardiography for the measurement of absolute CO values.[13]

Okwose et al.[14] showed that the RB of an inert gas and TB methods had acceptable levels of agreement to estimate the CO at higher degrees of metabolic demand during a CPT. However, they concluded they could not be used interchangeably because of the great disparity in results at rest and in low-to-moderate intensity exercises. Unlike this study, Torto et al.[15] showed that cardio-impedance could be less ideal for supramaximal exercise intensities.

In this issue, Coll et al.[16] evaluated the test-retest reliability of CO and cardiac work during CPT by TB in healthy adults under routine clinical conditions in an uncontrolled environment.

They concluded that, according to the findings, there is an obstacle to the clinical use of TB in healthy individuals whereas outliers are not identified (32% of the initial sample). That is, under routine clinical conditions, almost one-third of the patients showed measurement errors and, according to the authors, these outliers were probably due to an underlying technical reason; thus, further improvements in TB are required, such as regarding the use and the quality of the electrodes. This study contested the results of the study by Jones et al.,[11] which had demonstrated that TB could be viable under strict control conditions and in the research environment.

The results of the studies published to date showed that even in situations of in-hospital use and controlled environment (anesthesia, intensive care and even outpatient clinics) in which patients were at rest, noninvasive monitoring of CO showed great variability between the non-invasive methods and frequently showed unacceptable errors in relation to procedures considered as "gold standard", such as thermodilution. In an uncontrolled exercise scenario, both for the diagnosis of diseases and for the improvement of athlete conditioning, the non-invasive methods for CO monitoring seem to be more of a myth than a reality at present, when compared to the standard methods for calculating the CO.

Further studies are needed to determine CO through noninvasive methods at rest and during exercise. Our hope is that in the near future, and with the progress in technological development, the non-invasive monitoring of CO can be used in controlled and uncontrolled environments, in addition to the current perioperative scenario.

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Cardiovascular Risk in Psoriasis Patients: Clinical, Functional and Morphological Parameters

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Abstract

Background: **Psoriasis correlates with metabolic disorders, early atheromatosis and increased cardiovascular risk.**

Objectives: **To assess markers of cardiovascular disease in psoriatic patients.**

Methods: **Cross-sectional, observational study involving 11 psoriatic participants and 33 controls. Anthropometric, biochemical, hemodynamic and imaging parameters were evaluated. Arterial stiffness was assessed by oscillometric measurement of the brachial artery. Intima-media thickness (IMT) and left ventricular diastolic function were assessed by Doppler echography and echocardiography. Between-group comparisons of numerical variables were performed by the Student's t-test or Wilcoxon Mann-Whitney test for independent samples. Significance level was set at 5%.**

Results: **Psoriatic patients showed increased pulse wave velocity (PWV) (9.1 ± 1.8 vs 8.0 ± 2 m/s, p = 0.033), IMT of the left common carotid artery (p = 0.018) and a higher percentage of patients above the 75th percentile according to the ELSA table when compared with controls (54.5 vs 18.2%, p = 0.045). Psoriatic patients also showed an increase in peripheral/central systolic blood pressure (137.1 ± 13.2 vs 122.3 ± 11.6 mmHg, p = 0.004)/(127 ± 13 vs 112.5 ± 10.4 mmHg, p = 0.005), peripheral/central diastolic blood pressure (89.9 ± 8.9 vs 82.2 ± 8, p = 0.022)/(91 ± 9.3 vs 82.2 ± 8.3, p = 0.014), total cholesterol (252 ± 43.5 vs 198 ± 39.8 mg/dL, p < 0.001), LDL cholesterol (167 ± 24 vs 118 ± 40.8 mg/dL, p < 0.001) and C-reactive protein (7.6 ± 35.4 vs 1 ± 1.2 mg/L p < 0.001) compared with controls.**

Conclusion: **Psoriasis patients show increased PWV, IMT, peripheral and central blood pressures, and serum cholesterol and C-reactive protein levels, denoting a higher cardiovascular risk. (Arq Bras Cardiol. 2019; 113(2):242-249)**

Keywords: **Cardiovascular Diseases; Psoriasis; Arterial Stiffness; Hypertension; Hypercholesterolemia; Oscillometry/mehods; Brachial Artery.**

Introduction

Psoriasis is an immune-mediated, recurrent chronic inflammatory disease of the skin and joints, affecting 2-4% of the adult population in the world.[1,2] Vulgar psoriasis is the most common type and occurs in 85-90% of psoriasis patients. It is phenotypically characterized by dry, red, scaly, silvery-white, well-defined plaques that appear mainly on elbows, knees, scalp, and the lumbar area.[3] The cause of psoriasis is multifactorial, with numerous key components including genetic susceptibility, environmental triggers in combination with skin barrier disruption and immune dysfunction.[3,4]

Similarly to other autoimmune diseases, psoriasis is associated with well-documented systemic changes, including joint, endocrine, and cardiovascular dysfunctions.[5-8] Atherosclerosis is considered a chronic inflammatory disease of blood vessels and one of the most common mechanisms involved in the development of cardiovascular diseases (CVDs). The incidence of atherosclerosis is increased in psoriatic patients and seems to be directly associated with the severity of skin manifestations in these patients.[6] In addition, previous epidemiological studies have shown the high prevalence of cardiovascular risk factors in psoriatics, including metabolic syndrome, obesity, hypertension, diabetes mellitus, insulin resistance and dyslipidemia.[6,7,9-11]

CVDs are the main cause of mortality in Brazil and in the world. For this reason, it is important to identify and correct their risk factors.[12-14] There are several clinical and subclinical markers for early detection of cardiovascular risk, including physical examination findings, and metabolic, functional and imaging tests.[15]

Considering the close relationship between psoriasis and cardiovascular events, this study aimed to investigate subclinical cardiovascular change, measured by arterial stiffness (AS), common carotid artery intima-media thickness (IMT), and left ventricle diastolic dysfunction (LVDD), in addition to clinical and laboratory parameters in patients with moderate-to-severe psoriasis. The detection of these changes would contribute to early preventive and therapeutic measures.

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Methods

Type of study

This was a cross-sectional, analytical, observational study conducted between May 2016 and March 2018.

Participants

Psoriasis group (PG) was composed of 11 male volunteers, without evidence of CVD, aged between 40 and 65 years, with Psoriasis Area and Severity Index (PASI) > 7.[16] All patients were consecutively included during their medical visit at a public health care center in Belo Horizonte, Brazil. All patients were classified as PASI > 10, indicating severe skin manifestations of the disease. For the control group (CG), we selected 33 healthy men, without evidence of CVD or psoriasis, matched by age, recruited from the same health care center and from a private clinic in the same city. For the CG, patients seen for dermatological assessment due to conditions other than psoriasis. The number of subjects recruited was obtained by specific sample calculation proposed by Siqueira et al.[17] Sample size was calculated assuming that variations in AS between PG and CG were similar. We also considered a proportion of three controls to one case, due to the low prevalence of severe psoriasis.

Exclusion criteria for both groups were: chronic diseases requiring nonsteroidal anti-inflammatory drugs (NSAIDs) or systemic corticosteroids, treatment for neoplasms or diagnosis of neoplasms less than five years, severe chronic kidney failure (glomerular filtration rate < 30 mL/min), liver failure or previous coronary diseases, peripheral vascular disease and HF with reduced ejection fraction. We also excluded from the study psoriasis patients with PASI < 7.

All patients were seen by a cardiologist and assessed for smoking habit (smokers were considered those patients who smoked at least one cigarette per day in the last 12 months),[18] alcohol consumption (15 doses/week in the last 12 months – 1 dose corresponded to one can of beer),[19] systemic arterial hypertension (according to the 2017 Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis),[12] diabetes mellitus (according to the 2018 American Diabetes Association guidelines),[20] use of medications, and any other factor that may be related to the exclusion criteria of the study.

All volunteers had their body weight and height measured for body mass index (BMI) calculation, body surface area (BSA) measured, and waist and hip circumferences measured for waist-to-hip ratio (WHR) calculation. These measurements were obtained using calibrated and certified (by INMETRO/ANVISA) equipment.

Blood samples were collected for laboratory tests and measurement of C-reactive protein (CRP), LDL cholesterol, HDL cholesterol, and total cholesterol (TC).

Patients of the PG were classified according to the PASI, developed by Fredriksson and Pettersson in 1978 to assess the extent of the psoriatic plaques.[21] This is the method of choice for the classification of the disease severity,[16] and was applied by a dermatologist. Analysis of the severity and extent of the disease was made in four anatomical regions: head, trunk and upper and lower limbs.

Measurements of blood pressure (both peripheral/arm and central) and AS were obtained non-invasively using the monitor Mobil-O-Graph NG (IEM, Stolberg, Germany), with ARC Solver algorithm (the ARC Solver method, Austrian Institute of Technology). This is an oscillometric, 24-hour ambulatory blood pressure monitoring device, approved by the USA Food and Drug Administration and the Conformité Européenne. The method was validated according to the British Hypertension Society and recently by the American Heart Association's Council on Hypertension.[22-24] After the measurement of the arm circumference and selection of the arm cuff, the device was positioned as proposed by the Brazilian Society of Cardiology.[12] Three consecutive readings were taken automatically and the results were expressed as the mean of these three measurements. AS was estimated using the variables pulse wave velocity (PWV) and augmentation index (AIx) adjusted for a heart rate (HR) of 75 beats per minute (AIx@75). The monitor also provided the measurements of HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and peripheral and central pulse pressure (PP).

The analysis of IMT was performed by duplex scanning of the carotid arteries using the two-dimensional mode, and linear probe 10-MHZ Vivid S6 (GE healthcare, Telaviv, Israel), according to the recommendations of the Department of Cardiovascular Imaging of the Brazilian Society of Cardiology.[25] The measurement of IMT was semi-automatically obtained one centimeter from the posterior wall of the common carotid artery. To determine the IMT percentile, the mean IMT (without including the plaque) of each segment was compared with those of the reference tables. The highest percentile for age of each participant was obtained. We used the tables obtained from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil),[26] that evaluates chronic diseases in the Brazilian population aged from 40 to 65 years, of white, mulatto and black ethnicity, and from the Multi Ethnic Study of Atherosclerosis (MESA).[27] Measures above the 75th percentile were considered as significant increases.

A two-dimensional echocardiography with Doppler and tissue Doppler was performed following the American Society of Echocardiography (ASE) recommendations.[28] We analyzed the electrocardiographic images of three cardiac cycles for the dimensions of the left ventricle, left atrial volume (LAV), parietal thickness, left ventricular mass index, left ventricular ejection fraction and color Doppler images of all valves. Analysis of the left ventricular diastolic function (LVDF) was performed according to the 2016 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[29] The following parameters were obtained: early left ventricular filling (E-wave), peak atrial filling wave (A-wave), E/A ratio, E-wave deceleration time, and isovolumic relaxation time. Tissue Doppler velocity measurements were obtained in the medial and in the lateral mitral annulus, in the four-chamber view, for the measurement of the peak early diastolic velocity (e'). The 2016,[29] American Society of Echocardiography recommendations were also used for classification of diastolic function – normal function, diastolic dysfunction grade II (pseudonormal pattern), and diastolic dysfunction grade III (restrictive pattern). Subclinical dysfunction (i.e., asymptomatic condition) was diagnosed by left ventricular systolic and/or diastolic dysfunction.

The echocardiographist could not be blinded to psoriasis, since skin manifestations of the disease are clinically evident.

Statistical analysis

Categorical variables were expressed as counts and percentages. Numerical variables were tested for normality by the Shapiro-Wilk test and expressed as mean ± standard deviation (SD) (normally distributed variables) or median and interquartile range (variables without normal distribution). Association between categorical variables was assessed by Fisher's exact test or the chi-square test of independence. Between-group comparisons of numerical variables were performed by the Student's t-test or the Wilcoxon Mann-Whitney test, according to the normality of data distribution. The analysis was performed using the R software, version 3.3.2 and a 5% significance level was used.

Mean differences of AS between PG and CG were estimated, and the sample size was calculated to test the difference between two means. For calculation of the sample size, we assumed that the variance of the AS measurements in PG and CG would be the same. In addition, we used a ratio of three controls to one psoriatic patient, due to the difficulty in identifying patients with moderate or severe psoriasis (PASI ≥ 7), not using corticosteroids, considering a significance level of $\alpha = 5\%$ and power $(1 - \beta)$ of 80%.

Results

The study sample was composed of 44 subjects, 11 of the PG and 33 of the CG. Mean age was 60.5 ± 11.3 years and 59.1% was white. Mean values of BSA, BMI and WHR were 1.93 ± 0.20 m^2, 28.1 ± 5.2 kg/m^2 and 0.96 ± 0.06, respectively. Age was not different between the groups (Table 1).

Regarding lifestyle and comorbidities, 29.5% of participants consumed alcohol, 29.5% were smokers, 40.9% had systemic arterial hypertension, 20.5% had diabetes and 29.5% dyslipidemia, with no difference between the groups. With respect to laboratory tests, PG showed higher levels of TC, LDL cholesterol, and C-reactive protein ($p < 0.01$) (Table 1).

The most common medication in the study group was angiotensin II receptor blockers (29.5%), statins (22.7%) and diuretics (18.2%), with no difference between the groups (data not shown). For the psoriasis treatment, two patients (18%) of the PG used methotrexate. Only one patient of the PG (9%) used topical corticosteroids regularly for the skin lesions during the study period.

PG patients showed increased PWV (9.1 ± 1.8 and 8 ± 2 m/s, $p = 0.033$), increased IMT of the left common carotid artery ($p = 0.018$) and higher percentage of patients above the 75th percentile according to the ELSA table (54.5 and 18.2%, $p = 0,045$) when compared with the CG.

Compared with the CG, the PG also showed increased peripheral SBP (137.1 ± 13.2 *vs*. 122.3 ± 11.6 mmHg, $p = 0.004$), central SBP (127 ± 13 *vs*. 112.5 ± 10.4 mmHg, $p = 0.005$), peripheral DBP (89.9 ± 8.9 *vs*. 82.2 ± 8 mmHg, $p = 0.022$), central DBP (91 ± 9.3 *vs*. 82.2 ± 8.3 mmHg, $p = 0.014$), total cholesterol (252 ± 43.5 *vs*. 198 ± 39.8 mg/dL, $p < 0.001$), LDL cholesterol (167 ± 24 *vs*. 118 ± 40.8 mg/dL, $p < 0.001$) and C-reactive protein (7.6 ± 35.4 *vs*. 1 ± 1.2 mg/L, $p < 0,001$).

There was no difference in AIx@75 between the groups (Table 2).

Discussion

Psoriasis has been considered an autoimmune, inflammatory disease with important consequences in other systems.[5,6,8] There are evidences of higher incidence of obesity, diabetes mellitus, arterial hypertension and CVDs – such as acute myocardial infarction and stroke among psoriatic patients.[30,31] Thus, skin manifestations seem to be just one of the factors associated with this complex condition. It has been speculated that the high amounts of blood inflammatory mediators in psoriatics, in addition to C-reactive protein, such as TNFa and IL-6 may be associated with the inflammatory response to vascular remodeling and cardiovascular changes.[31,32]

In the present study, we included psoriasis patients with PASI>7, *i.e.*, with moderate and severe psoriasis. High C-reactive protein levels found in PG compared with the CG suggests increased inflammatory response, which was associated with higher blood pressure and LDL-cholesterol levels, may contribute to arterial remodeling, as well as to structural and hemodynamic changes observed in these patients.[7,10] Coban et al.[33] showed that systemic inflammation in psoriasis leads to insulin resistance, which, in turn, causes changes in the synthesis of adipokines, including visfatin, vaspin, omentin and adiponectin, which can increase blood pressure, and LDL-cholesterol and TC levels.[33] In the pathogenesis of atherosclerosis, factors like an altered lipid metabolism, and inappropriate immune response are involved, resulting in arterial wall inflammation. The increased levels of circulating inflammatory mediators contribute to vascular inflammatory response associated with migration of monocytes and oxidation of LDL-cholesterol, which are key elements in the formation of atherosclerotic plaque.[31,32] However, there are also reports describing the so-called "lipid paradox" in inflammatory diseases, mainly rheumatoid arthritis, marked by a significant decrease in LDL-cholesterol and TC levels 3-5 years before the onset of signs of the disease.[34,35] There also evidences of possible influence of pharmacological interventions on lipid profile of these patients.[36]

In our study, despite considerable impairment observed in psoriatic patients, this group showed significant increase in atherogenic lipoprotein levels compared with the CG. Only two (18%) patients used systemic medication, particularly methotrexate. None of the patients used biological drugs. The use of systemic corticosteroids was an exclusion criterion to avoid a bias in the findings.

A systematic review evaluated the metabolic effects of methotrexate in patients with rheumatoid arthritis;[37] while one study reported differences in lipid profile after one year of treatment, another study reported improvement in lipid concentrations, and their correlation with changes in C-reactive protein levels and blood sedimentation rate, and another study did not find any change in the levels of

Table 1 – Anthropometric and lifestyle data, comorbidities, and laboratory test results of patients with psoriasis (n=11) and control subjects (n = 33)

Variables	Control group (n = 33)	Psoriatic group (n = 11)	p-value
Age (years)	60 ± 9	64 ± 12.5	0.391*
Ethnicity			**0.479†**
White	21 (63.6%)	5 (45.5%)	
Pardo (multiracial)/Black	12 (36.4%)	6 (54.5%)	
BSA (m^2)	1.92 ± 0.20	1.94 ± 0.23	0.835‡
Weight (kg)	79.8 ± 15.1	84.7 ± 21.6	0.494‡
BMI (kg/m^2)	27.2 ± 4.7	30.9 ± 5.9	0.079‡
Waist-hip ratio	0.96 ± 0.06	0.97 ± 0.05	0.576‡
Habits			
Smoking	7 (21.2%)	6 (54.5%)	0.086†
Alcohol consumption	10 (30.3%)	3 (27.3%)	1.000§
Comorbidities			
Hypertension	11 (33.3%)	7 (63.6%)	0.093§
Dyslipidemia	10 (30.3%)	3 (27.3%)	1.000§
Diabetes mellitus	6 (18.2%)	3 (27.3%)	0.669§
Laboratory tests			
Total Cholesterol (mg/dL)	198 ± 39.8	252 ± 43.5	< 0.001*
HDL Cholesterol (mg/dL)	46 ± 13.5	38 ± 16.5	0.283*
LDL Cholesterol (mg/dL)	118 ± 40.8	167 ± 24	< 0.001*
C-reactive protein (mg/L)	1 ± 1.2	7.6 ± 35.4	< 0.001*

**Wilcoxon Mann-Whitney test for independent samples (mean ± SD), †chi-square test of independence; ‡Student's t-test for independent samples (mean ± SD), §Fisher's exact test; BMI: body mass index; BSA: body surface area.*

lipoproteins, even with reduced C-reactive protein levels. Thus, in light of the conflicting results of these studies and the low percentage of patients using methotrexate, we infer that the possible influence of medications is not relevant on our result.[37]

Among the hemodynamic changes in the PG, the increase in AS, illustrated by an increased PWV, indicates an early vascular aging.[38] Our results are in accordance with previous studies that reported an increase in PWV in psoriasis patients.[39-45] Increased PWV has been considered an important predictive factor for cardiovascular outcomes and higher mortality.[38]

Carotid atherosclerosis can be assessed by the IMT measurement and presence of plaques. In our study, we also used imaging test, which confirmed the increased left IMT in the PG. This is in agreement with other studies that showed similar results regardless of other risk factors.[43,44] Comparison of our results with reference values obtained in the ELSA, we showed a higher percentage of patients above the 75th percentile in the PG. However, this was not true when the results were compared with the MESA. This finding highlights the need for the use of reference tables developed in specific populations.

Regarding the presence of plaques, the apparently higher incidence of plaques in PG compared with the CG was not statistically significant, probably due to the sample size. Also, although a higher incidence of diastolic dysfunction in patients with psoriasis was found in the study by Shang et al.,[45] we did not find significant differences in echocardiographic parameters between the groups. The increased peripheral and central SBP and DBP values found in the PG may be related to the vascular changes observed in these patients, which has also been described in other studies.[46,47] Although the small number of patients in the PG is a limitations of the study, because of the difficulty in detecting patients who met the inclusion criteria including a PASI>7, we were able to show a close relationship between psoriasis and the factors associated with higher probability to develop cardiovascular outcomes. Such associations, found in moderate-to-severe psoriasis patients, are significantly greater than those reported in the general population. More comprehensive studies, including larger sample sizes are suggested, to demonstrate the importance of other predictive factors of CVDs, including an increased AIx@75 and the IMT of the right carotid artery, which did not show statistical difference in our study.

Current guidelines recognize the increased risk for CVDs in patients with psoriasis and the need for its early identification and better stratification.[48] However, predictive algorithms of cardiovascular risk, such as the Framingham risk score, do not consider the systemic inflammatory effect secondary to psoriasis.[9,49] Functional parameters, such as the measurement of the AS, as well as structural parameters, such as the use of cardiac and vascular imaging tests, and laboratory biomarkers could be used to improve the sensitivity of traditional algorithms of risk stratification in patients with psoriasis.

Table 2 – Ultrasound and oscillometry parameters of the brachial artery

Parameters	Control group (n = 33)	Psoriatic group (n = 11)	p-value
IVRT (ms)	94 ± 15	104 ± 12	0.106*
DT (ms)	180 ± 43	190 ± 36.5	0.322*
E/A ratio	0.86 ± 0.47	0.88 ± 0.18	0.456*
Lateral E/e' ratio	5.96 ± 1.42	5.90 ± 2.28	0.937‡
Septal E/e' ratio	6.92 ± 1.82	7.17 ± 3.14	0.616*
LA volume (mL/m^2)	18.41 ± 4.55	17.50 ± 5.48	0.626‡
LVESV (mL)	34 ± 9	38 ± 8	0.086*
LVEDV (mL)	106 ± 26	113 ± 17	0.606*
LVEF (%)	68 ± 3	68 ± 3	0.763*
Right IMT (mm)	0.60 ± 0.12	0.62 ± 0.16	0.481*
Left IMT (mm)	0.61 ± 0.14	0.72 ± 0.21	0.018*
MEDA > 75th percentile	6 (18.2%)	3 (27.3%)	0.669§
ELSA >75th percentile	6 (18.2%)	6 (54.5%)	0.045§
Plaques	9 (27.3%)	5 (45.5%)	0.287§
Peripheral SBP (mmHg)	122.3 ± 11.6	137.1 ± 13.2	0.004‡
Peripheral DBP (mmHg)	82.2 ± 8	89.9 ± 8.9	0.022‡
MBP (mmHg)	99.2 ± 11.5	108.3 ± 16	0.105‡
PP (mmHg)	39.8 ± 6	47.3 ± 11.4	0.058‡
Heart rate (bpm)	70 ± 14	72 ± 11	0.989*
Central SBP (mmHg)	112.5 ± 10.4	127 ± 13	0.005‡
Central DBP (mmHg)	82.2 ± 8.3	91 ± 9.3	0.014‡
Central PP (mmHg)	29.3 ± 7	36 ± 8.8	0.020*
AIx @75(l/min/m^2)	17.64 ± 10.84	19.15 ± 10	0.675‡
PWV (m/s)	8 ± 2	9.1 ± 1.8	0.033*

**Wilcoxon Mann-Whitney test (mean ± SD), ‡t-Student (mean ± SD) for independent samples and § Fisher's exact. IVRT: isovolumic relaxation time; DT: deceleration time; E/A ratio: ratio of the E-wave and A-wave of the left ventricular diastolic filling, LA: left atrial; LVESV: left ventricular end-systolic volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; IMT: intima-media thickness; MESA: Multi-Ethnic Study of Atherosclerosis; ELSA: Brazilian Longitudinal Study of Adult Health; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PP: pulse pressure. AIx @75: Augmentation Index adjusted for a heart rate of 75 beats per minute; PWV: pulse wave velocity.*

Conclusion

Our study shows that psoriatic patients have elevations in carotid IMT and PWV, in addition to increased central and peripheral blood pressure, and serum cholesterol and C-reactive protein levels.

Limitations

One possible limitation of this study is the small sample size, due to the difficulty in recruiting patients with moderate and severe psoriasis (PASI>7), not using corticosteroids, which could affect the outcome measures. Another possible limitation is the recruitment of patients from one location only.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Oliveira AN, Simões MM, Simões R, Rezende BA, Malachias MVB; Acquisition of data: Oliveira AN, Simões MM, Rezende BA, Malachias MVB; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Oliveira AN, Rezende BA, Malachias MVB.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Ciências Médicas de Minas Gerais under the protocol number 1.267.197. 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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Psoriasis and Cardiovascular Disease: Lesion Beyond the Skin

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Short Editorial related to the article: Cardiovascular Risk in Psoriasis Patients: Clinical, Functional and Morphological Parameters

Interesting to find an article[1] that apparently belongs to the dermatology field in a cardiology journal. Why read about psoriasis? A disease that, for several years, many colleagues regarded as eminently skin-related and of benign course, especially in its plaque form. As it happens, epidemiological studies[2,3] and an international registry[4] revealed that the risk of cardiovascular (CV) events increased approximately 50% in the group of psoriatic individuals compared to the general population, markedly in younger patients.[5] How to explain this situation? Systemic inflammation seems to be the "missing link" between CV diseases, neoplasms, and chronic systemic inflammatory diseases (e.g., psoriasis or rheumatoid arthritis).[6]

The interest of cardiology in this interdisciplinary theme is not new. In the past two decades, the understanding of atherosclerosis as a systemic vascular inflammatory disease and that sustained systemic inflammatory activity accelerates its physiopathological mechanisms has been consolidated. In 2003, Sattar et al.[7] used rheumatoid arthritis as a physiopathological model to systematize the process of accelerated atherosclerosis. Systemic inflammation would increase the hepatic synthesis of C-reactive protein (CRP), induce lipolysis with the release of free fatty acids, and intensify insulin resistance and oxidation of low-density lipoproteins (LDL), culminating in endothelial dysfunction associated with increased expression of adhesion molecules and accelerating the atherosclerotic disease. In 2011, Boehnck et al.[8] coined the term "psoriatic march" to describe possible mechanisms that could justify the increase in CV events in the physiopathological model of psoriasis. As expected, the foundation and steps of the process are extremely similar to those found in rheumatoid arthritis. The sustained systemic inflammation caused by psoriasis would increase the synthesis of CRP, vascular endothelial growth factor (VEGF), P-selectin, resistin, and leptin. Such proteins would be involved in raising insulin resistance, which ultimately would intensify the endothelial dysfunction and stimulate the expression of adhesion molecules. These steps reveal the importance of the subclinical atherosclerotic phase (endothelial dysfunction, vascular stiffness, and overexpression of vascular adhesion molecules) and biomarkers (CRP, leptin, and resistin) in this physiopathological process. In the article that prompted this short editorial, the authors compared arterial stiffness with pulse wave velocity (PWV), carotid intima-media thickness (IMT), metabolic syndrome data, and CRP levels in a cohort of psoriatic individuals and volunteers. The results reported were statistically significant and corroborated the hypothesis that psoriatic patients with intense disease activity are more prone to have metabolic syndrome, elevated CRP, and signs of subclinical atherosclerosis (increased IMT and arterial stiffness) compared to the control group.

The development of biomarkers to aid in the diagnosis, prognosis, and therapeutic follow-up of atherosclerotic disease is a reality. CRP and natriuretic peptides are well established for coronary artery disease and heart failure, respectively. Several biomarkers were studied specifically for psoriasis and risk of CV events: CRP, interleukin-6 (IL-6), leptin, and adiponectin. The results were similar to those of the general population, with increased CV risk in the presence of high CRP and IL-6 levels. Leptin presents conflicting findings, and adiponectin, as an adipokine with CV protective effects, is reduced in most studies.[9] In addition, a new molecule might become a protagonist biomarker: GlycA – molecule analyzed by nuclear magnetic resonance spectrometry. This marker is correlated with the risk of coronary artery disease and vascular inflammation. In psoriatic patients, it was associated with both disease activity – estimated by the psoriasis area and severity index (PASI) – and risk of CV events, regardless of traditional risk factors, including CRP. Moreover, GlycA and vascular inflammation levels decreased in patients undergoing drug therapy with anti-tumor necrosis factor-alpha (anti-TNF-α),[10] suggesting a correlation with therapeutic clinical response.

Given the importance of the theme, the American Academy of Dermatology[11] and the European League Against Rheumatism (EULAR)[12] have published recommendations on how to evaluate CV risk and make the necessary interventions to reduce such risks. Among the various scores that estimate CV risk factors, the EULAR group adopted the Systematic Coronary Risk Evaluation (SCORE), designed by the European Society of Cardiology. Unfortunately, no score or tool that estimates the probability of events can safely determine them in these high-risk populations (due to the chronic systemic inflammation). The dermatology guideline suggests increasing the estimated CV risk by 50% in psoriatic patients with active disease in >10% of the body surface or who have been indicated for phototherapy or systemic drug therapy to compensate. The EULAR group recommended the same procedure, proposing an adjustment of 1.5 times for patients with rheumatoid arthritis with extra-axial involvement, >10 years of disease, and presence of rheumatoid factor (RF) or serum anti-cyclic citrullinated peptide antibody (anti-CCP).

Another factor as important as risk stratification is the treatment. What are the possible drug interventions to control CV events in psoriasis? Reducing inflammation

Keywords

Cardiovascular Diseases; Atherosclerosis; Inflammation; Risk Factors; Systemic Atherosclerotic Disease.

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seems to be crucial to decrease CV diseases. In a cohort of psoriatic patients, the use of anti-TNF-α drugs decreased carotid IMT in men, and aortic stiffness in both genders.[13] Even more impressive was the analysis of data collected by a Danish registry of psoriatic arthritis, in which the use of immunobiologicals and methotrexate reduced overall mortality.[14] A meta-analysis helped to estimate the impact of anti-inflammatory therapies on the psoriatic population.[15] The use of anti-TNF-α reduced major adverse cardiovascular events (MACE) – cardiovascular death, acute myocardial infarction (AMI), or non-fatal cerebrovascular accident (CVA) – robustly by 70%. Methotrexate led to a 19% drop in the risk of AMI and 28% in global events. On the other hand, treatment with selective COX-2 inhibitor non-steroidal anti-inflammatory drugs more than doubled the risk of CVA, while corticosteroid raised MACE by 62%.

Until now, the most debated randomized clinical study was the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS),[15] which confirmed the hypothesis that the control of systemic inflammation reduces CV events in very high-risk patients (those who had AMI and even after optimized secondary therapy maintained high t-CRP levels). This study revealed that interleukin 1β blockade with a monoclonal antibody controlled the systemic inflammation and, additionally to the optimized treatment, decreased CV mortality, AMI, and CVA by 15% in a population with a high risk of recurrence of CV events. This fact opened doors for paradigmatic changes in the understanding of the physiopathology of the coronary artery disease and will contribute very significantly to the future development of new medicines, with targets unexplored until now.

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Healthcare Utilization and Costs Reduction after Radiofrequency Ablation For Atrial Fibrillation in the Brazilian Private Healthcare System

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Abstract

Background: Atrial fibrillation (AF) is the most common arrhythmia worldwide, with significantly associated hospitalizations. Considering its growing incidence, the AF related economic burden to healthcare systems is increasing. Healthcare expenditures might be substantially reduced after AF radiofrequency ablation (AFRA).

Objective: To compare resource utilization and costs before and after AFRA in a cohort of patients from the Brazilian private healthcare system.

Methods: We conducted a retrospective cohort study, based on patients' billing information from an administrative database. Eighty-three adult patients who had an AFRA procedure between 2014 and 2015 were included. Healthcare resource utilization related to cardiovascular causes, including ambulatory and hospital care, as well as its costs, were analyzed. A p-value of less than 0.05 was considered statistically significant.

Results: Mean follow-up was 14.7 ± 7.1 and 10.7 ± 5.4 months before and after AFRA, respectively. The 1-year AF recurrence-free rate was 83.6%. Before AFRA, median monthly total costs were Brazilian Reais (BRL) 286 (interquartile range [IQR]: 137-766), which decreased by 63.5% (p = 0.001) after the procedure, to BRL 104 (IQR: 57-232). Costs were reduced both in the emergency (by 58.6%, p < 0.001) and outpatient settings (by 56%, p < 0.001); there were no significant differences in the outpatient visits, inpatient elective admissions and elective admission costs before and after AFRA. The monthly median emergency department visits were reduced (p < 0.001).

Conclusion: In this cohort, overall healthcare costs were reduced by 63.5%. A longer follow-up could be useful to evaluate if long-term cost reduction is maintained. (Arq Bras Cardiol. 2019; 113(2):252-257)

Keywords: Catheter Ablation; Arrhythmias Cardiacs; Hospitalization; Hospital Costs; Atrial Fibrillation; Care Costs/trends.

Introduction

Atrial fibrillation (AF) is a public health problem. Estimates of incidence and prevalence vary worldwide.[1] AF incidence will rise from 1.2 million cases per year in 2010 to 2.6 million cases in 2030; in the same period, prevalence will increase from 5.2 million to 12.1 million.[2] In Brazil, estimates are less clear; a recent study showed a prevalence of 1.8% in the general population.[3] However, considering the ageing of the population in rapidly developing countries such as Brazil, this number will probably increase in the near future.[4]

The disease is associated with high healthcare expenditures. In the USA, the annual cost of AF was an estimated US$26 billion, while in the Euro Heart Survey the estimated combined annual cost in 5 countries (Greece, Italy, the Netherlands, Poland and Spain) was €6.2 billion.[4] Such expenditures represent a large economic burden: AF is estimated to contribute with more than 1% of total healthcare costs in projections made in 10 high-income countries.[5] The clinical burden is also significant, especially relating to stroke: about a third of patients with the cerebrovascular disease have AF, which in turn incurs in a greater probability of a larger stroke area in brain imaging exams and, therefore, worse prognosis.[6-8]

Catheter ablation is an established treatment option for restoration of sinus rhythm, which can increase the quality of life and possibly lead to health care expenditure savings in the long term.[9,10] The reduction in resource consumption and costs can be seen already in the first year of the procedure, and this is maintained in the following years.[11] Even considering the cost of the procedure, it can lead to total healthcare costs reduction after 2 years, especially in younger patients.[12-15]

To date, there is scarce data of the economic impact of catheter ablation in middle-income countries, such as Brazil.

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The aim of this study was to compare medical costs and ambulatory and hospital service use before and after catheter ablation in a cohort of Brazilian AF patients treated in the private healthcare system.

Methods

Study design and dataset

This was a retrospective cohort study. The dataset used for the analyses was a patients' reimbursement information from Orizon which contains a date-stamped log of all billed items by the cost-accounting department, including medications (only in-hospital use); laboratory, diagnostic, and therapeutic services; and primary and secondary diagnoses for each patient's hospitalization. Both ambulatory and inpatient resource utilization are available in the dataset. About 12 million patients – which accounts from approximately 25% of patients in the Brazilian private healthcare system – are included in the Orizon patients' billings databases. No informed consent was required because all data were from the patients' reimbursement information and their personal information was anonymous.

All adult patients (over 18 years old) who had a hospital admission between January 2014 and December 2015 and underwent catheter ablation with an ICD-10 code of AF (I48) were potentially eligible for the current analysis. The following eligibility criteria must have been met for patient inclusion in the current analysis:

- Elective radiofrequency ablation procedure, with a previous three-dimensional electrophysiologic mapping;
- Available age, gender and ICD code information;
- No registry of previous ablation procedures in the dataset;
- Use of point by point ablation (standard irrigated, irrigated with contact force sensors and non-irrigated);
- Minimum of 3 months of follow-up before and after the ablation procedure.

Outcomes were evaluated both in the perioperative admission as well as in any readmission that occurred up to 2 years after the ablation procedure.

Study variables

The following variables were evaluated for each patient: age, gender, comorbidities (such as ischemic heart disease [IHD], chronic heart failure [CHF] and conduction disorders, among others), perioperative complications, short- and long-term AF recurrence-free rate, cardiovascular events, healthcare resources utilization (including ambulatory and emergency care) and costs. Details regarding variable definitions of these variables are described in the next paragraphs.

Comorbidities were defined according to ICD-10 codes registered in the ambulatory and emergency visits from the patients in the database. AF recurrence was defined when a new ablation or a cardioversion procedure was performed or upon resumption of antiarrhythmic drug use in the follow-up period, after the three-month blanking period. The cardiovascular events evaluated (both in the pre- and post-procedural follow-up) were: acute coronary syndromes (ACS), stroke and arrhythmias. ACS was defined whenever a patient had requests for electrocardiogram plus either troponin or MB fraction of creatine kinase (CK-MB), as well as one of the following, billed items: any thrombolytic, angioplasty procedure, or a combination of medications highly suggestive of ACS (such as any form of heparin, antiplatelet drugs, nitrates, and statins). Ischemic stroke was defined when a patient had a request of either a computerized tomography or nuclear magnetic resonance of the brain, a prescription of antiplatelet agent or low-molecular-weight heparin, and billing of exams such as an echocardiogram, carotid doppler ultrasound, and an intensive care unit (ICU) admission. Hemorrhagic stroke was defined when a patient had a brain imaging exam (magnetic resonance or computerized tomography) and a compatible ICD-10, and admission to ICU. Arrhythmic events were defined when there were billed items related either to: electric cardioversion, internal cardioverter-defibrillator implantation, ablation procedure, surgical correction of arrhythmia, or prescription of in-hospital antiarrhythmic drugs suggestive of an acute arrhythmic event in patients where and electrocardiogram was also requested.

The use of resources and their related costs were computed by summing all billed items (both ambulatory and emergency/in-hospital care). Only cardiovascular related resources and costs were computed. To calculate mean monthly costs, we divided total costs by the number of follow-up months. Costs were further divided into ambulatory care, emergency related and elective admissions.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) when they followed a normal distribution, and as median and interquartile range (IQR) when the distribution was non-normal. However, considering that cost (expressed as Brazilian Reais [BRL]) is usually a non-normal variable, but it is interesting to know the mean value since the total costs of any given sample of patients is equal to its mean times the total number of individuals, we present cost data in both ways. Categorical variables are presented as absolute values and proportions.

Comparison between variables employed the Wilcoxon test for non-normally distributed variables and the paired student T-test for the ones with normal distribution. Fisher's exact test was used to compare categorical variables between groups. The AF recurrence-free rate was evaluated with the Kaplan Meier methods. In the evaluation of possible predictors of better event-free survival, we used the log-rank test. When the same predictors were analyzed regarding their impact on the before-and-after cost difference, the Mann-Whitney test was employed. All analyses were performed using SPSS version 20.0. A p-value of less than 0.05 was considered statistically significant.

Results

Among 179 potentially eligible patients, 83 fulfilled the eligibility criteria and were included in the analysis (Figure 1).

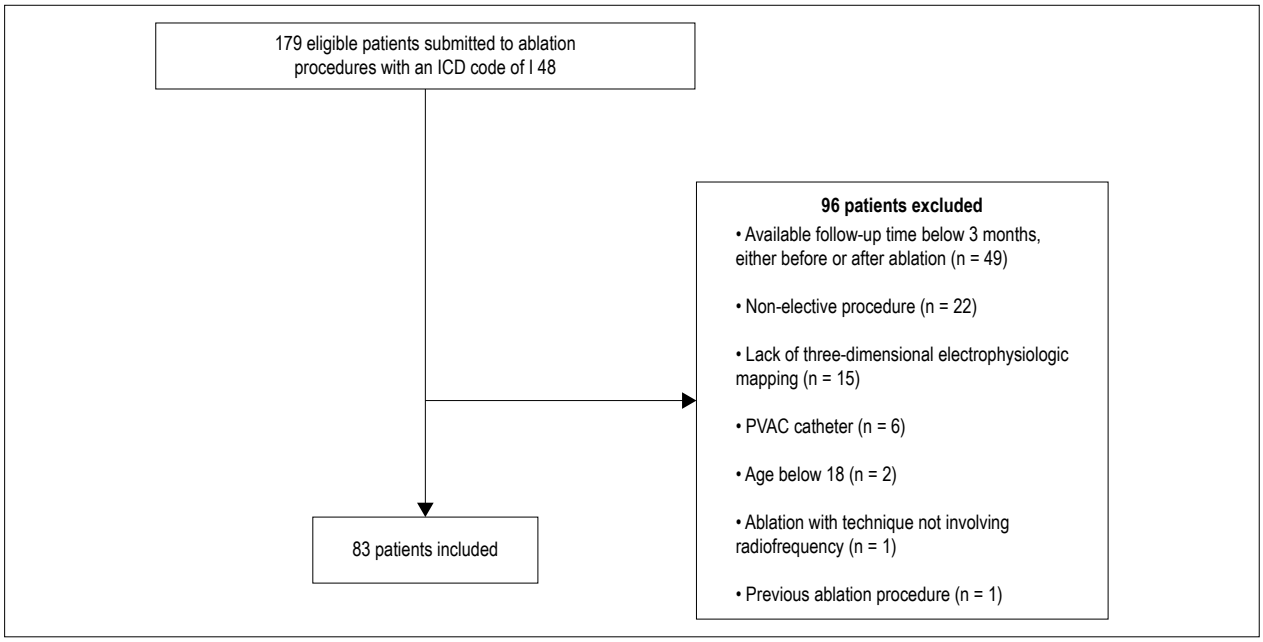

Figure 1 – *Flow chart of patient selection*

Demographics and perioperative patients' data are presented in Table 1. Approximately 70% of the study sample was comprised of male patients, with a mean age of 52.8 years (SD: 14.6). The most common comorbidities were hypertension (18%) and IHD (12%).

In one year, the success rate was 83.6%. In the evaluation of possible predictors of longer event-free rate, none of the comorbidities investigated (hypertension, heart failure, and ischemic or valvular heart disease) was associated with this outcome ($p > 0.05$ for all variables in the log-rank test). Only one patient suffered peri-procedural complications (a hemorrhagic stroke).

Table 2 presents monthly resource use and costs before and after the ablation procedure. The monthly median number of emergency department visits reduced from 0.10 (IQR: 0.04 – 0.23) in the pre-ablation period to 0 (IQR: 0 – 0.11) in the post-ablation period ($p < 0.001$). Median monthly total costs had a 68.5% decrease, from 330.95 (IQR: 142.36 – 754.17) to 104.21 (IQR: 56. 35 – 226,51, $p < 0.001$). Outpatient and emergency-related costs were also reduced, by 48.8% and 100%, respectively ($p < 0.001$ for both variables). The monthly number of elective hospital admissions and its related costs, as well as outpatient office visits, did not have a statistically significant change between pre- and post-ablation periods.

In the analysis of variables associated with a greater reduction in total monthly cost after the ablation procedure, none of the comorbidities evaluated – hypertension, heart failure, and ischemic or valvular heart disease – showed statistical significance ($p > 0.10$ for all variables).

Table 1 – Demographics and perioperative information of study patients

Variable	Total (%)
Male gender	58 (69.9)
Age*	52.8 (14.6)
Comorbidities	
Hypertension	15 (18)
Heart failure	5 (6)
Ischemic heart disease	10 (12)
Valvular heart disease	4 (4.8)
Conduction system disease	3 (3.6)
Diabetes	4 (4.8)
Sleep apnea	7 (8.49)
Thyreoid disease	5 (6)
Pre-procedural follow-up time (months)*	14.4 (7.2)
Post-procedural follow-up time (months)*	10.9 (5.4)
Prucedural LOS (days)*	1.93 (1.6)
Catheter cost	11,468 (4,591)

* *Mean ± standard deviation.*

Discussion

In this study, we found that catheter ablation resulted in reduced ambulatory and hospital care costs during a mean post-procedural follow-up of 10.7 months, with a monthly median cost reduction of 68.5%: from BRL 330.95 before to BRL 104.21 after the procedure. Cost reduction occurred both in the outpatient setting (from BRL 121.48 to BRL 62.70) and in the emergency-related component (from BRL 65.21 to BRL 0). The procedure presented a success rate of 83.6% after 1 year of follow up which is compatible with recent studies conducted elsewhere using contact-force catheters.[13,14] The number of serious complications was 1.2%, which is not different from other small cohorts in the literature.[16,17]

Table 2 – Monthly resource use and costs before and after the ablation procedure

Outcome	Before ablation - mean (SD)	Before ablation - median (IQR)	After ablation - mean (SD)	After ablation - median (IQR)	p value
Number of outpatient office visits	0.05 (0.15)	0 (0 - 0)	0.04 (0.10)	0 (0 - 0)	0.770
Number of emergency department visits	0.17 (0.21)	0.10 (0.04 – 0.23)	0.08 (0.16)	0 (0 – 0.11)	< 0.001
Number of emergency department visits - arrhythmic ICD	0.05 (0.07)	0 (0 – 0.09)	0.01 (0.04)	0 (0 – 0)	< 0.001
Number of elective hospital admissions	0.01 (0.02)	0 (0 – 0)	0.01 (0.04)	0 (0 – 0)	0.134
Total costs (BRL)	747.75 (1,315.38)	330.95 (142.36 – 754.17)	589.93 (1,779.83)	104.21 (56,35 – 226,51)	< 0.001
Outpatient costs (BRL)	156.81 (161.90)	121.48 (56.35 – 206.87)	83.74 (95.17)	62.70 (32.91 – 105.15)	< 0.001
Emergency related costs (BRL)	500.95 (1,268.61)	65.21 (3.54 – 433.88)	110.57 (358.86)	0 (0 - 36.98)	< 0.001
Elective admissions related costs (BRL)	89.99 (416.33)	0 (0 - 0)	395.61 (1,720.18)	0 (0 - 0)	0.215

SD: standard deviation; IQR: interquartile range; BRL: Brazilian Reais. P values were calculated with non-parametric tests since all variables had a non-normal distribution.

Other reports from the literature have also seen the impact of post-ablation cost reduction. In the larger study published to date, Ladapo et al.[11] included 3,194 patients from administrative databases in the US.[11] In that research, the approach was slightly different: they considered that costs can actually increase in the 6 months following the procedure, as a result of the need of reablation in a fraction of the sample, as well as the treatment of peri-procedural complications. Therefore, they analyzed the period from 6 to 36 months after ablation, divided into 6-month cycles. In the time frame of 6-12 months after ablation, mean monthly costs reduced around US$ 800, in comparison with the 6 months immediately before ablation. This number reduced until 18-24 months (where the reduction, compared to before ablation, was around US$ 200), and then increased again to around US$ 800 in the 30-36 months period. However, only 1/3 and 1/10 of patients had at least 24 months and 36 of follow-up time, respectively, making this long-term data more imprecise. Regardless, it seems considerably robust that cost reductions are noted already in the first year, and that it is retained over a longer follow-up period.

Some studies in the literature have estimated how long after catheter ablation the procedure would become "cost-neutral". In a French retrospective cohort study that included 118 consecutive patients submitted to radiofrequency ablation for paroxysmal AF during a mean follow-up of 32 ± 15 weeks, it was estimated that from the 5th year onwards, total accumulated costs would be smaller in patients submitted to ablation, as compared to medical treatment.[14] In two Canadian economic models, the cost-neutrality would occur between 2 and 4 years of follow-up.[13,15] These three studies, however, were not fully based on collected data and included some future projections and modelling.

Some limitations of our study must be acknowledged. The dataset used for all analyses was based on patient billing information and the patients were made anonymous to the researches. Therefore, direct contact to establish the recurrence was not possible. This could overestimate the success rate because the recurrence was only based on the use of healthcare resources (use of antiarrhytmic drug in the emergency room, cardioversion or repeated procedures) or indirectly by the purchase of antiarrhythmic drug in the pharmacies by the patient. The use of an administrative database carries the risk of bias as any retrospective study, as well as the problems associated with the lack of individual clinical patient information. Moreover, we did not included costs with ambulatory medications, since this information was not available in the patients' billings information dataset, which did not included out-of-pocket patients expenditures. Finally, the sample size was not large, and the analysis of possible predictors of greater cost reductions after the ablation procedure was probably underpowered.

Conclusion

In this sample of patients from the Brazilian private healthcare sector, catheter ablation of AF was associated with significantly decreased costs – both ambulatory and hospital-based.

Author contributions

Conception and design of the research: Saad EB, Tayar DO, Ribeiro RA, Junqueira Jr. SM, Andrade P, d'Avila A; Acquisition of data: Tayar DO; Analysis and interpretation of the data: Saad EB, Tayar DO, Ribeiro RA, Andrade P, d'Avila A; Statistical analysis: Ribeiro RA; Obtaining financing: Junqueira Jr. SM, Andrade P; Writing of the manuscript: Saad EB, Tayar DO, Ribeiro RA, d'Avila A; Critical revision of the manuscript for intellectual content: Saad EB, Tayar DO, Junqueira Jr. SM, Andrade P, d'Avila A.

Potential Conflict of Interest

Dr. Eduardo Benchimol Saad received lecture fees from Bionese Webster and Biotronik. Dra. Daiane Oliveira Tayar is employed by Johnson and Johnson Medical Brasil (Department of Economics and Access Market). Rodrigo A. Ribeiro received a research grant from Johnson & Johnson Medical Brazil to conduct the database, statistical analysis and to draft this manuscript. Dr. Silvio Mauro Junqueira Jr. is employed by Johnson and

Johnson Medical Brasil (Department of Economics and Access Market). Dra. Priscila Andrade is employed by Johnson and Johnson Medical Brasil (Department of Economics and Access Market). Dr. Andre d'Avila no potential conflict of interest.

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Study Association

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

Ethics approval and consent to participate

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

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Healthcare Utilization and Costs Reduction after Radiofrequency Ablation for Atrial Fibrillation in the Brazilian Private Healthcare System

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Short Editorial related to the article: Healthcare Utilization and Costs Reduction after Radiofrequency Ablation For Atrial Fibrillation in the Brazilian Private Healthcare System

Atrial fibrillation (AF) is the most common cardiac arrhythmia, constituting an important public health problem and leading to excessive spending on health care worldwide.[1,2] It has important repercussions in clinical practice, associated with an increased risk of stroke, development of heart failure, cognitive alterations, decreased quality of life and increased risk of death.[1]

It is estimated that in the American adult population the incidence of AF will increase from 1.2 million cases per year in 2010 to 2.6 million in 2030 and, in the same period, its prevalence will increase from 5.2 million to 12 million people.[3] In Brazil, AF estimates are less accurate. However, a recent epidemiological study with the Brazilian population reported a prevalence of AF of about 1.8% in the general population.[4] However, considering the aging of the population in middle-income countries such as Brazil, the prevalence of AF in our country is likely to increase in the near future.[5]

A recent study[2] reported that in 2010 the total annual cost for treatment of AF was about 26 billion dollars in the United States and, due to the epidemic growth of this arrhythmia, the cost of its treatment should increase substantially in the coming years all around the world. Much of this cost is due to recurrent hospitalizations, emergency room visits, and outpatient follow-up. In this sense, an immediate evaluation of the health costs used in the treatment of this arrhythmia becomes a priority in our environment.

About 20 years ago, percutaneous radiofrequency ablation of the pulmonary veins (PVs) was described by Haissaguerre et al.[1,6] as an effective and curative technique for the treatment of paroxysmal AF. Subsequently, the ablation procedure of the PVs was progressively modified, evolving to the current predominant technique of enlarged antral circumferential ablation of PVs (an enlarged area of 1 to 2 cm of the PV ostia) in order to modify the arrhythmogenic substrate responsible for the triggering and maintenance of AF.[1]

In this context, it has consistently been shown in several randomized clinical studies that percutaneous ablation of AF reduces the recurrence of this arrhythmia, greatly improving patients' quality of life[7,8] and cardiac mortality in patients with left ventricular dysfunction,[9] as compared to antiarrhythmic therapy. Additionally, nonrandomized clinical studies have reported that AF ablation also reduces the risk of stroke.[10]

Thus, it is possible to speculate that patients with AF undergoing catheter ablation should present a significant reduction in the use of health care and its related costs, both due to the decrease in hospitalizations, as well as the reduction of emergency room visits and outpatient follow-up.[11]

In this issue of *Arquivos Brasileiros de Cardiologia*, Saad et al.[11] report their findings on the use of health care, including outpatient and hospital care, as well as their costs, in a retrospective cohort of Brazilian private health care patients, before and after catheter ablation for AF. Between January 2014 and December 2015, 83 patients undergoing AF ablation were identified as the study cohort, and their data were analyzed for the mean period of 14 months prior to ablation and 10 months after the procedure.

In the study under analysis, in agreement with the world literature, there was a significant reduction of the health costs for the treatment of AF after catheter ablation.[12,13] The 1-year AF recurrence-free rate was 86%. As a result, the median of the total monthly costs had a reduction of 68.5% ($p < 0.001$) after ablation. Ambulatory and emergency costs were also reduced by 48.8% and 100%, respectively, ($p < 0.001$ for both variables) after AF ablation.

However, as pointed out by the authors, the study has several limitations. The data set used for all analyzes was based on patient billing information, which may have overestimated the success rate of AF ablation, since AF recurrence was based only on the use of health resources (use of antiarrhythmic drugs in the emergency room, cardioversion or repetition of procedures), or indirectly, in the purchase of antiarrhythmic drugs in pharmacies. The use of an administrative database carries the risk of bias, with the problems associated with the lack of individual clinical information of the patients, as well as the retrospective design of the study. In this sense, the results of this study can not be applied to all subgroups of patients with AF (for example, newly detected AF, persistent or long-standing persistent AF), since the patients' AF characteristics were not reported. Finally, the sample size was small and the analysis of the possible predictors of the greatest cost reduction after ablation was probably poor.

Finally, the present study has the merit of demonstrating that, in relatively young patients with few comorbidities and in need of increased health care for the treatment of AF, catheter ablation of this arrhythmia can significantly reduce the costs of outpatient and hospital care in the medium term follow-up after ablation.

Keywords

Arrhythmias, Cardiac; Atrial Fibrillation; Radiofrequency Ablation/methods; Arrhytmias/drug therapy.

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Quality of Intra-Hospital Nutritional Counseling in Patients with STEMI in the Public and Private Health Networks of Sergipe: The VICTIM Register

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Abstract

Background: **Having appropriate dietary habits is part of the recommendations after ST-Elevation Myocardial Infarction (STEMI), however, the quality of intra-hospital nutritional counseling in the different health services has been minimally explored.**

Objective: **To evaluate the quality of intra-hospital nutritional counseling among patients with STEMI in the public and private health systems in Sergipe.**

Methods: **A cross-sectional, with data from the Via Crucis for the Treatment of Myocardial Infarction (VICTIM) Register, conducted from April to November of 2017, with individuals aged ≥ 18 years diagnosed with STEMI, in one public health service hospital and three private hospitals. The occurrence and quality of nutritional counseling were analyzed based on current guidelines and the administration of questionnaires. A significance level of 0.05 was adopted.**

Results: **A total of 188 patients were analyzed; 80.3% were from the public health service facility. Among the interviewees, 57.6% of the public health service, and 70.3% of the private hospital patients received intra-hospital nutritional counseling ($p = 0.191$). The documentation of this practice, in medical records, was lower in the public service (2.6% vs. 37.8%, $p < 0.001$). A predominance of restrictive orientations was found in the public and private sectors, mainly regarding salt and fat, 52.3% and 70.3% respectively ($p = 0.064$). Patients from the private service were more counseling to introduce of cardioprotective foods, mainly fruit, vegetable/legume consumption (48.6% vs. 13.2%, $p < 0.001$). Among those who received counseling, nutritional knowledge was higher in the private sector (68.2% vs. 26.3%, $p < 0.001$).**

Conclusion: **The intra-hospital nutritional counseling provided to patients with STEMI, in Sergipe, still presents poor quality in both services, especially in the public health system. (Arq Bras Cardiol. 2019; 113(2):260-269)**

Keywords: **ST Elevation Myocardial Infarction; Health Education/methods; Healthy Diet; Risk Reduction Behavior; Healthcare Disparities; Nutritional Support; Hospitals,Public; Hospitals, Private.**

Introduction

Cardiovascular diseases (CVD) are the leading causes of death in the world, with a higher prevalence in low- and middle-income countries. They are responsible for approximately 30% of deaths in Brazil annually, and the ischemic heart diseases are the main causes of this high mortality, with an emphasis on acute myocardial infarction (AMI), due to its magnitude and the severity of its clinical prognosis.[1-5]

After the acute coronary event, actions are necessary for secondary prevention of the disease, which should consist of adherence to prescribed medication therapy and lifestyle changes, with an emphasis on the practice of programmed physical activity, adoption of healthy eating habits, and smoking cessation.[6-10]

Changes in dietary patterns were highlighted in the prevention and treatment of CVD in epidemiological studies. These studies reinforced that a free of trans-fatty acid diet, restriction of saturated fat, salt, alcoholic beverages, and increase in dietary fibre with a predominance of whole grains, fruits, vegetables and legumes, brought cardioprotective

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benefits associated with the reduction of important cardiovascular outcomes.[11-15]

Quality indicators and guidelines related to AMI recommend that these dietary changes must be guided by health professionals, even still during the in-hospital period. This contributes to the empowerment of the individual, and provides greater awareness of his role in relation to his own health, in addition to guiding his food choices, and increasing his nutritional knowledge.[7,9,16-20]

Previous studies demonstrated the existence of disparities in the quality of care between public and private health services, related to the time to perform examinations, and the use of cardiovascular medications.[21,22] This finding is concerning because approximately 72% of the Brazilian population is exclusively dependent on the Unified Health System (SUS).[23] However, the type of care provided by health professionals regarding nutritional counseling is poorly explored, and possible differences in the quality of this orientation in the in-hospital environment between the two health services are not yet known.

Thus, the present study aims to evaluate the quality of nutritional counseling received in the in-hospital environment in patients with ST-segment elevation myocardial infarction (STEMI) receiving care in the public and private health services in Sergipe.

Methods

This was a cross-sectional, quantitative study which used data from the Via Crucis for the Treatment of Myocardial Infarction (VICTIM) Register, which aims to evaluate the quality of care provided to patients with STEMI in the public and private health systems in Sergipe.

Data collection occurred from April to November of 2017, in the only four hospitals in the state with the capacity to perform primary angioplasty, all located in the Aracaju capital, one with SUS coverage and three with private coverage.

Patients of both sexes, older than 18 years of age, with a STEMI diagnosis confirmed by electrocardiogram were included, according to the defining criteria proposed by the Brazilian Society of Cardiology.[24] Individuals excluded were those who: died prior to concluding all stages of the study; did not meet the Via Crucis criteria, that is, those patients who did not travel the course from the beginning of the symptoms until arrival at the hospital with the ability to perform angioplasty, because they were already in the hospital when they experienced the STEMI; did not agree to participate in some stage of the research; those whose acute STEMI event was characterized as reinfarction (occurred within 28 days of the primary infarction); presented a change of diagnosis during hospitalization; were funded by private health insurance in a philanthropic hospital; and, were unable to be contacted by telephone within seven days after hospital discharge.

This research was approved by the Research Ethics Committee of the Federal University of Sergipe (UFS), under opinion nº 2,099,430. All procedures involved in this study are in accordance with the Declaration of Helsinki of 1975, updated in 2013. All patients signed the Terms of Free and Informed Consent form.

The data collection was performed in two stages: in the hospital environment and after discharge by telephone interview. In the hospital, a study instrument was used, the Case Report Form (CRF), which is composed of sociodemographic variables, previous pathological history, cardiovascular risk factors, physical examination on admission, and nutritional counseling recorded in the clinical patient records.

The second stage of the research occurred via telephone contact with the patients, within seven days after hospital discharge; this interval was determined after the pilot study and pondered the need for an immediate interview with them. At that time, the occurrence of nutritional counseling during the hospital period was evaluated, even though it was not recorded in the patient records by the health professional. In addition, the National Health Interview Survey Cancer Epidemiology was administered, a nutritional knowledge scale adapted for the present study.[25]

At this moment in time, the quality of in-hospital nutritional counseling was also assessed, using a closed-ended questionnaire based on the items proposed in the guidelines.[9,18,26,27] The categories of responses were "oriented", "not oriented", and "do not know". The presence or absence of a recommendation on physical activity after AMI, as established in the aforementioned guidelines, was also observed.

The nutritional status of the patients was obtained using the Body Mass Index (BMI), calculated by means of the body mass (weight) (kg) divided by the square of the body height (m^2), and classified according to the cutoff points proposed by the WHO.[28]

Statistical analysis

The Kolmogorov-Smirnov test was applied to evaluate the assumption of sample normality. Continuous variables that presented a normal distribution were described using mean and standard deviation; those that did not present a normal distribution were represented using median and interquartile range. The Student's t-test or the Mann-Whitney test was used for the independent groups, based on the normality standard of the sample. Absolute frequency and percentage were used for the categorical variables. To compare characteristics of the categorical variables between the two groups, the chi-square test or the Fisher's exact test were used, when appropriate. The significance level of 5% was used as a reference. A sampling plan was established in order to detect differences in the magnitude of mean between public and private health service samples. A significance of 1% and a power of 90% were established for comparisons between these two groups. Non-parametric tests were also used, and in order to obtain the same test power, a correction of 0.86429 was established.[29] In the data collection, the final sample remained similar in proportion to what was initially established ($X^2 = 0.01$, $p = 0.912$), preserving the initial conditions of power, level of significance, and design, as well as preserving the initial intention for detecting differences of mean magnitude between the two groups (public vs. private). The SPSS for Windows program, Version 17, was used for statistical analysis.

Results

A total of 188 patients was analyzed, 80.3% received care in the public service and 19.7% in the private health service, in the state of Sergipe.

Demographic characteristics

The patients who received care in the public service – the Unified Health System (Sistema Único de Saúde [SUS]) showed a predominance of non-white ethnicity, lower social class, with prevalence of the two lowest socioeconomic classes, and lower level of education (Table 1).

Clinical characteristics

Both groups, who received care in the two health services showed similar clinical characteristics, except for the smoking risk factor, in which the patients who received care in the SUS facility presented a significantly higher smoking rate (35.1% vs. 13.5%, p = 0.010). With regards to the previous history of AMI, patients who received care in the private health service presented a higher prevalence (Table 2).

Intra-hospital nutritional counseling

Based on the total sample, telephone contact with the patients occurred within five days (IIQ 3-6 days); when analyzed, for the patients from SUS, the median was 4 days (IIQ 4-6 days), and for those in the private service, it was five days (IIQ 3-6 days).

Although most patients reported having received in-hospital nutritional counseling, this was documented in the records of only 9.6% of the patients. Overall, according to the patient reports, the physician was the health professional who provided the most information about diet (85.8%) (Table 3).

Compared with the SUS, a larger contingent of patients from the private service reported having received verbal and written nutritional counseling. Regarding the professional who provided this information, the nutritionist was mentioned significantly more by the private service patients (50% vs. 11.5%, p < 0.001). In the private service, more documentation of nutritional orientation occurred in the patient records (37.8% vs 2.6%, p < 0.001), and more patients had nutritional counseling prior to hospitalization (64.9 % vs. 33.8%, p < 0.001) (Table 3).

Types of self-reported intra-hospital nutritional counseling

When compared to the SUS, more patients from the private service mentioned receiving guidelines on restriction of: sausages (p < 0.001); refined carbohydrates (p = 0.008); alcoholic beverages (p = 0.002). More also mentioned the introduction of: skimmed milk and dairy products (p = 0.01); grilled and steamed cooking preparations (p < 0.001); fish (p < 0.001); extra virgin olive oil (p = 0.035); fruits and vegetables (p < 0.001); and, whole grains and fiber (p = 0.001) (Figure 1).

In both health services, there was a predominance of restrictive of salty and salty foods, and of fats and fries with a prevalence of 52.3% and 70.3% in public and private, respectively (p = 0.064) (Figure 1).

Table 1 – Sociodemographic characteristics of patients with STEMI receiving care at hospitals in Sergipe, based on the type of service (Public vs. Private)

Variables	Total (188)	Public (151)	Private (37)	p value
Age, years (Mean ± SD)	61.5 ± 11.7	61.3 ± 11.7	62.5 ± 11.7	0.798[T]
Male sex, n (%)	126 (67.0)	98 (64.9)	28 (75.7)	0.246[Q]
Ethnicity, n (%)				
White	70 (37.2)	48 (31.8)	22 (59.5)	0.002[Q]
Nonwhite	118 (62.8)	103 (68.2)	15 (40.5)	
Social class, n (%)*				
A/B	11 (6.0)	2 (1.4)	9 (25.7)	< 0.001[Q]
C	30 (16.5)	15 (10.2)	15 (42.9)	
D/E	141 (77.5)	130 (88.4)	11 (31.4)	
Level of education, n (%)				
Elementary school or less	130 (69.1)	122 (80.8)	8 (21.6)	< 0.001[Q]
High school	38 (20.2)	20 (13.2)	18 (48.6)	
Higher education or graduation	20 (10.6)	9 (6.0)	11 (29.7)	
Marital status, n (%)				
Single	12 (6.4)	10 (6.6)	2 (5.4)	1.000[Q]
Married/Living with a partner	129 (68.6)	103 (68.2)	26 (70.3)	
Divorced/Widower	47 (25.0)	38 (25.2)	9 (24.3)	

SD: standard deviation; (*) Social classification (IBGE, 2010) according to family income: A- Above 20 minimum wages, B- 10 to 20 minimum wages, C- 4 to 10 minimum wages, D- 2 to 4 minimum wages, E- Up to 2 minimum wages; T-Test T for independent samples; Q- Chi-square test.

Table 2 – Clinical characteristics of the patients with STEMI receiving care at hospitals in Sergipe, based on the type of service (Public vs. Private)

Variables	Total (188)	Public (151)	Private (37)	p value
SBP, mm Hg*	140 (128-160)	140 (128-160)	140 (123-160)	0.909#
DBP, mm Hg†	86 (80-92)	84 (79-92)	90 (79-96)	0.190#
HR, beats/min‡	85 (72-98)	85 (72-97)	80 (68-100)	0.849#
GRACE Score	136 (119-157)	135 (119-155)	142 (117-168)	0.228#
GRACE Score, n (%)				
<140 (low risk)	98 (55.1)	81 (57.0)	17 (47.2)	0.349**
≥ 140 (high risk)	80 (44.9)	61 (43.0)	19 (52.8)	
Killip, n (%)				
I	169 (90.4)	139 (92.1)	30 (83.3)	0.108**
II	12 (6.4)	9 (6.0)	3 (8.3)	
III	5 (2.7)	3 (2.0)	2 (5.6)	
IV	1 (0.5)	0 (0.0)	1 (2.8)	
Cardiovascular risk factors, n (%)				
Family history of early CAD §	70 (37.2)	53 (35.1)	17 (45.9)	0.256**
Systemic Arterial Hypertension	129 (68.6)	103 (68.2)	26 (70.3)	1.000**
Dyslipidemia	76 (40.4)	57 (37.7)	19 (51.4)	0.139**
Diabetes Mellitus	60 (31.9)	48 (31.8)	12 (32.4)	1.000**
Smoking	58 (30.9)	53 (35.1)	5 (13.5)	0.010**
Clinical history, n (%)				
Previous PVD//	20 (10.6)	17 (11.3)	3 (8.1)	0.769††
Previous myocardial infarction	12 (6.4)	6 (4.0)	6 (16.2)	0.015**
Cardiac insufficiency	7 (3.7)	6 (4.0)	1 (2.7)	1.000††
Previous PCI¶	10 (5.3)	5 (3.3)	5 (13.5)	0.027**
Nutritional Diagnosis, n (%)				
Low weight	3 (1.6)	2 (1.5)	1 (2.9)	0.171**
Eutrophic	64 (37.6)	53 (39.3)	11 (31.4)	
Overweight	70 (41.2)	58 (43.0)	12 (34.3)	
Obesity	33 (19.4)	22 (16.3)	11 (31.4)	

(*) SBP: systolic blood pressure; (†) DBP: diastolic blood pressure; (‡) HR: heart rate; (§) CAD: coronary artery disease; (//) PVD: peripheral vascular disease; (¶) PCI: percutaneous coronary intervention; (#) Mann-Whitney test; (**) Chi-square test; (††) Fisher's exact test.

In both public and private services, the most prevalent guidelines had restrictive characteristics. The most prevalent were salt and salty food restriction, and fat and fried food limitations (50.3% vs. 70.3%, p = 0.064, respectively), as can be seen in Figure 1.

Relationship between self-reported, intra-hospital nutritional counseling and nutritional knowledge

Among the patients who received counseling, the nutritional knowledge was higher in the private service when compared to the SUS patients. However, among the non-counselled patients, no differences were observed in the level of nutritional knowledge between the SUS and private health services (Table 4).

Discussion

The main finding of this investigation was the underutilization of in-hospital nutritional counseling for patients with STEMI, both in the private service and, especially, in the public service. In the SUS hospital, documentation of nutritional counseling was practically non-existent in the patient records. This finding is of concern, because the change in dietary habits is a class one recommendation for the post-AMI patient, and if it is encouraged in the in-hospital setting, there is an increase of adherence to this therapy, due the recent coronary event.[9,16,17,19,20,26]

In the ideal setting, nutritional counseling should continue to be offered, even after hospital discharge, because it would enhance the work initiated in that environment.

Table 3 – Presence of nutritional counseling registered by professionals and self-referenced by patients with STEMI receiving care at hospitals in Sergipe, based on the type of service (Public vs. Private)

Nutritional counseling	Total (188)	Public (151)	Private (37)	p value
Nutritional counseling, self-referenced by patient, n (%)*	113 (60.1)	87 (57.6)	26 (70.3)	0.191†
Counseling presentation method, n (%)*				
Verbal only	63 (55.8)	50 (57.5)	13 (50.0)	0.288†
Writing only	38 (44.2)	33 (37.9)	5 (19.2)	0.064‡
Verbal + Writing	12 (10.6)	4 (4.6)	8 (30.8)	<0.001‡
Professional that counseled, n (%)*				
Physician	97 (85.8)	77 (88.5)	20 (76.9)	0.196†
Nutritionist	23 (20.4)	10 (11.5)	13 (50.0)	< 0.001†
Others	3 (2.7)	3 (3.4)	0 (0.0)	1.000‡
Counseling documented in patient record, n (%)	18 (9.6)	4 (2.6)	14 (37.8)	< 0.001‡
Professional who registered the counseling in the record, n (%)				
Nutritionist	9 (50.0)	0 (0)	9 (64.3)	0.082‡
Physician	9 (50.0)	4 (100)	5 (35.7)	
Pre-hospitalization counseling, n (%)	75 (39.9)	51 (33.8)	24 (64.9)	0.001†

(*) Information declared by the patient via telephone call, after discharge from the hospital; (†) Chi-square test; (‡) Fisher's exact test.

However, with the current weakening in the structure of counter-referral in the country, it is clear that individuals, who depend exclusively on the SUS, need logistics to be easy in order to attend these sessions. In this context, the existence of adequate in-hospital nutritional counseling could, in theory, partially repair this deficiency.[30-32]

The physician was the professional who acted the most, transferring these guidelines. This fact can be interpreted in some ways: inexistence, or lack of communication between the multidisciplinary team in the institution where the patient was hospitalized; conduct of important lifestyle changes, only at the time of discharge, is routinely performed by the physician.

Current guidelines indicate that nutritional counseling should be performed and encouraged by the entire, specialized, multi-professional team involved in patient care. This team must be composed of a cardiologist, nurse, nutritionist, and other professionals, with the purpose of promoting health education for the patient, and encouraging changes in lifestyle habits.[9,16,20,26] In more specific situations, the nutritionist can intercede with more individualized guidelines, as she is the most qualified professional for such intervention.

Another important finding is the disparity in the quality of nutritional guidance between public and private health services. The observation of the constituent elements of the guidelines provided reveals that private service users were privileged, especially with the inclusion of foods considered to be cardioprotective. It should be emphasized that this type of guidance is part of the nutritional recommendations currently recommended.[7,9,10,26,27]

Although private service patients reported receiving more nutritional counseling than public service patients, both received less than 50% on most of the items analyzed. This low prevalence evidences that the moment of providing information to the patient and/or companion still needs greater attention by health professionals, in both services, as the change in eating habits is related to the cardioprotective effect.[7,11,14,15]

One of the pioneer studies with AMI survivors, conducted by Lorgeril et al.,[11] the Lyon Diet Heart Study, showed that adherence to a diet rich in fruits, vegetables, α-linolenic acid, as well as low saturated fats and salt can reduce up to 70% cardioprotective effect of up to 4 years after the first AMI. More recently, Miller et al.[15] in the Prospective Urban Rural Epidemiology (PURE) study, demonstrated that the daily consumption of fruits, vegetables, and legumes was inversely associated with the onset of CVD, especially AMI, and, mortality.

The low prevalence of nutritional counseling in the public service may have been affected by the lower concentration of health professionals in this type of service. Although SUS serves the majority of the Brazilian population, the private health network now has three times as many physicians than the public service.[33] In relation to other professions, in Sergipe, this scenario is not different. Despite the fact that the SUS hospital has a larger number of beds, compared to the private health network, a lower number of nutritionists were observed in this service, in accordance with CFN resolution 600/2018.[34] This lower number of professionals for a high demand can affect the integral care of the patient, and, consequently, the quality of the nutritional orientation.

The manner of providing this orientation may also have been another point that influenced the low prevalence of nutritional orientation in the SUS, as the majority of respondents of this service reported that it was done verbally. On the other hand, many of those who received the recommendations in written form reported that they were brief, precarious and lacked verbal information, making

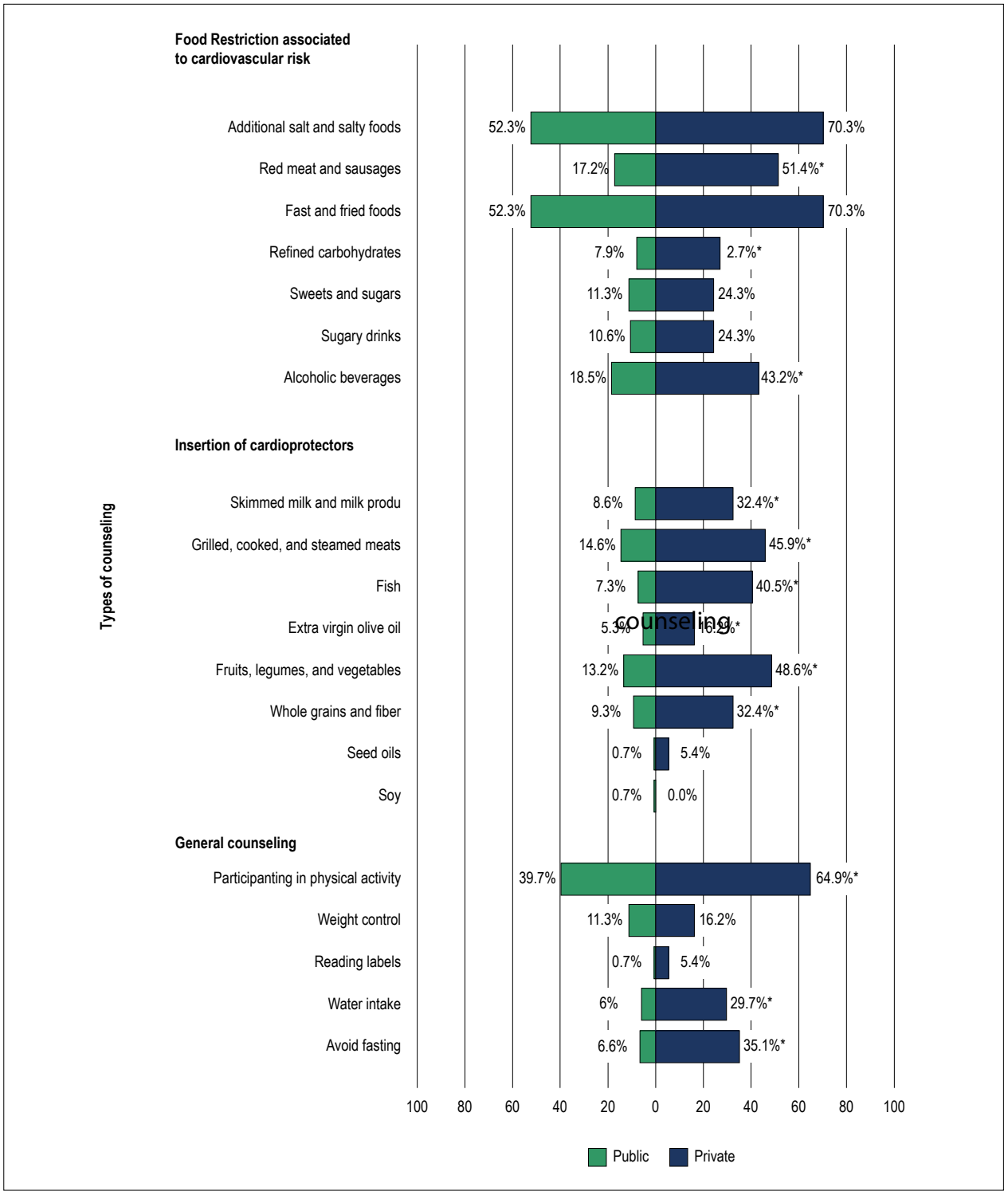

Figure 1 – *Types of self-reported intra-hospital nutritional counseling of the patients with STEMI receiving care at hospitals in Sergipe, based on the type of service (Public vs. Private). (*) p < 0,05; Fisher's exact test*

it difficult to understand. Such issues may have made it difficult for the patients to remember the information in the interviews of the present investigation.

In general, predominance of prohibitive guidelines was identified in both services (restriction of salt and/or salty foods, and restriction of fats and fried food). This finding is probably

Table 4 – Relationship between self-reported in-hospital nutritional counseling and the nutritional knowledge in patients with STEMI receiving care at hospitals in Sergipe, based on the type of service (Public vs. Private)

Level of nutritional knowledge	Patients counseled (102)		p value	Patients not counseled (68)		p value
	Public	Private		Public	Private	
Low, n (%)	21 (26.3)	1 (4.5)	0.001*	14 (23.7)	0 (0)	0.240*
Moderate, n (%)	38 (47.5)	6 (27.3)		23 (39.0)	4 (44.4)	
High, n (%)	21 (26.3)	15 (68.2)		22 (37.3)	5 (55.6)	

(*)Chi-square test.

due to the greater practicality of such conduct, and the fact that it was performed, most often, by the physician. It is known that the promotion of the integration and/or replacement of food into the diet requires more in-depth knowledge about the characteristics of the nutrients; this competence is part of the nutritionist's knowledge.[35,36] This attitude, due to an incomplete nutritional orientation or even the absence of such orientation, does not educate the patient to make healthy food exchanges, which can compromise their nutritional status, by restricting their dietary options.

Furthermore, during the data collection, most of the interviewees did not know what the guidelines meant, they only knew, in general, what they should restrict, without having a specific list with the food.

Similar results were found by Gomes et al.,[36] who verified that the guidelines distributed by the family health professionals to the patients with hypertension and/or diabetes mellitus were simplistic or insufficient. The patients did not have detailed information, with a higher prevalence of prohibitive recommendations, and without taking into account the daily habits of the individuals, and without the benefit of a participatory dialogue with them.

The nutritional knowledge among the patients was higher in private health service. These findings lead to the reflection of the possible positive influence of their level of education in the assimilation of the information provided. We cannot forget, however, that nutritional knowledge is also constructed through information throughout the lifespan, and most patients in the private service already had some kind of nutritional orientation prior to hospitalization. This is a factor that could have influenced these findings.[37,38]

The presence of nutritional counseling facilitates the improvement of nutritional knowledge, and according to the knowledge-attitude-behavior model, there is not a single condition for adherence to healthy eating practices, and may not cause significant positive changes in eating behavior. However, having nutritional knowledge facilitates the beginning of contemplation phases of the individual's behavior change.[38,39]

This worrying scenario of underutilization of in-hospital nutritional orientation can be modified with the adherence of simple behaviors in the work routine of the multi-professional team. Improving the communication of the multi-professional team of care, dedicating more time and attention to the information given to the patient, and jointly dispensing individualized, well-written information to complement the orientation provided is a simple, low-cost alternative that can lead to a positive clinical outcome.[36,40]

In addition, due to the fact that the time of hospital discharge represents a moment of anxiety for the patient and family, this can compromise the assimilation of information. Thus, nutritional counseling does not have to be restricted to this moment but can be performed during the entire in-hospital period, which will also prevent the patient from being discharged before being instructed.

It is also important to note the need for better linkage between the different care levels, to guarantee the integral care of the cardiac patient. The adequate preparation of health professionals to perform the counter-referral, as well as the best quality of specialized care services to meet demand, are fundamental for a successful referral.

Limitations

Some inherent limitations deserve to be highlighted: (1) much information was self-reported, and was dependent on the interviewee's memory, which may have been influenced by some independent factors, such as level of education and clinical condition at the time of the interview. In addition, many patients were elderly, which could lead to a larger memory bias; (2) As part of the research was performed by telephone, the contact with some patients was compromised, due to difficulty in understanding, or to health problems such as hearing or mental deficiencies.

In order to reduce the limitations of the study, a pilot study was conducted prior to data collection, aiming to identify the ideal time interval for the telephone follow-up, in order to reduce memory loss, and also to standardize the interview questions, so that all patients, regardless of socioeconomic status, understood the points raised.

Conclusion

The results of this research demonstrate the lack of documentation of in-hospital nutritional counseling, as well as the low quality of this orientation given to patients with STEMI in both health services of Sergipe especially in the public service.

These data cannot only represent the reality of the state of Sergipe, but also a national situation that needs to be better investigated in order to achieve improvements in the quality of the health service as a whole in the country, mainly the quality of in-hospital nutritional status counseling. This is a low-cost action that currently is not well performed; if achieved in an equitable manner, it can be very favorable for increasing the nutritional knowledge and clinical prognosis of patients with STEMI.

Author contributions

Conception and design of the research: Lima TCRM, Silva DG, Oliveira JC, Oliveira LCS, Arcelino LAM, Oliveira JC, Sousa ACS, Barreto Filho JAS; Acquisition of data: Lima TCRM, Oliveira JC, Oliveira LCS, Arcelino LAM, Oliveira JC; Analysis and interpretation of the data: Lima TCRM, Silva DG, Barreto IDC, Sousa ACS, Barreto Filho JAS; Statistical analysis: Lima TCRM, Barreto IDC; Obtaining financing: Oliveira JC, Oliveira LCS, Oliveira JC, Barreto Filho JAS; Writing of the manuscript: Lima TCRM; Critical revision of the manuscript for intellectual content: Silva DG, Barreto IDC, Oliveira JC, Oliveira LCS, Arcelino LAM, Oliveira JC, Sousa ACS, Barreto Filho JAS.

Potential Conflict of Interest

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 2099.430. 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 Lack of Nutritional Counseling during Hospitalization

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Short Editorial related to the article: Quality of Intra-Hospital Nutritional Counseling in Patients with STEMI in the Public and Private Health Networks of Sergipe: The VICTIM Register

During the nutritional follow-up of hospitalized individuals, the nutritionist has as activities to perform the diagnosis, dietary prescription, supervise the distribution of the diets and evaluate their acceptance, and also perform nutritional counseling so that these individuals understand how a standard specific diet may be more appropriate taking into account their diagnoses and nutritional status. The number of nutritionists issued by Resolution 600 of 2018 of the Federal Council of Nutritionists is 1 professional every 15 beds of high complexity and every 30 beds of medium complexity.[1]

Lima et al.[2] evaluated in an article published in this edition whether nutritional counseling was performed in the hospital environment for patients with Acute Myocardial Infarction (AMI) and the quality of this orientation. The authors found that 57.6% of the individuals hospitalized in the public network and 70.3% private hospitals, both in Sergipe, Brazil, had received in-hospital nutritional counseling.

One possible cause of this low rate of counseling provided may be the amount of nutritionists available in hospital institutions, which is lower than predicted by the resolution.[1]

Seta et al.,[3] 2010, evaluated 8 public hospitals in 4 Brazilian states, of which none of the nutritionists evaluated reported nutritional counseling.[3]

Another problem is the quality of the guidance provided. It should be checked whether it meets the guidelines for preventing the occurrence of new cardiovascular events.

In the cited article there was a predominance of restrictive guidelines, especially salt and fat. About the insertion of cardioprotective foods, patients from the private network were more benefited, mainly regarding the consumption of fruits and vegetables.

The diet for prevention after acute myocardial infarction requires caloric adequacy, applied calorie restriction when necessary for the adequacy of nutritional status. It is important that the macronutrients are adequate within normality, taking into account the restriction of saturated fats and balance between the other fats as recommended by the dyslipidemia guideline.[4-6] In Addition, current guidelines on prevention of cardiovascular events recommend a diet similar to the Mediterranean diet, salt intake of < 5 g per day; 30–45 g fibre per day; regular consumption of fruits and vegetables per daily; regular consumption of fish and unsalted nuts daily; limited alcohol intake; and discouraging sugar-sweetened drinks.[7,8]

The better understanding of the food behavior is indispensable to deepen the knowledge of the determinants of the alimentary behavior, which include a complex range of nutritional, demographic, social, cultural, environmental and psychological factors. Several studies point out that the transthoracic model,[9] developed by two US researchers, James O. Prochaska and Carlo DiClemente,[10] in the 1980s, can be considered a promising instrument to help understanding health-related behavioral change, and is widely used in research and clinical practice. The transthoracic model of behavior change presents 5 stages. In the pre-contemplation stage, it has not yet been considered by the individual or no changes were made to the behavior and there is no intention to adopt them in the near future. In the stage of contemplation, the individual begins to consider behavioral change. That is, it is intended to change the behavior in the future, but a deadline has not yet been set, therefore.

The decision-making individual, also called the preparation, intends to change his behavior in the near future, as in the next month. Generally, after overcoming previous attempts frustrated, small changes are made and a plan of action is adopted, still not making a serious commitment to the same. Already the individuals in action correspond to those who have in fact altered their behavior, their experiences or their environment so as to overcome barriers previously perceived. Such changes are visible and have occurred recently, as in the last six months. In the maintenance stage, the individual already changed his behavior and kept him more than six months.[10]

The study by Vieira et al.,[11] carried out with individuals after angioplasty at a hospital specialized in cardiology, in São Paulo, identified the stages of behavior change in which they were. 36% were in maintenance, 26% in preparation, 17% in pre-contemplation, 12% in action and 9% in contemplation. It is necessary for the nutrition team to create adequate food education strategies for the individuals at each stage, in order to promote adherence to a more favorable food plan and the adequacy of nutritional status.

A study with individuals from the northern region of Paraná after AMI or angioplasty aimed at identifying changes in attitudes and habits in these survivors. The main changes identified were an increase in the number of meals, an increase in fruit consumption, a reduction in the consumption of fats and fried foods, and the use of the salt shaker on the table. The number of patients who did not perform physical activity decreased.[12]

It is very important to evaluate the achievemente and the quality of nutritional counseling to allows the implementation of appropriate actions, since the moment after the recent cardiovascular event may favor the adoption of favorable dietary changes for these individuals.

Keywords

Hospitalization; Healthy Diet; Risk Reduction Behavior; Inpatients; Dietetics.

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Does the Mean Platelet Volume Decrease in the Presence of Coronary Artery Fistula?

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Short Editorial related to the article: Does Mean Platelet Volume Decrease in the presence of Coronary Artery Fistula?

It has long been known that platelet activation is involved in the genesis of several cardiovascular diseases, especially acute coronary syndromes and other atherosclerotic diseases.[1] Studies carried out in the 1970s already showed that the endothelial lesion was capable of triggering a cascade of inflammatory events leading to platelet activation and consequent vascular thrombosis.[2]

Activated platelets have a larger size due to their increased enzymatic and metabolic activity.[3] These observations led to a series of studies that evaluated the correlation between mean platelet volume (MVP) and cardiovascular disease. Most of these studies found a positive correlation between these variables, with a higher risk of ischemic events in patients with higher MPV.[4,5] These studies were replicated in several different situations, with similar results. Despite this, they have never been tested in large clinical trials as part of the decision-making. Therefore, there is no robust evidence to use MPV or even more complex platelet activity tests in daily clinical practice as a cardiovascular risk factor up to the present time.[6,7]

Coronary artery fistulas (CAF) are rare findings, present in approximately 0.2% of adults submitted to coronary angiography.[8] The main etiology is congenital, with a recent increase in the etiology of acquired CAF due to the increased number of invasive procedures with the development of hemodynamics.[9]

Most of the time, the CAF are small and clinically asymptomatic, not requiring specific treatment. In exceptional cases, when there is drainage to the right chambers and the fistula flow rate is high, the phenomenon of "coronary steal" may occur, with decreased blood flow to the myocardium and local ischemia, especially in situations of increased oxygen demand, such as during physical exertion. In these situations, the patient may have chest pain and need some interventional treatment.[10] Most fistulas are not correlated with an increased risk of myocardial ischemic events, but early atherosclerosis may occur in case of persistent high-debt fistulae.[11]

The study carried out by Sincer et al.[12] sought to evaluate the presence of a correlation between MPV and CAF. In the analyzed population, a negative correlation was observed between these factors, with the lower MPV being related to the presence of CAF. This finding differs from that seen in other cardiovascular diseases, in which there is an increase in MPV, as previously mentioned. Since the coronary fistula is not an inflammatory disease and is not correlated with an increased risk of atherosclerotic events, this finding may be real.

The pathophysiological explanation for this finding, however, is unknown and its practical applicability is extremely limited. The observation of the correlation between MPV and CAF may also have been merely a random fact, albeit statistically significant.

This is a common occurrence when one tests the correlation of several variables with one outcome. Further studies involving the analysis of platelet activation in atherosclerotic and non-atherosclerotic coronary diseases are still necessary to add this information to our daily clinical practice, both as a risk marker and, eventually, as therapy-guiding factor.

Keywords

Platelet Activation/genetic; Acute Coronary Syndrome; Mean Platelet Volume; Inflammation; Coronary Angiography.

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Importance of Genetic Testing in Dilated Cardiomyopathy: Applications and Challenges in Clinical Practice

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Abstract

Dilated cardiomyopathy (DCM) is a clinical syndrome characterized by left ventricular dilatation and contractile dysfunction. It is the most common cause of heart failure in young adults. The advent of next-generation sequencing has contributed to the discovery of a large amount of genomic data related to DCM. Mutations involving genes that encode cytoskeletal proteins, the sarcomere, and ion channels account for approximately 40% of cases previously classified as idiopathic DCM. In this scenario, geneticists and cardiovascular genetics specialists have begun to work together, building knowledge and establishing more accurate diagnoses. However, proper interpretation of genetic results is essential and multidisciplinary teams dedicated to the management and analysis of the obtained information should be considered. In this review, we approach genetic factors associated with DCM and their prognostic relevance and discuss how the use of genetic testing, when well recommended, can help cardiologists in the decision-making process.

Introduction

Primary cardiomyopathies (PCMs) are a heterogeneous group composed predominantly by genetic diseases associated with pathological alterations of myocardial structure and function.[1-3] These diseases often progress to heart failure (HF), with dilated cardiomyopathy (DCM) being the main indication for heart transplantation (HTx).[3] Currently, the prevalence of idiopathic DCM is estimated at around 1 case per 2,500 population, but authors such as Hershberger et al.[4] describe a frequency ten times greater.[4] Particularly in the last two decades, a greater understanding on the etiology and clinical course of many of these diseases has been achieved.[5,6] This has been possible by substantial advances in the use of genetic diagnosis at cardiomyopathy clinics and research centers around the world.

Traditionally, DCM is defined as dilatation of the left ventricle or both ventricles, with consequent impairment in myocardial contractility, in the absence of abnormal overload and/or ischemic heart disease.[4-6] However, this syndrome can encompass a wide range of genetic and acquired disorders that can be expressed to a greater or lesser impact over the patient's life course. Some individuals with specific mutations detected in the early DCM-stages may present intermediate phenotypes that do not meet the classical definition of the disease.[2,4] For this reason, the formulation of some concepts that define subgroups of patients with this syndrome would be relevant, such as the case of hypokinetic non-DCM,[2] where systolic dysfunction may occur without left ventricular dilatation. In fact, the observed clinical heterogeneity is the partial reflex of the various genes related to sarcomere proteins, cytoskeleton, intercellular connections, the cell membrane, and ion channels (Table 1),[2,4,7,8] which have been implicated in DCM. Many of these genes have been also associated with other forms of cardiomyopathies (left ventricle non-compaction [LVNC], arrhythmogenic, hypertrophic, and restrictive), and the prevalence of pathogenic variants in each of these genes is distinct for each disorder.[4,7] Mutations with pathogenic potential are identified in up to 40% of cases described as idiopathic DCM, depending on the cohort.[9,10] Indeed, it has been suggested that genetic testing would have a higher yield (up to 70%) in cohorts of patients with idiopathic DCM already waitlisted for HTx.[11,12]

In the last decade, recommendations for the use of genetic testing in familial DCM have been established by respective guidelines.[9] Genetic testing can help in the management of patients and their relatives, as well as optimize the risk stratification. Careful clinical evaluation, a thorough family history, and the results of genetic testing are the cornerstones of this approach. Considering the incipient use of genetics in DCM management in Brazil, the aim of this review is to present and discuss the importance of molecular testing in the DCM spectrum.

Keywords

Cardiomyopathy, Dilated/genetics; Ventricular Dysfunction, Left; Heart Failure; Genetic Testing/methods; Heart Transplantation.

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Table 1 – Main genes associated with dilated cardiomyopathy

Gene	Protein	Estimated contribution	Association with other cardiomyopathies	Other phenotypes	Inheritance	Level of evidence*
Sarcomere						
TTN	Titin	18-25%	LVNC	Myopathies	AD	1
TNNT2	Troponin T type 2	2-3%	HCM, LVNC	-	AD	1
TNNI3	Troponin I3, cardiac type	1-2%	HCM, RCM	-	AR	1
TPM1	Tropomyosin 1	1-2%	HCM, LVNC	Congenital heart disease	AD	1
MYH7	Miosina-7 (beta-myosin heavy chain)	3-5%	HCM, LVNC	Myopathies	AD	1
MYBPC3	Myosin-binding protein C	2%	HCM, LVNC	-	AD	1
BAG3	Bcl-2-associated athanogene 3	2%	-	Myofibrillar myopathy	AD	1
ACTC1	Actin alpha cardiac muscle 1	<1%	HCM, LVNC	-	AD	1
Cytoskeleton						
ACTN2	Actin alpha cardiac muscle 2	< 1%	HCM	Congenital heart disease	AD	2
FLNC	Filamin C	2.2%	HCM, RCM	-		1
LDB3	LIM domain binding 3	<1%	NA	Myofibrillar myopathy	AD	2
ANKRD1	Ankyrin repeat domain 1	< 1%	HCM	Congenital heart disease	AD	3
VCL	Vinculin	1%	NA	-	AD	3
JUP	Junction plakoglobin	1 %	ACM	Naxos disease	AD/AR	1
DMD	Dystrophin	1%	NA	Duchenne and Becker muscular dystrophy	X-linked	1
DES	Desmin	1-2%	HCM, RCM	Myofibrillar myopathy	AD	1
Cell Membrane						
LMNA	Lamin A/C	5-10%	HCM	Muscle myopathies, lipodystrophies, progeria	AD	1
EMD	Emerin	NA	ACM	Emery-Dreifuss muscular dystrophy	X-linked	1
Ion Channels						
SCN5A	Sodium voltage-gated channel alpha subunit 5	2-3%	LVNC	Brugada syndrome/LQTS	AD	1
ABCC9	ATP binding cassette subfamily C member 9	< 1%	-	Osteochondrodysplasia	AD	3
Desmosome						
DSC2	Desmoscollin-2	1-2%	ACM	Palmoplantar keratoderma	AD	1
DSG2	Desmoglein 2	1-2%	ACM	-	AD/digenic	1
DSP	Desmoplakin	3%	ACM	Carvajal syndrome	AR	1
PKP2	Plakophilin 2	<5%	ACM	-	AD	1
Lysosome						
LAMP2	Lysosome-associated membrane protein 2	4%	HCM	Danon disease	X-linked	1
Sarcoplasmic Reticulum						
PNL	Phospholamban	1%	HCM, ACM	-	AD	1
RYR2	Ryanodine receptor 2	NA	-	CPVT	AD	2
RBM20	RNA binding motif protein 20	2%	LVNC	-	AD	1

*HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy; LVNC: Left ventricle non-compaction cardiomyopathy; ACM: arrhythmogenic cardiomyopathy; CPVT: catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; NA: not available; AD: autosomal dominant; AR: autosomal recessive. *The genes were classified according to three levels. Level 1: Multiple studies, variants and families reported and cosegregation with established disease. Level 2: Single or few studies, variants and families reported and limited cosegregation observed. Level 3: Single or few studies, variants and families reported and unestablished cosegregation.*

Methods for genetic diagnosis in dilated cardiomyopathy

The use of next-generation sequencing (NGS) platforms has enabled two approaches for the genetic diagnosis of DCM:

1. Whole-exome sequencing: this approach covers "all" exons and flanking regions of the human genome (in practice, it considers only those genes for which correlated clinical information already exists). Exome sequencing has been more used in applied clinical research, resulting in the discovery of new genes potentially associated with DCM.[13,14] These "new" genes are also called candidate genes because the level of evidence supporting its pathogenic potential is still low or uncertain. It would result in a greater number of unknown clinical significance variants;
2. Targeted NGS: NGS panels sequence a certain number of genes for which there is higher evidence of a causal association with DCM (Table 1).[15,16] The large volume of cases already described in carriers of pathogenic/likely pathogenic variants in these genes raised useful information for clinical decision-making;[17] it is important to emphasize that most of the mutations reported in DCM are exclusive to a single family, which leads to barriers in the interpretation of the genetic data. Therefore, integration of clinical manifestations and family history is essential in the decision-making process.[17] There are around a hundred genes associated with DCM, with different levels of evidence for their associations. Furthermore, it bears stressing that the presence of a genetic mutation does not always mean that the disease will develop.[18] The best-documented genes are listed in Table 1.

In recent years, the increasingly widespread use of NGS panels has allowed the identification of a significant number of individuals with variants in the same gene. This population has been enabling relevant clinical descriptions in DCM, as in the most recent studies addressing different genes (*TTN*, *LMNA*, *FLNC*, or *BAG3*).[19-21] Cosegregation of variants in these genes has been demonstrated as disease-causing in multiple DCM-families, and the ever-increasing number of identified carriers has enabled genotype-phenotype correlation analyses on the prognosis of the disease.[22,23]

Briefly, genetic testing through the aforementioned techniques can help cardiologists in three important clinical scenarios:[8-10,24,25]

1. familial management;
2. etiological definition and;
3. assertive risk stratification.

Importance of family screening in dilated cardiomyopathy

A cohort study with advanced HF patients waiting in the transplant list shows that the diagnosis of familial DCM (FDCM) was systematically neglected.[26] The mere use of the pedigree tool increased the prevalence of this diagnosis from 4.1%to 26%. Prospective cohorts have since found that 25 to 40% of non-ischemic DCM cases are in fact familial,[9,24] drawing attention to the hereditary component of this syndrome, as well as to the importance of early detection and treatment of affected relatives. In this context, pedigree with at least three generations and the use of genetic testing is strongly recommended.[9]

The identification of a pathogenic or a likely pathogenic variant in an index case (proband) allows the entire family of the patient may benefit from genetic screening.[4,9] This is particularly useful in cases where clinical evaluation alone has not been able to establish the diagnosis in a relative.[2,4] In addition, the early identification of a family member carrier who is asymptomatic, or in the subclinical phase of the disease, may be particularly relevant when genetic testing reveals etiologies with greater arrhythmogenic potential or known to evolve faster.[19,20] Moreover, in this scenario, it would be possible to apply measures to delay disease progression or even avert a fulminant outcome. On the other hand, regular follow-up of the index case's relatives that are identified as non-carriers of a pathogenic variant is not recommended;[9] this avoids unnecessary health expenditures and prevents additional psychological stress to the patient/family.

Etiological definition and associated prognosis

TTN truncating variants: a milestone in knowledge about the role of genetics in DCM was a study by Herman et al.[11] In this publication, titin-truncating variants (TTNtv) were identified in 25% of cases of FDCM and in 18% of sporadic DCM-cases. These prevalence were obtained across three different cohorts, with a frequency of TTNtv between 8 and 40%. It is worth noting that higher frequencies were observed in subjects undergoing HTx or with severe systolic dysfunction. Since then, other studies have sought to ascertain the natural history of DCM by assessing TTNtv patients.[24,27,28] No difference was observed in the incidence of outcomes among affected carriers vs. non-carriers,[27] as there was no difference in mesocardial fibrosis between these groups.[28] However, males with TTNtv manifested the disease at younger ages than female carries (78% vs. 30% of women at age 40).[27] Other authors have identified that affected TTNtv carriers would have an earlier outcome event (death from any cause, waiting for HTx, or requiring a ventricular-assist device) than non-carriers.[28] In this same line, male carriers had a lower survival rate (28% of men had a cardiovascular event vs. 8% of women before age 50), considering the outcomes death by HF, HTx, or use of a ventricular assist device.[27]

In a robust sample (n = 558), a high incidence of cardiovascular death starting at age 40 years was observed in patients with TTNtv.[29] In this cohort, the incidence of cardiovascular events was again higher in men than in women "(1.25% vs. 0.75%/year between the ages of 40-60), with sudden cardiac death being the most frequent outcome. In addition, several publications have described a high incidence of atrial fibrillation, as well as sustained and non-sustained ventricular tachycardia, in these patients.[24,25,28,30]

Although according to the literature, the presence of TTNtv is associated with early onset of arrhythmic manifestations, it has not yet been possible to define a characteristic phenotype for these patients, unlike for patients with mutations in other DCM-related genes. Moreover, it has been proposed that TTNtv may be acting as a susceptibility genetic substrate to different DCM-types (anthracycline-induced, peripartum, and alcoholic).[27-29] Finally, patients with titin cardiomyopathy

appear to have a more favorable clinical course and respond better to drug therapy than those affected by variants in the lamin (*LMNA*) gene.[31-33]

Lamin: *LMNA* pathogenic variants produce a well-characterized DCM phenotype associated with conduction disease/malignant arrhythmias, also called cardiolaminopathies.[34] Phenotypic expression have been described as a progressive atrioventricular conduction disease which usually precedes ventricular dysfunction and/or ventricular arrhythmias, although ventricular or supraventricular arrhythmias (especially atrial fibrillation) may be identified as the first manifestation.[19,34] Diagnosis is usually established after age 20, with high penetrance (>90%) after 40 years.[35] Once the first symptoms have manifested, cardiolaminopathies can progress to advanced HF faster than primary DCM of other etiologies.[19,36] *LMNA* mutations prevalence ranges from 5-10% in FDCM cohorts and 2-5% in sporadic cases, accounting for up to 30% of the DCM-cases associated with conduction disease/arrhythmias. Their prevalence is lower in cases of isolated DCM (non-arrhythmic).[34,35]

Between 2013 and 2015, Hasselberg et al.[37] identified a 6% prevalence of *LMNA* gene mutations in a cohort of 79 Norwegians young with FDCM. A particularly high proportion of carriers (19%) required HTx. In another study, 122 affected *LMNA* carriers were followed for seven years; 27 progressed to terminal DCM or death. It is worth noting that, in this same cohort, asymptomatic carriers had a 9% annual incidence of any documented cardiac event over 4 years of follow-up.[19] These findings suggest a significant unfavorable prognosis and faster progression to HTx/death than in DCMs with other etiologies.

These clinical and epidemiological profile supports the recommendations for genetic testing of patients with non-ischemic DCM. Furthermore, an early implant of a cardioverter/defibrillator (ICD) should be considered when a *LMNA* pathogenic variant is identified (Class of recommendation IIa, level of evidence B) in a patient with risk factors.[38] Based on the study published in 2012 that enrolled 269 patients with cardiolaminopathy, the risk of cardiac events is highest when the patient has two or more of these risk criteria at the time of diagnosis: 1) non-sustained ventricular tachycardia; 2) left ventricular ejection fraction <45%; 3) male sex; and 4) a truncating-type variant.[39] Since then, other authors have proposed that not only truncating variants but also missense-type genetic variants, would be relevant due to the potential for sudden death.[40] Finally, a new risk score for patients with DCM associated with *LMNA* variants should be published soon. We hope that it will increase the accuracy of risk stratification in these patients.

Other genes: Some sarcomere genes more often associated with hypertrophic cardiomyopathy (HCM) may also cause DCM.[25] The beta-myosin heavy chain (*MYH7*), troponin T (*TNNT2*), and tropomyosin (*TPM1*) sarcomere genes are those for which associated prognostic information is available. Depending on the location of the genetic variant in the *MYH7* gene, the natural history may be particularly severe, similarly to that observed occurs in cases of DCM caused by *TNNT2* mutations.[25] *TPM1* variants cause less than 1% of DCM cases but account for a significant portion of pediatric forms of this disease, in which rapid progression to death or HTx is not uncommon.[25] A meta-analysis of nearly 8,100 patients evaluated genotype-phenotype correlations of DCM with the *TTN* and *LMNA* genes, as well as genes encoding sarcomere proteins such as myosin-binding protein C (*MYBPC3*), *MYH7*, *TNNT2*, troponin I (*TNNI3*), RNA-binding protein 20 (*RBM20*), and phospholamban (*PLN*).[41] A significantly higher frequency of HTx was observed in patients with *LMNA* mutations (27%) than for carriers of *RBM20* and *MYBPC3*mutations (~10% each). Across the different genes examined, those affected were predominantly male (79% for *MYBPC3* mutations and 69% for *LMNA* and *MYH7* variants), except for *PLN* mutations (46% men).

More recently, the filamin C (*FLNC*) and Bcl-2-associated athanogene 3 (*BAG3*) genes have had their role in the DCM natural history characterized in high-impact publications.[20,21,42] *FLNC* was associated with a more arrhythmogenic profile, and *BAG3*, with a greater number of HF-related events. *FLNC* truncating variants were found cosegregating in 28 affected families with a particular form of arrhythmogenic/DCM.[20] The most prevalent clinical features were ventricular dilatation (68%), systolic dysfunction (46%), and myocardial fibrosis (67%). Ventricular arrhythmias were documented in 82% of the patients, and cases of sudden death were reported in 21/28 families. Another study identified *FLNC* truncation variants in 2.2% of DCM-patients, 85% of whom had ventricular arrhythmias and/or sudden death.[42] Additional right-heart involvement was reported in 38% of the cases. Thus, early ICD implantation could be considered in these patients, even when they do not meet the criteria established in current DCM guidelines.[9,20]

In recent years, several isolated BAG3 reports have been described in DCM-families.[43-47] In a meaningful way, BAG3 associated phenotype was recently defined with data from a cohort of 129 carriers.[19] After a mean follow-up of 38 months, the number of carriers affected with DCM raised from 57% to 68%. It represents 26% of the carriers who initially had a negative phenotype but manifested the disease. Considering carriers over the age of 40, 80% were phenotype-positive. In this sample, the incidence of cardiac events in carriers of *BAG3* variants with DCM was 5.1% per year (outcomes: sustained ventricular tachycardia, sudden death, HF death, need for ventricular assist device and HTx), with a predominance of HF-events versus a lower number of arrhythmic outcomes. Male patients, those with systolic dysfunction, or increased ventricular diameter had the highest incidence of events during the follow-up.[21] Based on these findings, variants of the *BAG3* gene do not appear to be related to a need for early ICD implantation, unlike *FLNC* mutations.

Genetic heterogeneity and overlapping phenotype

Many of the genes described as disease-causing in patients with DCM are also associated with the development of other forms of PCMs (Table 1). This fact may result in the presence of more than one phenotype in the same pedigree or overlapping phenotypes in the same individual, as occurs, for example, with LVNC and DCM.[48,49]

In a cohort of 95 patients with LVNC (68 unrelated individuals and 27 relatives, 23% of cases familial), a genetic variant was identified in 38% of the cases.[49] The most frequent genes were

TTN, *LMNA*, and *MYBPC3*; one family was affected by a *RBM20* mutation. In this family, three generations were affected on the maternal side, and the index case underwent to HTx at the age of 21 (3 years after diagnosis). The number of major cardiovascular events in this cohort was significantly higher in patients with LVNC than those probands with non-ischemic DCM of known etiology. Approximately 10% of the patients with LVNC required HTx vs. 2.8% in the non-ischemic DCM group.[49] One of the families with LVNC in this cohort was found carrying a *MYH7* gene variant which has been associated in different studies with malignant-HCM. Although the affected individuals did not meet definitive criteria for HCM, several had an appreciable increase in myocardial wall thickness.[49] This should draw the attention of cardiologists to the phenotypic heterogeneity of PCMs, as well as to the need to bear in mind what an etiological diagnosis can represent in terms of the natural history of the disease.

Genes usually related to arrhythmogenic cardiomyopathy (ACM) may produce indistinguishable clinical phenotype from those with DCM. Patients affected by desmoplakin (*DSP*) or *FLNC* truncating variants, for instance, may be affected by a form of ACM with exclusive left ventricle involvement.[20,50,51] There are several reports of DCM-patients affected by mutations in desmosomal genes that do not fulfil any (or only some) of the arrhythmogenic right ventricular dysplasia diagnostic criteria.[50-52]

In a study of 89 unrelated end-stage DCM patients requiring HTx, screening of the five most common desmosomal genes (*PKP2*, *DSP*, *JUP*, *DSC2*, *DSG2*) identified genetic variants in 18% of the probands.[51] Genetic testing in relatives identified additionally 38 carriers, including some with subclinical DCM. Histopathological analysis of explanted hearts was heterogeneous; some cases showed fibro-fatty infiltration of the right ventricle, some of the left ventricle, and some had no observable fibro-fatty replacement.[52]

Final considerations

In view of the foregoing, we conclude that the PCMs, particularly the dilated form (DCM), reflect a complex, highly heterogeneous syndrome of challenging diagnosis, prognosis, and treatment. In this scenario, molecular NGS diagnosis can be a very useful tool for clinical cardiologists practice. Although still incipient in Brazil, the use of genetic testing in DCM and HTx services should be considered, since etiological diagnosis often allows a more assertive clinical management and risk stratification. Moreover, clinical and genetic screening of patients' relatives with these conditions is somewhat neglected, although it is a recommended approach. In this way, cardiomyopathy units and HTx services, as well as correlated research groups, should address this topic more incisively and focus on disseminating knowledge among health professionals and in the society as a whole.

Despite its potential benefits, the limitations of genetic testing should not be overlooked. The possible psychological impact of the genetic testing results on patients and their families should be anticipated and discussed. In addition, genetic testing cannot determine whether the proband will develop symptoms, as well as the severity of these potential symptoms.[53]

Finally, we illustrate the present article with a clinical case from our practice in which genetic testing was part of the clinical evaluation.

Clinical case: A 30-year-old male was hospitalized due to congestive HF (NYHA functional class III). After 1 year of occasional palpitations, a diagnosis of DCM was established. Cardiac magnetic resonance imaging, which revealed diffuse hypokinesis, left ventricular dysfunction (left ventricular ejection fraction, 46%), and diffuse mesoepicardial fibrosis (Figure 1). Comparison with a previous echocardiogram performed two years latter suggested a rapid clinical progression (left ventricular ejection fraction, 32%); systolic and diastolic diameters, 49 and 58 mm, respectively; left atrial diameter, 44 mm. Echocardiogram showed atrial fibrillation and the coronary angiography did not reveal any evidence of coronary heart disease. Taking into consideration, the severity of the case and a positive family history of sudden death (Figure 2), genetic testing was performed (NGS panel for DCM). A *LMNA* p.Leu176Pro variant was identified, providing etiological confirmation for familial DCM. Based on these findings an ICD was implanted for primary prevention, despite of the left ventricular ejection fraction > 30%. Consistent with descriptions in the literature, cardiolaminopathy of the patient did not respond adequately to optimized clinical treatment and progressed rapidly to HTx. One year later, the patient developed anasarca and was hospitalized again, requiring positive inotropic supporting with intravenous agents. HTx was performed 2 months later. The patient's children (both under 10 years of age) were apparently healthy. As the mean age of diagnosis of *LMNA* gene carriers is from the third decade of life onward, ethical recommendations for genetic testing in underage relatives were followed, respecting the appropriate age for genetic counseling.[54] However, it is important to mention that cases of children affected by *LMNA* cardiomyopathy have been reported rarely, which should call into question the current expectant management of young children of patients with cardiolaminopathies.[55]

Author contributions

Conception and design of the research: Lamounier Júnior A, Stein R; Acquisition of data and Analysis and interpretation of the data: Lamounier Júnior A, Ferrari F, Stein R; Obtaining financing: Stein R; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Lamounier Júnior A, Ferrari F, Max R, Ritt LEF, Stein R.

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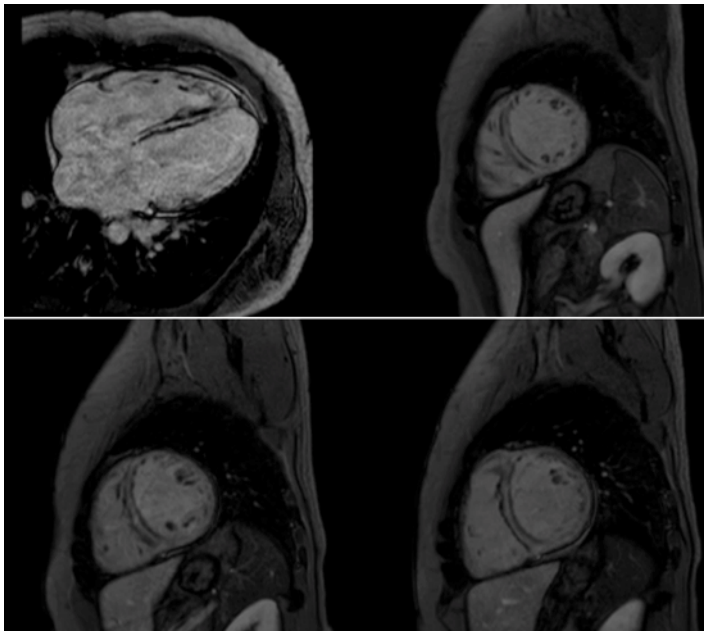

Figure 1 – *Cardiac magnetic resonance imaging showing extensive and diffuse area of mesocardial fibrosis.*

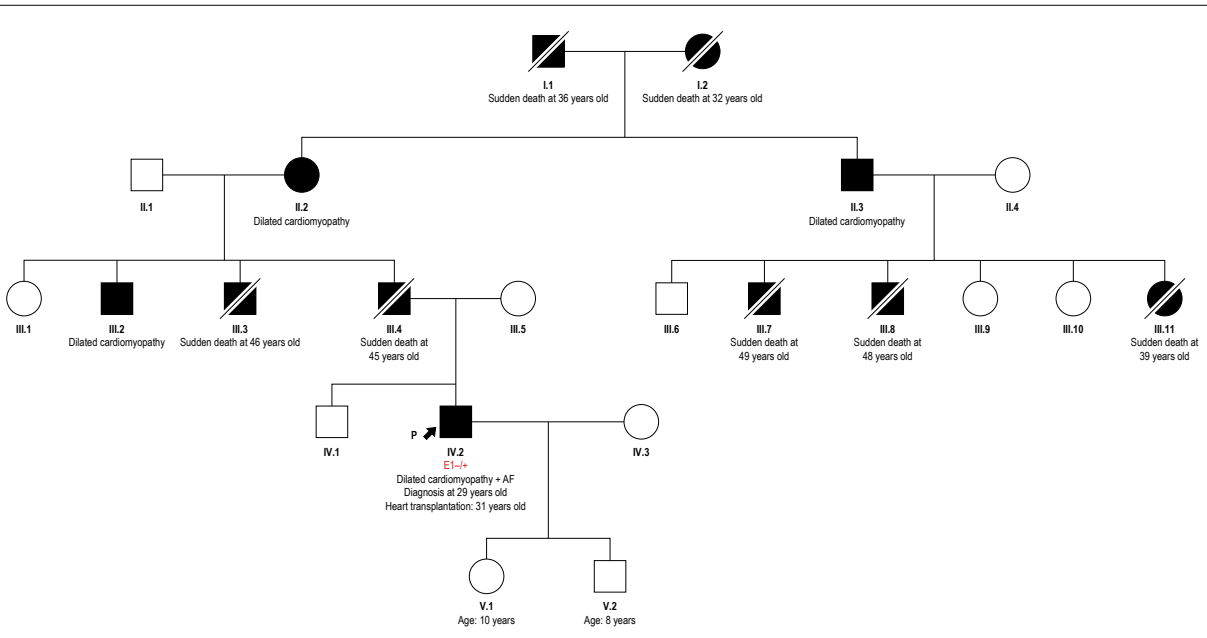

Figure 2 – *Index case heredogram showing involvement in first, second and third degree relatives. AF: atrial fibrillation.*

Study Association

This article is part of the thesis of master submitted by Filipe Ferrari, from Graduate Program in Cardiology and Cardiovascular Sciences, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre.

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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Update on Coronary Angiography-Based Physiology Technologies

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From the early stages of percutaneous coronary intervention (PCI), Andreas Grüentzig had advocated that the direct measurement of the trans-stenotic pressure gradient after balloon PCI should be used as a marker of successful PCI.[1] Since Grüentzig's time, the physiologic assessment of coronary artery disease (CAD) has been tested and validated.[2] Currently, fractional flow reserve (FFR) is the standard of care for the online assessment of CAD physiology, identifying hemodynamically significant lesions in stable angina patients.[3,4]

Albeit FFR is a relatively simple procedure, with a low complication rate, it comes with some intrinsic procedural risks and cost. Recently, non-hyperemic, resting index based physiology modalities have become an alternative to FFR but still require invasive assessment. Coronary angiography-based physiology technology was developed to overcome the intracoronary wiring and additional medication administration that were necessary with invasive physiology.[5]

Based on the principle of FFR, coronary angiography-based physiology technology incorporates computational power by combining the 3-dimensional (3D) meshing (i.e. virtual reconstructions) of the coronary artery and the use of computational fluid dynamics (CFD) as a surrogate marker of the antegrade coronary artery blood flow.[6]

Computational fluid dynamics

The basis for CFD is derived from Navier-Stokes equations, a mathematical generalization of Euler's flow of incompressible and frictionless fluids equation.[6] In its current state, CFD now can compensate for 3 dimensionality and interactions in the non-perfect cylindrical shape of the coronary arteries.[6] However, due to intrinsic cardiovascular physiology particularities, CFD cannot compensate for pulsatile blood flow effects; physiologic differences of coronary blood flow velocity in the proximal vs. distal segments of the vessel; and predictable loss of energy over a diseased vessel.[6-10] Moreover, CFD still cannot address the high complexity interactions in vessel geometry that may lead to a chaotic vortex or turbulence formation and more importantly, the trans-lesional pressure drop.[6,10]

There are significant differences in the complex rheological properties of blood and normal blood flow along the coronary artery tree branches by itself that are not taken into account in these models. This includes the Newtonian versus Non-Newtonian fluid properties of blood that depend on the vessel diameter, the presence of a bifurcation, and slow blood flow shear stress effects (e.g. the non-Newtonian fluid property in that context).[6] CFD simulation generalizes the differences of Newtonian and Non-Newtonian fluids properties by the assumption that large vessels can be approximated to a Newtonian fluid property with constant viscosity.[11,12] Therefore, these data provide a consistent explanation of why these methods were not standardized to evaluate severe stenosis or antegrade blood flow in small vessels.[11]

Computational time: Online vs. offline assessment

One of the major limitations for the clinical adoption of CFD in the online software is the computational time. The computation time required to estimate the antegrade blood flow in the 3D-mesh model using CFD considerably prolongs the procedure duration.[11] In order to reduce the computational time and provide an online assessment of the vessel, most software developers substituted the CFD with mathematical coefficients.[11,12] The impact of this substitution was studied by Collet et al. and demonstrated no significant difference between the results obtained using either method to estimate vessel blood flow.[13]

Online coronary angiography-based physiology software

The development of online coronary angiography-based physiology software solutions occurred in parallel with different initiatives. Most commonly, their software solutions were tested and validated against invasive FFR, including Quantitative Flow Ratio (QFR), Cardiovascular Angiographic Analysis Systems-Vessel Fractional Flow Reserve (CAAS-vFFR) and Fractional Flow Reserve Derived From Coronary Angiography (FFR_{angio}).[11,12,14] Each software solution however used different metrics (i.e. pressure vs. TIMI frame count) and anatomic considerations (i.e. single vs. multi-vessel) to build the 3D-mesh and solve the CFD challenges of non-invasively predicting invasive FFR measurements, making a fair comparison among them unlikely.[11,12,14]

In its current state, the overall performance of online coronary angiography-based physiology was evaluated in a Bayesian meta-analysis showing a pooled sensitivity of 0.89, specificity of 0.90, the positive likelihood ratio of

Keywords

Coronary Artery Disease/physiopathology; Percutaneous Coronary Intervention; Angina, Stable; Coronary Angiography; Fractional Flow Reserve, Myocardial; Software/trends.

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9.3, the negative likelihood ratio of 0.13 and the summary area under the receiver-operating curve of 0.84 compared to invasive FFR.[13] The individual characteristics of online coronary angiography-based physiology software solutions will be described below.

Quantitative flow ratio (QFR)

QFR (QAngioXA-3D prototype, Medis Medical Imaging System, Leiden, the Netherlands) is an angiography-based physiology software that uses the TIMI frame count of a single-vessel in two orthogonal views as the surrogate marker of blood flow to calculate the trans-lesional gradient ratio (Figure 1 A to D). In the latest reports, Favor II China trial, Xu B et al.[11] showed a linear correlation (r) between invasive FFR and QFR (online assessment) of 0.86 ($p < 0.001$) with a mean agreement difference of -0.01±0.06 ($p = 0.006$).[11] Spitaleri et al.[15] reported that the absence of revascularization of non-culprit lesions in ST-elevation segment myocardial infarction (STEMI) patients with QFR ≤ 0.80 increased the risk of clinical events in this population (HR 2.3; CI 95%, 1.2–4.5; $p = 0.01$).[15] Mejía-Rentería et al.[16] highlighted that coronary microcirculatory dysfunction (CMD) affects the overall diagnostic performance of QFR.[16] The QFR system has CE Mark and *ANVISA* clearance for clinical use. Clinical guidelines have not yet established the appropriate role of QFR in routine practice. Ongoing clinical trials including FAVOR III China (NCT03656848) may ultimately impact future guidelines.

Cardiovascular angiographic analysis systems for vessel fractional flow reserve (CAAS-vFFR)

CAAS-vFFR, Pie Medical Imaging, Maastricht, The Netherlands is single-vessel, two orthogonal view angiography-based physiology software (Figure 1 E to H). The CAAS-vFFR validation study included 100 patients with intermediate lesions and stable CAD or non-STEMI. The CAAS-vFFR and FFR mean value were 0.84 ± 0.07 and 0.82 ± 0.08, respectively.[14] The linear correlation of CAAS-vFFR vs. FFR was 0.89 ($p < 0.001$) and CASS-vFFR showed a high inter-observer correlation of 0.95 ($p < 0.001$). In addition, CAAS-vFFR diagnostic accuracy for lesions with FFR ≤ 0.80 was 0.93 ($p < 0.001$).[14] CAAS-vFFR was the first angiography-based physiology system to receive Food and Drug Administration (FDA) *"USA 510(k) approval"* market clearance.

Fractional flow reserve derived from coronary angiography (FFR_{angio})

Unlike QFR and CAAS-vFFR, the Fractional Flow Reserve Derived From Coronary Angiography (FFR_{angio}, CathWorks Ltd., Kfar-Saba, Israel) reconstructs the entire coronary artery tree using 3 single-plane angiographic projections (at least) and the mean aortic pressure to calculate a virtual FFR mapping of the 3D-model.[12,17] Fearon et al.[17] performed a global, multi-center validation study of FFR_{angio} enrolling 301 all-comer patients (319 lesions).[17] FFR_{angio} and invasive FFR measurements varied from 0.74-0.90 (median 0.83) and 0.5-0.97 (median 0.85), respectively. The coefficient of correlation between FFR_{angio} and invasive FFR was 0.80 ($p < 0.001$) and Bland-Altman's confidence limits were between -0.14 and 0.12 (95%). For lesions with invasive FFR ≤ 0.80, FFR_{angio} (per vessel) demonstrated the sensitivity of 0.94, the specificity of 0.91 and area under the curve of 0.94. The overall FFR_{angio} diagnostic accuracy was 0.92 and 0.87 for invasive FFR values between 0.75-0.85.[17] Finally, the inter-observer consistency of agreement between the methods was 0.96 ($p < 0.001$).[12]

Physiology assessment cost-effectiveness

A recurrent criticism of the routine use of invasive physiologic assessment (i.e. FFR) of CAD in the cardiac catheterization laboratory is the additional procedural cost.[18,19] For the non-invasive angiography-based physiology methods, cost-effectiveness data needs to be further investigated. This technology involves upfront institutional hardware and software costs, rather than a specific case-by-case cost of an invasive wire.

Impact of physiologic lesion assessment on clinical outcomes

Currently, with contemporary stents, target lesion failure (TLF, a composite of cardiac death, target vessel MI, or ischemia-driven target lesion revascularization - TLR) rates are similar (i.e. 4.0% to 6.0% at 12 months) to the rate of combined endpoint in the group of patients in whom PCI was deferred on the basis of FFR (i.e. overall unplanned revascularization of 5.0% at 12 months).[20] Thus, the rate of composite events for the treatment or deferral of PCI are similar, perhaps limiting the appropriate utilization of FFR for informing PCI decisions.[20-22] This needs to be further investigated in a contemporary clinical trial using 2nd generation drug-eluting stents (2G-DES).

Conclusion

The majority of angiography-based physiology software solutions are currently available for research only. Clinical trials demonstrating clinical feasibility and reproducibility with a significant impact on clinical outcomes are needed. However, real-world studies are also needed to evaluate the reliability, integration and cost-effectiveness of these technologies in a clinical catheterization laboratory, since the prevalence of ischemic lesions in most studies is limited (i.e. 17% to 43%).[17] The angiography-based physiology technologies have great potential, but still need to be observed with a word of caution and the impact of these technologies remains unknown.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Hideo-Kajita A, Garcia-Garcia HM, Shlofmitz E, Campos CM.

Potential Conflict of Interest

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

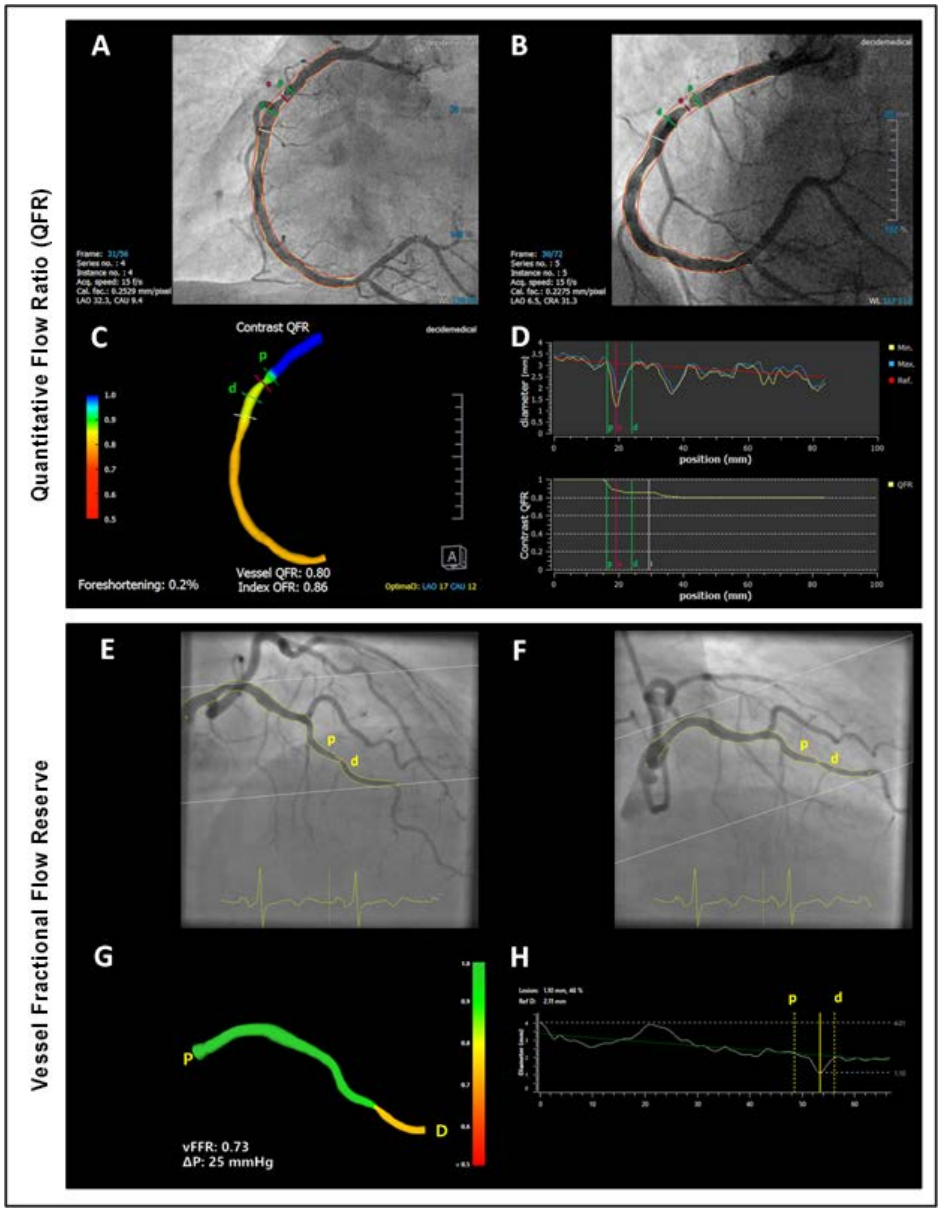

Figura 1 – *As imagens de A a D referem-se à artéria coronária direita (ACD) e avaliação da lesão pela Razão de Fluxo Quantitativo (QFR). As imagens E a H apresentam um vaso da artéria descendente anterior esquerda (ADA) com análise de lesão utilizando o Sistema de Análise Angiográfica Cardiovascular para Fluxo Fracionado de Reserva de vasos (SAAC-FFRv). Análise coronária quantitativa de duas projeções angiográficas ortogonais da ACD (A e B); Análise da QFR sobre a reconstrução tridimensional (3D) da ACD (C); Gráficos da QFR mostrando o diâmetro do vaso de referência proximal e distal da lesão e o ponto mais estreito da lesão (D). Análise do SAAC-FFRv mostrando projeções angiográficas ortogonais da ADA (E e F); Análise do SAAC-FFRv sobre a reconstrução em 3D da ADA (G); Gráficos de análise do SAAC-FFRv apresentando todo o diâmetro do vaso, marcando o diâmetro do vaso de referência proximal e distal da lesão, seguido pelo ponto mais estreito dentro da lesão (H). "P": proximal; "D": distal.*

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Ethics approval and consent to participate

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

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Case 4/2019 - 26-Year-Old Man with Congenital Chagas Disease and Heart Transplantation

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A 26-year-old man with cardiopathy due to congenital Chagas' disease was submitted to heart transplantation for heart failure; amastigote forms of *Trypanosoma cruzi* were found in an endomyocardial biopsy in the third month after transplantation.

The patient had been diagnosed with Chagas' disease due to transplacental transmission and was followed at Hospital das Clínicas of Faculdade de Medicina of Universidade de São Paulo (FMUSP) until the age of 2 years, when he was discharged from the follow-up. He was diagnosed with cardiopathy due to Chagas' disease at age 20.

He sought emergency medical care on July 23, 2016, at age 25, for dyspnea on moderate exertion and paroxysmal nocturnal dyspnea and edema for three weeks.

The physical examination disclosed blood pressure of 118/98 mmHg, heart rate of 87 bpm, respiratory rate of 28 breaths/min, oxygen saturation of 99% and pulmonary auscultation showed decreased vesicular murmur at the bases. Cardiovascular examination disclosed increased jugular venous pressure, thin pulses, cardiac stroke deviated 2 cm beyond the nipple line, 2 digital pulps, arrhythmic heart sounds, normal heart sounds with the presence of a third heart sound and mitral systolic murmur. Abdominal examination revealed painful hepatomegaly, with the liver palpated 6 cm from the right costal border and ++ /4 edema in the lower limbs.

The electrocardiogram showed sinus rhythm, heart rate of 107 bpm, PR interval of 187 ms, QRS duration of 146 ms, left atrial overload, right bundle-branch block and anterosuperior left bundle-branch block and probable left ventricular overload (Figure 1).

The posteroanterior chest x-ray disclosed veil-like opacification of the both hemithoraces, compatible with pleural effusion, increased pulmonary hila with signs of pulmonary congestion and cephalization of the pulmonary vasculature network and ++++ / 4 global cardiomegaly (Figure 2).

Keywords

Heart Defects, Congenital; Chagas Cardiomyopathy; Heart Transplantation; Heart Failure; Diagnosis Imaging.

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The patient was re-hospitalized on July 29, after two episodes of syncope that occurred on the day before hospitalization.

The physical examination disclosed a patient in regular overall status, hydrated, eupneic, acyanotic, conscious and oriented. Blood pressure was 90x60 mmHg, heart rate was 88 bpm, oxygen saturation was 97%; pulmonary auscultation was normal; cardiac auscultation disclosed an irregular heart rhythm, with no heart murmurs or accessory sounds; the abdominal examination showed no visceromegaly, no lower-limb edema, and no calf stiffness.

Laboratory tests (July 29, 2016) showed: red blood cells: 5200000/mm^3, hemoglobin 15.6g/dL, hematocrit of 47%, leukocytes 14,570/mm^3 (74% of neutrophils), platelets 157,000/mm^3, potassium 3.8 mEq/L, sodium 137 mEq/L, BNP 1,128 pg/mL, ALT 54 U/L, AST 42 U/L, gamma-GT 99 U/L. Urinalysis was normal.

The chest x-ray (July 29, 2016) disclosed clear pulmonary fields and cardiomegaly at the expense of the right ventricle (Figures 3A and B).

The transthoracic echocardiogram (July 29, 2016) showed: left atrium, 52 mm; right ventricle, 43x32 mm; septum, 8 mm; posterior wall, 8 mm; left ventricle 66x60 mm; left ventricular ejection fraction, 20%; pulmonary artery systolic pressure, 39 mmHg. There was a marked increase in left atrium (volume measured by Simpson's rule was estimated at 61 mL/m^2, normal value < 34 mL/m^2); moderate enlargement of the left ventricle and right atrium; slight enlargement of the right ventricle. Systolic function was decreased due to diffuse hypokinesia. The right ventricle showed mild hypokinesia. There was also mild to moderate mitral regurgitation, as well as mild to moderate tricuspid regurgitation.

The heart MRI (August 1, 2016) showed marked right ventricular dilatation with an ejection fraction of 17%, left ventricle with diffuse hypokinesia, with late mesocardial enhancement in the basal segment of the septum and transmural enhancement in the basal, middle and apical segments of the anterior, lateral and inferior walls, and less than 50% in the basal inferosseptal segment. The ejection fraction of this ventricle was also 17% (Figure 4).

In the electrophysiological study (August 4, 2016) there was no onset of atrial or ventricular arrhythmias after the extra stimuli.

Right catheterization (August 23, 2016) showed mean right atrial pressure of 11 mmHg, right ventricular end-systolic and diastolic pressures of 45/29 mmHg, and pulmonary capillary pressure of 30 mmHg. The pulmonary vascular resistance was 3.6 Wood Units (normal: 0.25 to 1.6 Wood U) and the cardiac index was 2.1L / min / m^2. After the use of 10 μg/kg/min of dobutamine, pulmonary vascular resistance decreased to 1.6 Wood U.

The patient was placed on a transplant waiting list with a priority status, as vasoactive drug weaning was not achieved

Anatomopathological Correlation

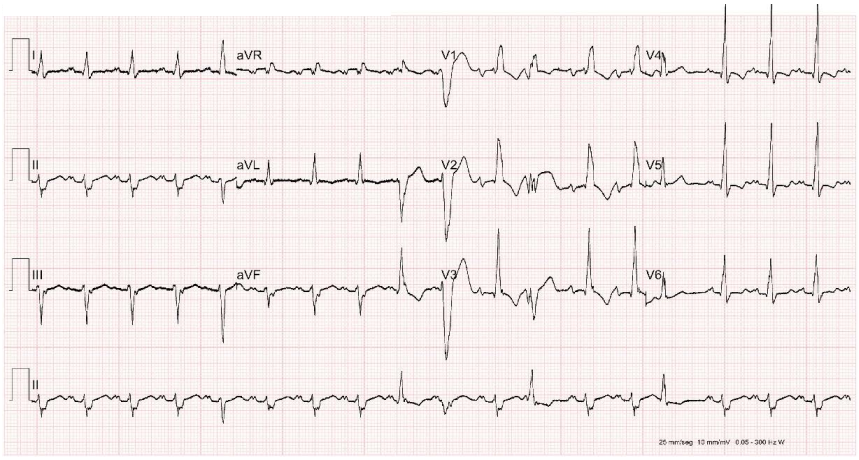

Figure 1 – *Electrocardiogram. Sinus rhythm. Left atrial enlargement, right bundle branch block, left anterior hemiblock, premature ventricular contraction, premature atrial contraction.*

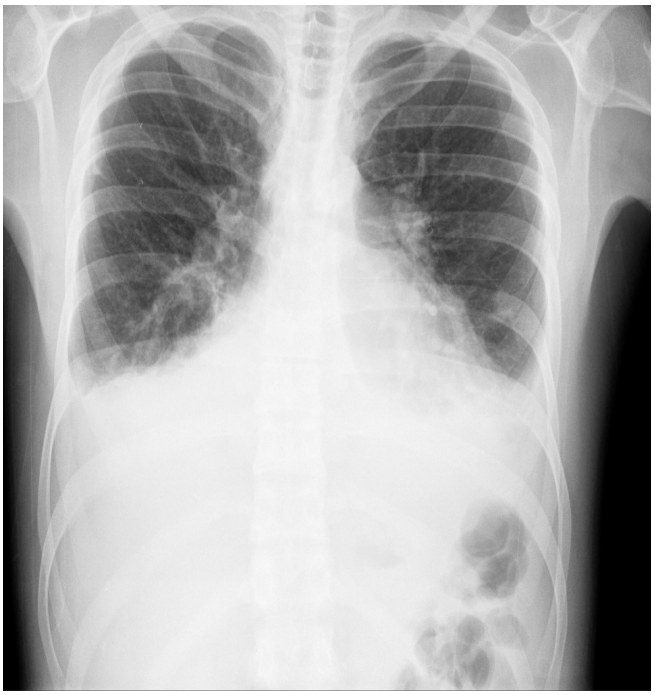

Figure 2 – *PA chest x-ray: veil-like opacification of pulmonary bases (pleural effusion), global cardiomegaly.*

due to hypotension. Orthotopic heart transplantation was performed with no complications on December 6, 2016. The donor was positive for cytomegalovirus.

The anatomopathological analysis of the para-aortic lymph nodes revealed reactive lymphadenitis with no granulomas.

The post-transplantation electrocardiogram (December 09, 2016) showed low voltage in the frontal plane and end-conduction disorder (Figure 5).

The biopsy on December 16, 2016 showed focal mild-degree fiber aggression; focal mild histiocytic proliferation and mild focal lymphocytic infiltrate; there was moderate diffuse edema. Compatible with acute grade 1R cellular rejection (low grade mild rejection). The search for antibody-mediated rejection by immunohistochemical reaction to complement C4d fraction was negative.

The serology was negative for cytomegalovirus; however, molecular biology screening for the parasite was positive since the end of December and viral load reached 47417 U/mL in February 2017, when the patient received ganciclovir for 21 days.

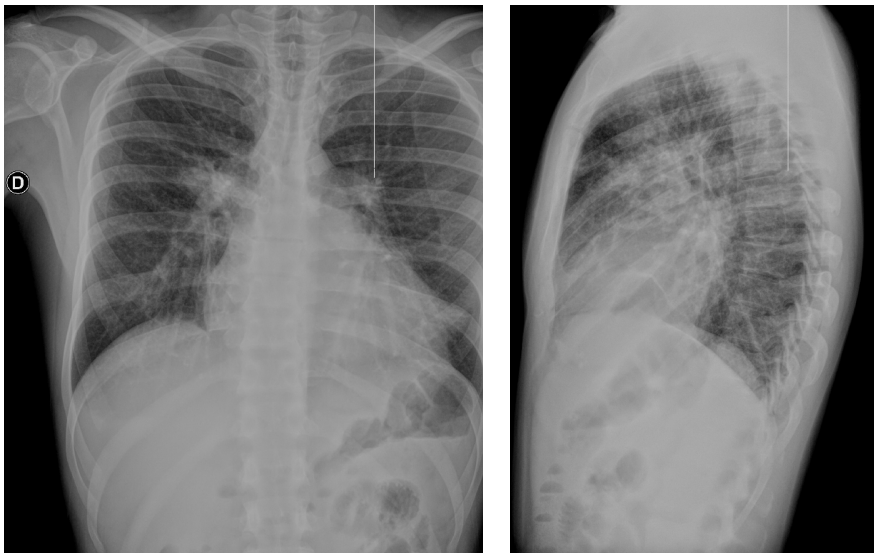

Figure 3 – *X-rays: global cardiomegaly, larger increase of the right ventricle.*

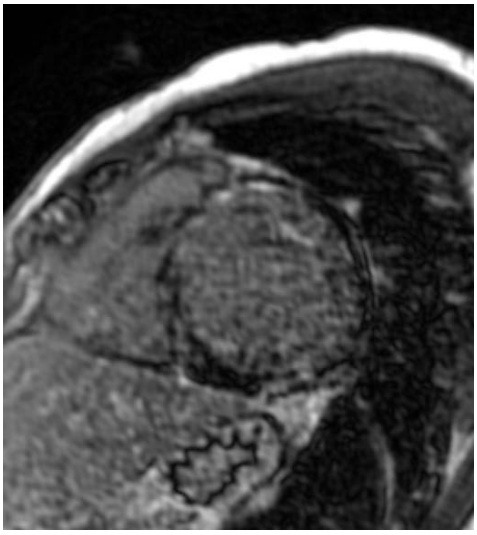

Figure 4 – *Magnetic resonance image: transmural, mid-wall and subepicardial late gadolinium enhancement not involving subendocardium.*

The echocardiogram performed in February 2017 was normal, except for an increase in the left atrium, whereas the one performed in March showed all measures within the normal range.

In a biopsy carried out in March 2017, moderate and focal fiber aggression, moderate diffuse proliferation, moderate focal lymphocytic infiltrate and mild diffuse edema were observed. Amastigote nests were observed inside the myocytes, with protozoal myocarditis. This biopsy was suggestive of Chagas' disease reactivation, with moderate mononuclear myocarditis. Kinetoplasts were observed in the parasites and the immunohistochemistry was positive for *Trypanosoma cruzi* antigens. Benznidazole was then prescribed.

A biopsy carried out in September 2017 disclosed acute grade 2R cellular rejection (moderate rejection, intermediate grade). Both histological and immunohistological analysis were negative for *Trypanosoma cruzi*.

The serology for Chagas' disease was negative in November 2017.

At an outpatient consultation on May 3 2019, the patient was asymptomatic and the physical examination was normal.

Clinical aspects

Chagas' disease was first described by Brazilian physician and scientist Carlos Chagas in 1909.[1] This multifaceted disease is caused by the protozoan *Trypanosoma cruzi*, which can be

Anatomopathological Correlation

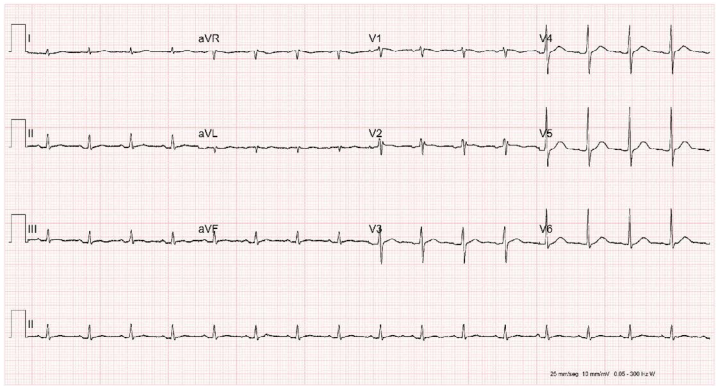

Figure 5 – *Post-transplantation electrocardiogram: low frontal plane voltage and end-conduction disorder.*

transmitted in different ways. Vector transmission through hematophagous insects is the most classic one, although it has declined in importance in recent years with measures to control the vector population.[2] Transfusion transmission, as well as vector transmission, have shown a drastic reduction in the last decades, and no cases have been reported in Brazil for years.[3] In contrast, there was an increase in reports of oral transmission. This form of contagion was little known but gained importance, with several descriptions of micro-epidemic events in the country, especially related to the consumption of açai berry. The development of the acute phase of the disease is more common in the oral transmission.[4] In the context of controlling the main forms of contagion, vertical transmission has become relevant.

The World Health Organization (WHO) estimates there are approximately 8 million individuals infected with Chagas disease worldwide, with an annual mortality of 10,000 people due to disease complications.[5] Most of these cases are found in Latin America, and Brazil is the country with the majority of infected individuals (approximately 4.6 million individuals). The decrease in transmission was accompanied by a reduction in mortality, estimated in 2007 to be 2.78 deaths/year for every 10,000 inhabitants.[6] Another change in the disease epidemiology in recent years has been the increase in cases in non-endemic regions, such as the USA and Europe, which has contributed to the increased attention given by the international scientific community to Chagas' disease.[5]

The pathophysiology of Chagas' disease is multifactorial, depending on several characteristics of both the host and the parasite.[7] It is known that the inflammatory response triggered by the parasite plays a crucial role in this pathophysiology.[8] This hypothesis is supported by low tissue parasitism and low parasitemia in the chronic phases of the disease. More recent studies have identified an autoimmune response triggered by the cross-reaction between parasite antigens and host proteins, such as troponin.[9] Diagnosis is attained by serological tests in the vast majority of cases, with the direct investigation of the parasitic agent being reserved for acute phases or reactivations, situations in which the parasitemia may be higher.[7]

Congenital Chagas' disease is a separate group. It occurs when there is vertical transmission, that is, during pregnancy. In Brazil, Martins-Melo et al.[10] demonstrated that the mean prevalence of infected pregnant women is 1.7%, with a mean percentage of congenital transmission of 1.7%. Extrapolating these data to the population based on the 2010 census, Brazil would have approximately 34,629 infected pregnant women, with an incidence of 587 children born with congenital Chagas per year.[10] Due to these numbers, the WHO recommended in 2018 increased attention to cases of congenital Chagas through maternal-fetal transmission, not only in Brazil, but in all countries with endemic disease.

In a study carried out in Argentina in 2014, Fabbro et al.[11] demonstrated that children of pregnant women who received treatment with antitrypanosomal drugs during their lives have a much lower chance of developing congenital Chagas' disease than children of women who have not been treated.[11] Thus, in addition to indications of etiological treatment included in the I Latin American Guideline for Chagas' disease in 2011, it is recommended that women of childbearing age also receive antitrypanosomal drugs. In Brazil, the available drug is benznidazole, which should be used at a dose of 5mg/kg/day divided into 2 or 3 doses a day for 60 days.[7] It is worth noting that benznidazole use is contraindicated during pregnancy, due to the risk of teratogenicity found in animal studies.[12]

The clinical picture of congenital Chagas disease is extremely variable and non-specific, being similar to several other infections seen in the neonatal period, such as toxoplasmosis, rubella, HIV and syphilis. The main symptoms are preterm birth, intrauterine growth restriction, neuropsychomotor development deficit, low Apgar score, respiratory distress syndrome, jaundice, and hepatosplenomegaly. These symptoms may appear days or even weeks after birth. Mortality is approximately 5% and is usually related to more severe manifestations, such as meningitis and myocarditis.[13] The diagnosis, in addition to the clinical picture, is based on the direct screening for the parasite up to 6 months of age and on the serological tests after 9 months, due to the presence of circulating antibodies from the mother. All cases should be treated with antitrypanosomal drugs as soon as the diagnosis is confirmed.[14] The earlier treatment is implemented, the lower the incidence of side effects and the higher the cure rate, which is 100% when implemented in the first year of life.[12]

Chagas' disease reactivation can affect any individual with the chronic forms of the disease, especially when they are submitted to immunosuppression. In this context, the most important conditions are HIV coinfection and/or organ transplantation.[14] Among patients with Chagas cardiopathy submitted to heart transplantation, the incidence varies between 21 and 45% depending on the studied series.[15] Review studies show that mortality is low when appropriate treatment is implemented and, therefore, diagnosis is a crucial part of a favorable outcome.[16]

The diagnosis of reactivation in the transplanted patient is based on the clinical picture and the routine screening for the parasite in endomyocardial biopsies, because often there are no symptoms, or the symptoms are non-specific. Symptoms may be cardiac, such as congestive and low-output symptoms in cases of myocarditis or changes in the electrocardiogram, such as cardiac rhythm disturbances or new blocks. The most frequent extracardiac symptoms are fever and skin lesions. Thus, a high degree of suspicion is necessary for diagnosis to be attained. When the endomyocardial biopsy is altered, the main differential diagnosis is acute cellular rejection, since there is lymphocyte/monocyte infiltration in both cases. The difference is that nests of *Trypanosoma cruzi* amastigotes may be present in the Chagas' disease reactivation biopsy, observed by hematoxylin-eosin staining or by immunohistochemistry analysis.[15]

When the reactivation diagnosis is made, the recommended treatment is benznidazole use, at the previously mentioned doses. It should be emphasized that this treatment does not result in the cure of the chronic infection, and the patient is subject to recurrent reactivations. As a consequence of this risk, it is recommended that the immunosuppression in these patients be as little as possible, aiming at an adequate balance between the risk of reactivation and rejection.[15]

Azathioprine use should be preferred instead of mycophenolate in the Chagasic population, since it is associated with a lower reactivation rate, without worsening of other outcomes.[17] Thus, despite the drastic decrease in the disease transmission in the country, Chagas' cardiopathy continues to be very frequent in Brazil, both due to the number of patients with the chronic forms of the disease and to other forms of transmission that were not previously very relevant, such as vertical transmission. The care of pregnant women and the treatment of those infected at reproductive age should be improved. The active screening for infection in the children of infected mothers is essential, aiming at establishing the earliest possible antitrypanosomal treatment in infected children, thus achieving the cure and reducing the potential number of patients with the chronic forms of the disease. **(Dr. Henrique Trombini Pinesi)**

Diagnostic hypothesis: Chagas disease reactivation in transplanted heart. **(Dr. Henrique Trombini Pinesi)**

Infectious aspects

The laboratory monitoring of Chagas' disease reactivation after cardiac transplantation is recommended. Due to the difficulty of attaining a clinical diagnosis of Chagas' disease reactivation, with the exception of skin lesions, the laboratory monitoring of transplanted patients is recommended.[15] For this purpose, peripheral blood samples should be collected for direct detection of the parasite in the buffy coat, which increases the likelihood of its finding, and for parasite screening by molecular biology. This method seems to be more sensitive, detecting the increase of the parasitic load before the onset of clinical and/or histopathological manifestations. It can be qualitative or quantitative. Monthly or quarterly monitoring is recommended in the first year after cardiac transplantation, when the level of immunosuppression is higher and after the treatment of rejection episodes. **(Prof. Dr. Tânia Mara Varejão Strabelli)**

Anatomopathological report

The explanted heart weighed 332g. It had a globose shape and the external surface was covered by smooth serosa, with small white and prominent nodules being noticed, focally, in the trajectory of the coronary vessels. The opening showed dilatation of all chambers (Figure 6), predominantly of the ventricles. The endocardial surface was smooth, showing no thrombi. The left atrial endocardium was quite thick. The left ventricular tip showed a dilated lesion measuring 1.2 cm in diameter, where the wall was tapered and partially replaced by whitish tissue (Figure 7). The epicardial coronary arteries showed no macroscopic alterations, as well as the atrioventricular and arterial valves. Histological analysis showed chronic mononuclear myocarditis and diffuse fibrosis, of which intensity varied from one region to another. We did not find parasites in the histological sections of the explanted heart.

The post-transplantation endomyocardial biopsy carried out in March 2017 showed good tissue representativeness, with a moderate inflammatory process and several cardiomyocyte aggression foci (Figure 8).

As this was a patient with Chagas' disease, an immunohistochemical reaction was carried out for *Trypanosoma cruzi* parasites, which were positive in pseudocysts containing amastigotes (Figure 9). New sections of the same block stained with hematoxylin-eosin also showed the presence of pseudocysts (or nests) containing several amastigote forms (Figure 10). **(Dr. Vera Demarchi Aiello)**

Anatomopathological diagnoses

Explanted heart: Chronic myocarditis with diffuse fibrosis, compatible with cardiac involvement in chronic Chagasic cardiopathy.

Post-transplantation endomyocardial biopsy: Chagas' disease reactivation, with moderate mononuclear myocarditis and presence of several parasite nests. **(Dr. Vera Demarchi Aiello)**

Comments

This case shows a young patient with chronic Chagasic cardiopathy who had clinical manifestations around the age of 20 years, after a diagnosis of congenital Chagas' disease. There was no clear history of childhood disease treatment. The explanted heart showed a typical picture of Chagas' chronic heart disease.

Anatomopathological Correlation

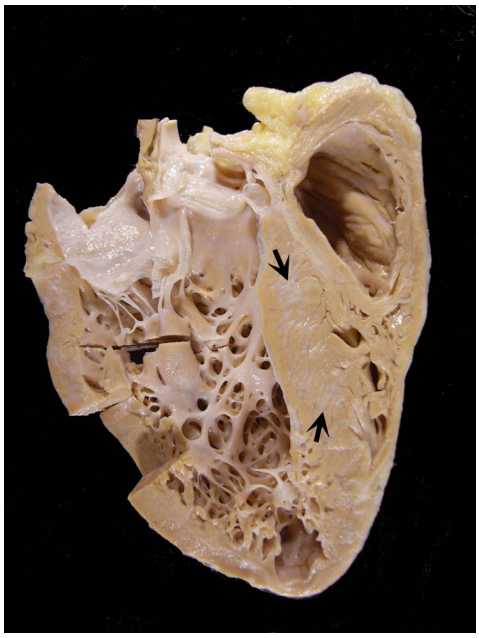

Figure 6 – *Longitudinal section of the explanted heart, showing chamber dilatation and areas of fibrosis in the ventricular septum (arrows).*

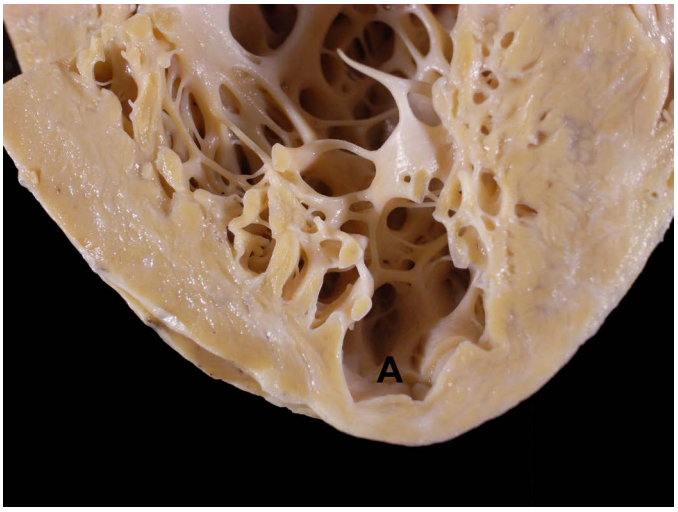

Figure 7 – *Detail of the left ventricular tip showing the typical lesion of chronic Chagasic cardiopathy, characterized by myocardial tapering with aneurysm formation (A).*

Regarding the post-transplant endomyocardial biopsy findings, the presence of inflammation with more than one focus of cardiomyocyte aggression is, at first, compatible with the diagnosis of acute grade 2R cellular rejection.[18] However, as this is the case of a patient with Chagas' disease as the primary cardiopathy, one must carry out a more detailed investigation of parasites, since the histological picture of acute 2R cellular rejection is identical to that of disease reactivation. The investigation was then carried out by immunohistochemistry and then in more detailed sections of the biopsy block, we concluded it was a reactivation of Chagas' disease in the transplanted heart, which allowed the appropriate treatment to be implemented.

It is known that the rate of reactivation depends on the implemented immunosuppressive treatment, as previously described. The work of Vidal et al.[19] also showed that the first episode of reactivation occurred at a median of 6.6 months post-transplantation. Therefore, the routine evaluation of endomyocardial biopsies in Chagasic patients with heart transplantation should include, whenever there is an R2 or higher grade acute cellular rejection, a very detailed evaluation of the histological sections for possible detection of parasites. **(Dr. Vera Demarchi Aiello)**

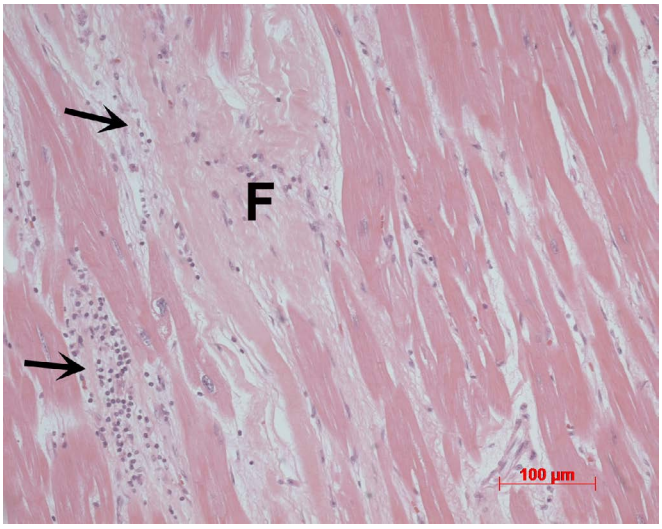

Figure 8 – *Myocardial photomicrography of the explanted heart, showing extensive fibrosis (F) and active myocarditis foci (arrow). Hematoxylin-eosin staining, magnification = 20X.*

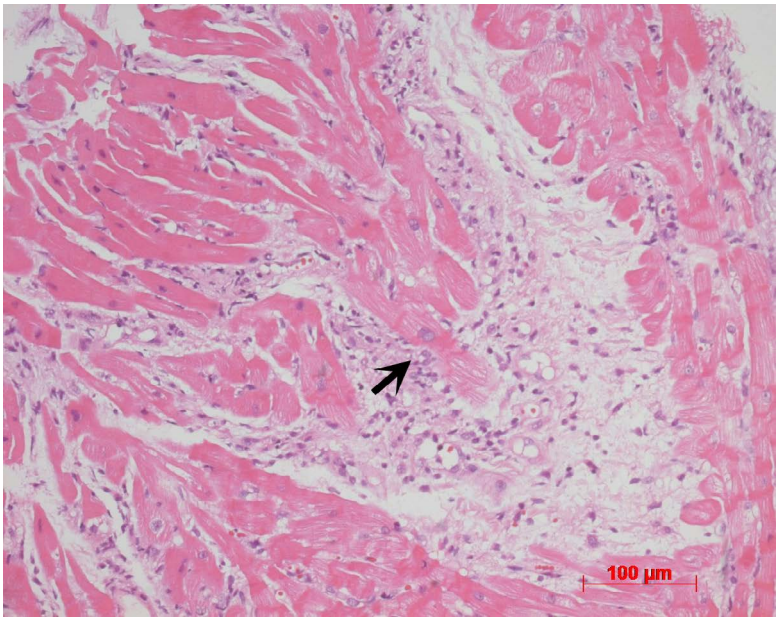

Figure 9 – *Endomyocardial biopsy photomicrography for post-transplant rejection control. Diffuse inflammatory picture with cardiomyocyte aggression foci can be observed (arrow). Hematoxylin-eosin staining, magnification = 20 X.*

Anatomopathological Correlation

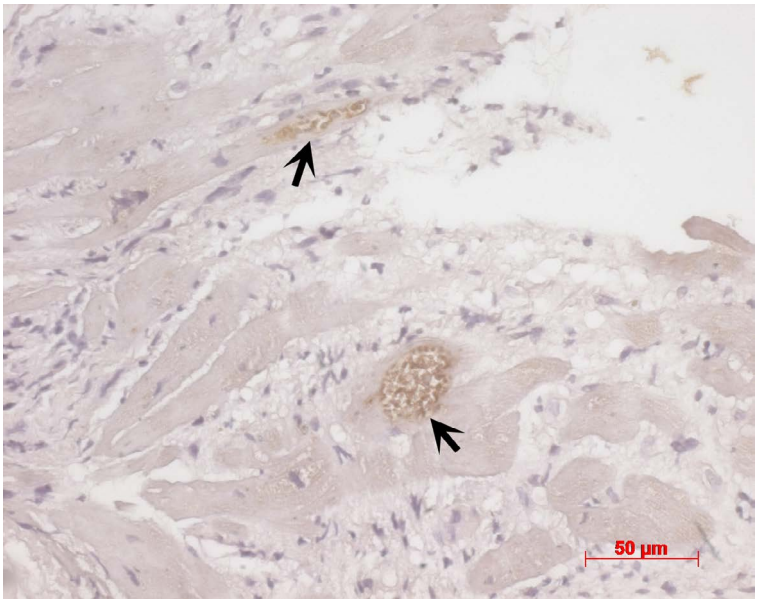

Figure 10 – *Photomicrograph of the endomyocardial biopsy histological section, submitted to immunohistochemical reaction for T. cruzi parasites. Nests of parasite amastigotes (arrows) are shown in brown. Harris hematoxylin counterstaining, magnification = 40X.*

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Exertional Rhabdomyolysis after Military Training Paralleled by Systemic Microvascular Dysfunction and Plasma Cytokine Increase: A Case Report

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Introduction

Exertional rhabdomyolysis (ER) is diagnosed by the presence of intense muscular pain and sudden elevation of total plasma levels of the enzyme creatine kinase (CK), with or without myoglobinuria,[1] is closely associated with acute fatigue during exercise,[2] as well to the associated risk of acute renal injury, disseminated intravascular coagulation, cardiac arrhythmias, and electrolyte disturbances.[3]

ER is highly prevalent in military training, particularly when performed in adverse climatic conditions, and many cases progress rapidly to acute, life-threatening renal failure. Moreover, it is estimated that about one-third of the cases of ER involve young male afro-descendants with low physical conditioning and extreme dehydration, occurring during summer military training courses.[4] In those situations, clinically healthy young subjects are submitted to strenuous exercise routines performed with combat uniforms and equipment and without adequate hydration possibilities.[4]

The assessment of systemic endothelial microvascular reactivity has already been proven to be essential in the investigation of the pathophysiology of cardiovascular and metabolic diseases.[5] Additionally, the cutaneous microcirculation is now considered as an accessible and representative vascular bed for the assessment of systemic microcirculatory reactivity and density.[5] Considering that ER has already been shown to be related to decreased systemic endothelium-dependent vasodilation in the systemic circulation in the experimental setting,[6] it is reasonable to speculate that ER is also associated with significant systemic microcirculatory dysfunction. Moreover, there is no description in the specialized literature of the association of ER with microvascular endothelial function is humans. To the best of our knowledge, this is the first report on the detrimental outcomes of ER on endothelium-dependent systemic microvascular reactivity in human beings.

Keywords

Rhabdomyolosis; Exercise; High-Intensity Interval Training; Myalgia; Cytokinase/blood; Creatine Kinase; Muscle, Skeletal.

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Case report

This case report is part of an observational research study without any intervention investigating the impact of special military training courses on cytokine profile and microvascular reactivity and the risk of developing ER in Brazilian Air Force military personnel who fully completed a five-week training period. This study was performed in accordance with the Declaration of Helsinki of 1975 (revised in 2013). The case report was approved by the Institutional Review Board (IRB) of the National Institute of Cardiology of the Ministry of Health, Rio de Janeiro, Brazil under protocol number # CAAE 49792515.6.0000.5272. The subject read and signed the informed consent form approved by the IRB. The patient was encouraged to share his perception of the clinical event that occurred during special military training with his colleagues.

The patient was a 21-year-old and physically fit afro-descendant Brazilian Air Force military trainee, who spontaneously applied for riot control military training. The military was considered to have excellent aerobic endurance for his age range (20-29 years of age), using the Cooper run test (VO_2max of 54.66 ml/kg/min). The patient presented no significant information on past personal or familial past medical history, including ER, and did not use any medication nor oral supplements during the period of military training. We tested the patient's blood using hemoglobin electrophoresis, which showed the absence of hemoglobin S. Thus, we can consider that the patient did not present sickle-cell trait. He was diagnosed with ER on the second day of military training. He had performed running exercise in a combat uniform and transporting a 15 Kg kit including shield and gun, with a limited intake of water, and after being exposed to tear and pepper gases for 45 minutes. On the day before, he had run 2,400 meters in 12 minutes, and on both occasions, the running exercises were performed in warm (32°C) and humid (86% relative humidity) conditions typical of the summer season in Rio de Janeiro, Brazil.

The patient had vomiting, postural hypotension, myalgia and muscle weakness in the hip region and lower limbs and was promptly referred to the Air Force Hospital. He soon developed fever (41°C axillary temperature), dark-colored urine, lower limb edema and gait difficulty.

The evaluations of microvascular reactivity were performed one day before the beginning of military training and one day after hospital discharge, both in the morning between 8 and 12 AM and after a 12-hour fast. Microcirculatory tests were performed after a 20-minute rest in the supine position in a temperature-controlled room (23 ± 1°C). Microvascular reactivity was evaluated using a laser speckle contrast imaging

system (PeriCam PSI system, Perimed, Järfälla, Sweden) in combination with skin iontophoresis of acetylcholine (ACh) for noninvasive and continuous measurement of cutaneous microvascular perfusion changes (in arbitrary perfusion units, APU).[7] During the post-occlusive reactive hyperemia (PORH) test, arterial occlusion was performed with supra-systolic pressure using a sphygmomanometer for 3 min. Following the release of pressure, the maximum flux was measured. Measurements of skin blood flow were divided by the mean arterial pressure to yield the cutaneous vascular conductance (CVC) in APU/mmHg. The capillary density, defined as the number of perfused capillaries per mm^2 of skin area, was assessed by high-resolution intra-vital color microscopy (Moritex, Cambridge, UK). The dorsum of the non-dominant middle phalanx was used for image acquisition. Images were acquired and saved for posterior off-line analysis using a semi-automatic integrated system (Microvision Instruments, Evry, France). The mean capillary density was calculated as the arithmetic mean of the number of visible (i.e., spontaneously perfused) capillaries in three contiguous microscopic fields of 1 mm^2 each, as described previously.[8]

Laboratory testing of the subject is shown in table 1. The plasma levels of the enzyme CK were more than 5 times higher than reference laboratory ranges, and together with the symptoms suggested the diagnosis of ER. The creatinine clearance, calculated using the Cockcroft-Gault formula, was markedly reduced. Treatment consisted primarily of intravenous infusion of saline solution (≥ 2,5 L/day) with bicarbonate for pH normalization and myoglobin washout[9] and to maintain adequate urine output. The plasma cytokine analysis is presented in table 2, showing increased levels of IL-1β, IL-6, IL-10, IL-1Ra even after hospital discharge.

Of note, one day after hospital discharge, systemic endothelium-dependent microvascular reactivity was severely impaired. These results can be observed both in the pharmacological (acetylcholine-induced) and physiological (PORH-induced) microvascular vasodilator responses (Figure 1). Finally, cutaneous endothelium-dependent capillary recruitment was also impaired (Figure 1).

After six days of hospitalization and two additional weeks of rest at home, the subject had fully recovered and was able to return to his normal activities. Prognosis of ER is generally good if full recovery occurs.[9]

Discussion

This case report demonstrates that ER after strenuous physical exercise, performed in adverse environmental conditions and with limited water access, can be paralleled by persistent systemic microvascular dysfunction, detectable up to 1 week after the beginning of symptoms and even after normalization of muscle enzymes and complete resolution of renal dysfunction. In fact, a marked reduction of the endothelium-dependent systemic microvascular reactivity induced by both pharmacological (acetylcholine) and physiological (post-occlusive reactive hyperemia, PORH) stimuli was observed one week after the diagnosis of ER. Moreover, skin capillary function, measured as post-ischemic capillary recruitment, was also significantly impaired, suggesting a loss of vasodilatory reserve and autoregulatory capacity and the existence of severe microvascular endothelial dysfunction.

Exercise training of moderate intensity is well-known to induce beneficial effects on the occurrence of cardiovascular diseases through the preservation of vascular endothelial function.[10] On the other hand, strenuous exercise increases oxidative metabolism and produces a pro-oxidant environment, and consequent endothelial dysfunction,[11] while regular and moderate physical activity promotes an antioxidant state and preserves endothelial function.[10] Thus, high-intensity exercise training in previously untrained individuals, such as that of special military training, could be detrimental to the promotion of vascular health.

The microvascular alterations described above were simultaneous with alterations of the profile of plasma cytokines. Nevertheless, it is clearly not possible to establish a link between both phenomena in the present case report, since other metabolic changes could also be involved in the initiation of microvascular dysfunction. It is well known that ER is acutely associated with the production of pro-inflammatory cytokines.[12] Even though we did not obtain cytokine plasma levels on the day of hospital admission, we observed an increase both in pro-inflammatory (IL-1β, IL-6) and anti-inflammatory (IL-10, IL-1Ra) cytokines after hospital discharge, compared to values obtained immediately before military training. The plasma levels of muscle-derived IL-6, which is considered to be a key mediator released during exhaustive exercise,[13] usually starts to increase within the first hour of prolonged exercise and continues to rise depending on the duration of the exercise.[13] In fact, it is well established that the elevation of pro-inflammatory cytokines at the time of muscle injury influences the synthesis of acute phase proteins and the expression of anti-inflammatory cytokines, as a physiological response to offset the inflammatory response.[13] Moreover, it has been consistently shown that there is a rise in anti-inflammatory cytokines, IL-1ra and IL-10, following endurance exercise lasting longer than 2 h.[13] Yet, the plasma levels of TNF-α were not increased one week after ER, suggesting that this cytokine has a different kinetics profile, compared with the aforementioned pro-inflammatory cytokines. Plasma levels of INF-γ did not show important variations in the present case. Actually, most studies in the literature failed to demonstrate a significant rise in plasma IFN-γ after exercise.[13]

Strengths and limitations of our experimental approach should be considered. The use of laser-based skin microvascular flowmetry, as well as the evaluation of the levels of plasma cytokines, is not yet possible in clinical practice. One major strength of the present case report is the demonstration of persistent systemic endothelial microvascular dysfunction and systemic inflammatory reaction after clinical and laboratory regression of ER. The long-lasting vascular inflammatory process observed in the present clinical case could have implications in the prognosis of patients presenting with ER. Nevertheless, it was impossible to retest these parameters in longer time intervals in the present case.

Table 1 – Laboratory testing of the patient before military training, during hospitalization (D, days) and one day after hospital discharge

Parameters	BEFORE	D1	D2	D3	D4	D5	AFTER	Reference ranges
Red blood cells (10^6/µL)	5.3	5.8	5.0	4.6	4.4	4.9	5.3	4.5 – 6.2
Hemoglobin (g/dL)	15.8	16.9	14.5	13.5	13.0	15.1	15.4	13.5 – 18.0
Hematocrit (%)	47.5	51.5	43.3	40.5	38.1	43.2	47.0	40 – 54
White Blood Cell Count (µL)	9,000	18,600	9,580	7,120	6,470	8,920	9,200	5,000 – 10,000
Platelet counts (x1000/µL)	278	313	233	201	195	267	269	150 – 450
Urea (mg/dL)	39	67	47	31	25	27	40	15 – 40
Creatinine (mg/dL)	1.05	2.1	1.3	1.6	1.4	1.2	1.03	0.6 – 1.2
Creatinine Clearance (mL/min)	121	60	98	80	106	123	120	97 – 137
Calcium (mmol/L)	2.34	10.9	9.8	8.7	8.2	9.6	2.72	2.23 – 2.55
Magnesium (mg/dL)	1.9	2.3	2.1	1.8	2.5	2.4	2.1	1.6 – 2.6
Sodium (mmol/L)	138	140	136	142	155	141	138	137 – 145
Potassium (mmol/L)	3.6	4.2	3.6	3.7	3.3	4.2	4.1	3.6 – 5.0
Creatine kinase (U/L)	370	1,100	2,116	1,496	306	211	158	30 – 170
TSH (µIU/mL)	2.10	-	-	-	-	-	2.60	0.35 – 4.94
T3 (ng/ml)	1.13	-	-	-	-	-	1.49	0.59 – 1.49
T4 (ng/dl)	1.19	-	-	-	-	-	1.16	0.70 – 1.48

T3: triiodothyronine; T4: thyroxine; TSH: Thyroid-Stimulating Hormone.

Table 2 – Cytokine plasma levels (in pg/mL) of the patient before military training and one day after hospital discharge

Cytokines	BEFORE	AFTER
IL-1β	0.29	29.44
IL-6	0.41	0.74
IL-10	0.038	6.089
IL-1Ra	5.86	156.57
TNF-α	19.28	3.75
INF-γ	0.88	0.69

IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-1Ra: IL-1 receptor antagonist; TNFα: tumour necrosis factor alpha; INF-γ: Interferon gamma.

Conclusion

ER may be accompanied by systemic microvascular dysfunction even after the resolution of symptoms and normalization of conventional laboratory tests. The microcirculatory disturbance is concurrent with alterations of plasma levels of both pro- and anti-inflammatory cytokines. Accordingly, ER should always be considered in the clinical scenario of muscle pain and disability, fever and dark urine after heavy exercise, including that performed for professional reasons. Besides that, the case report shows that ER may be associated with other complex and potentially severe conditions, which are microvascular dysfunction and systemic inflammation. These are novel findings which we would like to add to the clinicians´ reasoning. If the evaluation of microvascular function is made available clinically, it may be another potentially interesting evaluation to be performed in patients with ER. Nevertheless, more studies are needed to clarify the association between microvascular dysfunction and ER, as well as its clinical implications.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Pereira F, Moraes R, Bavel D, Lorenzo AR, Tibirica E; Acquisition of data: Pereira F, Bavel D; Statistical analysis and Obtaining financing: Tibirica E; Writing of the manuscript: Pereira F, Moraes R, Lorenzo AR, Tibirica E.

Potential Conflict of Interest

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

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Study Association

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

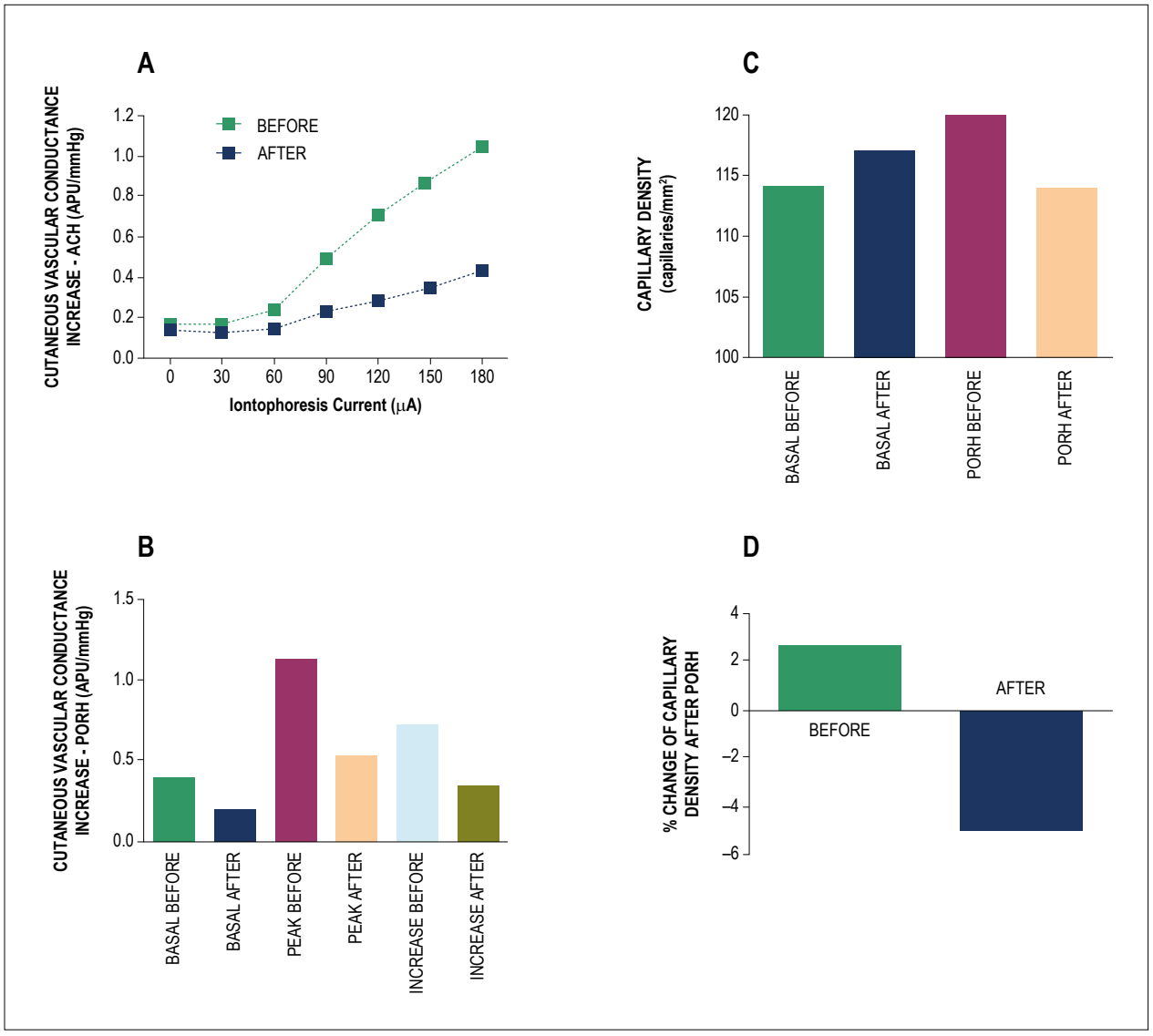

Figure 1 – *Effects of skin iontophoresis of acetylcholine (ACH) on cutaneous microvascular conductance (A, expressed in arbitrary perfusion units, APU, divided by mean arterial pressure, in mmHg) before military training (BEFORE) and one day after hospital discharge (AFTER). (B) Effects of forearm post-occlusive reactive hyperemia (PORH) on cutaneous microvascular conductance. (C) Functional capillary density before (BASAL) and during post-occlusive reactive hyperemia (PORH) before military training (BEFORE) and one day after hospital discharge (AFTER). (D) Percentage change in endothelial-dependent increase in capillary density after PORH before military training (BEFORE) and one day after hospital discharge (AFTER). BASAL: values before PORH; PEAK: maximum values after PORH; INCREASE: the difference between peak and basal values.*

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Gender Equity in Healthcare: An Issue of Justice or Need?

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With great interest on the topic, we read the article "The Profile of the Brazilian Cardiologist – A Sample of the Members of the Brazilian Society of Cardiology", by Faganello et al.,[1] where the professional and personal characteristics of Brazilian cardiologists are reported. The significant gender differences were highlighted in the mini-editorial "Profile of Brazilian Cardiologists: A look on Female Leadership in Cardiology and Stress – Challenges for the Next Decade" by Mesquita et al.,[2] where peculiarities such as payment and the small number of women in Cardiology are analyzed according to an intriguing point of view.

These articles resonate with the "Women's Letter" by Oliveira et al.,[3] a document based on current objectives, which require long-term efforts and structural changes in the medical culture, especially regarding the participation of women in executive positions in medical specialty societies and healthcare-related government bodies.

The important study "Medical demographics in Brazil 2018" by Scheffer et al.,[4] reports a reality which is already known by cardiologists: despite the fact that women currently represent the majority of students at Medical schools, indicating that doctors up to 34 years of age are mostly women, 70% of Cardiologists are men. This reality further contributes for the small number of women choosing Interventional Cardiology as their specialty.

Acknowledging the need for a greater and more effective participation of women in Medicine and Science as a whole, the Brazilian Society of Hemodynamics and Interventional Cardiology has created the so called "Mulheres INTervencionistas – MINT (Women Interventionists), whose objective is to pursue gender equality at a professional and patient level, encouraging female doctors to choose Interventional Cardiology as their specialty, thus helping improve the odds to have equal career opportunities as men, in addition to increasing the awareness of the interventional and research community about gender-related disparities in the diagnosis and treatment of patients with cardiovascular diseases, supporting the routine participation of women in clinical trials to guarantee women are present in all aspects of scientific literature, be it in clinical trials, guidelines or regulatory processes.

Finally, going back to the remark made by the mini-editorial, sexism cannot bel et aside in the analysis as one for the factors that discourage women to take up medical careers. Struggling for equal conditions and payment must be more than an objective, since, as reported in the important Lancet editorial in February 2019, "Feminism is for everybody", gender equality is not only a matter of justice and rights, it is essential to produce better research and provide better patient care. It is the duty of medical societies to head this change of paradigma for opportunities to be akin to all, adding forces so that the well known female characteristic, caring for others, may benefit all of our patients.

Keywords

Cardiologists; Women; Medicine/trends; Leadership; Gender Identity; Interventionals.

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In the "The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine Updated Guidelines for Sports and Exercise Cardiology - 2019", the following names have been omitted from the publication: Japy Angelini Oliveira Filho, associate editor and fifth name in the authorship, from the Universidade Federal de São Paulo (UNIFESP); Antonio Claudio Lucas da Nobrega, from the Universidade Federal Fluminense; Luiz Gustavo Marin Emed, from the Hospital Cardiológico Costantini; and Roberto Vital, from the Comitê Paralímpico Brasileiro (CPB) and Universidade Federal do Rio Grande Do Norte (UFRN), inserted at the end of the authorship, in this order, and their respective institutions.

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In original article "The Olympic Experimental Gymnasium Program and its Association with the Prevalence of Cardiovascular Risk Factors in Adolescents: A Cross-Sectional Study", consider Carlos Scherr as the correct form for the name of the author Carlos Scheer.

July issue of 2019, vol. 113(1), pages 62-68

In figure 1 of the original article "The Profile of the Brazilian Cardiologist – A Sample of Members of the Brazilian Society of Cardiology" there is an error for the category of women with 0 children. Instead of 4.5% consider correct 45%.

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