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EDITORIAL

Digital Tools and Cardiovascular Rehabilitation

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Cardiovascular diseases are the leading cause of death worldwide. The inclusion of patients with such diseases in cardiovascular rehabilitation (CR) programs is an evidence-based conduct, since it has the potential to improve the individual's clinical condition and manage several risk factors associated with these diseases.[1] The association of aerobic and resistance exercises is a recommended combination in many CR programs. However, technological tools have been studied and used in order to increase the range of methods to optimize the results in the scenario of secondary prevention of cardiac diseases. In addition, combining modern strategies and conventional models can be a form of motivation for the patient by making CR interactive and funnier. In this case, virtual reality (VR) has also been used, including in our country.[2,3]

A study published by Silva et al.[4] in this issue of the International Journal of Cardiovascular Sciences compares the effects of conventional rehabilitation with VR on body composition and functional capacity of patients with cardiac diseases. It is a randomized controlled trial (RCT) in which 27 patients with cardiac diseases were enrolled to participate in an eight-week CR program. The sample was divided into two groups: a) conventional rehabilitation; b) rehabilitation with VR. The sessions lasted 60 minutes for both groups and the weekly frequency was twice a week. Conventional rehabilitation consisted of two parts: 25 minutes of aerobic exercise followed by 25 minutes of exercises with weights (upper and lower limbs). The intensity control during aerobic exercise was performed by monitoring the heart rate reserve determined by the Karvonen equation (50% and 80%). For resistance exercises, intensity was controlled by rating of perceived exertion (up to 13 on the Borg scale). Rehabilitation with VR was performed using Microsoft's Xbox 360 with Kinect. The twenty-five minutes of games consisted of exercises for the upper and lower limbs and 25 minutes of dancing with the Dance Central 3 game. In the first part, velcro weights were used in the ankle and dumbbells in the hands for the resistance exercises. The intensity was only controlled in the first part of the activity. Functional capacity was measured through a 6-minute walk test, which significantly increased in both groups. Similarly, both groups had the capillary blood glucose reduced. However, as opposed to what was expected, none of the two strategies significantly reduced fat percentage and body weight. In fact, the VR group presented a significant increase in these two variables compared to the conventional rehabilitation group.

The research question studied seems relevant and original and the results contribute to the knowledge on RC. However, this is an experiment with many limitations, some of which have been reported by the authors themselves. The sample size was small and the intervention period may not have been sufficient to promote positive results in the participants' body composition.[5,6] The absence of a proper nutritional assessment may have directly influenced the results on body composition.[7] In addition, it would be recommended to control exercise intensity and volume in order to quantify the isocaloric protocols for both groups. Therefore, the researchers did not control such measure and, because of this, each exercise protocol may have promoted unequal energy expenditures. Besides, controlling the heart rate of the VR group would have been important to respect the same training zones as the group exposed

Keywords

Cardiovascular Diseases/physiopathology; Virtual Reality; Cardiac Rehabilitation; Exercise Movement Techniques/methods; Quality of Life.

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to conventional rehabilitation.[8] Another strategy to control exercise intensity would be to quantify METS in the rehabilitation sessions. It should also be noted that the increase in fat percentage and fat weight may be related to the absence of nutritional counseling (food control was only performed through a reminder). Through nutritional counseling, the individuals participating in the experiment would have received proper guidance so they could change their eating habits rather than simply record their food intake.[9]

Despite some major biases and limitations, we believe the study has some merits. In a nutshell, the researchers entered in a field that mixes the present with the future, by showing in this RCT the effectiveness that a strategy of rehabilitation through VR has the potential of inducing similar gains to conventional CR on variables such as functional capacity and capillary blood glucose. In this regard, functional capacity is a powerful measure and is directly related to death by cardiovascular outcomes.[10] Improving the functional capacity of individuals with heart diseases can qualify the protocol that uses VR as a tool to be used in CR. Now, it is evident that studies with a more robust sample size, longer intervention period and with well-structured protocols are necessary to answer some questions about the real role of VR in the CR scenario.

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International Journal of Cardiovascular Sciences. 2018;31(6)560-561

EDITORIAL

To Occlude or not to Occlude. That is the Question

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In this issue of the International Journal of Cardiovascular Sciences, Madeira et al.[1] evaluated the influence of percutaneous left atrial appendage (LAA) occlusion device on left atrial (LA) function. They assessed several parameters of atrial function, including LA strain and strain rate by speckle-tracking echocardiography (STE) of 16 patients, 75% with permanent atrial fibrillation, undergoing percutaneous LAA closure. No differences were found in maximum and minimum LA volume or LA emptying fraction before and 3 months after the procedure. Similarly, no differences were noted in LA strain (13.7 ± 11.1 vs. 13.0 ± 8.8%; p = 0.63) or strain rate (1.06 ± 0.26 vs. 1.13 ± 0.34 s^{-1}; p = 0.38) in the reservoir phase. Based on those results, the authors concluded that LAA occlusion had no impact on LA function.

This is among the first studies to examine the effect of this procedure on LA function, for which the authors should be congratulated.

The LA function is difficult to be assessed in patients with atrial fibrillation, and an addition analysis of strain and strain rate can be of great help.

Since the concept of "strain" was introduced with respect to myocardial contraction[2] and in echocardiographic field,[3] many discoveries have been made in the areas of myocardial, valvular, congenital and coronary diseases. With these studies, the use of ventricular strain has become the standard of practice in cardiology today.

On the other hand, the study of atrial performance has been a great challenge in clinical cardiology in the past decade, and a hard task to accomplish in several imaging modalities, especially echocardiography and magnetic resonance imaging (MRI).

Due to its advantages over MRI, recent advances in the quantification of tissue motion, triggered by the discovery of speckle tracking imaging (STI), and the known value of 2D and Doppler echocardiography, echocardiography is undoubtedly the gold standard method to evaluate atrial anatomy and function in humans.

The results of the study by Madeira et al. are in agreement with the first rule of medicine in patient care: "first do no harm - primum non nocere" (Thomas Inman,1860)[4]. The authors demonstrated that the LAA implantation in patients with high embolic risk, expressed by a median CHA_2DS_2-VASc score of 5 and HAS-BLED score of 3, did not negatively affect their left atrial function.

Despite these results, we must view them with caution, since they apparently apply to a population of elderly patients with well-preserved left ventricular function and poor atrial function at baseline. The average longitudinal strain was ~13% in the reservoir phase, which is very low and is similar to what is seen in heart failure patients.

In a study performed in our institution, in patients admitted to the emergency department for heart failure,[5,6] patients with new or worsening heart failure symptoms, and LA strain lower than 11.7% in absolute values had higher chance of developing a short-term cardiac event.

In another study,[7] in a population of 286 outpatients with heart failure and reduced ejection fraction, the authors measured global peak atrial longitudinal strain at the end of the reservoir phase and concluded that the global peak atrial longitudinal strain, especially those with strain values bellow 12,5%, were among those with a higher incidence of hard cardiac events.

Keywords

Atrial Fibrillation. Atrial Appendage; Balloon Device; Diagnosis Imaging; Echocardiography / methods

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Therefore, the study by Madeira et al. adds to the current literature, but we must understand that their results are limited to the studied population, i.e., a group of subjects with severe atrial dysfunction, in whom no significant worsening is expected.

Moreover, these results suggest, at best, what can be expected to occur at short term (3 months), in elderly patients with well-preserved left ventricular function. Nevertheless, this opens the possibility of studying the effect of percutaneous LAA on LA function in younger subjects with many forms of cardiac diseases.

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International Journal of Cardiovascular Sciences. 2018;31(6)562-568

ORIGINAL ARTICLE

Option for the Radial *versus* Femoral Access in Coronary Intervention in Acute Coronary Syndromes: A Risk-Treatment Paradox

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Abstract

Background: In coronary procedures, although the radial approach protects patients from hemorrhagic complications, it is technically more complex than the femoral approach.

Objectives: To test the hypothesis that the radial approach is the procedure of choice in ACS patients due to the high risk of bleeding; and to identify independent predictors of the choice for radial access.

Methods: Patients admitted for ACS who underwent invasive coronary procedure were included. We registered the type of access (femoral or radial) chosen by the physician for the first angiography; the investigators did not interfere with this choosing process. Student's t-test was used for comparisons between the CRUSADE and ACUITY scores. Predictors of radial access were compared between the groups. Statistical significance was defined by $p < 0,05$.

Results: Radial access was chosen in 67% of 347 consecutive patients. Patients who underwent radial approach had lower risk of bleeding determined by CRUSADE (30 ± 14 vs. 37 ± 15; $p < 0.001$) as compared with femoral access. In multivariate analysis, four variables were identified as independent predictors negatively associated with radial access – age (OR = 0.98; 95%CI = 0.96 – 0.99), creatinine (OR = 0.54; 95%CI = 0.3 – 0.98), signs of left ventricular failure (OR = 0.45; 95% CI = 0.22 – 0.92) and previous CABG (OR = 0.022; 95%CI = 0.003 – 0.166).

Conclusion: The propensity to choose radial over femoral access in coronary intervention was not primarily influenced by patients' bleeding risk. Predictors of this decision, identified in the study, indicated less complex patients, suggesting that the difficulty in performing the technique was a stronger determinant than its potential antihemorrhagic effect. (Int J Cardiovasc Sci. 2018;31(6)562-568)

Keywords: Angioplasty; Catheterism; Coronary Artery Disease; Percutaneous Coronary Intervention; Radial Artery; Femoral Artery; Stents.

Introduction

Percutaneous coronary intervention (PCI) is the main revascularization procedure performed in acute coronary syndromes (ACS) due to its efficacy in preventing recurrent coronary events and less invasiveness as compared with surgical procedures.[1] However, PCI is not free of complications, with access site bleeding as the most common adverse effect.[2]

Femoral access has been the predominant site for PCI for decades, due to its relative feasibility to perform. Radial access, in turn, has shown to be efficient in preventing bleeding and therefore has become the preferred procedure in the last years.[2-5] The radial approach, however, is a more complex technique, requiring greater technical ability and experience.[6] Thus, considering the higher feasibility and reproducibility of the femoral access and the lower risk of bleeding of the radial access, both techniques are available for PCI.

Efficacy is the intrinsic property of the treatment, described in the ideal world of clinical trials, in which intervention occurs in a random fashion, excluding

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the effect of medical decision making. Effectiveness represents the performance of the therapy in the real world, in which allocation depends on the medical decision making. Effectiveness is then optimized when allocation of treatment prioritizes patients at high risk for the outcome expected to be prevented by the intervention in question. Radial access would be more effective for patients at higher risk of bleeding who are allocated to this intervention. In a recent study, Wimmer et al.,[7] reported a risk-treatment paradox, in which the radial approach was less frequent in patients at higher bleeding risk than in those at lower risk.

The present study aimed to explore this phenomenon. Using the Prospective Registry of ACS, we tested whether the radial access was the first choice for PCI in patients at high risk of bleeding, which was evaluated by the CRUSADE[8] and the ACUITY[9] scores. Also, we identified predictors of radial access and developed a propensity score of representative, predicting factors of medical decision making.

Methods

Sample selection

We included in the study patients consecutively admitted to the coronary unit of a tertiary hospital between December 2011 and January 2016 with diagnosis of ACS (unstable angina or myocardial infarction) with previous diagnostic or therapeutic invasive cardiac procedures. ACS was defined as precordial discomfort in the 48 hours prior to admission, associated with at least one of the following criteria: 1) myocardial necrosis markers, defined as troponin T ≥ 0.01 ug/L or troponin I > 0.034 g/L, corresponding to values above the 99th percentile;[10] 2) ischemic electrocardiographic changes, consisting of T-wave inversion (≥ 0.1 mV) or ST-segment changes (≥ 0.05 mV); 3) previous coronary artery disease, defined as previous Q-wave myocardial infarction or coronary obstruction ≥ 70% confirmed by angiography. Patients who declined to participate were excluded from the study. The study protocol was in accordance with the Helsinki declaration and approved by the local ethics committee. All patients signed the informed consent form.

Study protocol

This is a registry of ACS, composed by collection of prospective data. Variables of these data were used for calculation of bleeding scores. Access site for the first arterial puncture in the first (diagnostic or therapeutic) coronary procedure was systematically registered on data collection form. Major bleeding was defined as BARC (Bleeding Academic Research Consortium) type 3 or type 5.[11] The criteria for type 3 bleeding were as follow – decrease in hemoglobin of 3-5 g/dL or need for transfusion (type 3a); hemoglobin drop ≥ 5 g/dL, cardiac tamponade, requirement of surgical intervention or hemodynamic instability for control (type 3b); and intracranial or intraocular bleed (type 3c). Type 5 bleeding is a definite fatal bleeding (direct causal relationship, type 5a) or a probable fatal bleeding (indirect causal relationship, type 5b). Minor bleeding (type 1 or type 2) or cardiac surgery-related bleeding (type 4) were not included in the analysis.

Bleeding risk scores

The CRUSADE score was used to evaluate the baseline risk of bleeding. This instrument is composed of eight variables – four categorical variables (female sex, signs of heart failure, diabetes and peripheral arterial disease) and four numerical variables (baseline hematocrit, creatinine clearance, heart rate, and systolic blood pressure). The point scores were calculated based on the value of each variable; the sum of all variables indicated predetermined levels (low, intermediate and high).[8] Bleeding risk was also confirmed by the ACUITY score, composed of seven variables – four categorical variables (female sex, anemia, bivalirudin therapy and type of ACS) and three numerical variables (age, creatinine clearance, white blood cell count).[9]

Statistical analysis

Although the collection of the variables included in the primary analysis was predetermined, the association between bleeding score and the access route was a posteriori exploratory analysis. Nevertheless, we estimated that a minimum of 100 patients with radial or femoral access would allow the insertion of 10 covariables into the propensity model, based on the logistic regression principle, which establishes the need of at least 10 patients with the outcome in question for each covariable.[12]

Numerical variables were described as mean and standard deviation or median and interquartile range, as appropriate. Normality of numerical variables was verified by the Shapiro-Wilk test. Categorical variables

were described as absolute and relative frequencies. The CRUDADE and ACUITY scores were compared between radial and femoral groups by the unpaired Student's t test. Predictors of the radial access were compared between both groups by the chi-square test or the unpaired Student's t test. Variables with $p < 0.10$ in the univariate analysis were inserted into the logistic regression, with radial access as dependent variable; the odds ratio of each predictor was determined. A $p < 0.05$ was set as statistically significant in all tests. The analysis was performed using the SPSS software version 21.

Results

Sample description

A total of 347 patients were included; mean age was 63 ± 14 years, 63% were men, 27% of them were hospitalized for ST-segment elevation myocardial infarction (the others had ASC with non-ST-segment elevation myocardial infarction). Invasive coronary angiography showed that 38% of patients had three-vessel disease or left coronary artery occlusion. Mean GRACE score was 119 ± 37, compatible with an intermediate risk of cardiovascular events. Mean CRUSADE score was 32 ± 15 and mean ACUITY score was 14 ± 7, both corresponding to moderate risk of bleeding according to validation studies.[8,9] Bleeding occurred in 64 patients (18%) and major bleeding in 12 (3.5%). The CRUSADE score was higher in patients with major bleeding (47 ± 17 *versus* 32 ± 15; p = 0.01), confirming its predictive value. The same was observed with the ACUITY score (20 ± 9 *versus* 14 ± 7; p = 0.02). Patients treated with the radial approach showed a higher incidence of major bleeding as compared with those treated with femoral access (1% *versus* 8%; p < 0.01).

Risk of bleeding and the choice for the radial access

The radial artery was chosen as the primary vascular access in 64% of patients, whereas the femoral access was chosen for the others. The mean CRUSADE score showed that patients treated with the radial access showed a lower risk of bleeding (30 ± 14) compared with those treated with femoral access (37 ± 15; p < 0.001) (Figure 1). According to the literature, these values corresponded to a bleeding risk of 5.5% and 8.6%, respectively.[8]

Analysis of the ACUITY score corroborated the fact that patients treated with radial access had a higher risk of bleeding than patients treated with femoral access (13 ± 6 *versus* 15 ± 7; p = 0.002). These values correspond to a bleeding risk of 3.3% and 6.9%, respectively.[9]

Propensity to choose the radial access

With respect to general characteristics of patients, those with a radial access were younger (61 ± 13 years), compared with patients with femoral access (66 ± 14 years; p < 0.001). Sex, self-reported race, weight, height,

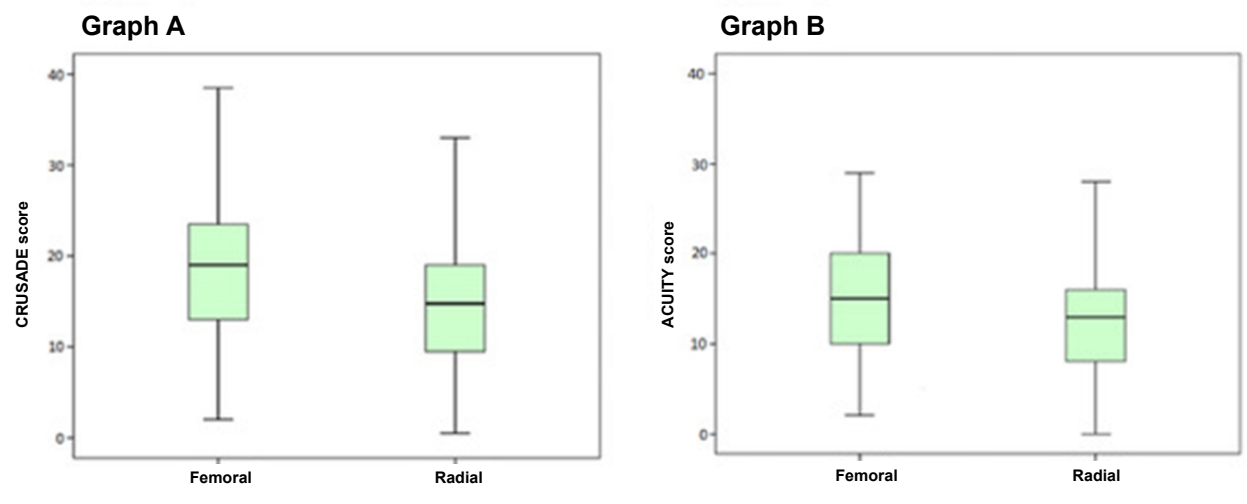

Figure 01 - Box-plot comparing the CRUSADE score (Graph A) with the ACUITY score (Graph B) values between radial access and femoral access groups.

body mass index and body surface were not different between the groups (Table 1).

Regarding ACS presentation, compared with patients treated with femoral approach, patients with radial access had a lower mean GRACE score (114 ± 34 *versus* 128 ± 41; p < 0,001), better renal function according to creatinine levels (1.0 ± 0.3 *versus* 1.2 ± 1.1; p < 0.001) and lower prevalence of signs of left ventricular failure (Killip > 1: 8% *versus* 19%; p < 0.003). The type of ACS, heart rate, systolic arterial pressure, positive troponin, electrocardiographic ischemia, three-vessel disease, coronary angiography showing involvement of the trunk and hemoglobin levels at admission were not different between the groups (Table 1).

Regarding comorbidities, there was a lower prevalence of previous coronary disease in patients treated with radial access (24% *versus* 46%, p < 0.001). Previous history of stroke (3% *versus* 9%; p < 0.021) and myocardial

Table 1 - Comparison of clinical characteristics of the radial and femoral access groups

Variables	Radial (n = 223)	Femoral (n = 124)	p-value
Female sex	85 (38%)	38 (31%)	0.62†
Age	61 ± 13	66 ± 14	0.001*
Weight	78 ± 13	76 ± 18	0.27*
Height	1.67 ± 0.1	1.65 ± 0.9	0.12*
Body mass index (kg/m²)	27.9 ± 4.5	27.6 ± 5.9	0.57*
Body surface (m²)	1.89 ± 0.2	1.86 ± 0.2	0.25*
Black/pardo race	132 (63%)	72 (62%)	0.88†
ST-segment elevation myocardial infarction	63 (29%)	32 (26%)	0.62†
Positive troponin	171 (77%)	95 (77%)	0.98†
Ischemic electrocardiography	88 (40%)	50 (40%)	0.87†
Three-vessel disease or left coronary trunk	42 (19%)	28 (23%)	0.1†
Signs of left ventricular failure	18 (8%)	23 (19%)	0.003†
Heart rate (bpm)	79 ± 16	82 ± 19	0.13*
Systolic arterial pressure (mmHg)	153 ± 30	154 ± 34	0.7*
Creatinine	1.0 ± 0.3	1.2 ± 1.1	0.001*
GRACE score	113.9 ± 33.5	128.1 ± 41	0.001*
Hemoglobin	14.0 ± 1.8	13.8 ± 1.9	0.29*
Diabetes mellitus	76 (34%)	48 (39%)	0.34†
Peripheral arterial occlusive disease	9 (4%)	11 (9%)	0.1†
Previous coronary disease	53 (24%)	57 (46%)	0.001†
Previous revascularization	1 (0.5%)	24 (19.5%)	0.001†
Stroke	7 (3%)	11 (9%)	0.021†
Smoking	23 (10%)	8 (6.5%)	0.23†
Previous heart failure	7 (3%)	7 (6%)	0.25†
Previous bleeding	2 (5%)	1 (8%)	0.65†

**Student's t-test; †chi-square test.*

revascularization surgery (0.5% *versus* 19.5%; p < 0.001) was also different between the groups, whereas no difference was observed in the presence of diabetes mellitus, peripheral artery disease, smoking, previous history of heart failure or bleeding (Table 1).

The variables described above as significant in the univariate analysis were inserted into the logistic regression model, with radial access as dependent variable. In this analysis, the variables with independent association with radial access were age (OR = 0.98; 95%CI = 0.96 – 0.99), creatinine (OR = 0.54; 95%CI = 0.3 – 0.98), signs of left ventricular failure (OR = 0.45; 95%CI = 0.22 – 0.92) and previous myocardial revascularization surgery (OR = 0.022; 95%CI = 0.003 – 0.16), all with a discouraging effect on the use of the radial access (Table 2).

Discussion

In the present study, patients treated with radial approach for coronary procedures had lower baseline risk of bleeding as compared with the femoral access group. This finding contrasts with the logical expectation that the access related to lower incidence of bleeding is the one more commonly used in patients at higher risk for this complication, characterizing a risk-treatment paradox.

This paradoxical result raises the need for discussing potential causes of this phenomenon in a critical perspective of the cognitive process of the medical decision-making process. This, in turn, is presumedly influenced by several factors. One may expect that such decision is based on the main objective of the radial approach, i.e. to prevent bleeding; however, other factors may be determinant in this process. Interventionists have a natural sense of achieving success with their techniques. By intuition, the chance of success is expected to be lower from procedures considered technically more difficult. Hence, the operator tends to avoid the access considered more difficult in attempt to reduce the challenge. Nevertheless, that would be a biased view, since the risk of failure in the radial approach is lower than the risk of increased bleeding in femoral approach (eight times greater in the present study). Besides, a migration from radial to femoral vascular access when needed is also possible. Although the results of this study were exploratory, they suggest that the physician's decision may be more strongly influenced by a sense of self-protection rather than a protection of the treated patients. This is quite possible, since while bleeding tends to be seen as a natural complication, failure in the intervention tends to be considered a medical failure. Further studies should explore these potential mechanisms.

Intuitive estimation of probabilities in conditions of uncertainties is influenced by cognitive biases.[13-15] For example, when we opt to treat less complex patients, we are seeking cognitive comfort; and in search of this, we underestimate the risk of more complex patients, intuitively reducing the magnitude of the benefits that these patients could obtain from the procedure. In consequence, patients with more complex conditions receive less treatment than needed. This generates a risk-treatment paradox, typical of this intuitive process of decision making.

To understand the mechanisms of this paradox, we built a propensity model to identify potential determinants to the choice for the radial access. In this model, we identified variables that had a negative association with the radial access only, not including variables that may increase the chance for this choice. This propensity score allows us to make interpretations of the decision-making process. It is possible that our interventionist had the radial access as the first-choice option (in fact, this approach was the most frequent in the study) and then used other criteria for secondary options. These criteria were represented in our model by independent predictors of the radial access. Analysis of these predictors showed that all of them concerned more complex patients, with predictors representing each of the domains: patient's baseline constitution (age), comorbidities (creatinine), severity of ACS presentation (acute heart failure) and previous history (surgery). These observations suggest that the physician

Table 2 - Multivariate analysis that generated the propensity model of radial access

	Odds ratio	95% CI	p-value
Creatinine	0.54	0.3 – 0.98	0.041*
Age	0.98	0.96 – 0.99	0.037*
Killip class > 1	0.45	0.22 – 0.92	0.029
Previous revascularization	0.022	0.003 – 0.166	0.001
Stroke	0.366	0.13 – 1.07	0.066
Previous coronary disease	0.75	0.43 – 1.31	0.313
GRACE score	1.0	0.99 – 1.01	0.543*

**Numerical variables.*

tends to avoid the radial access as the patient's condition gets more severe, disregarding patient's higher risk of bleeding. On the other hand, we should recognize that this is not a conscious choice.

The risk-treatment paradox has been described in situations in which the most effective approach is also the most complex. For example, in atrial fibrillation, anticoagulant therapy is more frequently provided to patients with a low risk of embolic events than patients at high risk.[16] In the ACS scenario also, there has been no association between risk and the choice for an invasive strategy.[17,18] In PCI, the prospective, observational, multicenter study by Wimmer et al.,[7] also reported this phenomenon by showing that patients at higher risk of femoral access site complications were less susceptible of receiving the radial access approach. An additional contribution of our study is the identification of independent predictors involved in the generation of this paradox. Other previous studies[19,20] evaluated the predictors involved in the choice for the radial access, however, in none of them a multivariate analysis was performed to minimize confounding bias.

Once the presence of the risk-treatment paradox is detected in certain situation, a possible adjustment strategy is the use of probabilistic models to estimate the risk.[21,22] In other words, the use of scores for allocation of more complex resources induces the physician to make decisions based on probability. In case of bleeding in ACS, the best validated models are the CRUSADE[8] and the ACUITY scores.[9]

Our findings were obtained in a single center, in which five interventional cardiologists were working during the study period. Thus, we must recognize the limited external validation of these findings. Nevertheless, the real aim of this study was not to describe interventionists' behavior, since in fact it may vary considerably among regions. Actually, the impact of the present study is not the inference of the prevalence of a phenomenon, but rather to call attention to a situation in which the decision-making process may suffer a risk-treatment paradox.

A natural thought would be to suggest an evaluation of medical practice variation, to verify the uniformity of this phenomenon. However, we avoided this analysis, since in the Registry design, the unit of analysis was the patient who was treated and not the physician himself, whose consent to be observed was not sought. We also believe that individual evaluation of each of the five interventionists involved in the study would not be accurate due to the sample size of the study.

Conclusion

In this exploratory study, we observed that the choice for the radial access was not primarily influenced by its potential benefit on bleeding prevention, since baseline bleeding risk was negatively associated with this access, characterizing a risk-treatment paradox. Determinants of the preference for the radial access were variables that connote patients' clinical status/severity, suggesting that in highly complex patients, the access is primarily chosen for its easiness and not for its antihemorrhagic effect.

Author contributions

Conception and design of the research: Lacerda YF, Sá NC, Suerdieck JG, Viana MS, Fonseca L, Lopes F, Rabelo MMN, Correia LCL. Acquisition of data: Lacerda YF, Sá NC, Suerdieck JG, Sodré GS. Analysis and interpretation of the data: Lacerda YF, Suerdieck JG, Viana MS, Sodré GS, Fonseca L, Rabelo MMN, Correia LCL. Statistical analysis: Suerdieck JG, Viana MS, Sodré GS, Fonseca L, Lopes F, Correia LCL. Obtaining financing: Lacerda YF. Writing of the manuscript: Lacerda YF, Suerdieck JG, Fonseca L. Critical revision of the manuscript for intellectual content: Lacerda YF, Sá NC, Lopes F, Rabelo MMN, Correia LCL. Supervision / as the major investigador: Lacerda YF, Sá NC, Rabelo MMN, Correia LCL.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital São Rafael* under the protocol number 35/11. 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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ORIGINAL ARTICLE

Does Percutaneous Left Atrial Appendage Closure Affect Left Atrial Performance?

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Abstract

Background: Percutaneous left atrial appendage (LAA) occlusion may be an alternative therapy for atrial fibrillation (AF) patients with contraindication for anti-coagulation therapy. However, the influence of LAA occlusion on left atrial (LA) performance has not been studied.

Objective: Our aim was to evaluate the influence of percutaneous LAA occlusion device on LA function by transthoracic echocardiography plus speckle-tracking echocardiography (STE).

Methods: We included 16 patients undergoing percutaneous LAA closure with adequate echocardiographic window for the study of LA mechanics. Transthoracic echocardiography was performed before and after the procedure. LA volumes were calculated using the biplane method, and LA mechanics were assessed using STE. The analysis focused on the LA reservoir phase strain and strain rate.

Results: Seventy-five percent of patients had permanent atrial fibrillation. Embolic and bleeding risk scores used were CHA_2DS_2-VASc [median of 4-5] and HAS-BLED [median of 2-3]. Major bleeding (62%) was the most common indication for the procedure. Percutaneous LAA closure was performed successfully in all patients, without major complications. No differences were found in maximum LA volume (44 ± 11 vs. 46 ± 13 mL/m^2; p = 0.54), minimum LA volume (32 ± 8 vs. 37 ± 14 mL/m^2; p = 0.09) or LA emptying fraction (26 ± 17 vs. 21 ± 14%; p = 0.33) before and after the procedure. Similarly, no differences were noted in left atrial strain (13.7 ± 11.1 vs. 13.0 ± 8.8%; p = 0.63) or strain rate (1.06 ± 0.26 vs. 1.13 ± 0.34 s^{-1}; p = 0.38) in the reservoir phase.

Conclusions: Our data suggest that percutaneous LAA closure does not affect LA reservoir function. (Int J Cardiovasc Sci. 2018;31(6)569-577)

Keywords: Atrial Fibrillation; Atrial Appendage; Heart Atria; Echocardiography, Transthoracic.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia,[1] with a current estimated prevalence of 1.5% to 2%.[2] It is considered a major cause of systemic embolism, increasing the risk for ischemic stroke by 5 times.[2,3] Oral anticoagulation has been shown to effectively reduce the risk for stroke in patients with atrial fibrillation and is one of the cornerstones of management.[2] However, a significant proportion (30% - 50%) of eligible patients do not receive oral anticoagulation due to the presence of absolute contraindications or a perceived high risk of bleeding.[3] Several studies have shown that, in patients with nonvalvular atrial fibrillation, 90% of thrombus formation occurs in the left atrial appendage (LAA).[4,5] Therefore, devices for LAA closure have been developed as an alternative to oral anticoagulation in patients at high risk for stroke with contraindications to anticoagulation therapy.[6] Recently, the non-inferiority of LAA exclusion over warfarin for stroke prevention was demonstrated in patients with nonvalvular atrial fibrillation.[7]

It was previously believed that the LAA was a vestigial structure with no meaningful function. LAA is now thought to play an important role in normal cardiac

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hemodynamics.[8] The appendage is more compliant than the left atrium, acting as a reservoir to attenuate the rise in intra-atrial pressure in response to various hemodynamic factors.[9] Surgical clamping or removal of the LAA has been shown to cause an immediate increase in left atrial pressure, left atrial size, and pulmonary- and mitral-inflow velocities.[10] However, both the relative contribution of appendage distensibility to the passive elastic-chamber properties of the left atrium and the physiological and hemodynamic importance of the LAA are currently uncertain. Furthermore, the influence of the LAA occlusion device on left atrial performance has not yet been defined.

Two-dimensional speckle-tracking echocardiography (2D-STE) is a recently developed, angle-independent, semiautomated technique used to evaluate the myocardium.[11] It uses standard B-mode images to track blocks of speckles from frame to frame, and measures myocardial lengthening and shortening relative to the baseline – the Lagrangian method. 2D-STE provides local myocardial information from which displacement, velocity, strain, and strain rate can be derived, allowing an accurate assessment of longitudinal, radial, and circumferential myocardial mechanics.[11] In recent years, left atrial mechanics have been used as a surrogate for left atrial performance, which is influenced by the left atrial wall properties, left atrial volume, and left atrial pressure, and also by the left ventricular longitudinal systolic function.[12] Measurements of left atrial strain (ƐR) and strain rate (SR_R) during the reservoir phase can be used to describe atrial function physiology and are sensitive to detect early functional remodeling before anatomical changes occur.[12,13]

We hypothesized that left atrial function, assessed by echocardiographic parameters and 2D-STE, would decrease after percutaneous LAA closure. Therefore, our aim was to evaluate the influence of the LAA closure device on left atrial physiology.

Methods

Patients

Twenty-five patients with non-valvular atrial fibrillation and a high risk for stroke with a CHA_2DS_2-VASc Score of ≥ 1 admitted to our centre for percutaneous LAA closure between August of 2010 and August of 2015 were enrolled in this retrospective study. Nine patients were excluded due to lack of adequate echocardiographic evaluation before or after the procedure or poor echocardiographic window for the evaluation of left atrial mechanics.

Referral indications for percutaneous LAA closure were contra-indication for long-term oral anticoagulation, bleeding events during oral anticoagulation, labile international normalized ratio (INR) or embolic events despite proper anticoagulation.

Clinical data included past medical history, current medication, the CHA_2DS_2-VASc and HAS-BLED scores, and diagnostic evaluation by routine laboratory testing, electrocardiography, and echocardiography.

Sixteen patients with good echocardiographic window for assessment of the left atrial mechanics were included in our study.

The study was approved by the ethics committee of our institution.

Echocardiographic evaluation

Echocardiography was performed on the day before and 3 months after percutaneous closure of the LAA.

Echocardiographic examinations were performed using an ultrasound system (Vivid 7, General Electric®, Horten, Norway) and tissue harmonic imaging at 1.7/3.4 MHz. A complete echocardiographic study was performed using standard views according to current guidelines.[14] Three consecutive heart cycles were acquired for quantification of the left atrial size and 2D-STE analysis for sinus rhythm patients, and five consecutive heart cycles were obtained for atrial fibrillation patients.

Left atrial volume was assessed by the biplane method of disks from the apical 4- and 2-chamber views and the measurements were indexed to the body surface area according to established recommendations.[15] Minimum left atrial volume was measured at left ventricular end-diastolic volume, and maximum left atrial volume at end-systole. Left atrial emptying fraction was calculated as (maximum left atrial volume - maximum left atrial volume)/ maximum left atrial volume.[15]

The 2D-STE method was used to calculate regional and global longitudinal ƐR and SR_R (Figure 1). A minimum frame rate of 60 frames/sec was required for a reliable operation of the program. The recordings were processed using an acoustic-tracking dedicated software (EchoPAQ 9.0, GE Healthcare®, Horten, Norway), which allowed for an off-line semi-automated analysis of speckle-based strain. Left atrial endocardial surface was manually

traced in end-systole in both four- and two-chamber views by a point-and-click approach. An epicardial surface tracing was then automatically generated by the system, generating the region of interest (ROI). For definition of the ROI at the discontinuity of the left atrial wall (corresponding to pulmonary veins and left atrial appendage), the limit of left atrial endocardial and epicardial surfaces at the junction of these structures was extrapolated. After manual adjustment of ROI width and shape to ensure optimal tracking, the software divided the ROI into six segments (basal, middle and apical segments of the atrial septum and lateral wall), and the tracking quality of each segment was automatically scored as either acceptable or non-acceptable, with possible further manual correction. Segments from which good quality images could not be obtained were rejected by the software and excluded from the analysis. In subjects with good quality images, a total of twelve segments were analyzed. The software displayed peak longitudinal ƐR and strain rate for each of the twelve segments and the average global strain. Peak ƐR were expressed in percentages and SR_R in s^{-1}. Since left atrial wall strain is reliably imaged and is not constrained by other cardiac chambers, recent consensus of imaging for evaluation of atrial fibrillation patients recommend the evaluation of this parameter rather than global ƐR.[16] Therefore, we also performed a comparison between left atrial lateral wall strain and SR_R at baseline and after device implantation. Since we included patients with atrial fibrillation and sinus rhythm, we used the first left ventricular systolic frame as the frame of interest – QRS timed analysis.

LAA closure procedure

LAA closure device was implanted in the catheterization laboratory. The device used was an Amplatzer® (St. Jude Medical, St. Paul, Minnesota, USA) and was delivered

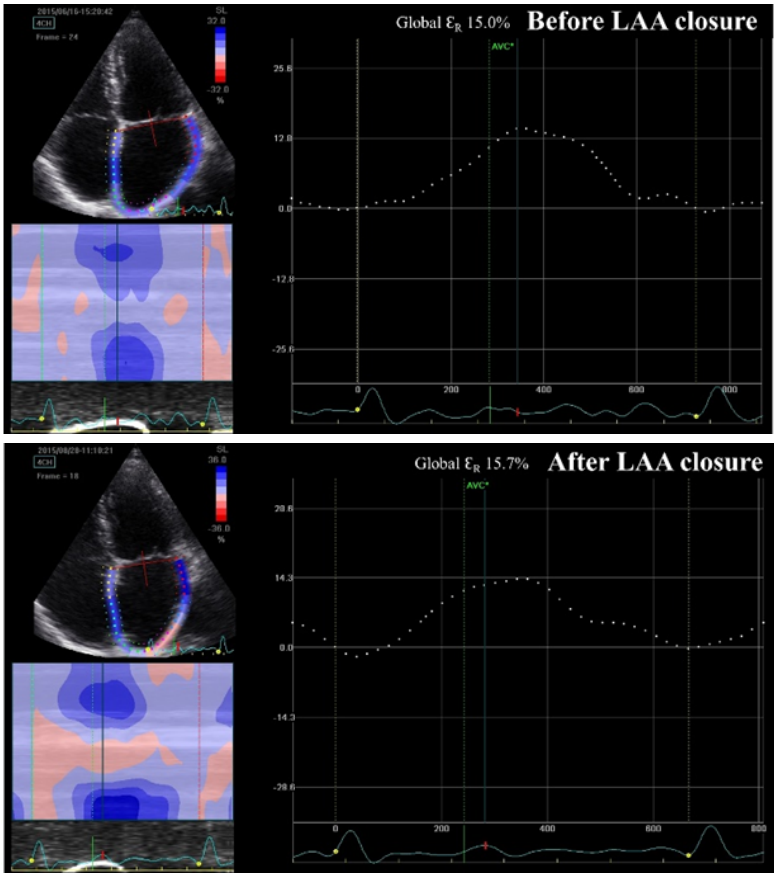

Figure 1 - Global left atrial strain during reservoir phase (ƐR) before and after percutaneous closure of the left atrial appendage (LAA). Differences between baseline and post-LAA occlusion device implantation data were analysed by paired sample t-test.

through an appropriate sheath depending on the size of the selected occluder through a puncture in the femoral vein. Deployment and position of the device were controlled by fluoroscopy, and by periprocedural transesophageal or intracardiac echocardiography. LAA was reached through a transseptal puncture. Decision on device size was made upon anatomical morphology, and measurements in echocardiography and fluoroscopy. Oral anticoagulation, if present, was discontinued 48 hours prior to the procedure. During procedure, heparin was administered with an activated clotting time of 250s. Dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg was recommended for 1 month, followed by long-term antiplatelet therapy with aspirin 100 mg daily. No oral anticoagulation was recommended after device implantation.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of the continuous variables. In the overall sample, all variables were normally distributed, except for ƐR and follow-up time; and when patients were separated by group (no change and decrease of ƐR and SR_R), the variables were not normally distributed. According to distribution normality, continuous data were presented as mean and standard deviation or as median and interquartile range. Quantitative variables with normal distribution were compared by the t-test and quantitative variables without normal distribution by the Mann-Whitney test. Qualitative variables were compared using the chi-square test. Differences between baseline and post-implantation of the LAA occlusion device were analysed by the paired sample t-test.

Statistical analysis was carried out with SPSS®15 and GraphPad Prism® 6.05. A two-tailed p value < 0.05 was considered statistically significant.

Results

Population characteristics

Mean age of our sample was 71 ± 9 years, with male predominance (63%). Seventy-five percent of patients had permanent atrial fibrillation. There was no history of percutaneous atrial fibrillation ablation attempt or surgical Maze procedure. Our population had a high embolic and bleeding risk, expressed by a median CHA_2DS_2-VASc score of 5 [4-5] and HAS-BLED score of 3 [2-3].

Major bleeding (62%) was the most common indication for the procedure, followed by labile INR (19%), embolic events despite anticoagulation (13%), and poor compliance with anticoagulation medication (6%). Percutaneous LAA closure was performed successfully in all patients using the cardiac plug device (size, 24 ± 2 mm), without any major complications during or after the procedure.

Characteristics of the study population are summarized in Table 1.

LA volume and emptying fraction

Maximum and minimum values of left atrial volume and the left atrial emptying fraction before and after the procedure are represented in Figure 2 and Figure 3, respectively. No differences were found in maximum left atrial volume (44 ± 11 vs. 46 ± 13 mL/m²; p = 0.54), minimum left atrial volume (32 ± 8 vs. 37 ± 14 mL/m²; p = 0.09), or the left atrial emptying fraction (26 ± 17%

Table 1 - General characteristics of the study group (n = 16)

Age, years	71 ± 9
Male sex	10/16 (63%)
Atrial fibrillation	
Permanent	12/16 (75%)
Persistent	1/16 (6%)
Paroxysmal	3/16 (19%)
CHA_2DS_2-VASc score	5 [4 - 5]
HAS-BLED score	3 [2 - 3]
Indication for LAA closure	
Major bleeding	10/16 (63%)
Labile INR	3/16 (19%)
Embolic event despite anticoagulation	2/16 (13%)
Poor compliance with anticoagulation	1/16 (6%)
Cardiac plug device size, mm	24 ± 2
Left ventricular ejection fraction	
Normal range	13/16 (81%)
Mildly abnormal	3/16 (19%)

LAA: left atrial appendage; INR: international normalized ratio. Data expressed as mean and standard deviation, percentage or median and interquartile range.

vs. 21 ± 14%; p = 0.33) after the intervention compared with the baseline values.

Left atrium reservoir ƐR and SR_R

Global and regional peak ƐR and SR_R of the 12 segments before and months after percutaneous closure of the LAA are listed in Table 2. Similar values of ƐR (10.1 [8.1–14.7] vs. 12.7 [5.4–16.5]%; p = 0.81) and SR_R (1.06 ± 0.26 vs. 1.13 ± 0.34 s^{-1}; p = 0.38) were observed before and after the procedure (Figure 4).

Assessment of left atrial lateral wall revealed similar ƐR (11.0 [6.5–19.8]% vs. 8.2 [2.7–15.9]%; p = 0.60) and SR_R (1.01 [0.78–1.54] vs. 1.02 [0.85–1.56] s^{-1}; p = 0.75) before and after the procedure.

In 44% of patients, there was a decrease in ƐR. There were no differences regarding patient age, baseline left atrial volume, left atrial emptying fraction, ƐR, SR_R, CHA_2DS_2-VASc or HAS-BLED scores, cardiac-plug device size, or incidence of cardiovascular adverse events during follow-up between patients with decreased and unaltered postoperative ƐR values (Table 3).

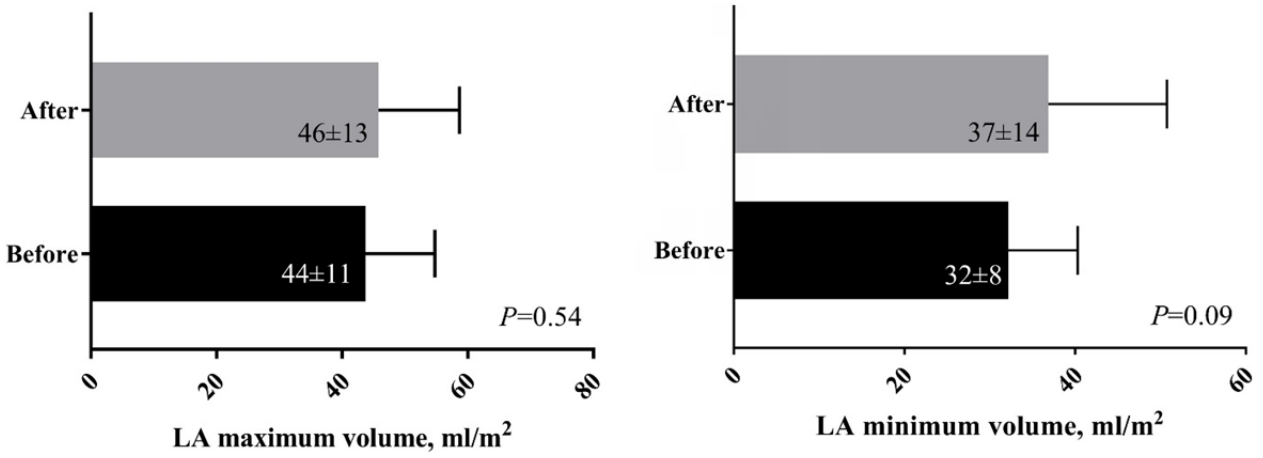

Figure 2 - Maximum and minimum volume of the left atrium before and after percutaneous closure of the left atrial appendage (LAA). Differences between baseline and post-LAA occlusion device implantation data were analysed by paired sample t-test.

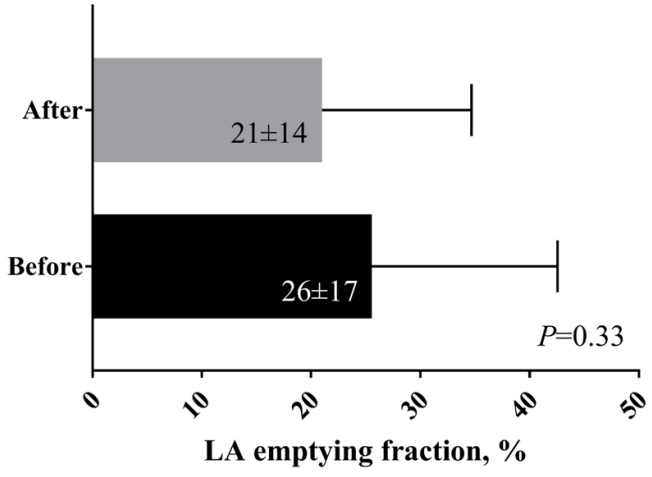

Figure 3 - Left atrial emptying fraction before and after percutaneous closure of the left atrial appendage (LAA). Differences between baseline and post-LAA occlusion device implantation data were analysed by paired sample t-test.

Table 2 - Global and regional peak left atrial strain (ƐR) and strain rate (SR_R) during reservoir phase of the 12 segments before and after percutaneous closure of the left atrial appendage (LAA)

	Basal	After LAA occlusion	p
Global ƐR, %	10.1 [8.1 - 14.7]	12.7 [5.4 - 16.5]	0.81
Lateral basal ƐR, %	18.6 [10.5 - 28.8]	17.6 [11.0 - 22.3]	0.49
Lateral mid ƐR, %	10.1 [6.0 - 18.8]	9.0 [4.4 - 16.4]	0.40
Lateral apical ƐR, %	7.1 [3.9 - 13.6]	5.9 [2.0 - 15.7]	0.84
Septal apical ƐR, %	9.1 [4.9 - 18.4]	8.5 [3.9 - 16.8]	0.38
Septal mid ƐR, %	12.0 [8.1 - 17.5]	9.8 [3.2 - 22.5]	0.86
Septal basal ƐR, %	13.2 [5.2 - 21.8]	12.2 [2.7 - 23.6]	0.84
Global SR_R, s^{-1}	1.06 ± 0.26	1.13 ± 0.34	0.38
Lateral basal SR_R, s^{-1}	1.14 ± 0.49	1.20 ± 0.62	0.60
Lateral mid SR_R, s^{-1}	1.04 ± 0.42	1.10 ± 0.56	0.61
Lateral apical SR_R, s^{-1}	1.18 ± 0.50	1.05 ± 0.48	0.41
Septal apical SR_R, s^{-1}	1.00 ± 0.54	1.10 ± 0.45	0.50
Septal mid SR_R, s^{-1}	0.94 ± 0.45	1.01 ± 0.29	0.45
Septal basal SR_R, s^{-1}	1.39 ± 0.53	1.35 ± 0.62	0.86

ƐR: left atrial strain during the reservoir phase; LAA: left atrial appendage; SR_R: left atrial strain rate in the reservoir phase. ƐR values compared by the Mann-Whitney test and SR_R values by the t-test.

Discussion

Our investigation demonstrates that changes in left atrial fraction volume are minimal after LAA percutaneous closure, and mechanics of the left atrial reservoir phase assessed by 2D-STE are not significantly different before and after the procedure.

Structural and functional remodelling of the left atrium has been proposed as a surrogate for diastolic dysfunction and a predictor of cardiovascular outcomes such as new-onset atrial fibrillation, stroke, heart failure, mortality after myocardial infarction, severity of diastolic dysfunction, and cardiovascular death.[12] 2D-STE is a novel method for quantitative real-time assessment of regional myocardial deformation. The technology tracks acoustic speckles or kernels rather than using Doppler myocardial velocities.[17] Considering the limitations of the classical indices of left atrial function, assessment of ƐR by 2D-STE may represent a relatively rapid and easy-to-perform technique for assessing left atrial function, due to its semiautomated nature and off-line processing. In fact, in contrast to Doppler-derived parameters, 2D-STE has the advantage of being angle-independent, and less affected by reverberation, side lobe and drop-out artefacts.[18] Furthermore, recent studies have shown that 2D-STE is feasible and reproducible.[18-20] It has been suggested that ƐR allows an excellent assessment of the atrial deformation profile during an entire cardiac cycle,

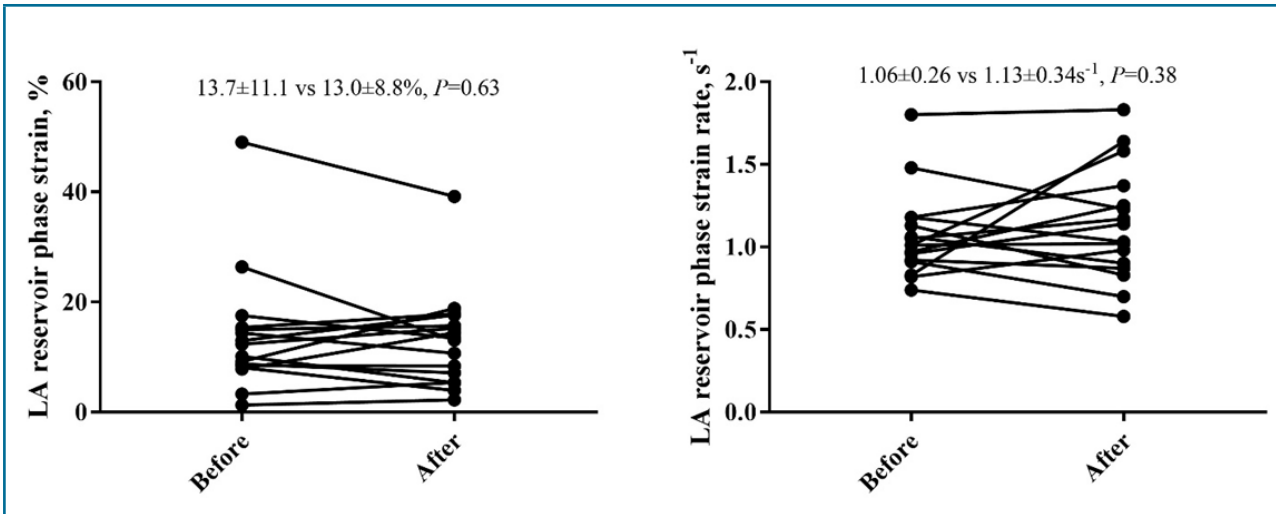

Figure 4 - Global left atrial strain (ƐR) and strain rate during reservoir phase (SR_R) before and after percutaneous closure of the left atrial appendage. Differences between baseline and post-LAA occlusion device implantation data were analysed by paired sample t-test.

Table 3 - Patients with reduction in left atrial mechanics in the reservoir phase

	Reduction in left atrial mechanics in the reservoir phase		p
	Yes (7/16 - 44%)	No (9/16 - 56%)	
Age, years	67 [66 - 73]	77 [69 - 81]	0.09
Permanent atrial fibrillation	4/7 (57%)	8/9 (89%)	0.26
CHA_2DS_2-VASc	5 [3 - 5]	5 [4 - 6]	0.35
HAS-BLED score	3 [2 - 4]	3 [2 - 3]	0.92
Cardiac plug device size, mm	24 [22 - 25]	24 [21 - 25]	0.83
Baseline mildly abnormal LVEF	0/0	3/9 (33%)	0.09
Baseline left atrium volume, mL	41 [33 - 45]	46 [40 - 62]	0.27
Baseline left atrium emptying fraction, %	25 [13 - 49]	18 [15 - 39]	0.43
Baseline global ƐR, %	14.4 [8.7 - 26.4]	9.2 [5.6 - 14.0]	0.14
Baseline global SR_R, s^{-1}	1.1 [0.9 - 1.2]	1.0 [0.8 - 1.1]	0.25

LVEF: left ventricle ejection fraction; ƐR: left atrium strain during the reservoir phase; SR_R: left atrium strain rate reservoir phase. Comparison of variables was performed with a Mann-Whitney test and SR_R values by the t-test. Data expressed as mean and standard deviation or median and interquartile range.

closely following left atrial physiology, and can be used to evaluate dynamic left atrial function.[18,19] It has also been demonstrated that the left atrial reservoir ƐR is associated with fibrosis and can thus represent left atrial stiffness.[21]

Contrary to earlier belief, LAA is now thought to play an important role in normal cardiac hemodynamics, acting as an adaptive chamber in conditions of volume overload to attenuate the rise in intra-atrial pressure.[22,23] Furthermore, the highest density of atrial natriuretic-peptide granules of the heart is found in LLA, and the release of atrial natriuretic peptide with consequent diuresis is an important compensatory mechanism involved in the maintenance of normal fluid homeostasis.[24] Hondo et al.,[23] in a study performed in 10 open-chest dogs, reported that the LAA is more compliant than the left atrial main chamber. They also found a higher dimensional increase in the LAA than the left atrial main chamber during left atrial volume overload. Davis et al.,[25] reported, in a study using 6 isolated canine left atria, that the LAA may enable the entire left atrium to better adapt reservoir function to physiologic conditions by protecting the pulmonary capillary system from encountering a rise in pressure.

In a study conducted by Kamohara et al.,[26] to investigate the short-term and midterm effects of LAA exclusion on left atrial function, involving 19 dogs with 90 days of follow-up, the authors showed no significant difference in the transmitral flow tissue Doppler imaging measurements, left atrial pressure, left ventricular volume, or stroke volume. Tabata et al.,[27] evaluated the role of LAA in left atrial reservoir function by assessing changes in left atrial flow dynamics after LAA clamping during cardiac surgery. The subjects of the study were 8 patients who had undergone coronary artery bypass grafting and 7 who had undergone valvular surgery for mitral regurgitation; all patients were in sinus rhythm. They demonstrated that, in both groups, mean left atrial pressure and maximum left atrial dimension significantly increased during LAA clamping. The authors concluded that the LAA is more compliant than the left atrial main chamber and plays an important role in left atrial reservoir function. Johansson et al.,[28] explored the effects on atrial and ventricular function of restoring sinus rhythm after epicardial cryoablation and closure of the LAA in 65 patients with mitral valve disease and atrial fibrillation. In patients who were in sinus rhythm, peak velocity during atrial contraction and the reservoir function were lower in patients that underwent LAA closure than in the control group at 6 months of follow-up. In summary, it seems that in patients who are in sinus rhythm, LAA occlusion might negatively influence left atrial reservoir function. In fact, our patients in sinus rhythm had a decrease in ƐR and SR_R after the procedure.

However, in patients with atrial fibrillation, closure of the LAA does not seem to have an impact on left atrial reservoir function. Hanna et al.,[29] conducted a study designed to evaluate the effects of percutaneous LAA transcatheter occlusion on anatomic and hemodynamic properties of the mitral valve and left upper pulmonary vein in 10 patients with atrial fibrillation. At 6 months of follow-up, left superior pulmonary vein diameter, peak systolic and diastolic flow velocities, left atrial size, severity of mitral regurgitation, and mitral valve peak E-wave velocity showed no significant change from baseline. In our sample, patients at baseline had decreased left atrial reservoir function, which was expressed by

increased left atrial volumes and decreased left atrial emptying fractions,[15] ƐR, and SR_R.[12] Furthermore, Sasaki et al.,[30] demonstrated that left atrial peak systolic ƐR is independently associated with LAA dysfunction in patients with atrial fibrillation. Hence, in our population of patients with left atrial chamber dysfunction at baseline, a reduced LAA function might also be present. Our results, along with those of Hanna et al.,[29] suggest that the exclusion of the LAA does not seem to have a further impact on compromised left atrial physiology.

Nevertheless, a recent study with 33 patients (20 patients with atrial fibrillation) demonstrated that LAA closure was associated with an improvement in left atrial mechanical function in a 45-day follow-up, and these changes appeared to be related to changes in loading conditions (Frank-Starling effect).[31] Despite favourable short-term outcomes, the long-term effects of an increase in left atrial volume might lead to deleterious effects, mainly in patients with sinus rhythm. We must also highlight that although there was an increase in peak atrial longitudinal strain at discharge compared to baseline, peak atrial longitudinal strain tended to be lower 45 days as compared with discharge ($p = 0.08$). Therefore, with a longer follow-up, peak atrial longitudinal strain might return to baseline levels as observed in our study.

Most previous studies were performed in patients with sinus rhythm and evaluated left atrial function immediately after LAA closure; the long-term hemodynamic effects of this procedure in patients who are in sinus rhythm are currently not known. Although we did not find any statistically significant difference between patients with decreased and with similar left atrial reservoir function after the procedure, the former group might have better left atrial function at baseline since a lower number of patients had lower left atrial volumes, higher left atrial emptying fractions, and higher ƐR values, consistent with the results of the studies mentioned above.

Limitations

Our study has several limitations. First, this was a single-center study with a relatively small sample size. However, there is a paucity of data regarding the effects of percutaneous LAA closure on left atrial function in the literature. Second, the retrospective nature of the study limited the evaluation of additional clinical and analytical parameters. Third, although we analyzed the impact of LAA percutaneous closure on left atrial mechanics, the design of our study made the assessment of clinical outcomes impossible. Finally, most of our patients had atrial fibrillation and left atrial dysfunction at baseline. It would therefore be important to study the influence of LAA percutaneous closure on left atrial function in patients who are in sinus rhythm with normal or slightly altered left atrial function.

Further studies including large populations of patients in sinus rhythm and in atrial fibrillation are needed to provide definitive evidence of the impact of LAA occlusion not only on left atrial physiology at long term, assessed by 2D-STE, but also on clinical outcomes.

Conclusion

We have demonstrated that in patients with atrial fibrillation and contraindication to oral anticoagulation, percutaneous LAA closure does not have a negative effect on left atrial reservoir function in patients with permanent atrial fibrillation. Further studies with a larger population of patients are warranted to confirm this finding.

Author contributions

Conception and design of the research: Madeira M, Teixeira R, Costa M. Acquisition of data: Madeira M, Teixeira R, Reis L, Dinis P, Paiva L, Botelho A, Costa M. Analysis and interpretation of the data: Madeira M, Teixeira R, Reis L, Dinis P, Paiva L. Statistical analysis: Madeira M, Teixeira R, Dinis P, Paiva L. Writing of the manuscript: Madeira M. Critical revision of the manuscript for intellectual content: Teixeira R, Reis L, Dinis P, Paiva L, Botelho A, Costa M, Gonçalves L.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina da Universidade de Coimbra under the protocol number 128 – CE - 2016.

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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ORIGINAL ARTICLE

Evolutive Study of Rheumatic Carditis Cases Treated with Corticosteroids in a Public Hospital

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Abstract

Background: Rheumatic carditis is a challenge for treatment and secondary prophylaxis, due to severe valve sequelae.

Objective: To evaluate the cases of rheumatic carditis in patients under 18 years old treated with corticosteroids.

Methods: An observational, longitudinal and retrospective study was carried out on the profile of patients, in the period of 2000-2015. We selected those who received corticosteroid therapy at immunosuppressive doses, for the treatment of carditis and were aged 5 to 18 years. Data were extracted from medical records. Calculations of: averages, standard deviations, medians and interquartile ranges, ratios and 95% confidence intervals were obtained. Chi-square and Wilcoxon tests were applied for comparisons. The level of significance was 5%.

Results: Of the 93 cases, 93.53% developed moderate or severe carditis. Mitral regurgitation was detected in 100% of the sample. Pulse therapy was administered in 11.83%. Surgery was performed in 23.69% of patients: mitral, aortic and/or tricuspid valve repair or replacement. The evolution of the cases was favorable in 70.96%. There was a good response among those who received only clinical treatment and those who belonged to the surgical group. The comparison of the initial and posterior valve lesions to the corticoid use was statistically significant ($p < 0.001$). A difference between the ejection fraction medians was observed ($p = 0.048$). Hospitalization was required twice or more for 45.16% of the patients. The mortality rate was 5.38%.

Conclusions: The patients showed significant clinical improvement. The treatment was effective, reducing trivalvular impairment. (Int J Cardiovasc Sci. 2018;31(6)578-584)

Keywords: Myocarditis/physiopathology; Myocarditis/complications; Rheumatic Fever; Mitral Valve Insufficiency; Adrenal Cortex Hormones; Penicilin G Benzathine.

Introduction

Although rheumatic fever (RF) occurs all over the world, in developing countries (such as Brazil), it is still a major cause of acquired heart disease among children and adolescents, which unfortunately still remains underreported.[1-3]

According to the National Census conducted by the Brazilian Institute of Geography and Statistics (IBGE), some 10 million cases of streptococcal tonsillitis are diagnosed each year, of which 0.3 to 10% develop into RF.[1,4] This indicates that, around 15,000 people must live with carditis each year.[1,5,6] Rheumatic damage to heart valves accounts for 40% of valve replacement operations,[7] costing the nation an average of R$ 89 million (close to US$ 28 million) a year.[8] Information from Brazil Unified National Health System database (DATASUS), indicates a cardiac mortality rate of about 7.87% from chronic RF.[8]

The dissemination of projects, such as the Rheumatic Fever Prevention Program (PREFERE), by the Ministry of Health (MH), aims to raise awareness among medical

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practitioners and the population in general about the importance of prevention and early diagnosis of this disease.[1] However, secondary prophylaxis is prone to failure, due to poor treatment compliance by patients[9] and/or gaps in nationwide antibiotic distribution networks, particularly Penicillin G Benzathine, breaching the directive issued by this MH that ensures no-cost distribution of this medication.[10]

Due to the importance of this issue, we decided to evaluate the cases of rheumatic carditis in individuals under 18 years of age treated with corticotherapy, in a public hospital in Rio de Janeiro State, and to verify the results obtained in the long-term follow-up.

Methods

An observational, longitudinal and retrospective study was carried out in patients treated in the pediatric cardiology department of a tertiary hospital in the city of Rio de Janeiro, Rio de Janeiro State, Brazil, for 15 years (2000–2015). All cases had the RF diagnosis made according to the reviewed and revalidated Jones criteria, plus evidence of prior pharyngotonsillitis caused by Lancefield's group A beta-hemolytic *Streptococcus* (GABHS).[1,11,12]

The inclusion criteria were: children and adolescents between 5 and 18 years of age undergoing corticoid treatment. The treatment followed the guidelines issued by the World Health Organization (WHO) and the Brazilian Cardiology Society (SBC).[1,2,13]

Corticoid treatment consisted of oral Prednisone, given as a single daily dose of 1 to 2 mg/kg/day (milligrams per kilogram per day), for eight weeks in cases of mild carditis or nine to 11 weeks in cases of moderate and severe carditis.[1,2] The full dose was given for approximately three weeks, tapering off by 20 to 25% of the initial dose each week, in response to clinical and laboratory improvement.[1]

Pulse therapy involved the administration of venous Methylprednisolone, at doses of 30 mg/kg/day,[1,14,15] for two weeks, with each cycle lasting three days, for severe carditis or when emergency surgery was required.[1,16] Immunosuppression was then completed with full-dose oral corticoids.

Streptococcus eradication required the administration of a single dose of 1,200,000 IU (International Units) of Penicillin G Benzathine through deep intramuscular injection, for patients weighing 20 kg (kilograms) or more and 600,000 IU for those weighing less than 20 kg. The oral medication used was Penicillin V, at a dose of 50,000 IU/kg/day (International Units per kilogram per day) every eight hours, for 10 days. As an option, treatment in some cases consisted of Amoxicillin at a dose of 50 mg/kg/day every eight hours, for 10 days.[1]

Secondary prophylaxis, with Penicillin G Benzathine, began while patients were still hospitalized and continued after their release, with outpatient control, prescribed at the same doses and with an interval of 21 days.[1,12,17] Some cases were treated with oral antibiotics, by administering 400,000 IU of Penicillin V every 12 hours; or daily Sulfadiazine at a dose of 500 mg for patients weighing less than 30 kg and 1 g (gram) for those weighing 30 kg or more;[1,18,19] or 250 mg of Erythromycin every 12 hours.[1,19]

Based on their clinical evolution, patients were divided into two groups: A – cases treated only with corticosteroids at immunosuppressive doses; B – cases that also required surgery.

Statistical analysis

The Stata program version 13.0 (*Stata Corp*) was used. The level of statistical significance was set at 5% ($p < 0.05$) as the statistically significant difference for all analyses. The Shapiro-Wilk's test was used to test the normality of the variables. Continuous variables with normal distribution were represented by mean and standard deviation and, otherwise, by median and interquartile range. The 95% confidence intervals were calculated, and the chi-square test was applied for the difference between proportions. Wilcoxon's test was used to compare left ventricular ejection fraction (LVEF) before and after treatment.

Ethical aspects

This research was approved by the Research Ethics Committee (REC) of the institute – National Research Ethics Commission (CONEP) and obtained a CAAE registration number: 21608213.0.0000.5265, available at the following website: http://www.saude.gov.br/plataformabrasil. As a retrospective study, there was no need to obtain the Free and Informed Consent form.

Results

The number of diagnosed cases of RF treated at the institute between January 2000 and December 2015 included 174 patients. We selected 93 of them that required immunosuppression with corticosteroids.

Between the ages of 5 and 18 years, the mean age of these patients was 9.89 years old, of which 47 (50.54%) were females. No significant gender-related differences were observed (Table 1).

Of the total number of patients, 11 (11.83%) did not adequately respond to oral Prednisone and were consequently given pulse therapy with Methylprednisolone.

Six (6.47%) of them had mild, 36 (38.69%) had moderate and 51 (54.84%) had severe carditis, indicating that 93.53% of the cases had the moderate or severe form of the disease. All 93 patients (100%) also had mitral insufficiency.

An initial daily dose of 30 mg of Prednisone was administered to mild cases, whereas 40 to 60 mg a day were administered to moderate or severe cases (Table 2).

In group A, 71 patients (76.31%) received corticoids, with no surgical intervention. Among them, only two (2.15%) were lost to follow-up. Group B consisted of 22 patients (23.69%) who required surgery in addition to corticoid treatment. Among them, 17 (18.31%) had good outcomes (decreased pressure gradient and intracavitary volume, with left ventricular systolic function improvement). Five (5.38%) died. The team performed surgical corrections of the mitral, aortic and/or tricuspid valves through repairs or replacements (Table 3).

As shown in Table 3, eight patients (8.64%) underwent surgery in only one valve. Two patients (2.15%) underwent surgery twice for the same valve, at different

Table 1 - Baseline characteristics of the study population (n = 93)

Variables	Results
Female gender - n (%)	47 (50.54)
Male gender - n (%)	46 (49.46)
Age (years old) - mean ± standard deviation	9.89 ± 3.10

Table 2 - Distribution of treatment with Prednisone (in mg) in patients with rheumatic carditis (n = 93)

Initial doses	Total weeks	n	%	95% confidence interval	
				Lower	Upper
60	11	51	54.84	43.4	64.5
50	10	23	24.72	17.6	34.0
40	9	13	13.97	7.9	21.1
30	8	6	6.47	2.2	12.9

Table 3 - Surgical cases in patients with rheumatic carditis (n = 22)

Surgery performed	Affected valve	n	%	95% confidence interval	
				Lower	Upper
Single repair	Mitral	1	1.08	0.0	13.6
Double repair	Mitral and Tricuspid	2	2.15	0.0	22.7
Repair / biological prosthesis	Mitral / Aortic	1	1.08	0.0	13.6
Repair and biological prosthesis two years later	Mitral	1	1.08	0.0	13.6
Repair and metal prosthesis in the same year	Mitral	1	1.08	0.0	13.6
Repair / biological prosthesis	Tricuspid / Mitral	3	3.23	0.0	31.8
Repair / metal prosthesis	Tricuspid / Mitral	1	1.08	0.0	13.6
Repair / double metal prosthesis	Tricuspid / Mitral and Aortic	2	2.15	0.0	22.7
Single biological prosthesis	Mitral	4	4.30	4.5	36.4
Single biological prosthesis	Aortic	1	1.08	0.0	13.6
Double biological prosthesis	Mitral and Aortic	3	3.23	4.5	27.3
Single metal prosthesis	Aortic	2	2.15	0.0	22.7

times. In 12 cases (12.90%), surgery was required for two or three valves damaged by carditis.

The median follow-up time in our service was 5 years.

During outpatient follow-up, we observed that secondary prophylaxis with Penicillin G Benzathine was administered on a regular basis to 55 patients (59.14%) and irregularly to 38 (40.86%) others.

As a result of one episode of carditis, 44 patients (47.31%) had only one hospitalization and five (5.38%) were maintained in outpatient control only. All of these were free of surgery.

There were indications of two to three subsequent hospital admissions for 31 patients (33.33%) and four to five or more returns to hospital for another 11 (11.83%).

In 12 cases (12.90%), the diagnosis was rheumatic carditis with bacterial endocarditis, using the modified Duke criteria.[20] Among them, three patients (3.23%) required surgery, of which one (1.08%) died after a double valve replacement using mitral and aortic biological prostheses. Evidence of vegetation at the two-dimensional Doppler echocardiogram was found mainly in the mitral valve (MV) of 10 patients (10.75%). In two others (2.15%), one showed damage to the aortic valve (AoV) only, while the other had mitral-aortic injury.

Microorganisms were identified through blood cultures in six patients (6.47%), as follows: two (2.15%) with coagulase-negative *Staphylococcus*; one (1.08%) had community-acquired methicillin-resistant *Staphylococcus aureus* (CA–MRSA); one (1.08%) had *Streptococcus pneumoniae*; one (1.08%) had *Streptococcus thermophilus*; and another (1.08%) had *Klebsiella pneumoniae*.

The initial clinical status of carditis related to arthritis or arthralgia was found in 63 cases (67.74%). Other 12 patients (12.90%) also showed an association with Sydenham's chorea (SC).

In terms of clinical evolution: improvement was observed in 66 patients (70.96%); one (1.08%) showed worsening; 19 (20.43%) showed no change in the clinical picture; two (2.15%) were lost to follow-up and did not return for control visits; and five (5.38%) died. Consequently, we currently have 86 patients (92.47%) still undergoing outpatient follow-up.

We observed good outcomes in the 49 patients (52.65%) who received clinical treatment only (valve regurgitation improvement) and the 17 (18.31%) submitted to successful surgical procedures (decreased pressure gradient and intracavitary volume, with an improvement in left ventricular systolic function).

After corticotherapy, echocardiography showed that of the 52 cases (55.91%) with an initial lesion in three heart valves, 36 (38.69%) had a favorable evolution, with regression to univalvular disease and only 16 (17.20%) remained with the trivalvular involvement (mitral, aortic and tricuspid). Therefore, at the end of the treatment, we demonstrated that most patients showed a decrease in the carditis intensity. Comparison of the frequencies of the initial and final lesions (triple, double and single) showed a reduction in the number of patients with trivalvular involvement, with a significant difference (p value < 0.001 and chi-square 34.7473).

LVEF determination by conventional transthoracic echocardiography (TTE) was performed before and after treatment was instituted. Subsequently, we verified the median ejection fraction (EF) values (Table 4).

It was observed that in both the echocardiographic study at the acute phase and in the final evolution assessment, the EF was preserved, although a statistical significance was found in the comparison between these LVEF medians (p value = 0.048). Only two patients (2.15%) showed ventricular systolic dysfunction (LVEF < 50%) and died. These were male patients with an initial estimated mean LVEF of 33.50% and final LVEF of 27.00%.

Table 4 - Median initial and final left ventricular ejection fraction (LVEF) in patients with rheumatic carditis (n = 93)

EF	n	Median	p value*	Interquartile range	
				Lower	Upper
Initial	93	69.0	0.0484	40	81
Final	93	71.0		66	76
Female gender					
Initial	47	69.0	0.0408	60	73
Final	47	71.0		66	77
Male gender					
Initial	46	69.0	0.4475	61	74
Final	46	71.5		67	75

Wilcoxon's test.

Discussion

Most of the cases already had severe carditis, as previously shown. Of the 93 patients assessed by this study, more than half developed triple valvular injury, indicating the severity of the disease during the initial examination. However, there was a predominance of preserved LVEF. In the study by Rocha and Silva et al.,[21] most patients underwent repairs at an advanced stage of valve damage, being in functional class IV of congestive heart failure (CHF), according to the criteria established by the New York Heart Association (NYHA). The MV surgical approach was performed in a large number of patients, due mainly to mitral insufficiency (MI). Most of the monitored children showed satisfactory responses to MV reconstruction. In the study by Travancas et al.,[22] more than half of the replacement surgeries were focused on this valve. In our sample, surgical valve repair occurred mainly in the MV, as mentioned above. Patients undergoing surgery at the ideal time evolved well and death occurred in those treated at the later stages, who already showed compromised myocardial function.

In our group, valve replacement was performed due to device deformity, being in agreement with the literature. According to Rocha and Silva et al.,[21] one of the causes of mitral repair failure was the advanced inflammatory process of the valve. In the study carried out by Travancas et al.,[22] patients with severe valve damage required surgical prosthesis implantation. It was also stressed that biological prostheses were appropriate, for children and adolescents, in case of difficulty resulting from the prescription or maintenance of laboratory control over anticoagulant use. Inadequate control of the international normalized ratio (INR) might lead to hemorrhagic or thrombo-embolic complications.

This study showed that, of the total number of cases with vegetation image, preferably in the MV, 50% had the bacteriological isolation of the triggering microorganism of infective endocarditis (IE), with the coagulase-negative *Staphylococcus* being the main pathogen identified. Similarly, the results of Torbey et al.,[23] showed that the mitral valve was predominantly affected, accompanied by significant regurgitation, and that *Staphylococcus* had been isolated, especially in newborns and patients with prosthetic valves.

In some of our patients, treatment with oral corticoids was not effective initially, requiring the introduction of intravenous Methylprednisolone. The protocol followed for intravenous immunosuppression continued to be used in severe cases, of which importance has been underscored in certain publications.[15,24] However, pulse therapy was not widely used in our sample, probably due to prior treatment optimization with oral medications.

Our clinical control and monitorization through the echocardiography series showed lesion improvement in most of the severe carditis cases treated with oral and/or intravenous immunosuppression and in those who remained in outpatient control with regular administration of secondary prophylaxis. This outcome was similar to that found in the follow-up study by Herdy et al.,[25] which showed that even critically-ill patients had achieved a satisfactory evolution.

Secondary prophylaxis failed in some of our adolescent patients. Adherence difficulty was observed regarding the systematic use of periodic injections of Penicillin G Benzathine, which has also been previously reported.[9,26] In the study by Herdy et al.,[25] carditis reappeared in 49% of the cases, due to secondary prophylaxis disregard. Furthermore, recent failures in the free distribution of medication in some parts of the country and at certain times, resulted in higher RF recurrence rates, constituting a serious national public health problem.

Our outpatient follow-up drop-out rate was lower than the initially expected one, comprising only two patients (2.15%). In the study carried out by Muller et al.,[6] 10.8% of the patients gave up on treatment. The drop-out rate and loss of follow-up in the group studied by Herdy et al.,[25] reached a considerably high rate of 51%. This difference of results may be explained through the efforts of our multi-disciplinary team to get patients and their families to understand the disease severity and the need to prevent further RF flare-ups, stressing the importance of prevention.

Limitations of the study

Due to the retrospective nature of the study, we considered the possibility of limiting the sample size, because it is time-defined.

Additionally, the data collection was restricted to a single hospital, not representing the entire State of Rio de Janeiro.

Conclusions

We observed a favorable clinical evolution in most cases of severe carditis treated through immunosuppression with corticoids and periodic outpatient follow-up. The

treatment proved to be effective, decreasing damage in the three valves.

Author contributions

Conception and design of the research: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Acquisition of data: Lemos FMCF. Analysis and interpretation of the data: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Statistical analysis: Valete COS. Writing of the manuscript: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Critical revision of the manuscript for intellectual content: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET.

Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were 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 Instituto Estadual de Cardiologia Aloysio de Castro under the protocol number 21608213.0.0000.5265. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. As a retrospective study, there was no need to obtain the Free and Informed Consent form.

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ORIGINAL ARTICLE

Effect of Mild Aerobic Exercise in Atrial Granules of Mice with Chronic Chagas Disease

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Abstract

Background: Chagas disease presents in different clinical forms, ranging from asymptomatic to acute, with destruction of heart cells and a possibility of death. In the chronic phase, the parasites can cause serious injuries to different tissues.

Objectives: Our objective was to study the effects of physical exercise (swimming) in atrial granules and components of cardiomyocytes in mice with chronic Chagas disease.

Methods: In total, 20 male mice were divided into four different groups: untrained control (UC), trained control (TC), untrained infected (UI), and trained infected (TI). In the UI and TI groups, 1,000 forms of *Trypanosoma cruzi* (Y strain) were inoculated intraperitoneally. After 40 days of infection and proof of chronic phase, the exercise protocol began. The UC and UI groups performed exercise for 10 min/day, and the TC and TI groups followed a training protocol five times a week for 30 minutes during 8 weeks. Ultrathin sections were subjected to morphometric and stereological analyses using electron photomicrographs (x15000) obtained by transmission electron microscopy.

Results: The TI group showed the lowest percentage of small granules (58%), while the UI group presented 80% of these granules. The volume density of the Golgi complex and myofibrils in the TI group were reduced compared with those in the UI group, while the parameters of atrial granules and mitochondria increased.

Conclusion: Our results suggest that mild physical exercise changes the morphological and morphometric parameters of granules and organelles in the cardiac atrium of mice infected with *T. cruzi*, and produces moderate beneficial effects on the cardiovascular system. (Int J Cardiovasc Sci. 2018;31(6)585-593)

Keywords: Chagas Disease; Exercise; Atrial Natriuretic Factor; Mice.

Introduction

Cardiac manifestations of Chagas disease remain the leading cause of death in several countries in Latin America and have become a public health problem in nonendemic countries due to migration.[1] Chronic Chagas heart disease is considered a major cause of nonischemic cardiomyopathy worldwide.[2] With an annual incidence of 28,000 cases in the region of the Americas, Chagas disease affects approximately 6 to 8 million people and causes, on average, about 12,000 deaths per year.[3]

Chronic Chagas heart disease is characterized by cardiac dysfunction in varying degrees evolving to heart failure, bradycardia, biventricular cardiomyopathy or right ventricular dysfunction, severe arrhythmias, thromboembolism, syncope, and sudden death. It is a cardiomyopathy with a prognosis determined by systolic dysfunction and diastolic failure, especially among patients with heart failure.[2,4-6]

Both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are synthesized and stored in the cytoplasm of atrial and ventricular cardiomyocytes

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in the shape of granules of varying size, and play an important role in the pathophysiology of heart failure, including that of Chagas etiology. ANP and BNP are very similar to each other with respect to amino acid sequence and pharmacological spectrum. Patients with congestive heart failure have high levels of ANP and BNP in the atrial and ventricular cardiomyocytes and increased secretion of their contents.[1,7-11] The pathophysiological role of ANP and BNP in cardiovascular diseases is related to their endogenous diuretic and vasodilator action, with both peptides working as protectors of the cardiovascular system in situations of volume and pressure overload.[12-14] In addition, ANP or BNP administration produces clinical improvement in patients with heart failure.[15,16]

According to Bianchi et al.,[17] the action of exercise on the normal heart provides benefits. The increase in blood volume caused by physical exercise raises the ANP and BNP levels, facilitating the metabolism of all organs involved.[17]

The effect of physical exercise on ANP levels in healthy subjects and in individuals with nonspecific heart failure is evident. In these cases, depending on the type and intensity, physical exercise increases ANP production and secretion in cardiomyocytes, greatly increasing the serum levels of this peptide.[18,19]

The aim of this study was to evaluate the effect of an exercise program on the cardiomyocytes of mice with chronic Chagas disease. The data showed an experimental basis for measuring the effects of regular exercise practice in patients with chronic Chagas disease.

Methods

Animals and procedures

Experimental animals

The experiment included 20 young, male, Swiss mice (20 - 25 g, 21 days old) from the Animal House of the Dante Pazzanese Institute of Cardiology, São Paulo, Brazil. The animals were housed in collective polycarbonate cages in a temperature-controlled room (21 - 24°C) with a 12 h dark-light cycle (light 7:00 am to 7:00 pm). Water and food were available *ad libitum*.

All procedures were approved by the Research Ethics Committee of the *Universidade São Judas Tadeu* (060/2007). This investigation was conducted in accordance with the Principles of Laboratory Animal Care formulated by the National Institutes of Health (Publication No. 96–23, Revised 1996).

The mice were randomly assigned to four groups: untrained control (UC, n = 5), trained control (TC, n = 5), untrained infected (UI, n = 5), and trained infected (TI, n = 5). The TC and TI groups were submitted to swimming exercise. The sample size was defined based on the parameters established by the *Conselho Nacional de Controle de Experimentação Animal* (CONCEA) concerning the use of animals in research. The number of animals used was sufficient to evaluate the hypothesis of this study.

Parasitemia and exercise training

Inoculum and strains of 20-day-old *Trypanosoma cruzi* were inoculated intraperitoneally in 10 Swiss mice (groups UI and TI) with 10^3 trypomastigotes of the Y strain of *T cruzi*.[19] The parasitemia curve and parasitemia peak were determined by collecting 5 μL blood samples from the animals' tails using the Brenner protocol.[19] Blood was collected daily from the second day of the infection until no parasites were observed (~40 days), characterizing the chronic phase of the infection.[20,21]

After 60 days of life, all animals were adapted to the liquid medium in collective tanks with a temperature of 30 ± 2ºC for a week during 15 minutes in order to reduce their stress during physical exercise in the water. The training protocol (swimming) adapted from Lancha et al.[22] was performed by the TC and TI groups for 8 weeks, 5 days a week, lasting 30 minutes per day. The training load was equal to 5% of the body weight of each animal. This protocol was characterized as low-intensity and long-term training.[22]

Tissue sample preparation

At the end of the experiment, when the animals were around 120 days old, they were sacrificed by decapitation. Subsequently, thoracotomy was performed, and the hearts in diastole were removed and weighed. After that, the hearts were perfused via the aorta at a constant pressure of 80 mmHg using 0.1 M cacodylate buffer (3 min), followed by 2.5% glutaraldehyde solution diluted in cacodylate buffer. Subsequently, in each animal, the atria were separated from the ventricles, and the right atrium (RA) was separated from the left atrium.

Right atrium

Fragments of the RA of approximately 3 mm wide and 5 mm length were fixed in 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M buffer for 2 h at 4°C and postfixed in 1% osmium tetroxide in the same buffer for 2 h at 4°C. The

samples were dehydrated in ethanol series and embedded in Epon resin. Thin sections were double-stained with uranyl acetate and lead citrate. Two randomly chosen blocks from each RA in which the myocytes were cut in cross sections were used for quantitative analysis. The ultrathin sections were placed on a copper grid and, using a JEOL transmission electron microscope, 10 randomly chosen fields per block were selected for micrographs.

Ultrastructural morphometry and stereology

Twenty RA electron micrographs per animal, chosen by systematic random sampling of squares, were taken at a final magnification of x15000, and the numerical density of granules / field and the diameter of all granules present in the field were determined. For the volume density of granules, mitochondria, myofibrils, Golgi complex, and interstitium present in the field, the electron micrographs were analyzed by a stereological test system with 82 points using the Image J software (version 1.47, National Institutes of Health; Collins, 2007), and the values were expressed as percentages.[23]

Statistical analysis

The data were evaluated with the software Stata 7.0 and are expressed as mean ± standard error of mean (SEM). All continuous variables were normally distributed (Friedman test), and statistical differences between the groups were obtained by two-way analysis of variance (ANOVA) and *post hoc* Tukey test. P values below 5% were considered statistically significant.

Results

Body and heart mass

At the beginning of the protocol, all study groups presented similar body mass values (35.7 ± 1.9 g). At the end of the study, body weight was similar in the UC (40.6 ± 0.94 g), TC (43.4 ± 0.62 g), UI (42.52 ± 1.4 g), and TI (41.94 ± 1.02 g) groups. Heart mass and heart mass / body mass ratio showed no significant difference among the groups (Table 1).

Morphology of atrial cardiomyocytes

The electron photomicrographs in Figure 1 show the structural aspects of the atrial cardiomyocytes in the UC and TC groups, and those in Figure 2 show the structural aspects of the atrial cardiomyocytes in the UI and TI groups.

The frequency distribution histogram of the atrial granules showed that *T. cruzi* infection (UI and TI groups) promoted an increase of small granules (16.7 to 29.9 nm) and a reduction of large granules (50.0 to 75.0 nm) when compared with the UC group. However, a comparison between the UI and TI groups showed a decrease in the diameter of the small granules and an increase in the diameter of large granules promoted by training in both control and infected animals, reversing the process induced by infection. The average granules (30.0 to 49.9 nm) were unchanged in all studied groups (Figure 3).

Volume density of the organelles of atrial cardiomyocytes

Table 2 shows morphological and quantitative data of the organelles of atrial cardiomyocytes in the RA of animals in the experimental groups. The organelle density parameters observed in the TI group were similar to those in the TC group, except for the myofibril density, which was lower in the TI group. In addition, the TI group showed increased density of atrial granules and mitochondria, and reduced density of myofibrils and Golgi complex compared with the UI group, but these parameters were comparable to those in the TC.

Table 1 - Body and heart mass of the four groups of studied animals

Parameters/groups (n = 5)	UC	TC	UI	TI
Body mass, initial (g)	37.8 ± 0.58	37.7 ± 0.56	36.80 ± 1.07	33.20 ± 1.58
Body mass, final (g)	40.6 ± 0.95	43.5 ± 0.52	42.52 ± 1.4	41.94 ± 1.02
Heart mass (g)	0.19 ± 0.01	0.19 ± 0.0073	0.176 ± 0.015	0.19 ± 0.02
Heart / body mass, $x10^{-3}$	4.69 ± 0.043	4.56 ± 0.012	4.12 ± 0.026	4.65 ± 0.039

Values are presented as mean ± standard error of mean. Abbreviations: UC: untrained control; TC: trained control; UI: untrained infected; TI: trained infected.

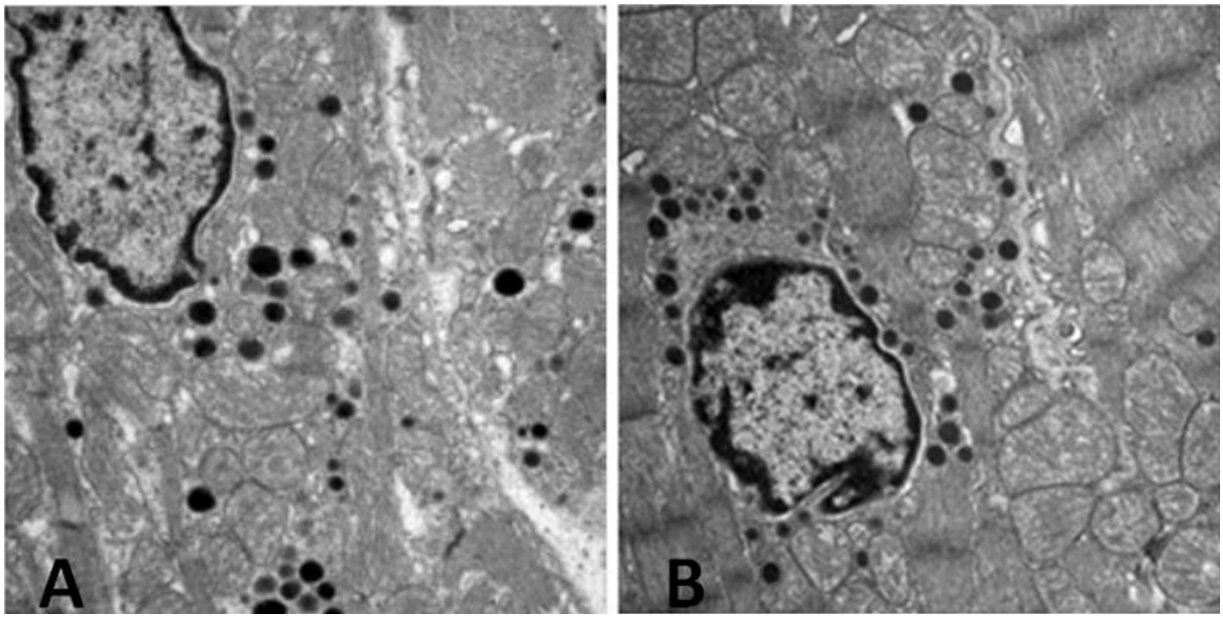

Figure 1 - Electron micrographs of atrial cardiomyocytes in the control groups. The image in (A) shows the untrained group (UC) with plenty of interstitium with regular architecture and presence of collagen fibers. Preserved mitochondria, Golgi complex, myofibrils, and Z line are observed in the cytoplasm. The nucleus shows nuclear chromatin with heterogeneous density, clear nuclear envelope, and irregular contour at the intersection with the cytoplasm. The atrial granules have different size and density and agglomerate closer to mitochondria, Golgi complex, and polar region of the nucleus. In (B), the trained control group (TC) shows numerous lined mitochondria, thickened myofibrils, and Z lines, reduced interstitium and, consequently, reduced collagen fibers. The nuclear envelope presents extremely irregular and electron-dense contour. Compared with the untrained control group (UC), in the TC, most atrial granules display variable size and electron density, are dispersed in the cytoplasm in less quantity around the nuclear envelope and closer to the mitochondria, Golgi complex, and the periphery of myocytes.

Together, the trained groups (TC and TI) showed a decrease in volume density of myofibrils and increase in volume density of mitochondria when compared with the untrained groups (UC and UI). The distribution of organelles of cardiomyocytes and interstitium in the RA (Figure 4) showed a greater presence of granules in the trained groups, especially in the TI.

Discussion

Our results show an influence of a nonpharmacologic treatment (physical exercise) on cardiovascular control in an experimental model of chronic Chagas disease. We showed an improvement promoted by moderate aerobic exercise in both endocrine activity and mechanical action of the heart in animals with chronic Chagas disease.

The histopathological analysis followed the Dallas criteria advocated by Aretz[24] and confirmed the occurrence of chagasic myocarditis in the studied animals. Moreover, the positive influence of light exercise on heart morphological and morphometric parameters in an experimental model of mice with Chagas disease has been reported with evaluation of the left and right ventricles of these animals.[25]

Corroborating previous data, our results indicated an increased density of atrial granules by area and number of mitochondria in cardiomyocytes promoted by exercise training, giving evidence of increased ANP plasma in animals submitted to physical exercise. Other studies have shown that physical activity modulates the increase in ANP gene expression in atrial receptors.[26,27] This effect is explained by increased pressure in atrial walls caused by blood volume during physical exercise, inducing an increase in ANP levels in the swimming animals, and regulating the cardiovascular response.[28]

During physical exercise, there is an increase in plasma levels of catecholamines and ANP, as well as physiological lipolysis with an increase in fatty acids, providing important nutrition to the heart.[29,30] Hu et al.[31] investigated the effects of physical exercise and ANP circulation in patients with and without ischemic

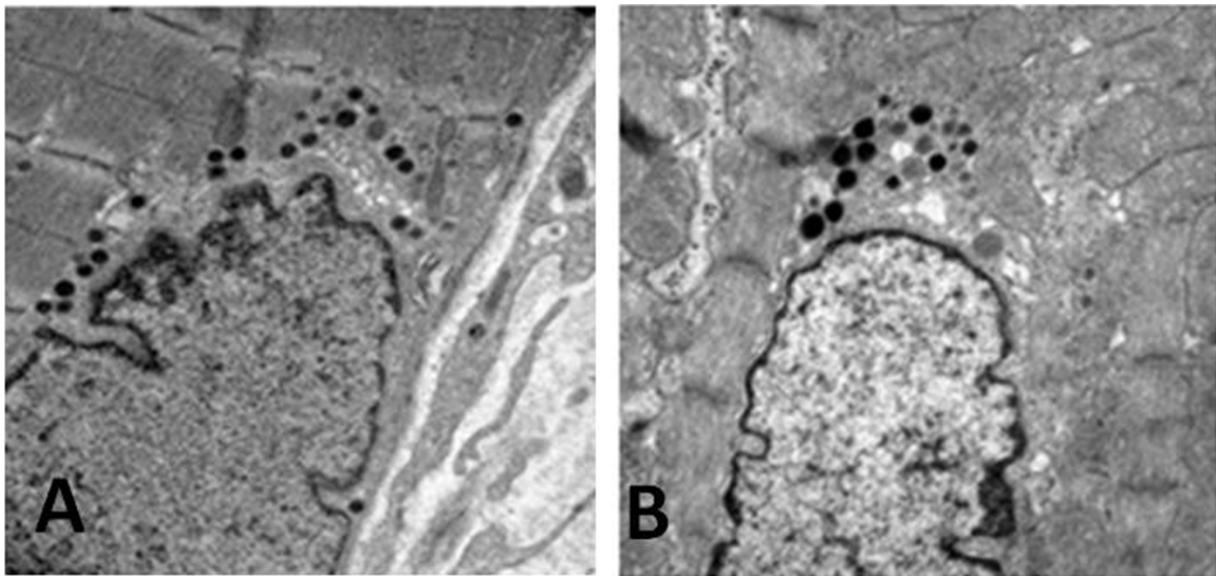

Figure 2 - Electron photomicrographs of atrial cardiomyocytes of infected groups. In (A), the untrained infected group (UI) presents a large amount of collagen fibers in the interstitium. Some nuclear envelopes have an irregular thickness and numerous invaginations, while others have a rectilinear thickness and precise contours with the cytoplasm. The nuclear chromatin shows heterogeneous electron density with intensely dense regions near the nuclear envelope, mitochondria without evident ridges, concentration of granules, mostly small, on the periphery of myocytes, and preserved structure of myofibrils and Z lines. In (B), the trained infected group (TI) presents irregular interstitium with plenty of collagen fibers. The cytoplasmic membrane in most myocytes has an irregular contour with numerous invaginations, and the cytoplasm has numerous scattered or grouped mitochondria and rare suggestion of degeneration. The nuclear chromatin is heterogeneous with electron-dense regions disseminated throughout the nucleus, and along the nuclear envelope. There is a predominance of small atrial granules scattered in the cytoplasm, in the nuclear poles, and the surface of the cytoplasmic membrane. Both myofibril and Z line are thickened.

Table 2 - Apparatus of atrial cardiomyocytes in mice in the untrained control (UC), trained control (TC), untrained infected (UI), and trained infected (TI) groups

Parameters /group	UC	TC	UI	TI
Vv [gr] (%)	4.43 ± 0.36	4.02 ± 0.66	3.18 ± 0.19*	6.16 ± 0.5+
Vv [mit] (%)	16.5 ± 1.05	26.91 ± 4.3*	15.56 ± 1.16*#	23.68 ± 2.08*+
Vv [miof] (%)	56.32 ± 1.67	46.01 ± 4.01*	55.43 ± 1.60#	44.45 ± 2.02*#+
Vv [golgi] (%)	4.74 ± 0.30	4.94 ± 0.60	7.15 ± 0.39*#	5.48 ± 0.38+
Vv[others] %	7.23 ± 1.63	11.82 ± 4.0	8.15 ± 1.6	9.64 ± 1.66
Vv [int] (%)	10.28 ± 1.17	7.55 ± 1.97	10.6 ± 0.94	9.02 ± 1.06

*Values are presented as mean ± standard error of mean. *p < 0.05 versus UC; #p < 0.05 versus TC and +p < 0.05 versus UI. Abbreviations: Vv[gr]: volumetric density of granules; Vv[mit]: mitochondria; Vv[myofib]: myofibrils; Vv[golgi]: Golgi complex; Vv[int]: interstitium; Vv[others]: others.*

heart disease, and found a disproportionate elevation of ANP after physical exercise in ischemia. Zhu et al.[32] analyzed postmortem pericardial ANP and showed that ANP levels correlated negatively with pericardial cardiac troponin levels, while Tanaka et al.[33] found that RA cardiomyocytes are prevalent in the production of ANP. Many studies have been performed analyzing the stimulation of ANP secretion by physical exercise.[34-38]

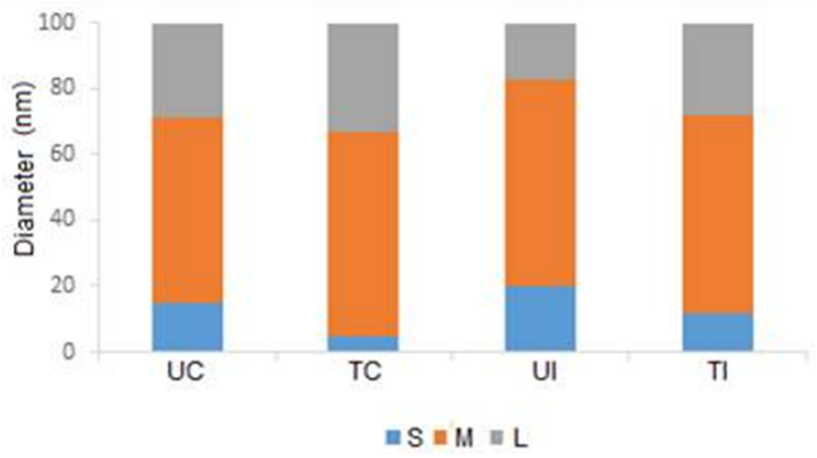

Figure 3 - Frequency distribution histogram of atrial granules in relation to their diameter (small [S], medium [M], and large [L]) in the studied groups.

In acute Chagas disease, there is intense myocarditis associated with changes in the secretory complex in atrial myoendocrine cells and consequent heart failure. Additionally, it is known that ANP and BNP levels also increase in patients with Chagas with echocardiographic changes.[1] Our data showed that the UI group had a significant reduction in the density of granules when compared with the UC group. However, this difference was not observed in the density per area, indicating no substantial difference in the amount of granules between the UI and UC groups.

Additionally, the TI group presented density parameters similar to those observed in the TC group and different from those in the UI group, indicating that exercise training can approximate the physiology of infected cardiac cells to that found in uninfected cells. As for the interstitium, there was no significant difference between the untrained groups compared with the swimming groups. The myofibril density was higher among groups that performed exercise (TC and TI) compared with those that did not exercise (UC and UI). This indicates that physical activity contributes to increasing the number of myofibrils in the heart muscle.[39,40]

When comparing the numerical density of atrial granules in all four groups of animals, we observed no statistically significant difference among the groups ($p > 0.05$). However, there were differences between large and small granules. Interestingly, physical training promoted a decrease in the diameter of small granules and an increase in the diameter of large granules in both controls and infected animals. Additionally, we also observed that the frequency distribution of granules in relation to the areas was significant in the UI group compared with the other groups, with 80% of small granules. The TI group showed the smallest percentage of large granules (0.9%) compared with the other groups. Activation of the renin-angiotensin-aldosterone system in congestive heart failure results in sodium and fluid retention, with increased blood volume and central venous pressure, and consequent stretching of the atrial wall,[41,42] as well as morphologic and morphometric changes in cytoplasmic organelles in atrial and ventricular cells.[43,44] The lowest concentration of large granules observed may represent a more effective elimination of the contents present in the granules, resulting in endocrine benefits to the cardiovascular and renal systems.

Structural differences were identified in untrained animals with Chagas disease when compared with those in the UC group. The granules of UI animals had a heterogeneous size and dispersed electron density in the cytoplasm permeating the sarcolemma, cytoplasmic condensation, and characteristic changes in cell chromatin and nuclear envelope with several indentations in the cytoplasm.

The chagasic swimming group (TI) presented reduced interstitium and plasma membrane of irregular contour with numerous invaginations containing electron-dense granules. Numerous mitochondria, some with signs of degeneration, were also observed. Nuclear chromatin appeared hazy and electron dense,

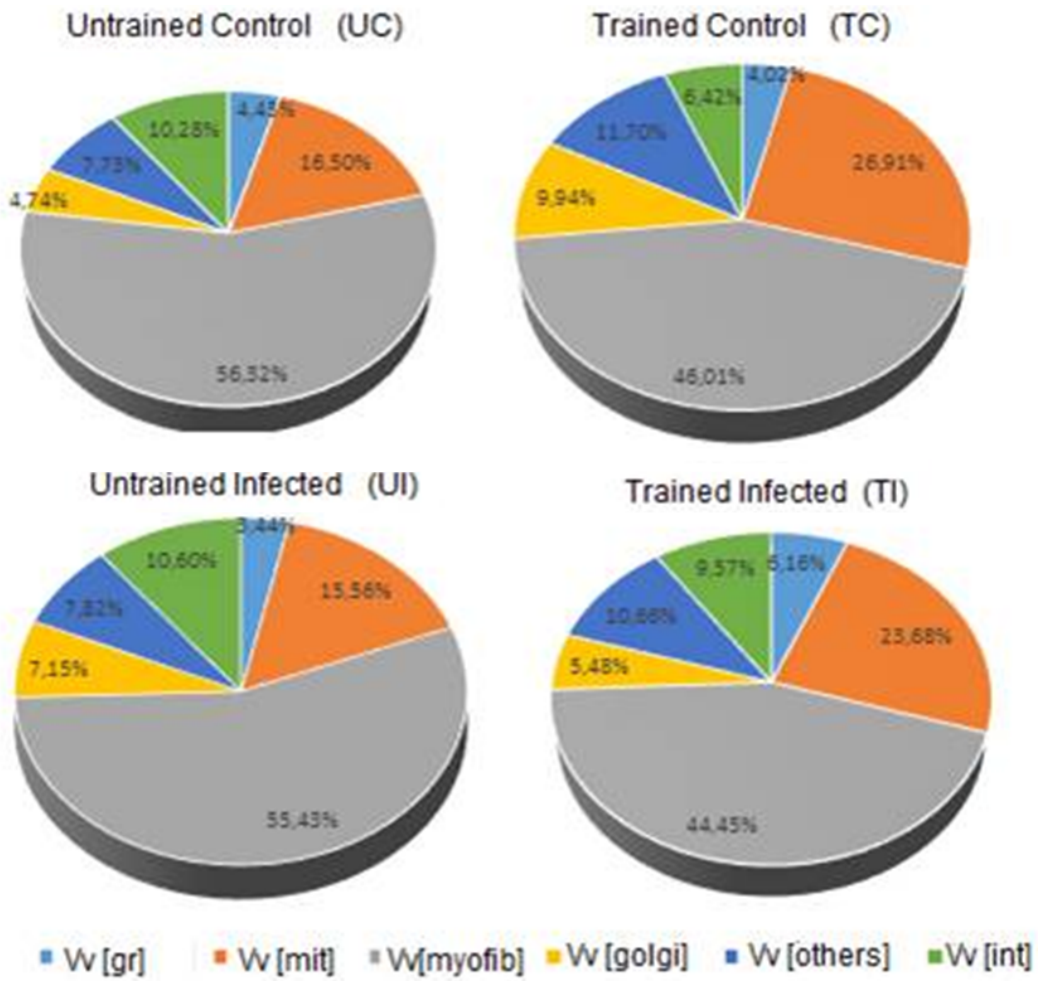

Figure 4 - Distribution of volume densities of cytoplasmic organelles and by interstitium between the UC, TC, UI, and TI groups. Volumetric density of granules (Vv[gr]), mitochondria (Vv[mit]), myofibrils (Vv[myofib]), Golgi complex (Vv[golgi]), interstitium (Vv[int]), and others (Vv[others]).

concentrated in the nuclear envelope and dispersed in the nucleus. A reduced number of granules was observed, with a predominance of small granules dispersed in the cytoplasm and around the Golgi apparatus and mitochondria, and in the peripheral region of the cytoplasmic membrane.

Conclusion

Our results suggest that physical exercise (light) performed by chagasic animals is beneficial to the heart, promoting rehabilitation of sequelae caused by myocyte injuries during parasitemia throughout the acute phase of the disease. This benefit was likely due to increased heart rate, which stimulates the production of electron-dense atrial granules and ANP in response, providing greater blood volume and pressure of the atrial walls, and consequently increased secretion of ANP.

Author contributions

Conception and design of the research: Ferraboli R, Ornelas EM, Fonseca FLA, Cardoso CG, Maifrino LBM. Acquisition of data: Ferraboli R, Ornelas EM, Fonseca FLA. Analysis and interpretation of the data: Ferraboli R, Ornelas EM, Fonseca FLA, Veiga GL, Marques MR, Maifrino LBM. Statistical analysis: Ferraboli R, Fonseca FLA. Obtaining financing: Maifrino LBM. Writing of the manuscript: Ferraboli R, Veiga GL, Cardoso CG, Maifrino LBM. Critical revision of the manuscript for intellectual

content: Ferraboli R, Ornelas EM, Fonseca FLA, Veiga GL, Cardoso CG, Marques MR, Maifrino LBM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Roberto Ferraboli, from *Universidade São Judas Tadeu*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade São Judas Tadeu* (060/2007) under the protocol number 060/2007 the National Institutes of Health (Publication No. 96–23, Revised 1996).

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ORIGINAL ARTICLE

Prevalence of Physical Inactivity and its Effects on Blood Pressure and Metabolic Parameters in a Brazilian Urban Population

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Abstract

Background: Cardiovascular disease is the leading cause of mortality in the world and physical inactivity represents an important risk factor.

Objective: This study aimed to evaluate the prevalence of physical inactivity in the adult population and its effects on blood pressure, blood glucose and lipid profile.

Methods: A population-based cross-sectional study with stratified simple random sampling was conducted in 1,717 adults divided by age groups: 18-39, 40-49, 50-59, 60-69 and ≥ 70 years. The participants answered the physical activity questionnaire and were classified as physically active or inactive. The bootstrap statistical method was used to assess physical activity, associated with lipid profile and blood glucose levels. The level of significance was 5%.

Results: The prevalence of physical inactivity in the general population was 65.8%. There was a significant difference in the group older than 70 years. There was a significant decrease in physical activity in the group with lower educational level, with a significant difference between social classes AB and C. The prevalence of hypertension was 27.5% among physically inactive and 21.4% among active individuals (p = 0.04). The prevalence of metabolic syndrome was 26.1% in inactive and 16.7% in the active individuals (p = 0.007). Total cholesterol, low-density lipoprotein and triglycerides levels were more elevated in the physically inactive group, which was not observed with high-density lipoprotein levels. Blood glucose was also higher in the inactive group.

Conclusion: This study shows a high prevalence of physical inactivity and a positive correlation between risk factors for cardiovascular disease, mainly blood pressure, glucose and lipids profiles. (Int J Cardiovasc Sci. 2018;31(6)594-602)

Keywords: Exercise; Diabetes Mellitus; Hypertension; Metabolic Syndrome; Risk Assessment.

Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality in high and low-income countries. In the last decades, CVD accounted, on average, for 30% of all deaths in Brazil.[1] A large number of cardiovascular events can be attributed to several risk factors, particularly physical inactivity. According to the World Health Organization (WHO), physical inactivity is the fourth-leading risk factor for global death, responsible for 3.2 million deaths annually, including an estimated 670,000 early deaths (people aged < 60 years).[2] Individuals who are insufficiently active have a 20% to 30% increased risk of all-cause mortality when compared to people who practice at least 150 minutes of moderate-intensity physical activity per week.[2] It is estimated that physical inactivity accounts for 6% to 10% of the world's burden of chronic diseases.[3]

Several studies have shown an inverse association between the practice of regular exercise and the

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risk of disease. The health benefits of moderate or vigorous intensity physical activity include lower risk of developing or dying from chronic diseases, such as type 2 diabetes mellitus (T2DM), hypertension (HT), coronary artery disease (CAD), stroke, kidney disease and some types of cancers.[4-9] Admittedly, physical activity improves lipid profiles and glycemic control; it reduces the risk of developing insulin resistance and glucose intolerance, and it plays an important role in the treatment of hypertension.

The prevalence of physical inactivity in the population is variable, depending of the assessed world region and of age.[10,11] Generally, older adults are more physically inactive than younger adults, showing about 55% versus 23% of inactivity, respectively.[10] About one in every three American adults (30.4%) do not engage in physical activity.[11] However, in Brazil, there is a lack of consistent data on the prevalence of physical inactivity and its effect on clinical and metabolic parameters in the general population at different age groups. Therefore, this study aimed to evaluate the prevalence of physical inactivity in a Brazilian urban adult population stratified by age groups, correlating it to demographic, anthropometric and biochemical parameters.

Materials and methods

Study design setting, and participants

This study was approved by the Research Ethics Committee of the Medical School (057/2004). All participants were informed about the purpose of the study and provided informed consent before starting it. This was a cross-sectional, population-based study with simple random sampling and stratified by age groups, which was carried out from March 2004 to November 2005 in the urban adult population (≥ 18 years) of São José do Rio Preto, São Paulo, Brazil.[12] The sampling was stratified according to age groups, based on the data provided by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE). At the time the survey, the city had a population of 370,000 inhabitants, predominantly white (82.8%) and with a balanced distribution between men (48.4%) and women (51.6%).[13] The groups were divided by age ranges: 18-39, 40-49, 50-59, 60-69 and ≥ 70 years. The parameters used to calculate the stratum sample sizes were number of inhabitants, expected prevalence of hypertension for each age group, a confidence interval of 95% and a maximum error of 3%.[14]

The city was divided into census sections according to IBGE. In each sector, the number of individuals was determined according to the proportionality of the population. For each region, streets, homes, an adult living for more than six months in a house, who met the inclusion criteria, was randomly chosen. After the visit to the first residence, houses located on alternating sides of the street, after skipping two households, were visited. If the selected individual did not agree to participate, the next-door neighbor was randomly chosen. Exclusion criteria included pregnancy, severe degenerative diseases, incapacitating mental disorders, severe psychiatric diseases or mental disability and bedridden patients.[12]

Interviewers were previously trained and monitored by a field coordinator. The participants answered a questionnaire that included their personal data, income and assets, in order to assess their socioeconomic status, formal education (number of years of schooling), personal and family medical history, lifestyle, awareness of hypertension and diabetes medication being used. After that, body mass index (BMI), pulse rate and blood pressure (BP) were assessed.

Data collection

The BP measurement technique was that standardized by the VII Joint National Committee:[15] 1) measurements were taken with a recently calibrated aneroid sphygmomanometer (Welch Allyn / Tycos) known to be accurate; 2) the cuff was placed so that the lower edge was 3 cm above the elbow crease and the bladder was centered over the brachial artery; 3) a standard, a large, and a small bladder were available for thicker and thinner arms, respectively; 4) the arm was bare and supported, with the blood pressure cuff positioned at the heart level 6) phase I and V (disappearance) Korotkoff sounds were used to identify systolic and diastolic BP, respectively; 7) the pressure was rapidly increased to 30 mmHg above the level at which the radial pulse was extinguished; 8) a cuff deflation rate of 2 mmHg per beat was used; 9) a minimum of 1-minute intervals were recommended between readings to prevent venous congestion; 10) BP was measured in both arms to detect possible differences due to peripheral vascular disease; in this case, the higher value was taken. Arterial hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or with the use of antihypertensive medications. For individuals with

borderline BP values, a new measurement was taken on a different day at the same hour of the last measurement.

The socioeconomic status was divided into classes A, B, C, D and E, and later into groups AB, C and DE (based on family income and assets). Groups AB had a monthly income higher than 10 minimum wages; Group C, between 3 and 5 minimum wages; and Groups DE, lower than 3 minimum wages.[12,16] Formal education was defined by the number of years of study, considering two levels: Level 1: 0-11 school years; and Level 2: > 11 school years, including university degrees.[12]

The short version of the International Physical Activity Questionnaire was used to assess the overall physical activity (OPA), including work-related physical activity (WPA), transport-related physical activity (TPA), domestic activities (DA) and leisure time physical activity (LTPA). The level of physical activity was classified as physically active individuals (PA), who performed more than 150 minutes of physical activity per week (including manual labor jobs, walking, running, swimming and cycling) and physically inactive individuals (PI), who performed < 150 minutes per week.

Clinical variables

The BMI was obtained by the weight/height^2 ratio (kg/m^2). A calibrated portable scale was used for weight measurements. Individuals were classified as normal weight (18.5 to 24.9), overweight (25 to 29.9) and obese (≥ 30 kg/m^2).[17]

The diagnosis of type T2DM was established based on the patient's medical history, on hypoglycemic medication and blood glucose measurements.[18]

The levels of blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TG) were analyzed after 12 hours of fasting by the colorimetric method. An RXL analyzer and the Dade Behringer reagent were used for the analysis. The low-density lipoprotein cholesterol (LDL-c) levels were calculated using Friedewald formula: LDL-c = TC - (HDL-c + TG /5) for TG < 400mg/dL.[19]

Metabolic syndrome (MetS) was classified according to the following diagnostic criteria: waist circumference (men ≥ 102 cm and women ≥ 88 cm), TG ≥ 150 mg/dL, HDL-c [< 40 mg/dL (for male) and < 50 mg/dL (for female)], BP (Systolic BP ≥ 130 or Diastolic BP ≥ 85 mmHg), fasting blood glucose (≥ 100 mg/dL or T2DM) or specific treatment for these conditions.[20]

Statistical analysis

Statistical analysis was carried out using the Minitab programs version 12.22 and R 2.4.1. Estimated frequency of physical activity according to factors (education, age, gender and socioeconomic status), characteristics (BMI, HT, MetS), and metabolic parameters (cholesterol, HDL-c, LDL-c, TG and blood glucose) was performed by estimation and population association testing by means of the method of weighted least squares. Correction for the weight of the population was made according to the age group: 55.33% for 18-39 years, 18.45% for 40-49 years, 12.29% for 50-59 years, 8.20% for 60-69 years and 5.73% for 70 years or more. The bootstrap statistical method (simulation method of convex combinations with the same weights used for the analysis of frequencies, where 1,000 bootstrap samples are generated for each comparison) was used to assess the physical activity, associated with serum lipid and glucose levels. This method (resampling technique) attempts to accomplish what would be desirable to do in practice if it were possible: to repeat the experiment. The observations are chosen at random and the estimates recalculated for the purpose of improving the final estimate.[21] The level of significance was 5%.

Results

Baseline characteristics

A sample of 1,717 urban adults (≥ 18 years) was evaluated in this study. Table 1 shows the distribution of the studied sample and the prevalence of PI individuals adjusted for the population according to age groups (in years) and the expected number of PI in the population. In the general population, the prevalence of PI individuals was 65.8% (95% CI: 62.2%-69.5%) and 34.2% (95% CI: 30.5%-37.8%) for the PA group. Regarding gender and age range, there was a higher prevalence of PI among women in both age groups 18 to 39 years and ≥ 70 years (women 73.9% and men 56.3%; p = 0.006 and women 83.1% and men 72.7%; p = 0.03, respectively). No differences were found between genders in the other age groups.

Table 2 demonstrates the levels of physical activity estimated for the population and related to demographic data (age, gender, education and socioeconomic status), as well as risk factors (HT, obesity and MetS). Table 2 also shows the prevalence ratios among the studied variables in the PI individuals.

Table 1 - Prevalence of physically inactive individuals according to age groups (in years) and the expected number in the population

Age groups (years)	Sample (n)	CP - PA (%)	CP - PI (%)	Number of inhabitants for each age group	Expected number of PI in the population
18 to 39	220	34.5	65.5	145,938	95,589
40 to 49	395	35.7	64.3	48,637	31,273
50 to 59	449	33.6	66.4	32,416	21,524
60 to 69	375	37.3	62.7	21,602	13,545
≥ 70	278	21.9	78.1 *	15,133	11,819
Total	1,717	34.2	65.8	263,768	173,559

*CP: corrected for population of the city, PA: physically active, PI: physically inactive. * p = 0.03: ≥ 70 group vs all groups.*

Table 2 - Characteristics of the population stratified according to gender, socioeconomic status, formal education, body mass index, hypertension and metabolic syndrome

		N	CP (95% CI)	PI (%)	PA (%)	PI prevalence ratio	p-value
Gender	Male (M)	837	48.4 (44.6-52.2)	60.1	39.9	PI F/M: 1.19	0.003
	Female (F)	880	51.6 (47.8-55.4)	71.2	28.8		
Socioeconomic status	AB	376	19.8 (17.0-22.7)	58.0	42.0	AB/DE: 1.13	
	C	719	43.2 (39.4-47.0)	69.7	30.3	C/AB: 1.20	0.03
	DE	622	37.0 (33.2-40.7)	65.7	34.3	C/DE: 1.06	
Schooling	< 11 Years	1225	60.7 (56.9-64.5)	69.5	30.5	PI < 11y/> 11y: 1.15	0.02
	> 11 Years	492	39.3 (35.5-43.1)	60.2	39.8		
BMI	Normal Weight	676	44.6 (40.7-48.4)	64.5	35.5	N/Ob: 0.94	
	Overweight	645	33.2 (29.7-36.7)	65.8	34.2	N/Over: 0.98	NS
	Obesity	396	22.2 (19.1-25.4)	68.7	31.5	Over/Ob: 0.96	
Blood pressure	Hypertensive	762	25.4 (22.8-27.9)	27.5	21.4	PI HT/PA HT: 1.28	0.04
	Normotensive	955	74.6 (72.2-77.4)	72.5	78.6		
MetS	with MetS	467	22.7 (19.4-26.0)	26.1	16.7	PI MetS/PA MetS:1.56	0.007
	without MetS	902	77.3 (72.2-79.0)	73.9	83.3		

The socioeconomic status is divided into 3 grouped social classes (AB, C and DE). All the data were corrected for the total population of the city. The statistical analysis was performed by estimation and population association testing by means of the method of weighted least squares. CI: confidence interval, CP: corrected for population of the city, BMI: body mass index, MetS: metabolic syndrome, PI: physically inactive, PA: physically active, N: normal weight, Ob: obesity; Over: overweight, NT: normotensive, HT: hypertensive.

The prevalence of PI individuals was higher among women as compared with men, with a prevalence ratio of 1.19 (p = 0.003). There was a lower prevalence of PI in class AB, in comparison with class C (p = 0.03). The prevalence rate of PI among those with lower educational levels when compared with those with higher educational

level was 1.15 (95% CI: 1.02 to 1.31%) (p = 0.02). There was no difference regarding PI prevalence ratios in the groups of evaluated BMI (table 2).

Hypertension

The corrected prevalence of HT in the studied population was 25.4% (95% CI: 22.8%-27.9%). The PI/PA prevalence ratio was 1.28 (95% CI: 1.01-1.64) (p = 0.04) showing a lower prevalence of HT in active subjects (table 2).

Metabolic syndrome

The corrected prevalence of MetS for the studied population was 22.7%. The sedentary / active prevalence ratio was 1.56 (95% CI:1.10-2.23; p = 0.007) (table 2).

Biochemical data (TC, LDL-c, HDL-c, TG, glucose) and the presence of MetS were evaluated in 1,369 subjects who completed the examinations.

Lipid profile and blood glucose

The bootstrap statistical method was used to assess the physical activity, associated with serum lipids and blood glucose levels. The levels of total cholesterol, LDL-c and TG were higher in the physically inactive than in physically active individuals (189.1 ± 1.8 vs 183.3 ± 3.1 mg / dL; 116.5 ± 1.4 vs 111.6 ± 2.6 mg / dL and 134.8 ± 4.2 vs 126.5 ± 0.9 mg / dL, respectively). The images demonstrate a rightward shift of the curve, with a tendency for higher plasma levels of these lipoproteins in physically inactive subjects (Figure 1, panels A, C and D for TC, LDL-c and TG, respectively). For HDL-c, the curves are practically superimposed (46.3 ± 0.7 mg / dL in the physically inactive and 46.9 ± 1.0 mg / dL in the active individuals) (Figure 1, Panel B). Concerning blood glucose, sedentary individuals showed a rightward shift of the curve, which demonstrated a clear tendency for higher levels of glucose in the physically inactive group (84.1 ± 1.2 mg / dL for PI and 79.4 ± 0.9 mg / dL for PA) (Figure 2).

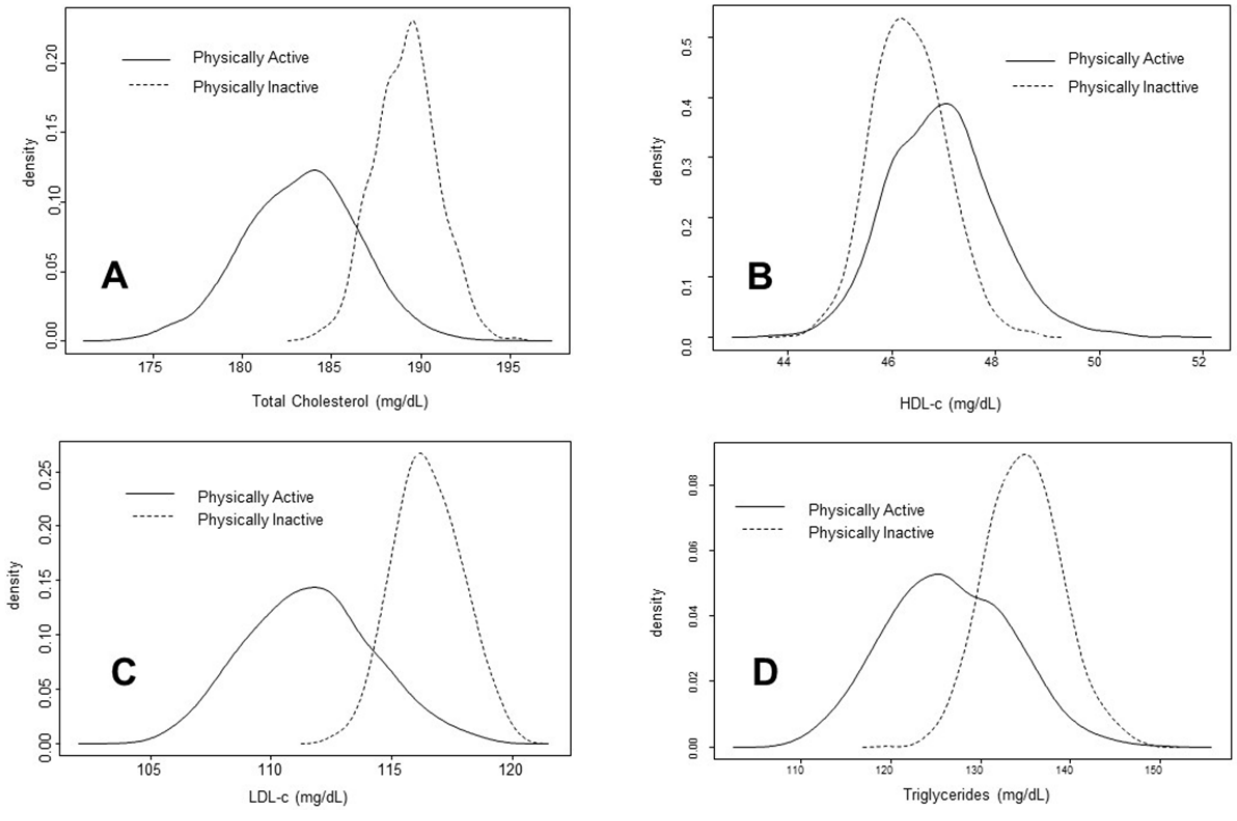

Figure 1 - Distribution of lipid parameters in relation to physical activity. The figure shows the following panels: total cholesterol level (A), HDL-c (B), LDL-c (C), TG (D) in relation to physical activity levels (physically active or inactive). The levels of total cholesterol, LDL-c and TG were higher in physically inactive individuals than in physically active ones (189 vs. 183 mg/dL; 116 vs. 111 mg/dL and 134 vs. 126 mg/dL, respectively) (Panels 1A, 1C and 1D). For HDL-c, the curves are practically superimposed (46.3 mg/dL in physically inactive individuals and 46.9 mg/dL in active ones) (Panel 1B). HDL-c: high density lipoprotein; LDL-c: low density lipoprotein; TG: triglycerides.

Discussion

This study assessed various aspects related to overall physical activity in the urban adult population and its importance in the prevention of risk factors for CVD and T2DM. A total of 1,717 individuals of different age groups and sample data adjusted for the population were studied. As expected, a high prevalence of physically inactive subjects was detected (65.8%). Indeed, previous studies have shown a large range in the prevalence of physical inactivity.[11,22-24] In addition, our findings showed prevalence of PI higher than 62% in all age groups, with the highest prevalence in the group > 70 years (78.1%), similar to that of previous studies.[11,24]

The difference between genders showed a high prevalence of PI in women in comparison with men (71.2 and 60.1%, respectively), mainly in the extremes of the age groups. In agreement with our data, studies have shown a greater PI in women (55.5%) as compared with men (42%).[25] The reason for the lower practice of physical activity at those age ranges might be the beginning of the career and/or professional activities for the young individuals, whereas for individuals aged > 70 years, it could be due to the lack of stimulus to perform physical exercise or mobility issues.

Regarding formal education levels, this study clearly showed that PI was 15% higher in the group with lower education. Other authors also showed a higher physical activity rate related to higher educational levels and an inverse association between the educational level and work-related physical activity.[26,27]

According to the socioeconomic level, there was a predominance of PI individuals in all the social classes. However, a significant difference was observed only between classes AB and C. The frequency of PI was 20% higher in class C compared to AB, probably due to increased LTPA in the AB group. Some authors have also reported the prevalence of PI during leisure time, rather than at work, as a risk behavior in relation to cardiorespiratory and metabolic health.[28,29] On the other hand, socioeconomic class DE showed a lower frequency of PI compared to C, due to a large number of workers with higher frequencies of domestic and transport-related physical activities, namely cycling or walking.[30]

Regarding BMI, 55.4% were overweight or obese, although the prevalence of PI in the studied groups was not significantly different. Overweight and obese individuals were probably advised to practice physical exercise, which might have led to the observed results. Interestingly, obese women with high levels of physical activity appear to have staved off the actual development of CAD and CVD.[31] Nonetheless, sedentary individuals have shown a higher risk of increasing BMI over the years.[32]

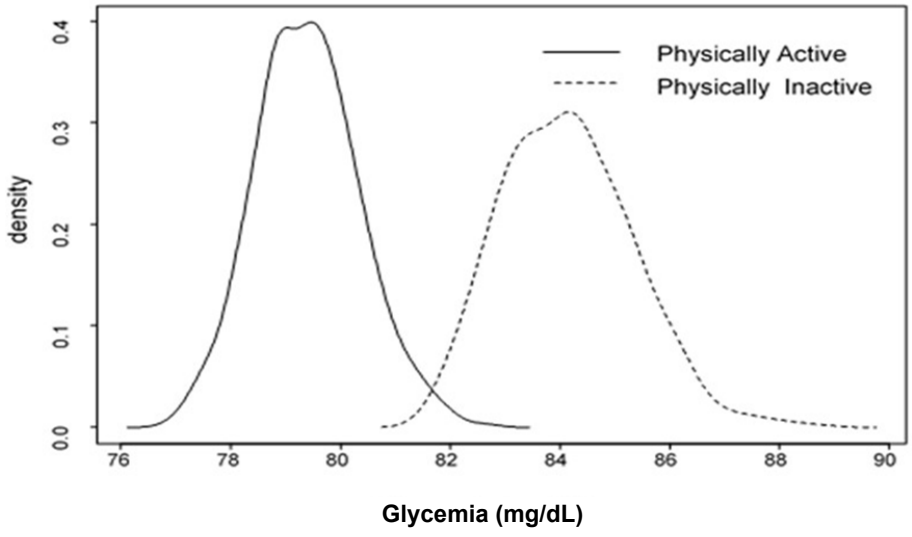

Figure 2 - Distribution of glycemic levels in relation to physical activity. The figure demonstrates a clear tendency for higher levels of glucose in the physically inactive group (84.1 mg/dL vs. 79.4 mg/dL).

Hypertension

In the present study, there was a 28% higher probability of HT in PI individuals. In turn, studies have shown a reduced prevalence of HT related to a higher rate of physical activity.[33,34] Physical activity decreases total peripheral resistance by improving endothelium-dependent relaxation, mainly mediated by a significant increase in vascular nitric oxide (NO) production and/or decrease in NO scavenging by reactive oxygen species (ROS). Moreover, exercise has also been shown to release several cytokines and anti-inflammatory peptides, which in turn increase NO bioavailability by decreasing ROS production. Exercise-related vasodilation was also associated with the growth of new arterioles and the reduction of nervous sympathetic activity.[34]

Metabolic syndrome

It was observed a 56% higher probability of MetS in PI individuals. Several studies have found that the practice of LTPA was associated with a reduction in MetS components.[35-37] Longer duration of daily physical activities leads to a lower prevalence of MetS, especially for the components of central obesity and HDL-c levels.[37] Moreover, a recent study showed that middle-aged individuals with MetS who usually perform physical activity had lower arterial stiffness and more favorable cerebral white matter integrity than their sedentary peers.[38]

Lipid parameters

The analysis of bootstrap in the PI group showed a tendency for higher levels of lipoproteins (TC, LDL-c and TG), when compared with PA subjects. Physical exercise has shown beneficial effects on plasma lipoproteins, such as decrease in TC, LDL-c, and TG levels.[39,40] Spending less time in sedentary behaviors, and having medium levels of intense physical activity may be associated with a more favorable blood lipid profile.[40]

Blood glucose

The bootstrap method curve showed a rightward shift in the PI group, and, consequently, lower glucose levels in the PA group. Data have shown an inverse association between physical activity and blood glucose.[34,35] Studies have demonstrated that improved blood glucose control is due to increased insulin sensitivity and glucose metabolism promoted by physical exercise.[37]

Strengths and limitations

Some limitations of this study should be mentioned. First, the guidelines of the American Diabetes Association[18] recommend the confirmation of hyperglycemia through a second blood glucose measurement, which was not performed in this study. However, epidemiological studies, including NHANES, used almost exclusively a single blood glucose measurement for the diagnosis of T2DM. Second, the interference of antilipemic drugs on lipid values determination was not assessed. Third, the association between physical activity and its benefits in preventing CVD risk and T2DM could be better evaluated in a cohort study rather than a cross-sectional one. Nevertheless, this fact does not invalidate the present study since that its main objective was to evaluate the prevalence of physical inactivity in the urban population. The benefits of physical activity could be better assessed through a cohort study, which is not the goal of this study. On the other hand, this population-based, age-stratified study, is unique as it gathers different demographic, epidemiologic and risk factors involved in the association between physical activity, hypertension and CVD in a single sample with a population assessment calculation, which might be extrapolated to other populations.

Conclusions

This study shows a high rate of physical inactivity in all age groups, higher among women and with differences in the prevalence according to the socioeconomic and educational levels. It also demonstrates a clear association between physical inactivity and the presence of cardiovascular risk factors, mainly hypertension, hyperglycemia and lipid changes, observed by the bootstrap method.

Author contributions

Conception and design of the research: Cipullo JP, Ciorlia LAS, Cesarino CB, Vilela-Martin JF. Acquisition of data: Cipullo JP, Ciorlia LAS, Cesarino CB, Vilela-Martin JF. Analysis and interpretation of the data: Rissardi GGL, Cipullo JP, Giollo Junior LT, Vilela-Martin JF. Writing of the manuscript: Rissardi GGL, Moreira GC, Vilela-Martin JF. Critical revision of the manuscript for intellectual content: Giollo Junior LT, Zanesco A, Vilela-Martin JF.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of Doctoral submitted by Geiza da Graça Leite Rissardi, from *Faculdade de Medicina de São José do Rio Preto*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Pesquisa da Faculdade de Medicina de São José do Rio Preto* (FAMERP) - SP under the protocol number 057/2004. 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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International Journal of Cardiovascular Sciences. 2018;31(6)603-609

ORIGINAL ARTICLE

Prevalence of Metabolic Syndrome in Three Regions in Venezuela: The VEMSOLS Study

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Abstract

Background: No previous study has evaluated the prevalence of metabolic syndrome (MS) in more than one region in Venezuela.

Objective: To determine the prevalence of MS in three Venezuelan regions.

Methods: From 2006 to 2010, a total of 1,320 subjects aged ≥ 20 years were selected by multistage stratified random sampling from the regions of Lara State (western region), Mérida State (the Andean region), and Capital District (Capital Region). Anthropometric measurements, blood pressure, and biochemical analysis were obtained from each participant. MS was defined according to the harmonized Joint Interim Statement (2009) definition.

Results: Mean age was 44.8 ± 0.39 years and 68.5% of the participants were female. The overall prevalence of MS was 35.7% (95% confidence interval 32.2 – 39.2%), while the prevalence was 42.5% (95% CI 38.8 – 46.1%) among men and 32.6% (95% CI 29.1 – 36.0%) among women ($p < 0.001$). In women, the prevalence of MS increased at almost every decade of life, while in men, the prevalence was similar from the age of 30 years onwards. The most prevalent abnormalities were low HDL-c levels (58.6%, 95% CI 54.9 – 62.1%), abdominal obesity (52.0%, 95% CI 48.4 – 55.7%), and elevated triglycerides levels (39.7%, 95% CI 36.1 – 43.2%). The prevalence of MS increased with increasing body mass index categories.

Conclusion: In Venezuela, MS is a highly prevalent condition, which increases the risk of type 2 diabetes and cardiovascular disease in a large number of subjects. (Int J Cardiovasc Sci. 2018;31(6)603-609)

Keywords: Metabolic Syndrome/epidemiology; Obesity; Venezuela/epidemiology; Risk Factors; Cardiovascular Diseases; Diabetes Mellitus, Type 2.

Introduction

Metabolic syndrome (MS) is a cluster of cardiometabolic risk factors characterized by dysfunctional adipose tissue and insulin resistance,[1,2] clinically expressed by atherogenic dyslipidemia, abdominal obesity, increased blood pressure, and elevated blood glucose concentration. Subjects with MS have increased risk of cardiovascular diseases and type 2 diabetes (T2D).[3]

Although many controversial issues exist around MS,[4] assessing this syndrome is pathophysiologically and epidemiologically relevant[5] to determine regional differences in cardiometabolic diseases and risk. The International Diabetes Federation, American Heart Association, and National Heart, Lung and Blood Institute have standardized their criteria for the definition of MS. These updated diagnostic criteria maintained the components defined by the last National Cholesterol Education Program/Adult Treatment Panel III (NECP/ATP-III) modification in 2005,[6] and recommended the use of specific cutoff values of waist circumference for each ethnic group or population. A cutoff for abdominal

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obesity (waist circumference ≥ 94 cm in men and ≥ 90 cm in women) in the Latin American population has been proposed.[7] Considering that the level of fat mass linked to MS differs among regions, applying these abdominal obesity ethnic-specific cutoffs can improve the detection of cardiometabolic risk factors. Comparing with Caucasians and similar to Asian populations,[8] MS is present at lower levels of waist circumference in Latinos[7] and Venezuelans.[9]

Two major studies have reported the MS prevalence in Venezuela. Florez et al.,[10] evaluating 3,108 adults from the Zulia Region, found the prevalence of MS according to the NCEP/ATP-III[11] to be 31.2%, and the prevalence of atherogenic dyslipidemia (elevated triglycerides and low high-density lipoprotein cholesterol [HDL-c]) to be 24.1%. In Barquisimeto city, located in the western region of the country, the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study,[12] which applied the NCEP/ATP-III definition[11] and included 1,848 adults, reported a prevalence of MS of 25.8%. The limitation of these studies was that they only included one Venezuelan region, prompting the design of the Venezuelan Metabolic Syndrome, Obesity and Lifestyle Study (VEMSOLS). This article presents the results of this study, specifically, the MS prevalence in five populations of three regions of Venezuela.

Methods

Design and subjects

An observational, cross-sectional study was designed to determine the prevalence of cardiometabolic risk factors in a subnational cohort in Venezuela. Five municipalities were evaluated in three regions in the country: Palavecino Municipality in Lara State (urban), located in the western region; Ejido Municipality (Mérida city), in Mérida State (urban) and Rangel Municipality (Páramo area) in Mérida State (rural), both located in the Andes region; and Catia La Mar Municipality in Vargas state (urban) and Sucre Municipality in Capital District (urban), both in the Capital Region. During the years 2006 and 2010, a total of 1,320 subjects aged ≥ 20 years who had lived in their homes for at least 6 months were selected by two-stage random sampling. The assessment included three different geographic regions in the country – the Andes, mountains in the south; Western, Llanos in the middle; and Capital District, coast in the north. Each region was stratified by municipalities, and one was randomly selected. Map and census of each location were required to delimit the streets or blocks, and to select the households to visit in each municipality. After selecting the sector to be surveyed at each location, the visits to the households started at house number 1 and moved up, skipping every two houses. Pregnant women and individuals unable to stand up and/or communicate verbally were excluded.

The sample size was calculated to detect a prevalence of hypercholesterolemia (the lowest prevalent condition reported in Venezuela) of 5.7%[12] with a standard deviation of 1.55%, which allows the calculation of a 95% confidence interval (95%CI). The minimum estimated number of subjects to be evaluated was 830. Overall, 1,320 subjects were evaluated (89.4% in the urban and 10.6% in the rural area).

Clinical and biochemical data

All subjects were evaluated in their homes or in a nearby health center by a trained health care team according to a standardized protocol. Each home was visited twice. In the first visit, the participants received information about the study and a written informed consent was obtained. Demographic and clinical information was obtained using a standardized questionnaire. Blood pressure was measured twice in the right arm supported at the level of the heart, with the subject in the sitting position, after 5 minutes of rest, and obtained with a calibrated aneroid sphygmomanometer. Weight was measured with the use of a calibrated scale with the individuals wearing as few clothes as possible and without shoes. Height was measured using a metric tape attached to the wall. Waist circumference was measured at the iliac crest, in a horizontal plane with the floor at the end of expiration. Body mass index (BMI) was calculated with the formula weight (in kg) divided by the squared height (in m^2).

In the second visit, blood samples were drawn after 12 hours of overnight fasting, centrifuged during 15 minutes at 3000 rpm within 30-40 minutes from the collection, and transported in dry ice to the central laboratory where the samples were properly stored at -40°C until analysis. Questionnaire information from the participants absent during the first visit was collected during this second visit. Plasma glucose, triglycerides, and HDL-c were determined by standard enzymatic colorimetric methods. The study was conducted according to the Declaration of Helsinki. The only invasive procedure performed was venipuncture, and no complications occurred.

Categorization of variables

MS was defined according to the definition of the harmonized Joint Interim Statement (2009)[13] as the presence of at least three of the following: abdominal obesity (waist circumference ≥ 94 cm in men or ≥ 90 cm in women),[7] triglycerides ≥ 150 mg/dL, HDL-c < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mmHg or antihypertensive treatment, and fasting blood glucose ≥ 100 mg/dL or self-reported diabetes. Additionally, the definition of MS according to the NCEP/ATP-III[11] was also applied to compare with previous reports. In this definition, elevated fasting blood glucose was set at ≥ 110 mg/dL, and abdominal obesity as waist circumference > 102 cm in men and > 88 cm in women. Individuals were classified according to their BMI as having normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2), or obesity (BMI ≥ 30 kg/m^2).

Statistical analysis

All calculations were performed using the program SPSS 20 (IBM Corp., Armonk, NY, United States). Data of continuous variables are presented as mean ± standard deviation. Blood glucose values are presented as median and interquartile range (IR) due to a nonnormal distribution. Differences between mean values were assessed by analysis of variance (ANOVA), with Bonferroni or Tukey adjustment for multiple comparisons. Differences between median levels of blood glucose were evaluated with the Mann-Whitney U test. The proportion of subjects with MS and its components are presented as prevalence rates and 95%CIs. The chi-square test was applied to compare different frequencies by gender and nutritional state. A p value < 0.05 was considered to be statistically significant.

Results

Subjects characteristics

Two-thirds of the study subjects were female. Men had higher weight, height, waist circumference, blood pressure, and blood glucose values than women (Table 1). There were no differences between genders for age and BMI.

Prevalence of metabolic syndrome

More than one-third of the subjects had MS (35.7%), and the frequency of this condition was higher in men than women (Table 2). Low HDL-c and abdominal obesity were the most frequent abnormalities. Most MS components were increased in men, except for low HDL-c levels, which were more frequent in women.

Table 1 - Subjects' characteristics

	Men	Women	Total	p
Participants (n, %)	412 (31.2)	908 (68.8)	1,320 (100)	
Age (years)	45.8 ± 0.73	44.4 ± 0.46	44.8 ± 0.39	0.086
Weight (kilograms)	80.1 ± 0.80	67.9 ± 0.48	71.7 ± 0.44	0.0001
Height (meters)	1.69 ± 0.00	1.56 ± 0.00	1.60 ± 0.00	0.0001
BMI (kg/m^2)	27.7 ± 0.25	27.6 ± 0.17	27.6 ± 0.14	0.633
Waist circumference (cm)	96.4 ± 0.65	89.8 ± 91.9	91.9 ± 0.35	0.0001
Systolic blood pressure (mmHg)	125.6 ± 0.94	118.9 ± 0.60	121.0 ± 0.51	0.0001
Diastolic blood pressure (mmHg)	80.8 ± 0.68	75.9 ± 0.39	77.4 ± 0.35	0.0001
Blood glucose (mg/dL)	88 ± 22.0	85.0 ± 19.0	85.0 ± 19.0	0.0001
HDL-c (mg/dL)	43.2 ± 0.51	47.2 ± 0.36	45.9 ± 0.30	0.0001
Triglycerides (mg/dL)	175.3 ± 6.90	140.0 ± 2.81	151.0 ± 2.93	0.0001

Data are represented as mean ± standard deviation. Blood glucose values are represented as median values ± interquartile range. BMI: body mass index. HDL-c: high-density lipoprotein cholesterol. LDL-c: low-density lipoprotein cholesterol.

In men, the prevalence of MS was lower in the 20 – 29 years age group, but was similar in all other age groups, ranging from 39.5% to 60.9% (Figure 1). In women, the prevalence of MS increased at almost every decade of life, and was lower in the 20 – 29 years age group (9.0%) and higher in the ≥ 70 years group (71.9%). Comparing genders, the prevalence of MS was higher in men until the fifth decade of life. The prevalence of MS increased at every category of BMI in women but was similar between men with overweight and obesity (Figure 2). The prevalence of MS in men with overweight and obesity was higher than that in women. The prevalence of MS according to the ATP-III was 30.6% (95% CI 28.1 – 33.0%) and was similar between genders, 30.1% (95% CI 25.6 – 34.5%) in men and 30.9% in women (CI 95% 27.8 – 33.9%, p = 0.415).

Table 2 - Prevalence of metabolic syndrome and its components by gender

	Men n = 412	Women n = 908	Total n = 1,320	p
Metabolic syndrome	42.5 (38.8 – 46.1)	32.6 (29.1 – 36.0)	35.7 (32.2 – 39.2)	0.0001
Elevated blood glucose	26.0 (21.7 – 30.2)	16.9 (14.4 – 19.3)	19.1 (16.9 – 21.2)	0.0001
Abdominal obesity	57.8 (54.2 – 61.2)	49.4 (45.8 – 53.1)	52.0 (48.4 – 55.7)	0.0001
Increased blood pressure	46.6 (42.9 – 50.2)	31.3 (27.9 – 34.6)	36.1 (32.6 – 39.5)	0.0001
Low HDL-c	42.2 (38.6 – 45.8)	66.0 (62.5 – 69.4)	58.6 (54.9 – 62.1)	0.0001
Elevated triglycerides	49.5 (45.8 – 53.1)	35.2 (31.7 – 38.7)	39.7 (36.1 – 43.2)	0.0001

Data are presented as percentages (95% CI). Chi-square test. Metabolic syndrome was defined as the presence of three of the following: abdominal obesity (waist circumference ≥ 94 cm in men and ≥ 90 cm in women), triglycerides ≥ 150 mg/dL, HDL-c < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mmHg or antihypertensive treatment, and elevated blood glucose ≥ 100 mg/dL or self-reported diabetes.

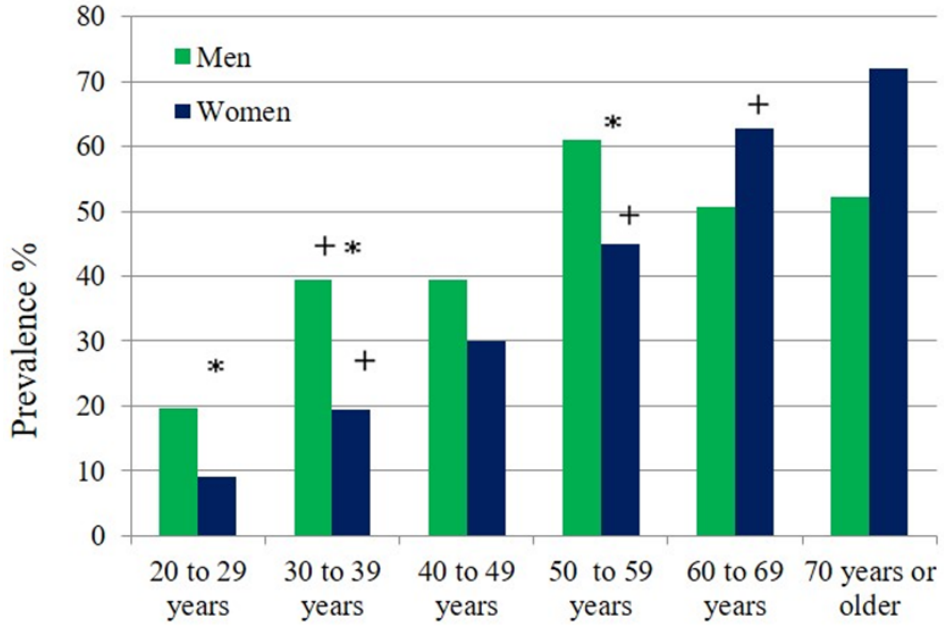

Figure 1 - Prevalence of metabolic syndrome (MS) by age and gender. (*) indicates a significant difference in MS prevalence between genders (p < 0.05; chi-square test). (+) indicates an increased MS prevalence in the indicated gender compared with the previous decade.

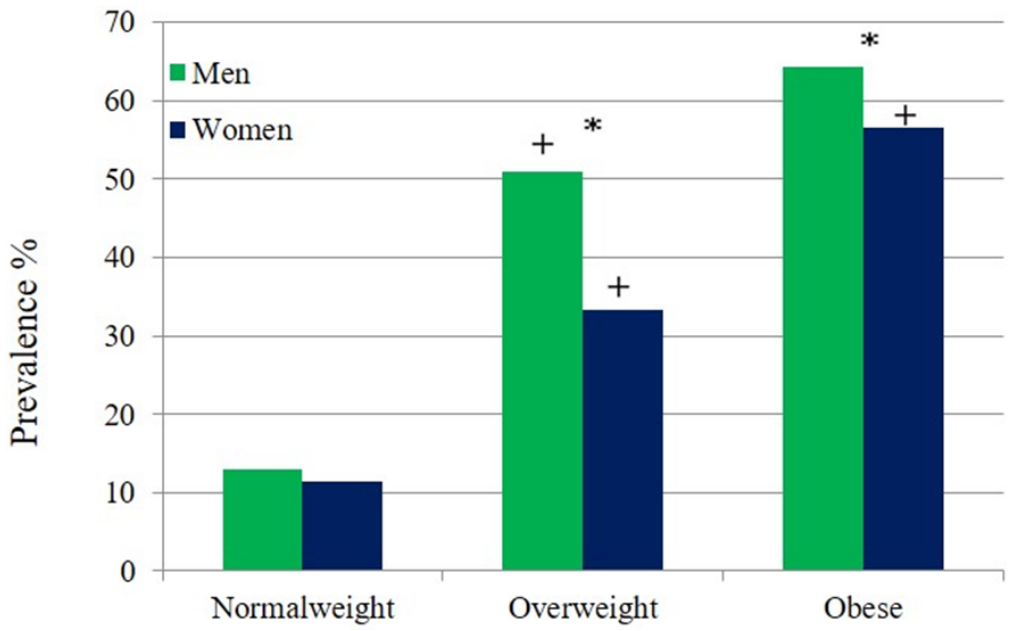

Figure 2 - Prevalence of metabolic syndrome (MS) by nutritional state and gender. (*) indicates a significant difference in MS prevalence between genders ($p < 0.05$; chi-square test). (+) indicates an increased MS prevalence in the indicated gender compared with the previous nutritional status.

Discussion

In this study, 35.7% of the subjects met the criteria for MS, while the most prevalent abnormalities were low HDL-c, abdominal obesity, and elevated triglycerides levels. These abnormalities increased with age and were more prevalent in men and subjects with overweight or obesity. These results are consistent with those of other studies conducted in Venezuela, which reported a prevalence of MS ranging from 27.4%, in 274 subjects from Mérida city[14] in the Andes region to 45.4% in 321 subjects in the Junquito municipality[15] in the Capital District. Using the NCEP/ATP-III definition, the prevalence of MS in this study was similar to that observed in the Florez et al. study (31.2%),[10] conducted in the Zulia region, but higher than that observed in the CARMELA study, conducted in Barquisimeto (25.8%).[12]

The prevalence observed in the present study is one of the highest reported in the American region. In a systematic review of MS in Latin American countries, the weighted prevalence of MS was 24.9% (range 18.8 – 43.3%).[16] A higher weighted mean for general MS prevalence has been reported in a Brazilian study (29.6%, range 14.9 – 65.3%).[17] The Central American Diabetes Initiative (CAMDI) study[18] included five major Central American populations and study data on 6,185 adults aged ≥ 20 years, with a survey response rate of 82.0%. This is higher than the data reported in the CARMELA study in Mexico City (27%).[12] The global prevalence of MS according to the NECP/ATP-III criteria was 30.3%, which is similar to the prevalence found in this study using the NECP/ATP-III definition. Compared with the population in the United States (US), the prevalence of MS in this report was similar to the one observed in Hispanics (35.4%) in the National Health and Nutrition Examination Survey (NHANES data 2003 – 2012); this population also showed an increasing prevalence of MS, from 34.3% in 2003 – 2004 to 38.6% in 2011 –2012.[19]

The higher prevalence of MS observed in this study using the most recent definition of MS can be explained, in part, by the different cutoff values applied. The NCEP/ATP-III definition[11] includes higher cutoff values for both elevated blood glucose (110 mg/dL) and abdominal obesity (using the cutoff values recommended for the US population). Therefore, the cutoff value to detect subjects with impaired fasting glucose was reduced to 100 mg/dL,[20] while the International Diabetes Federation[19] recommended the adaptation of the waist circumference cutoff values to ethnic and regional differences. Thus, for Latin American subjects, the values proposed are

lower than those for men in the US, which increased the prevalence reported. This most recent definition, with more strict cutoff values as in the GLESMO study,[7] represents more appropriately the real public health problem related to the prevalence of MS in Venezuela.

The prevalence of metabolic abnormalities also varies among studies. Low HDL-c values and abdominal obesity were the most prevalent abnormalities in Latin America (62.9% and 45.8%, respectively),[16] in the Zulia study (65.3% and 42.9%, respectively),[10] and in a Brazilian study, which found similar results as those in the present study (58.6 and 52%, respectively). Low HDL-c has been established as the most frequent lipid abnormality in Venezuela, observed in 90% of 100 subjects in Valencia city,[21] in the central region, and in 81.1% in those in the Junquito municipality.[15] Similar to the observations in men in the present study (49.5%), the above studies (Valencia and Junquito) also reported a high prevalence of elevated triglycerides values (51%),[15,21] compared with those found in Latin America, of 62.5%,[16] and in the CAMDI, of 48.1%.[18] These findings support the need to monitor lipid profile in those subjects with other metabolic abnormalities (abdominal obesity, high blood glucose levels, or hypertension), and not only total cholesterol, as frequently occurs in some Latin American countries.

The elevated prevalence of cardiometabolic risk factors in Venezuelan adults could explain the higher burden related to these conditions. Cardiovascular disease and T2D, the most important complications related to MS and dyslipidemia, were the leading disability-adjusted life years (DALYs) risk factors and the leading causes of death, with 44,100 deaths (31% of global death) in 2012.[22] Cardiovascular disease is the first cause of death in Venezuela.[22] Nutritional transition has promoted adverse nutritional and lifestyle habits in Venezuela and other Latin American countries, clearly contributing to the incidence of noncommunicable diseases, especially related to obesity and T2D.[23] Besides, an elevated weighted prevalence of physical inactivity (68%) has been reported in Venezuela in two studies involving 3,422 adults.[23]

The present study has some limitations. The cohort did not represent the entire population of Venezuela, as only three of the eight regions of the country were included. Additionally, in the VEMSOLS, the eating pattern and the physical activity of the population were not investigated in all regions. Despite these limitations, this study is the first to report on MS in more than one region in Venezuela. A national survey in Venezuela is currently ongoing (Estudio Venezolano de Salud Cardiometabólica, EVESCAM study) and data collection was completed in 2017.

Conclusions

One-third of the subjects assessed in this study presented MS, characterized by abdominal obesity and atherogenic dyslipidemia. These data suggest the need to explore possible environmental factors increasing the cardiometabolic risk, especially those related to lifestyle. Considering that MS is associated with a high risk of mortality and increased health care costs, the cardiometabolic consequences of an inappropriate lifestyle can be monitored through the detection of MS. The high prevalence of MS makes mandatory the implementation of national policies for the prevention of this condition. In practical terms, we recommend promoting the detection of subjects at risk, using both BMI and waist circumference routinely measured in primary care practice, and identifying all MS components when one of them is present.

Author contributions

Conception and design of the research: Brajkovich I,. González–Rivas JP, Rísquez A, Nieto-Martínez R. Acquisition of data: Brajkovich I, González–Rivas JP, Rísquez A, Nieto-Martínez R. Analysis and interpretation of the data: Brajkovich I, González–Rivas JP, Ugel E, Nieto-Martínez R. Statistical analysis: González–Rivas JP, Ugel E. Writing of the manuscript: Brajkovich I. Critical revision of the manuscript for intellectual content: González–Rivas JP, Rísquez A, Nieto-Martínez R.

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

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ORIGINAL ARTICLE

Comparison betweent the Effects of Swimming and Treadmill-Based Aerobic Training Protocols in Diabetic Rats

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Abstract

Background: Type 1 diabetes mellitus (DM1) can cause damage to several physiological systems.

Objectives: To compare and characterize the effects of aerobic exercise training (ET) performed by swimming with those of ET performed on a treadmill on the skeletal muscle and heart of rats with DM1.

Methods: 41 male Wistar rats were randomized into four groups: nondiabetic control (CTR), diabetic control (DMC), diabetic trained on the treadmill (DMT), and diabetic trained by swimming (DMS). The trained groups performed aerobic exercise training for 8 weeks, 5 times a week, 60 min per day. Exercise tolerance, blood glucose, body weight, wet weight of the skeletal muscles and left ventricle (LV), muscle glycogen, cross-sectional area of skeletal muscles, and cross-sectional diameter and collagen volume fraction of the LV were evaluated.

Results: The results were expressed as mean ± standard deviation of the mean and submitted to two-way ANOVA with post-hoc Bonferroni test. Aerobic ET protocols applied to animals with DM1, regardless of the ergometer, showed satisfactory results ($p < 0.05$) when compared to the control groups: improved exercise tolerance, increased glycogen content of the soleus and extensor digitorum longus (EDL) muscles and increased cross-sectional diameter of the left ventricular cardiomyocytes. In some variables, such as exercise tolerance and cross-sectional area of the soleus and EDL muscles, DMT showed better results than DMS ($p < 0.05$). On the other hand, DMS showed increased cross-sectional diameter of cardiomyocytes when compared with the DMT group.

Conclusion: Both aerobic ET protocols offered benefits to animals with diabetes; however, due to the specific characteristics of each modality, different physiological adaptations were observed between the trained groups. (Int J Cardiovasc Sci. 2018;31(6)610-618)

Keywords: Exercise; Physical Exertion; Rats, Wistar; Diabetes Mellitus; Exercise Test; Muscle, Skeletal.

Introduction

In Brazil, the current overall prevalence of diabetes mellitus (DM) is 7.6% and of these, 46% have not been diagnosed.[1] DM type 1 (DM1) is found in 5% to 10% of cases. This type is characterized by destruction of the insulin-secreting cells of the pancreas.[2] In the long term, DM1 can cause damage throughout the body and to several physiological systems, especially the kidneys, eyes, nerves, heart, and blood vessels.[3]

Cardiomyocytes are greatly affected by the disease. The development of "diabetic cardiomyopathy 1" (DC) may occur[4] and skeletal muscle can also be affected. In fact, a reduction in the muscle fiber size occurs and in cases of poor glycemic control, there can also be alterations in the distribution of muscle fiber types.[5]

Silva et al.,[4] showed that ET performed in a swimming pool increased the amplitude of cardiomyocyte contraction in animals with DM1 and controls. On the

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other hand, ET on a treadmill resulted in increased capillary density in Wistar rats and an increase in oxidative muscle fibers.[6] However, a comparison between the effects of ET performed on a treadmill and in a swimming pool is scarce in the literature.

We know that the environment where exercise is carried out influences the acquired adaptations. ET in water submersion tests requires different physiological adaptations than training performed on the ground.[7]

The main physical properties of water that show clinical relevance are density, buoyancy, hydrostatic pressure, turbulence, viscosity, surface tension, and refractivity.[8] Whereas in the swimming pool the individual is subject to the action of all of these properties to keep the upper airway above the level of water, on the treadmill, the gravitational force and the ground reaction force are the factors that most influence the movement performed out of water.[9]

Therefore, the aim of this study was to compare the effects of ET in animals with DM1 and thus perform the characterization of the cardiac and skeletal muscle adaptations following an ET protocol performed in two different ergometers, a treadmill and a swimming pool.

Material and methods

A cohort of 41 male Wistar rats was studied from 8 to 16 weeks of age. The animals were housed under controlled environmental conditions. The animals were assigned to four experimental groups: sedentary control (CTR) with 10 rats; sedentary diabetes mellitus (DMC) with 11 rats; diabetes mellitus submitted to swimming training (DMS) with 12 rats; diabetes mellitus submitted to treadmill training exercise (DMT) with 9 rats. This study was carried out in accordance with the National Research Council's Guidelines for the Care and Use of Laboratory Animals,[10] according to the Brazilian legislation on animal testing (Federal Law N°11,794 of 2008) and was approved by the Ethics and Research Committee (ERC) of UNIFESP (ERC #0384/12).

DM1 induction was carried out by administrating streptozotocin (STZ) (Sigma Chemical Company, St. Louis, MO, USA). A single dose of STZ (70 mg/kg) dissolved in citrate buffer (0.01 M, pH 4.5) was administered through the dorsal vein of the penis.[11,12]

Fasting blood glucose was estimated using a reagent strip and glucometer to confirm the diabetic state 7 days after the STZ injection. The animal was considered diabetic when glycemia was ≥ 200 mg/dL.[13,14] Animals with glycemia equal to or higher than 500 mg/dL were excluded from this experiment.

The animals in this experiment were trained individually with equal intensity in their respective tracks of aerobic/anaerobic transition (Lan). To identify the metabolic transition zone, a test to measure blood lactate during exercise was carried out to determine the maximum lactate steady state (MLSS).

Before performing the test cited earlier, the animals underwent a 5-day adaptation to their respective ergometers for 25 min/day.[15]

After 48 h of rest, the end of the adjustment period, the animals of the DMS group performed 20 min of continuous effort in the pool, bearing a load of 3% of their body weight on the first test day, 3.5% on the second day, 4% on the third day, and 4.5% on the fourth test day. Between each test, there was an interval of 48 h to allow for stabilization of serum lactate levels. The incremental load was tied to the back of the animals with an elastic band. During the test, blood samples were collected every 5 min from a cut in the tip of the tail for lactate determination.[15]

The animals submitted to treadmill training exercise (DMT) also underwent a lactate test similar to the group submitted to swimming training; however, the test was adapted to the treadmill. After 48 hours of rest at the end of the adaptation period, the animals performed 20 minutes of exercise on each test day. The protocol consists of 4 days of testing, starting on the first day with a velocity of 10m /min, and 5m / min added on each day of the test. Between each test day there was a 48-hour interval for the stabilization of lactate levels. Blood samples were taken every five minutes during the test at the distal end of the animals' tail to measure the lactate level of each animal.[15]

The exercise capacity of all groups was measured on the treadmill and estimated by the total distance. It was evaluated before the beginning of the exercise training protocols and after the end of the exercise training protocols on the eighth week, after 24 hours of rest. The test consisted of an initial walk with an initial speed of 3 m/min for 5 minutes for warming-up, with 3 m/min being added every 3 minutes until the animal showed signs of exhaustion.[16]

The exercise training protocol was initiated 20 days after DM induction.

Exercise training

Swimming

In the first week of the experiment, the animals from the DMS group were placed in a pool with 700 L of water, divided by glass tanks of different sizes. The water temperature was maintained at 33 ± 1º C. The training protocol consists of 1 session of 60 min/day, 5 days/week and intensity determined by the MLSS, for 8 weeks. At midpoint of the protocol, that is, the fourth week of training, there was a new lactate test to readjust the intensity of training, as animals suffer physiological adaptations and the intensity established at the beginning of the protocol would satisfy a lower intensity of animal Lan.

Treadmill

After the week of adaptation and determination of MLSS, the animals of the DMT group started the ET protocol over 8 weeks, 5 days/week, 60 min/day at an intensity corresponding to MLSS. At midpoint of the protocol, that is, the fourth week of training, a new lactate test was performed in order to readjust the intensity of training.

Glucose levels and body weight

Glucose measurement was performed at the tip of the tail in the following phases of the trial period: after 12 h of fasting; every 7 days during the experimental period. For the fasting blood glucose test, reagent strips were used and measured by a glucometer.

Body weight was evaluated under the same conditions and at the same time as glycemic control on a scale.

Euthanasia of animals

At the end of the experiment, rats were not handled for 24 h and after that they were anesthetized with ketamine (0.2 mL/100 g) and xylazine (0.1 mL/100 g), sacrificed by decapitation, and their tissues harvested. Cardiac chambers were dissected, and the left ventricle was weighed, as well as the right soleus and right extensor digitorum longus (EDL) muscles.

Skeletal muscle cross-sectional area

Soleus and EDL muscles were cut into 5-μm-thick sections using a cryostat and stained with hematoxylin and eosin for examination under light microscopy. Whole muscle cross-sectional area was evaluated at 200× magnification and further analyzed on a digitizing unit connected to a computer using the Axiovision program. All analyses were conducted by a single observer (EM), blinded to the rat's group.

Skeletal muscle glycogen content

The soleus and EDL muscles were digested in 30% KOH at 100°C and glycogen was precipitated by the addition of 100% ethanol. After precipitation, the sample was centrifuged at 3500 rpm for 30 min. The supernatant was then decanted off and the precipitated glycogen was obtained quantitatively by two successive extractions with trichloroacetic acid 5%. Glycogen was estimated using a colorimetric assay with an anthrone reagent (0.2% solution in 95% sulfuric acid). The protocol was adapted for skeletal muscle tissue from Balmain et al.,[17] and previously used by Voltarelli et al.[18] The values are expressed in microgram per gram of fresh weight.

Cardiac structural analysis

The left ventricles were then embedded in paraffin for histological processing. Sections (5 μm) were stained with hematoxylin and eosin for examination under light microscopy. Only nucleated myocytes from the transversally-cut muscle fiber areas were included in the cross-sectional diameter of cardiomyocyte analysis.[19] Quantification of left ventricular fibrosis was achieved using picrosirius red staining. Analyses were performed in a computer-assisted morphometric system.

Statistical analysis

The data are expressed as mean ± standard deviation. The normality of the data was verified through the Kolmogorov-Smirnov test. The effect of exercise training protocols was tested by one or two-way analysis of variance (ANOVA), as appropriate. When a statistically significant difference was achieved, post hoc comparisons between groups were performed using Bonferroni test. Statistical analyses were performed using Dell Statistica (version 12). The level of significance was set at $p < 0.05$.

Results

As expected, the diabetic groups (DMC, DMS and DMT) displayed statistically significant ($p < 0.05$) higher glycemia at the beginning of the protocol (Table 1) and the glycemia remained high at the end of the protocol. Moreover, DMT

group showed higher glycemia at the end of the protocol when compared to all other groups (Table 1).

In relation to body weight, diabetic groups (DMC, DMS and DMT) showed lower body weight when compared to the CTR at the end of the protocol. Only the CTR group showed a significant ($p < 0.05$) increase in body weight at the end when compared to the beginning of the protocol (Table 1).

Diabetic groups (DMC, DMS and DMT) displayed statistically significant ($p < 0.05$) lower exercise tolerance at the beginning of the protocol when compared to the CTR group. Only the DMT group showed a significant ($p < 0.05$) increase in exercise tolerance at the end when compared to the beginning of the protocol. Although the DMS group did not show a significant increase at the end compared to the beginning of the protocol, exercise tolerance was significantly higher ($p < 0.05$) than in the DMC group (Table 1) at the end of the protocol. The CTR group showed a decrease in exercise tolerance at the end compared to the beginning of the protocol.

The data related to the analysis performed in the soleus and EDL muscles are shown in table 2. The DMC group showed similar cross-sectional areas of soleus and EDL muscle fibers when compared to the CTR group. Only exercise training on the treadmill was able to increase this variable, since the DMT group showed greater areas in the fibers of both muscles when compared to the CTR, DMC and DMS groups ($p < 0.05$).

Regarding glycogen levels, the DMC showed similar levels in soleus but decreased levels in the EDL ($p < 0.05$) when compared to the CTR group. Both ET protocols were able to increase the glycogen levels in both muscles ($p < 0.05$). In addition, the DMS group showed a higher level in relation to the CTR group.

When comparing the wet weight of the soleus and EDL muscles, the DMC showed lower weights of both muscles corrected for tibial length when compared to the CTR group. The ET protocols used in this study had no effect on this variable, since no differences were found between the DMC, DMS and DMT groups. When correcting the weight of the muscles by body weight, there were no significant differences either and, for that reason, these data are not shown.

The data for the analysis carried out in the left ventricle are depicted in Table 3. The DMC group showed a cardiac cross-sectional diameter similar to that of the CTR group. However, the exercise-trained groups (DMS and DMT) showed higher ($p < 0.05$) cardiac cross-sectional diameter when compared to the sedentary groups (CTR and DMC). Moreover, the cardiac cross-sectional diameter of the DMS group was significantly ($p < 0.05$) higher than that of the DMT group. Left ventricular fibrosis assessed by collagen quantification was not different between the groups. Regarding the wet weight of the left ventricle, the DMC group showed a significant ($p < 0.05$) decrease when compared to the CTR group and the different

Table 1 - Glycemia, body weight and exercise tolerance before (pre) and after (post) 8 weeks of either sedentary status or exercise training

			Parameter		
			Glycemia (mg/dL)	Body weight (g)	Exercise tolerance (min)
Groups	Pre	CTR	70 ± 6	237 ± 15	29 ± 2
		DMC	229 ± 24 *a*	219 ± 8	19 ± 1 *a*
		DMS	282 ± 27 *a*	234 ± 8	21 ± 1 *a*
		DMT	250 ± 25 *a*	193 ± 7	20 ± 1 *a*
	Post	CTR	65 ± 8	381 ± 19 *	23 ± 2 *
		DMC	284 ± 18 *a*	196 ± 12 *a*	16 ± 1 *a*
		DMS	252 ± 12 *a*	227 ± 8 *a*	23 ± 2 *b*
		DMT	346 ± 27 *abc**	211 ± 10 *a*	28 ± 2 *b**

*CTR (n = 10), DMC (n = 11), DMS (n = 12), and DMT (n = 9). a ≠ CTR, b ≠ DMC, c ≠ DMS. * ≠ pre (p < 0.05). Results are presented as mean ± standard derivation of the mean; Two-way ANOVA with post-hoc Bonferroni test.*

Table 2 - Cross-sectional area, glycogen content and wet weight of the soleus and EDL muscles corrected for tibial length after 8 weeks of either sedentary status or exercise training

			Skeletal muscle		
			Cross sectional area (µm²)	Glycogen (ug/mg)	Wet weight (mg/cm)
Groups	EDL	CTR	82.0 ± 4.9	324.0 ± 23.8	74.8 ± 1.5
		DMC	50.9 ± 6.2	105 ± 14 *a*	26.1 ± 1.7 *a*
		DMS	70.3 ± 5.3	638.5 ± 57.8 *ab*	29.8 ± 1.2 *a*
		DMT	189.8 ± 17.0 *c*	500.6 ± 43.5 *ab*	27.5 ± 1.2 *a*
	Soleus	CTR	103.9 ± 39.3	90.4 ± 11.2	60.1 ± 2.8
		DMC	69.0 ± 1.9	46.1 ± 3.3	35.3 ± 1.5 *a*
		DMS	111.1 ± 7.8	162.7 ± 20.2 *ab*	38.7 ± 1.0 *a*
		DMT	318.4 ± 36.0 *c*	139.3 ± 8.9 *b*	36.1 ± 1.4 *a*

CTR (n = 10), DMC (n = 11), DMS (n = 12), and DMT (n = 9). a ≠ CTR, b ≠ DMC, c ≠ DMS, DMC and CTR (p < 0.05). Results are presented as mean ± standard derivation of the mean; One-way ANOVA with post-hoc Bonferroni test.

Table 3 - Cross-sectional diameter, collagen volume fraction and wet weight of left ventricle corrected for tibial length after 8 weeks of either sedentary status or exercise training

		Left ventricle		
		Cross-sectional diameter of cardiomyocytes (µm)	Collagen (%)	Wet weight (mg/cm)
Groups	CTR	18.8 ± 1.0	5.78 ± 0.45	225.8 ± 685
	DMC	17.8 ± 1.4	6.34 ± 1.03	162.2 ± 585 *a*
	DMS	34.6 ± 6.8 *ab*	8.15 ± 0.68	175.8 ± 449 *a*
	DMT	25.7 ± 1.0 *abc*	7.55 ± 0.69	161.3 ± 298 *a*

CTR (n = 10), DMC (n = 11), DMS (n = 12), and DMT (n = 9). a ≠ CTR, b ≠ DMC, c ≠ DMS (p < 0.05). Results are presented as mean ± standard derivation of the mean; One-way ANOVA with post-hoc Bonferroni test.

exercise training protocols were not able to change this variable (Table 4).

Discussion

Some studies show that aerobic ET aids in controlling blood glucose, whereas other studies showed no significant improvement regarding this control.[14,20] What is known and is widely discussed in the literature is that, physiologically, ET increases the expression of GLUT4 transporters, optimizing glucose uptake in muscle cells and accordingly, it is argued that this has a significant impact on the control of serum glucose, while maintaining hepatic glucose production stable.[21] However, this glucose control was not verified in our study.

Neither ET protocol was able to reestablish the body weight of the diabetic groups. Body weight maintenance is one of the variables affected by the clinical condition of DM1.[22] With the diminishing supply of glucose into cells, physiological mechanisms degrade other substrates that are available as energy sources, such as proteins and lipids, resulting in the loss of muscle mass, fat reserves, and consequently, loss of body weight. If a person has good glycemic control, these mechanisms

Table 4 - Demonstration of uncorrected weights in relation to the tibial length; soleus muscle, EDL muscle, left ventricle and tibial length

		Uncorrected weights and tibial length			
		Soleus (mg)	EDL (mg)	Left ventricle (mg)	Tibial (cm)
Groups	CTR	250.1	311.0	939.1	4.2
	DMC	131.6	97.3	604.5	3.7
	DMS	144.2	111.4	655.0	3.7
	DMT	134.5	102.8	600.5	3.7

are not triggered and this prevents progressive weight loss.[22,23] As the ET was not able to promote better glycemic control, the improvement of body weight did not occur, either.

The DMC group showed decreased exercise tolerance and the trained groups increased exercise tolerance after the ET protocol when compared with the DMC group. This result allows us to infer that DM1 had a negative influence on the exercise tolerance of the animal, and the ET, whatever the ergometer used, provided physiological adaptations to the diabetic animal, increasing exercise capacity. The DMT group was the only one with a significant improvement in exercise tolerance when compared to the results achieved before the experimental period. Adaptability and familiarity with the ergometer can explain this result,[24] as the exercise tolerance test was performed in the same ergometer in which the DMT group trained for 8 weeks.

Regarding the skeletal muscles, the diabetic groups showed lower weights when compared with the CTR group. This result confirms the activation of biochemical mechanisms to increase energy bioavailability in the bloodstream, as well as the difficulties of supplying energy to maintain the cell, which is caused by the lack of insulin caused by DM1.[22]

On the other hand, when we evaluated the cross-sectional area of the soleus and EDL muscles, we did not observe differences between the DMC and CTR groups. However, the ET on the treadmill was able to significantly increase the cross-sectional area of both muscles. ET leads to differentiation of muscle fiber types and the different types of fibers have different diameters. Although the soleus muscle has a predominance of type 1 fibers and the EDL muscle a predominance of type 2 fibers, there still exists a small percentage of other types of fibers that may influence this analysis. The histological technique used in this study did not allow us to differentiate between fiber types.[25,26] Furthermore, the biomechanics of movement in the ergometer should have favored the DMT group, as we analyzed agonist muscles.

Muscle fibers of different types also have different metabolic profiles. Thus, the soleus muscle has an oxidative metabolism and, consequently, greater reserves of glycogen, whereas the EDL muscle has a predominantly glycolytic metabolism and lower bioavailability of glycogen. As expected, the DMC group showed lower glycogen content when compared to the CTR group in the EDL because they had not received insulin 23. In the soleus muscle, this decrease in muscle glycogen levels did not show statistical difference.

Both ET protocols used in this study were able to increase glycogen content in both muscles when compared with the DMC group. This result corroborates the abovementioned data , where researchers claim that ET has the ability to increase the expression of the GLUT4 transporter.[21] This fact may have favored the entry of glucose into muscle cells. However, this action may not have been enough to affect serum glucose levels, which remained high even after the exercise training period. Possible explanations for the contrast observed in this study include the severity of STZ effects, which can vary between animals, and the intensity of the effort equivalent to metabolic transition, which may not be the most suitable one for obtaining the desired beneficial effects.[2]

Regarding the analysis carried out in the heart, although glucose was found to be high in the DMC group and to stay high in the trained groups, we found no differences in the collagen volume fraction between the groups, corroborating the results of Stilli et al.,[27] unlike the findings of other studies.[28,29]. Sears et al.,[30] also induced DM1 with STZ at similar doses to those

used herein. However, they found that diabetic rats had increased levels of collagen fibers after DM1 induction, which may indicate that there is some variability in the cardiac collagen fraction response of rats when DM1 is induced by STZ.[30] It may be possible that the period of DM1 may influence this response. Aside from that, the different techniques and types of collagen volume fraction assessment may also influence this response.

Bakth et al.,[31] induced mild DM1 in canines by administering low doses of alloxan for a period of 1 year. Despite the low doses and mild DM1, this greater period of DM1 led to increased collagen volume fraction in the myocardium of canines. Silva et al.,[28] also observed increased collagen in the left ventricle of rats. However, in this case, Silva et al. induced DM1 in rats by administering STZ, 60 mg/kg, intraperitoneally.[28]

Another cardiac morphological change that was observed in this study was the left ventricular wet weight. As expected, the DMC group had a decrease in ventricular weight when compared with the CTR group, similar to other studies that have found a decrease in heart weight[30,32] and left ventricular weight.[27] Neither of the exercise training protocols used in the present study was able to change the left ventricular wet weight.

On the other hand, cardiomyocyte hypertrophy was not observed in the DMC group, but the exercise training protocols used in the present study were able to increase the cross-sectional diameter of cardiomyocytes. There may have been a physiological hypertrophy since it is believed that ET can influence DNA replication and mitotic activity, which offsets the larger diameter induced by exercise training, compensating for the left ventricular weight. Thus, it may have decreased the number of cells, while increasing the size of those that remained. However, it is important to remember that we evaluated the wet weight of the ventricle, not the dry weight, which may result in other components influencing this remodeling of cardiomyocytes and ventricular mass.

The fact that swimming showed a more prominent increase in cardiac cross-sectional diameter may be due to the characteristics of this type of exercise, where the hydrostatic pressure exerted by water on the blood vessels leads to vasoconstriction and therefore, promotes increased venous return and preload.[33] It is known that increasing the preload promotes the addition of new sarcomeres in series, leading to an eccentric hypertrophy.[34] Furthermore, this increase in vasoconstriction also promotes increased post-load and stimulates the growth of cardiomyocytes by adding new sarcomeres in parallel and increasing the thickness of the heart wall to produce a stronger contraction to overcome this increased resistance.[34] In fact, swimming training was effective in increasing the width and cell volume of cardiomyocytes in rats with DM.[4]

Another factor that may have contributed to this more notable increase in cardiac cross-sectional diameter after swimming training is the increased adrenergic activity. There are studies in rats showing that swimming training leads to higher norepinephrine and adrenaline levels than exercise training on a treadmill, favoring the activation of the sympathetic nervous system.[35] It is known that catecholamines exert cardiac hypertrophic effects through adrenergic action, especially in pathological conditions.[36-39] Therefore, perhaps a higher cardiac adrenergic action may have contributed to increased cardiomyocyte hypertrophy in DMS, when compared with DMT. It is likely that this cardiac remodeling observed in the trained animals reflected an improvement in cardiac function, which must have influenced the superior performance in terms of exercise tolerance compared with the DMC group.

However, it is important to note that our study did not evaluate the number of cardiomyocytes, or the adrenergic activity of each training protocol and its association with cardiac hypertrophy is speculative. Nevertheless, it is undoubtedly an interesting topic for future investigations.

Conclusion

The aerobic ET protocols applied to animals with DM1, irrespective of the ergometer, offered benefits in some regards: increased glycogen content of the soleus and EDL muscles and increased cross-sectional diameter of cardiomyocytes. For some variables, such as exercise tolerance and the cross-sectional area of the soleus and EDL muscles, the DMT showed better results than DMS group. On the other hand, the DMS showed increased cardiac cross-sectional diameter when compared with the DMT group.

Author contributions

Conception and design of the research: Moura EOC, Nogueira E, Gomes R, Medeiros A. Acquisition of data: Moura EOC, Tanaka K, Mattos K, Brum PC. Analysis and interpretation of the data: Moura EOC, Tanaka K.

Statistical analysis: Gomes MFP. Writing of the manuscript: Medeiros A. Critical revision of the manuscript for intellectual content: Estadella D, Medeiros A.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade Federal de São Paulo* - UNIFESP under the protocol number 0384/12.

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ORIGINAL ARTICLE

Effects of Conventional and Virtual Reality Cardiovascular Rehabilitation in Body Composition and Functional Capacity of Patients with Heart Diseases: Randomized Clinical Trial

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Abstract

Background: Virtual reality is an alternative therapeutic resource to be inserted into cardiovascular rehabilitation, stimulating the practice of physical activity through man-machine interaction.

Objective: To compare the effects of conventional and virtual reality cardiac rehabilitation on body composition and functional capacity in patients with heart disease.

Methods: Randomized clinical trial with 27 cardiac patients divided into conventional rehabilitation group (CRG) and virtual reality rehabilitation group (VRG). They underwent a rehabilitation program with 60-minute training sessions twice a week for eight weeks. The VRG training consisted of exercises from the Xbox 360® with Kinect™, using YourShape™ and Dance Central 3™ games. The CRG used conventional treadmills for aerobic exercise and free weights for resistance exercise. Bioimpedance and 6-minute walk test (6MWT) were evaluated at baseline and after training. For main outcome analysis, Student t and Mann Whitney tests were used with a 5% significance level.

Results: The VRG showed a significant increase in body fat percentage and fat weight when compared to the CRG, and a smaller amount of total water. There was a significant improvement in functional capacity evidenced by the increase in the distance covered in the 6MWT (54.00 m and 32.25 m in the CRG and VRG, respectively), but the gains did not differ between the groups.

Conclusion: The two rehabilitation modalities had no effect on the body composition of the groups. In addition, the improvement in functional capacity was similar in both groups. (Int J Cardiovasc Sci. 2018;31(6)619-629)

Keywords: Cardiovascular Diseases; Cardiac Rehabilitation; Physical Therapy Modalities; Body Composition; Virtual Reality Exposure Therapy.

Introduction

Cardiovascular diseases (CVD) are a major cause of mortality worldwide, with approximately 17.5 million deaths, accounting for three in every ten deaths.[1] In Brazil, despite the progressive decline in deaths due to CVD, they remain the major cause of hospitalization and mortality, accounting for 31.3% of adult deaths.[2,3]

Therefore, cardiovascular rehabilitation programs, by use of physical activity, are essential to improve cardiovascular function and aerobic capacity, in addition to providing psychological benefits, risk factor control, improvement in CVD symptoms and mortality reduction.[4-6]

The advance of cardiovascular rehabilitation has witnessed the incorporation of technology to its methods, with virtual reality (VR) being included into physical therapy protocols[7,8] to boost physical activity practice[9] and encourage the rehabilitation process.[10] Virtual reality uses devices that promote man-machine integration,

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allowing real-time three-dimensional movement.[11] The videogames that adopt physical interaction with the user are called "exergames"[12,13] and provide body motion as a form of exercise.[14]

Physical exercise influences physical fitness, whose components include flexibility, muscle strength, cardiorespiratory endurance and body composition.[15] The studies by Mandic et al.,[16] and Calegari et al.,[17] have shown that the regular practice of physical activity has favorable effects on the body composition and functional capacity of individuals with CVD. However, whether the VR intervention as a physical exercise modality has benefits similar to those of the cardiovascular rehabilitation process remains controversial. This study hypothesized that, after implementing conventional and VR cardiac rehabilitation, individuals have similar improvement in body composition and functional capacity.

This study aimed at comparing the effects of conventional and VR cardiac rehabilitation on the body composition and functional capacity of individuals with CVD. In addition, food frequency and blood glucose levels were assessed.

Methods

Ethical aspects

The individuals included in this study were informed about all the procedures and provided written informed consent to participate. This study was approved by the Ethics Committee of the institution (CAAE: 62437816.4.0000.5515) and abides by the CONEP resolution 466/2012. The registration of this randomized clinical trial can be found at Clinicaltrials.gov (NCT03169387).

Sample characterization

This is a parallel group randomized clinical trial conducted at the physical therapy clinic of the Oeste Paulista University (UNOESTE), in the city of Presidente Prudente, São Paulo, Brazil, from February to October 2017. The sample comprised 27 individuals divided into two groups: a conventional rehabilitation group (CRG) and a virtual reality rehabilitation group (VRG). Based on sample calculation, each group had at least 12 individuals, using the study by Pimenta et al. (2013)[18] as reference. Fat-free mass was used, with standard deviation of 4.02, difference to be detected of 3.8 for the two-tail hypothesis test, power of 80%, and significance level of 5%. Figure 1 shows the flow diagram of the participants in every phase of the study, in accordance with the recommendations of the CONSORT Statement.[19]

The random allocation sequence was generated by a researcher without previous contact with the participants by use of the Microsoft Office Excel® program, at an allocation ratio of 1:1.

The study included individuals over the age of 45 years, of both sexes, with CVD (coronary heart disease, postoperative period of coronary artery by-pass grafting, acute myocardial infarction, systemic arterial hypertension, diabetes mellitus). The inclusion criteria were as follows: hemodynamic stability (systolic blood pressure < 200 mmHg and diastolic blood pressure < 110 mmHg at rest, absence of angina, controlled arrhythmias, and resting heart rate < 120 beats per minute);[20] absence of arteriopathy and muscle or orthopedic changes; and no supervised physical activity in the previous 30 days. The exclusion criteria were as follows: decompensations (circumstances posing a risk to individual integrity) during the training protocol; lack of adaptation to the protocol; and participation frequency lower than 75%.

Experimental design

Participants underwent an initial evaluation to detect comorbidities, to establish the diagnosis, to collect the clinical history and medications used, and to measure the anthropometric variables. The following parameters were assessed before the intervention and eight weeks after that: body composition; waist circumference; food frequency; functional capacity; and blood glucose levels.

Anthropometric variables

Weight (in kilograms) was measured with a WELMY W300® scale (accuracy to the nearest 100 g), with the individual barefoot wearing light and comfortable clothes. Height (in meters) was measured with a Sanny® stadiometer (accuracy to the nearest 0.1 cm), with the individual barefoot, standing with his/her back to the height rule, feet together, head positioned in the Frankfurt plane, and the measuring rod lowered to the individual's head. Body mass index (BMI) was calculated based on weight and height (weight/height^2).

Body composition

Body composition was the study's primary outcome, and body fat percentage was defined as the primary variable. Body composition was assessed by use of

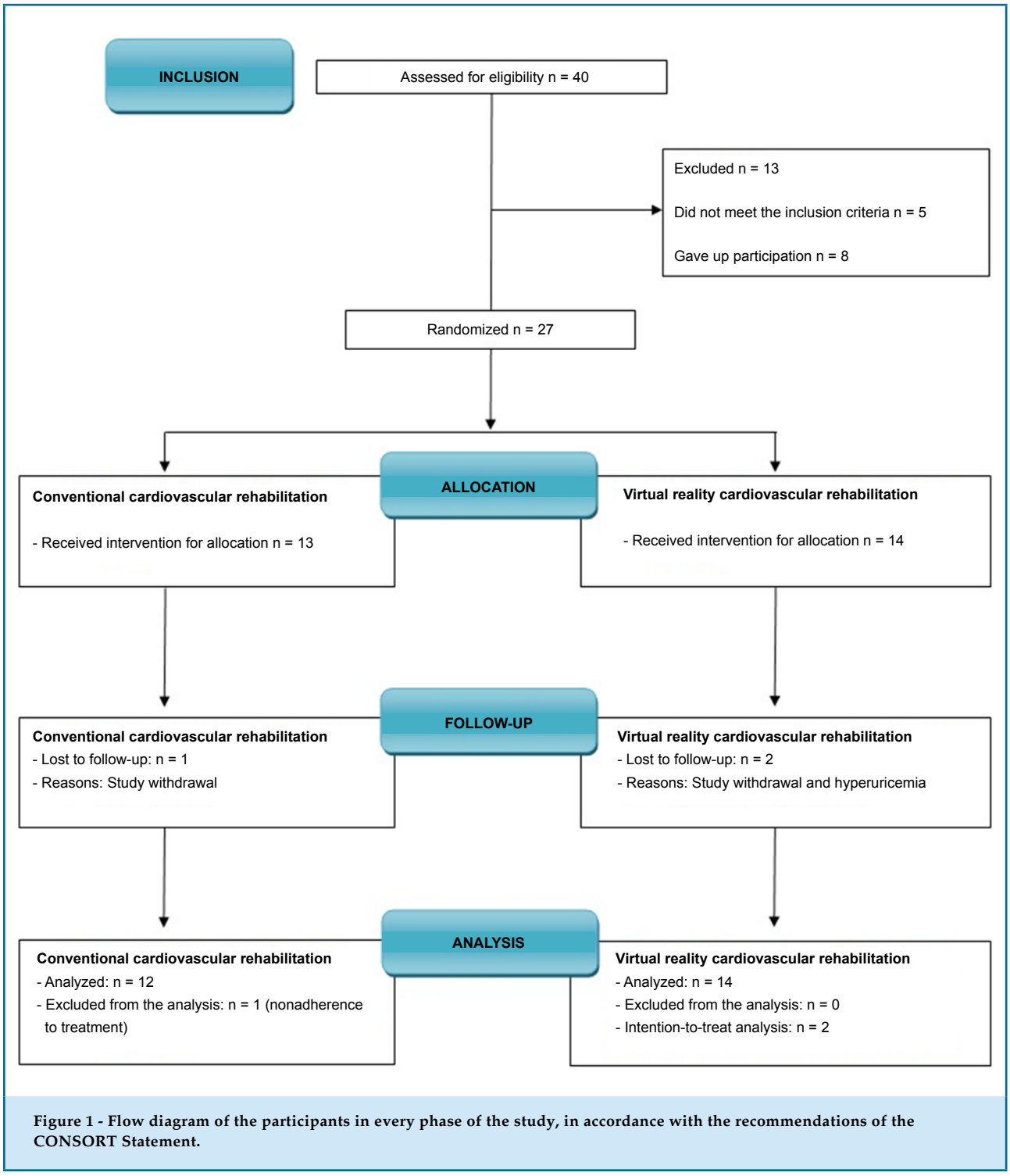

Figure 1 - Flow diagram of the participants in every phase of the study, in accordance with the recommendations of the CONSORT Statement.

bioimpedance analysis with a tetrapolar bioimpedance device (Biodynamics®, model 310e), analyzing and quantifying the body fat percentage, body fat weight, lean weight, basal metabolic rate, and percent and total water. Bioimpedance analysis measurements were taken in the morning, in fasting condition, after voiding the urinary bladder, having suspended diuretics for 24 hours, no alcohol and caffeine consumption for 24 hours, and no intense physical activity for 72 hours in both the initial and final assessment.[21,22]

Waist circumference

Waist circumference was measured with a non-distensible measuring tape (accuracy to the nearest 1 mm) and the subject standing, with parallel feet and arms hanging freely by the sides of the trunk. The measuring tape was placed in a horizontal plane around the abdomen, at the level of the umbilicus, just above the uppermost lateral border of the right iliac crest, not compressing the skin. Measurement (in centimeters) was taken three times, and the lowest value obtained was considered for analysis.[23]

Food frequency

The Food Frequency Questionnaire (FFQ) was used to assess the frequency of food consumption. The FFQ consists of a list of foods and beverages with response categories to indicate the frequency of consumption over the time queried. The frequency is registered in units of time (days, weeks, months or years) according to the need.[24]

Functional capacity

Functional capacity was assessed by use of the Six-Minute Walk Test (6MWT) performed according to the American Thoracic Society criteria.[25] The 6MWT was performed along a corridor of the UNOESTE gymnasium.

Blood glucose level

Postprandial capillary blood glucose level was assessed (milligram per deciliter) by use of an Optium Xceed® blood glucose meter that reads glucose in fresh capillary blood obtained by pricking the ring finger skin with a sterilized lancet. The measurements were taken before and after training in an individualized way.

Cardiovascular parameters

Heart rate was measured by use of a Sigma® cardiac frequency meter. Oxygen saturation was measured by use of a pulse oximeter (Choicemmed®, model Md300c1). With the subject in the sitting position, blood pressure was measured from the dominant arm, using a Premium® aneroid sphygmomanometer and a Littman® stethoscope, following the recommendations of the Brazilian guidelines on arterial hypertension.[26] The subjective perception of exertion was assessed by use of the Borg scale of perceived exertion.[27]

Training protocol

Both groups underwent 60-minute training sessions twice a week for eight weeks at the UNOESTE physical therapy clinic, adding up to 16 sessions. Four physical therapy students conducted the sessions, two for each group, and each student was responsible for two participants per session. In the initial and final 5 minutes, the following parameters were assessed: blood pressure, blood glucose level, oxygen saturation, and subjective perception of exertion by use of the Borg scale. During the entire session, the Borg scale was used and heart rate was assessed to ensure that the training heart rate calculated individually with the Karvonen formula would not be exceeded (50% to 80% of the reserve heart rate).[27,28]

The VRG training comprised the use of the Microsoft Kinect™ sensor for Xbox 360®, with a controller-free infrared camera that tracks user motion. Two games were used: Your Shape™ (Fitness Evolved) and Dance Central 3™. Your Shape™ (Fitness Evolved) is a program that allows users to exercise their upper and lower limbs in an isolated or combined way, and comprises mainly trunk rotation, diagonal flexion/adduction and extension/abduction movements, plantar flexion of ankle, hip flexion and squat. Dance Central 3™ is a music rhythm game involving performing given dance moves, which are tracked by Kinect. Both were performed for 25 minutes, the former in association with ankle Velcro weights and dumbbells as resistance. The increase in resistance was individualized and based on the Borg scale of perceived exertion (13: somewhat hard).[27]

The CRG training comprised the use of treadmills (Embreex®) for aerobic training for 30 minutes and free weights, with 1-4-kg dumbbells and 2-4-kg ankle Velcro weights, for resisted training, performed in three sets of 10 repetitions, with 1-minute recovery interval. The exercises comprised shoulder abduction, elbow flexion, knee extension and flexion, all performed in the sitting position, except for knee flexion, performed in the standing up position.[27] In the CRG training protocol, resistance was increased similarly to that in the VRG training protocol.

Statistical analysis

Data were assessed by use of the GraphPad Prism statistical software. Data normality of distribution was analyzed with Shapiro Wilk test. Proportion was compared by use of chi-square test. Paired analysis was carried out by use of paired Student t test in case

of normal distribution or Wilcoxon test for non-normal distribution variables. Intergroup comparisons were performed by use of absolute variation before and after the interventions, and nonpaired Student t test or Mann Whitney test were used according to data distribution. The magnitude of the differences between groups was described by calculating the effect size, using Cohen's d. The effect sizes considered were as follows: small ($d \leq 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$). Continuous variables were expressed as mean and standard deviation or median and interquartile range, according to normal data distribution. Categorical variables were expressed as absolute and percentage values with their respective confidence intervals. The significance level adopted was 5%.

Results

Clinical and anthropometric data

Table 1 shows the clinical and anthropometric data of the individuals assessed, whose mean age was 63.46 ± 8.12 years, most of whom were of the male sex. There was no significant difference between groups regarding age and anthropometry. Systemic arterial hypertension was the major comorbidity. Anti-hypertensives were the most frequently used medication.

Body composition

Table 2 shows the baseline and final body composition of both groups. The VRG showed a significant difference regarding the increase in body fat percentage and in fat weight, in addition to a decrease in basal metabolic rate and total water, while the CRG showed no significant difference. Waist circumference did not significantly differ between CRG and VRG.

Table 3 compares the absolute variation in body composition between the groups, evidencing significant differences regarding body fat percentage and fat weight, which were higher in the VRG, while total water was significantly lower in the VRG than in the CRG. The other variables showed no significant difference. The effect size

Table 1 - Baseline clinical and anthropometric characteristics of the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) expressed as mean ± standard deviation or absolute and percent value

Characteristics	CRG n = 12	%	VRG n = 14	%	p value
Age (years)	63.75 ± 8.65		63.21 ± 8.27		0.8734
Weight (kg)	78.48 ± 16.86		72.43 ± 10.69		0.2785
Height (m)	1.629 ± 0.08		1.635 ± 0.079		0.8598
BMI (kg/m²)	29.38 ± 4.80		27.02 ± 3.19		0.1491
Sex (m/f)	6/6	50/50	12/2	85.71/14.28	0.0492
Medications	**n**	**% / 95% CI**	**n**	**% / 95% CI**	
Antihypertensive agents	11	91.66 / 0.64-0.98	12	85.31 / 0.6-0.95	0.6358
Antiplatelet drugs	9	75 / 0.46 – 0.91	9	64.28 / 0.38 – 0.83	0.5551
Hypoglycemic agents	2	16.66 / 0.04 – 0.44	2	14.28 / 0.04 – 0.39	0.8668
Lipid-lowering drugs	8	66.66 / 0.39 – 0.86	10	71.42 / 0.45-0.88	0.7931
Beta-blockers	10	83.33 / 0.55 – 0.95	8	57.14 / 0.32-0.78	0.1492
Concomitant diseases	**n**	**% / 95% CI**	**n**	**% / 95% CI**	
SAH	11	91.66 / 0.64 – 0.98	13	92.85 / 0.68-0.98	0.9096
Diabetes mellitus	4	33.33 / 0.13 – 0.60	4	28.57/ 0.11-0.54	0.7931
AMI	8	66.66 / 0.39 – 0.86	6	42.85 / 0.21 – 0.67	0.2247

BMI: body mass index; m: male; f: female; n: number of individuals; CI: confidence interval; SAH: systemic arterial hypertension; AMI: acute myocardial infarction. Statistical tests: chi-square test to compare proportions, and nonpaired Student t test to compare continuous variables.

Table 2 - Body composition and waist circumference of the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) at baseline and study end, expressed as mean ± standard deviation

BIA / WC	CRG		p value	VRG		p value
	Baseline	Final		Baseline	Final	
Fat (%)	33.66 ± 4.83	33.25 ± 5.53	0.5271	28.34 ± 4.59	30.02 ± 4.28	0.0117*
Fat weight (kg)	26.27 ± 6.09	25.95 ± 6.9	0.5654	20.43 ± 4.1	21.79 ± 3.95	0.0191*
Lean weight (kg)	52.22 ± 12.62	52.33 ± 12.29	0.8512	51.87 ± 8.92	51.79 ± 9.08	0.9269
BMR (Kcal)	1605 ± 378.4	1591 ± 373.9	0.6638	1579 ± 269.4	1553 ± 276.6	0.0407
Water (%)	76.06 ± 1.50	72.99 ± 8.67	0.0664	76.16 ± 1.97	76.13 ± 1.83	0.8504
Total water (L)	39.73 ± 9.84	41.99 ± 14	0.3601	39.57 ± 7	38.61 ± 7.37	0.0241*
WC (cm)	102.2 ± 11.70	103.3 ± 12.64	0.3115	95.36 ± 8.758	96.64 ± 9.018	0.0823

*BIA: bioimpedance; WC: waist circumference; BMR: basal metabolic rate; * significant difference between study end and baseline. Statistical tests: paired Student t test or Wilcoxon test according to data normality.*

Table 3 - Comparison of the variations in body composition and waist circumference between the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) expressed as median and interquartile range (25%-75%)

BIA / WC	CRG	95% CI LL	95% CI UL	VRG	95% CI LL	95% CI UL	p value
Δ Fat (%)	0.10 [-1.87 - 1.32]	-1.784	0.9676	2.05 [0.75 - 3.00]	0.4408	2.916	0.0213*
Δ Fat weight (kg)	-0.30 [-1.70 - 1.30]	-1.493	0.8592	1.20 [0.50 - 2.37]	0.2621	2.466	0.0325*
Δ Lean weight (kg)	-0.25 [-1.12 - 1.12]	-1.133	1.35	-0.9 [-1.70 - (-0.15)]	-2.066	1.895	0.2683
Δ BMR (Kcal)	-6 [-47.00 - 49.25]	-83.98	55.65	-29.00 [-52.00 - (-4.00)]	-50.3	-1.269	0.2367
Δ Water (%)	-0.1500 [-1.75 - 0.0]	-8.648	2.515	0.05 [-0.62 - 0.62]	-0.4368	0.3653	0.1219
Δ Total water (L)	-0.2 [-0.67 - 1.45]	-2.947	7.463	-1.05 [-1.70 - (-0.37)]	-1.768	-0.1467	0.0371*
Δ WC (cm)	1.50 [-1.00 - 2.00]	-1.254	3.587	1.50 [-1.00 - 3.00]	-0.1894	2.761	0.9253

*BIA: bioimpedance; WC: waist circumference; Δ: amplitude; CI: confidence interval; LL: lower limit; UL: upper limit; BMR: basal metabolic rate; * significant difference between study end and baseline. Statistical tests: nonpaired Student t test or Mann Whitney test according to data normality.*

of body fat percentage between groups was considered high (d = 0.96), as was the effect size of fat weight (d = 0.89). The effect size of lean weight was small (d = 0.06).

Food frequency

Regarding food frequency, the paired analysis showed no significant difference in most food groups ($p > 0.05$), but a significant increase in the intake of sweets and desserts was observed in the CRG ($p = 0.0425$), while the VRG showed a significant increase in the intake of vegetables ($p = 0.0455$), sauces and seasonings ($p = 0.0245$). Table 4 compares the food frequency variation between the two groups, showing a significantly higher intake of vegetables, sauces and seasonings in the VRG as compared to that of the CRG. No significant difference was observed in the consumption of other food groups.

Functional capacity and blood glucose level

Figure 2 shows the functional capacity values of the individuals assessed. The distance covered increased significantly in both groups after undergoing the training protocols.

Figure 3 depicts the blood glucose levels during the training sessions and the significant differences found,

Table 4 - Comparison of the variations in monthly food frequency between the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) expressed as median and interquartile range (25%-75%)

FFQ (monthly)	CRG	95% CI LL	95% CI UL	VRG	95% CI LL	95% CI UL	p value
Δ Soups and pasta	-0.03 [-0.62 - 0.39]	1.086	2.679	0.47 [-0.61 - 1.00]	-0.3105	1.046	0.4253
Δ Meat and fish	5.69 [3.00 - 6.74]	3.793	6.639	-0.03 [-1.31- 1.48]	-1.616	3.148	0.959
Δ Milk and dairy products	-1.25 [-5.48 - 3.34]	-4.758	4.462	1.52 [-0.46 - 4.16]	-1.413	8.867	0.1052
Δ Pulses and eggs	0.61 [-0.01 - 2.05]	-0.8971	5.359	-0.62 [-6.67 - 1.37]	-4.76	1.79	0.0896
Δ Rice and tubers	0.35 [-2.50 - 3.75]	-1.465	2.93	1.32 [-0.25 - 4.49]	-0.4805	3.702	0.5351
Δ Vegetables	-1.14 [-7.37 - 1.96]	-5.797	0.9937	4.13 [-1.30 - 7.60]	0.1081	9.09	0.0147*
Δ Sauces and seasonings	-2.62 [-10.53 - 3.87]	-9.435	6.022	8.84 [-2.60 - 21.25]	2.479	17.8	0.0269*
Δ Fruits	2.35 [-0.20 - 6.09]	-1.871	5.892	1.25 [-1.49 - 5.56]	-0.6194	6.075	0.7617
Δ Beverages	0.44 [-3.66 - 3.40]	-8.269	17.58	-0.21 [-6.79 - 5.46]	-6.769	3.609	0.7381
Δ Breads and cookies	1.24 [-3.39 - 10.04]	-2.224	10.33	-0.69 [-4.19 - 3.69]	-4.104	6.035	0.3413
Δ Sweets and desserts	5.12 [0.26 - 7.68]	-1.185	7.903	2.50 [-0.90 - 8.75]	-0.3229	8.867	0.9181

*FFQ: food frequency questionnaire; Δ: amplitude; CI: confidence interval; LL: lower limit; UL: upper limit; * significant difference between study end and baseline. Statistical tests: nonpaired Student t test or Mann Whitney test according to data normality.*

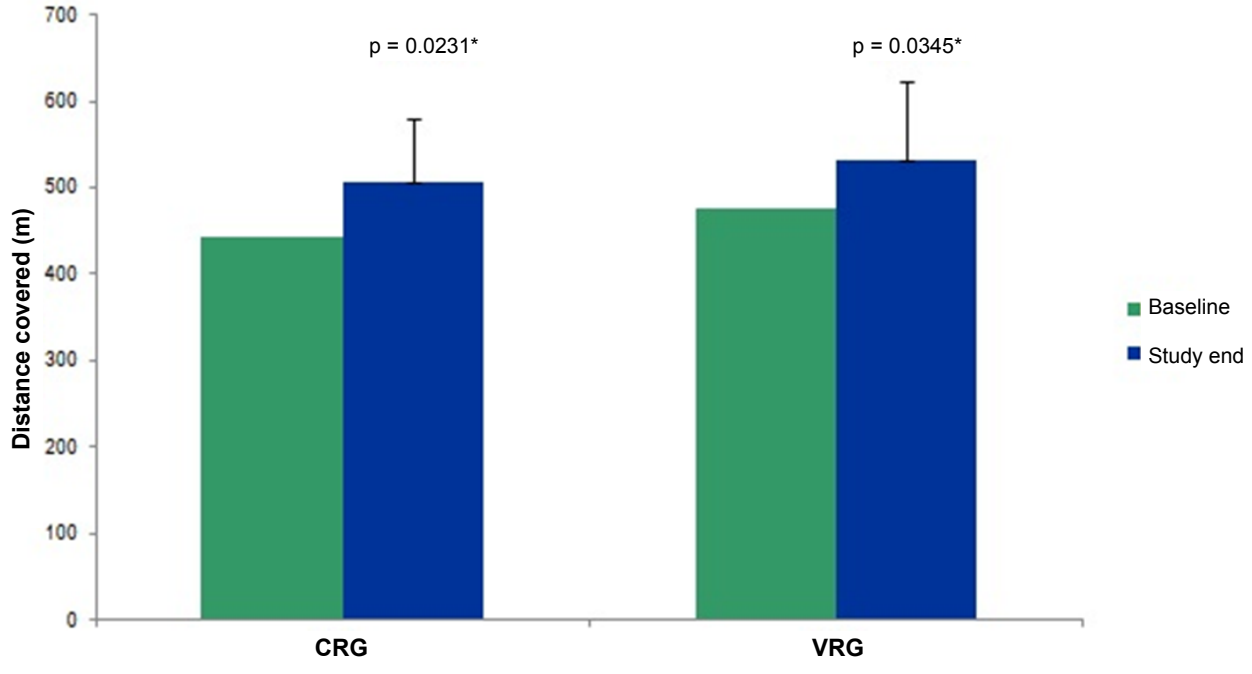

Figure 2 - Functional capacity (mean, standard deviation) of the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) at baseline and study end. *significant difference between study end and baseline.
CRG: conventional rehabilitation group; VRG: virtual reality rehabilitation group.

with a significant decrease in capillary blood glucose levels in CRG and VRG by the end of the sessions.

Table 5 compares the variation in functional capacity and blood glucose levels in the groups, but with no significant difference.

Unwanted effects

One individual reported dyspnea and intense fatigue when undergoing the VR protocol, which interrupted the session.

Discussion

The present study showed that conventional and VR cardiovascular rehabilitation influenced functional capacity and blood glucose level positively, which did not significantly differ between the training modalities. However, no favorable change in body composition and food frequency was observed in the individuals assessed.

Structured cardiovascular rehabilitation programs can provide several benefits to individuals with CVD, such as desirable changes in body composition.[29,30] After

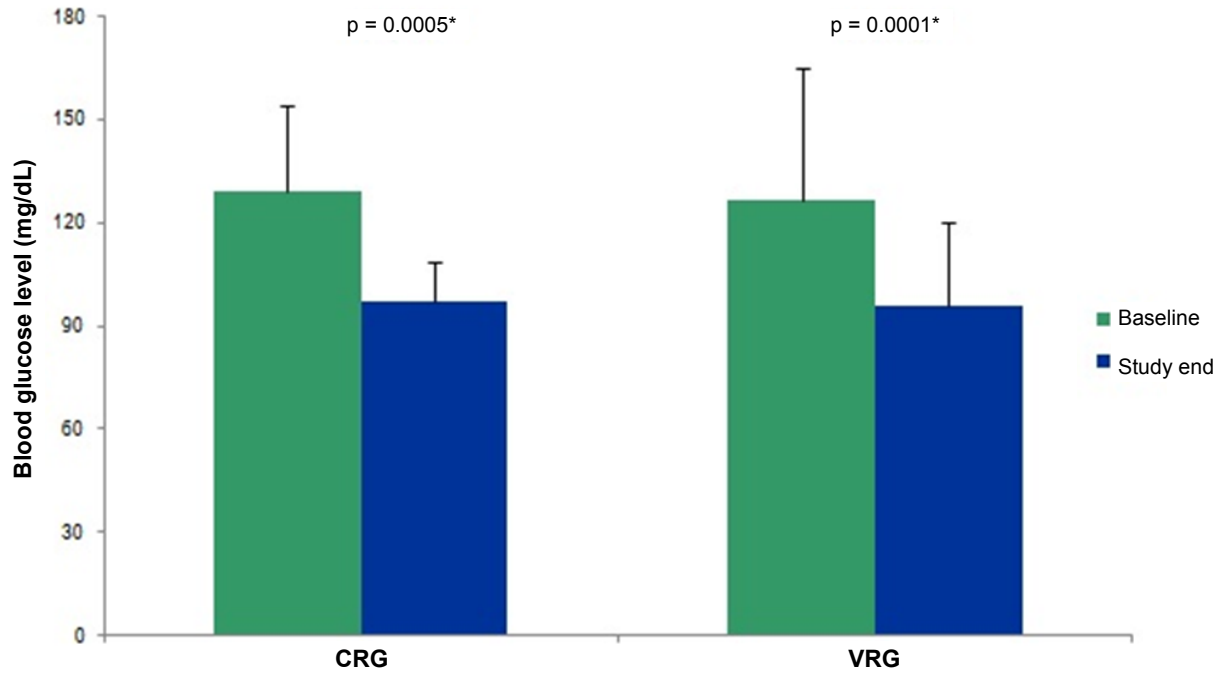

Figure 3 - Blood glucose levels (mean, standard deviation) of the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) at baseline and study end. *significant difference between study end and baseline.
CRG: conventional rehabilitation group; VRG: virtual reality rehabilitation group.

Table 5 - Comparison of the variations in functional capacity and blood glucose levels between the conventional and virtual reality rehabilitation groups (CRG and VRG, respectively) expressed as median and interquartile range (25%-75%)

6MWT/ BGL	CRG	95% CI LL	95% CI UL	VRG	95% CI LL	95% CI UL	p value
Δ Distance covered (m)	54.00 [23.43 - 71.39]	10.83	120.3	35.25 [6.875 - 93.63]	4.719	106.2	0.4253
Δ BGL (mg/dL)	-19.80 [-52.45 - (-17.74)]	-45.47	-17.66	-23.22 [-50.24 - (-12.56)]	-44.13	-18.17	0.7381

*6MWT: 6-minute walk test; BGL: blood glucose level; Δ: amplitude; CI: confidence interval; LL: lower limit; UL: upper limit; * significant difference between study end and baseline. Statistical test: Mann Whitney test according to data normality.*

undergoing the training protocol, unexpected higher fat mass gain was observed in the VRG as compared to the CRG. Ades et al.,[31] have reported that, of the behavioral changes for weight control, the following are worth noting: self-monitoring with systematic observation and recording of dietary habits; environmental change associated with eating and exercising to control stimuli; and strategies to control factors that can lead to excessive caloric ingestion.

The use of technologies that allow man-machine interaction in a real three-dimensional environment as a modality of treatment is increasing.[32] However, there is no substantial evidence of change in body composition by use of exergames as an alternative to other intervention types.

The methods used in this study included behavioral changes for weight control. However, the duration of the intervention might have influenced the results, and an intervention longer than eight weeks might benefit body composition.

Cardiovascular rehabilitation programs are usually 12-week long or shorter, and, changes in lifestyle, such as weight loss, require a longer period, such as 16 to 24 weeks. Thus, positive changes in body composition in a rehabilitation program might require a longer follow-up time. In addition, no nutritional guidance was provided. All those factors associated might explain the negative effects regarding body composition. Brennan B[33] has reported that a combined aerobic and resistance training is more effective than aerobic training alone to improve body composition in individuals with coronary artery disease.

Total body water is known to reduce as body fat increases; thus, a more metabolically active muscle tissue needs more water to perform the cellular exchange of metabolites and nutrients.[34] Thus, one can infer that the greater the amount of muscle and the lower the amount of adipose tissue, the higher the total body water proportion. This reflects on the decrease of total water in the VRG, which had an increase in fat percentage. However, the opposite can happen: the hydration level can change resistance and lean and fat weight, influencing the results.

Lima et al.,[35] have compared the effects of combined aerobic and resistance training with those of aerobic training alone on blood pressure and body composition of 44 hypertensive individuals, performing three training sessions per week for ten consecutive weeks. Regarding body composition, fat mass was reduced only in the combined aerobic and resistance training group, corroborating the findings of the present study, in which the CRG (aerobic and resistance exercises) showed a decrease in fat mass, although with no statistical significance.

This study showed inconsistent results regarding the food intake of individuals with CVD. The paired analysis showed an increase in the intake of sweets and desserts in a group without any significant change in body composition, while the group with an increase in the body fat percentage and fat weight showed a significant increase in the intake of vegetables, sauces and seasonings. These findings can be related to particularities of the FFQ used in the present study.

Slater et al.,[36] have reported sources of errors related to the FFQ due to the restrictions imposed by a defined list of food, dependence on recollection, food portion perception and the way the questions are interpreted. Thus, the FFQ proved to be a subjective tool of food frequency analysis, emphasizing the lack of nutritional guidance during the treatment protocol.

Despite the limitations of the questionnaires that assess food frequency and dietary habits, such parameters should be assessed, because inadequate dietary intake can be one of the major determinants of the increase in deaths from CVD in Brazil.[37]

Regarding the distance covered in the 6MWT,[25] significant improvement was observed in both groups, but, when compared, the gains did not differ. Klompstra et al.,[38] have reported similar results when adopting VR, by use of Nintendo Wii, at the home of individuals with heart failure for 12 weeks, with a significant improvement in the 6MWT.

In addition, a systematic review has evidenced the susceptibility of the 6MWT to changes in the clinical status after cardiac rehabilitation.[39] Thus, the improvement in functional capacity is believed to relate to the increase in the maximal consumption of oxygen in individuals with CVD, which results from training-induced adaptations, specifically the aerobic component, which leads to an increase in cardiac output, maximum systolic volume, tolerance to muscle acidosis, and elevation in the anaerobic threshold that characterize improvement of the tolerance to submaximal exercise.[40]

Regarding blood glucose levels, both groups showed a significant reduction after the sessions, but with no difference between them. Kempf et al.,[41] have reported that the use of exergames reduced blood glucose

levels in individuals with type 2 diabetes mellitus who exercised with Nintendo Wii® (*Wii Fit Plus)* for 30 minutes for 12 weeks.

That finding results from the fact that the intervention proposed is the physical exercise practice, which increases muscle capillarization, improves mitochondrial function and, via an insulin-independent mechanism, involves the muscle glucose transporter (GLUT 4), improving insulin resistance and decreasing blood glucose levels.[42]

This study evidenced similar gain potentials in certain variables for both training modalities, showing VR as a complementary and innovative tool that contributes in a motivational, interactive and functional manner. Thus, the use of technologies as an intervention can be added to cardiovascular rehabilitation programs.

This study has limitations, such as its reduced sample size and intervention duration, requiring further investigation to confirm its findings. In addition, there was no nutritional guidance, which might have influenced the results regarding body composition.

Conclusion

Both groups showed a positive effect of conventional and VR cardiovascular rehabilitation on functional capacity and blood glucose levels, but with no difference between them. However, neither body composition nor food frequency improved after the interventions.

Author contributions

Conception and design of the research: Silva JPLN, Novaes LFM, Santos LCR, Galindo BP, Cavalcante MA, Araújo BCG, Pacagnell FL, Freire APCF. Acquisition of data: Silva JPLN, Novaes LFM, Santos LCR, Galindo BP, Cavalcante MA, Pacagnell FL, Freire APCF. Analysis and interpretation of the data: Silva JPLN, Novaes LFM, Santos LCR, Galindo BP, Araújo BCG, Pacagnell FL, Freire APCF. Statistical analysis: Freire APCF. Obtaining financing: Cavalcante MA. Writing of the manuscript: Silva JPLN, Novaes LFM, Santos LCR, Galindo BP, Araújo BCG, Pacagnell FL, Freire APCF. Critical revision of the manuscript for intellectual content: Silva JPLN, Novaes LFM, Santos LCR, Galindo BP, Cavalcante MA, Araújo BCG, Pacagnell FL, Freire APCF.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Unoeste under the protocol number 6243.7816.4.0000.5515. 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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ORIGINAL ARTICLE

Echocardiographic Assessment of Right Ventricular Function by Two-Dimensional Strain In Patients with Left-Sided Valvular Heart Disease: Comparison with Three-Dimensional Echocardiography

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Abstract

Background: Right ventricular (RV) dysfunction is a well-known predictor of mortality in patients with valvular heart disease (VHD). The assessment of RV function is often difficult due to complex geometry and hemodynamic factors.

Objective: We aim to analyze RV function in patients with severe mitral and/or aortic valve disease using two-dimensional strain (2DS) imaging and conventional echocardiographic parameters, comparing it with right ventricular ejection fraction (RVEF) measured by three-dimensional echocardiography (3DE).

Methods: Fifty-three patients with severe mitral and/or aortic VHD underwent complete transthoracic echocardiogram in the preoperative setting for cardiac surgery, including conventional echocardiographic parameters of RV function and speckle-tracking derived 2DS indices: RV global longitudinal strain (RVGS) and RV free wall longitudinal strain (RVFWS). Conventional echocardiographic and 2DS parameters were compared with real-time 3DE RVEF using Spearman correlation test. For comparison between two groups of patients based on the presence of RV dysfunction (normal RVEF ≥ 44% - A, abnormal RVEF < 44% - B), we used nonparametric Mann-Whitney U test. ROC (receiver operating characteristic) curve analysis was used to assess the clinical utility of all RV function variables in defining RV dysfunction. P values <0,05 were considered statistically significant.

Results: We found a significant correlation between all parameters and RVEF ($p<0.05$), with best results for RV fractional area change (FAC), RVGS, and RVFWS. Dividing the population into two-groups based on RVEF, we found 14 patients with RV dysfunction (27.4%), and significant differences between the groups for all RV function variables. For detection of RV dysfunction defined by 3DE, ROC curve analysis showed the best area under the curve (AUC) for RVGS (0.872), RVFWS (0.851) and FAC (0.932).

Conclusions: We observed significant correlation between RVGS, RVFWS and RVEF, with good accuracy in detecting RV dysfunction, comparable to FAC and better than other conventional parameters of RV function assessment. The evaluation of RV myocardial deformation with 2DS may have additional diagnostic and prognostic value in patients with severe left-sided VHD. (Int J Cardiovasc Sci. 2018;31(6)630-642)

Keywords: Ventricular Dysfunction, Right/diagnostic, imaging; Ventricular Dysfunction, Right/physiopathology; Echocardiography, Tridimensional/methods; Stroke Volume; Valvular Heart Diseases; Prognosis.

Introduction

The accurate assessment of right ventricular (RV) systolic function plays an important role for the evaluation, follow-up and treatment of a myriad of cardiac and non-cardiac diseases.[1-4] The assessment of RV function by conventional echocardiographic parameters has major challenges, and its accuracy is limited by the irregular geometry of the RV chamber, the distinct pattern of contractility (mostly based on longitudinal deformation), the trabeculated inner contour of the cavity with poor endocardial border definition, separate

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inflow and outflow chambers which may be adequately visualized only from separate views, load-dependency, and influence of ventricular interdependency.[5,6]

In some pathologic conditions where changes in preload (e.g. severe tricuspid regurgitation) and afterload (e.g. pulmonary hypertension) are seen, the evaluation of RV function is particularly difficult. In patients with severe VHD, RV function assessment is challenging, not only because of the hemodynamic alterations frequently seen in these patients, but also because its primary etiopathogenic process itself may impair RV function, as we often see in rheumatic heart disease.[7]

In the last few years, studies have shown the applicability and clinical value of three-dimensional echocardiography (3DE) and two-dimensional strain (2DS) techniques in the evaluation of RV systolic function, with good accuracy for detecting RV dysfunction, and additional prognostic value in various diseases.[8] Speckle-tracking echocardiography (STE) derived techniques, specially 2DS, allows myocardial deformation analysis, is less dependent on angle and loading conditions, with great potential for RV evaluation (considering the complex geometry of the RV and great exposure to load changes), and has been shown to be a very sensitive technique, allowing early detection of subclinical RV involvement in a great variety of diseases.[9-12] Real-time 3DE is a well-established echocardiographic technique that has the great advantage of displaying the entire right ventricle in a single dataset, despite its irregular shape. The technique, hence, overcomes inherent limitations of tomographic methods for assessment of ejection fraction (EF), with good accuracy when compared with cardiac magnetic resonance (CMR).[13-17]

Objectives

The aim of this study was to analyze RV systolic function in patients with severe left-sided VHD using conventional echocardiography and 2DS techniques, testing the correlation of these techniques with RV ejection fraction (RVEF) measured by 3DE, and to evaluate the accuracy of these three techniques for the detection of RV dysfunction (RVEF < 44%).

Methods

This prospective observational cross-sectional study was approved by the local ethics committee.

Study population

From May 2013 to May 2014, in a tertiary cardiology hospital, we recruited consecutive adult patients with diagnosis of severe mitral and/or aortic valve disease[18] referred for preoperative evaluation for cardiac surgery (valve replacement, repair or both). We only included patients with no previous history of cardiac surgery, to avoid the influence of pericardiotomy on the accuracy of echocardiographic parameters of RV systolic function, and patients with no history of coronary artery disease to avoid confounding factors in determining the cause and severity of pulmonary hypertension and RV disease. We excluded patients with poor echocardiographic window for analysis of RV systolic function (either conventional parameters or 2DS), patients with severe tricuspid regurgitation (TR) and those who refused to participate in the study.

Conventional echocardiography

Echocardiography was performed using standard views, with the patient in the left lateral decubitus position, using a commercially available ultrasound machine (Vivid E9, GE Healthcare, Horten, Norway). Conventional echocardiographic images and cine loops of all patients were obtained by a single experienced examiner using a M5S transducer. Left ventricular (LV) EF was calculated using the biplane method of discs, and all the Doppler parameters necessary to quantitate the severity of valvular lesions and pulmonary artery systolic pressure (PASP) were obtained and analyzed in accordance with the criteria defined on the EAE/ASE/EACVI guidelines.[19,20] RV diastolic and systolic areas were measured to calculate RV fractional area change (FAC). With the pulsed-wave Doppler sample volume positioned at the lateral tricuspid annulus in the RV focused apical 4-chamber view, the peak systolic velocity (PSV) by tissue Doppler was obtained. We also measured the tricuspid annular plane systolic excursion (TAPSE), placing the M-mode cursor through the base of the lateral tricuspid annulus, quantitating its longitudinal motion at peak systole.

Speckle-tracking echocardiography

For STE analysis, digital loops of the right ventricle were obtained from apical 4-chamber and/or right ventricle-focused apical 4-chamber views. Three cardiac cycles were acquired from each view at a frame rate of

40-80 frames/sec in patients in sinus rhythm and five consecutive cycles in patients with atrial fibrillation (AF). The data were exported at the end of the test to a workstation (EchoPac BT12, GE Vingmed, Horten, Norway) for further offline analysis.

Preliminary analysis was performed online in the ultrasound machine was performed online in the ultrasound machine to check if the image quality of the loops was good enough to permit adequate tracking of the acoustic markers (speckles) of the myocardium during the entire cardiac cycle. STE analysis was performed semi-automatically by the system, after manual setting of 3 points on the endocardial border of the right ventricle by the operator (2 basal and one at the apex). When the region of interest (ROI) included the whole thickness of the right ventricle and excluded other structures such as trabeculae, moderator band and valvular tissue, the processing was started, and analysis proceeded on a frame-to-frame basis using an automatic tracking system (Figure 1). If the tracking was poor, the operator could repeat the the acquisition of loops, readjusting the endocardial tracing (editing) or change software parameters such as ROI width, frame rate or gain, until an adequate tracking of the entire myocardium was achieved.

The ROI generated by the software included basal, mid and apical segments of RV free wall and septum, dividing it into 6 segments (Figure 1). Longitudinal peak strain values were measured for each segment, and the RV free wall longitudinal strain (RVFWS) and the RV global longitudinal strain (RVGS), analyzed by 2DS, were calculated by averaging the values from the three segments of the RV free wall and all the six segments along the entire right ventricle, respectively. These initial results were blinded to the investigators until the offline analysis of the remaining parameters was performed.

Three-dimensional echocardiography

3DE was performed in all subjects immediately after the two-dimensional echocardiographic examination using the same ultrasound machine, equipped with a 4V probe. RV three-dimensional (3D) images were obtained in a full-volume dataset from the apical four-chamber view, optimized for analysis of RV function. Multi-beat (3-6 beats) data were obtained during apnea, on the multislice (short axis) visualization mode, to make sure that the right ventricle was entirely included in the dataset (Figure 2).

All the measurements of RV volumes and EF were made off-line, using a dedicated software (TomTec Imaging Systems GmbH, Munich, Germany). Semi-automatic analysis was performed, with manual tracing of the endocardial borders in end-systolic and end-diastolic frames in the sagittal, four-chamber and coronal views, obtained from the full-volume dataset. In addition, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume and EF were calculated using the software (Figure 2).

Assessment of reproducibility

Evaluation of inter- and intraobserver reproducibility were performed. Fourteen patients, chosen by simple random selection, were assessed by two observers for analysis of interobserver variability, and for intra-observer variability, the second analysis was performed with a minimum interval of two weeks from the first analysis. The readers were blinded to previous measurements. Interobserver and intraobserver variability were assessed using the intraclass correlation coefficient and Bland-Altman analysis.[21]

Statistical analysis

Demographic data are presented as mean ± standard deviation (SD) and categorical data are presented as frequencies. Normality of the distribution of numerical variables was tested by the Kolmogorov-Smirnov test; normally distributed variables were expressed as mean ± SD and variables with abnormal distribution as median with interquartile range. We compared all RV function parameters between subgroups of patients according to their predominant valvular lesion. To reduce the occurrence of alpha error, we used one-way ANOVA test with Bonferroni post-hoc correction. Conventional echocardiographic and 2DS parameters were compared with real-time 3DE RVEF using Spearman correlation test. For comparisons between groups of patients (A and B), based on the presence of RV dysfunction defined as RVEF (3DE) < 44%, we used nonparametric Mann-Whitney U test. ROC (receiver operating characteristic) curve analysis was used to assess the clinical utility of all RV function variables in defining RV dysfunction. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 13 (SPSS Inc, Chicago, IL).

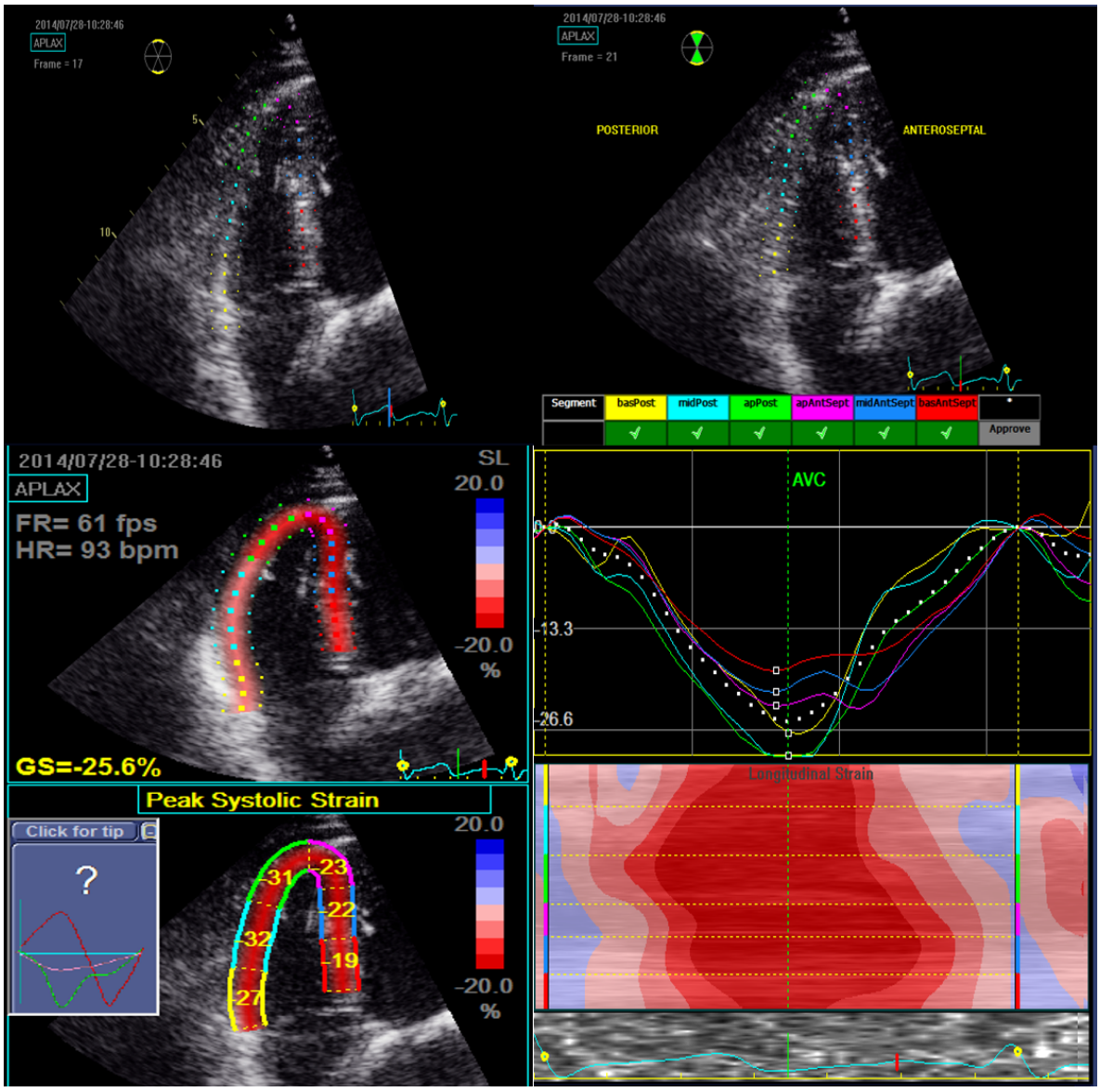

Figure 1 - Speckle-tracking analysis of right ventricular (RV) systolic function using the automated function imaging technique. (Top) Semi-automated delineation of endocardial borders and definition of the region of interest (ROI). Mid and lower images illustrate two-dimensional strain analysis: (middle-left) shows global longitudinal RV strain (-25.6%), (middle-right) two-dimensional strain (2DS)-time curves, (bottom-left) peak 2DS values per segment, and (bottom-right) 2DS-time parametric analysis.

Results

Patients' characteristics

A total of 57 consecutive patients with severe VHD were enrolled in this study. Of these, two had severe TR and other two refused to participate, thus the final study group was comprised of 53 patients (31 women; mean age, 52,4 ± 15,9 years). Most patients were symptomatic, with 50.9% classified as New York Heart Association (NYHA) functional class II and 43.4% as NYHA III (Table 1). The predominant etiology of valve diseases was rheumatic valve disease (53.6%), myxomatous valve disease (18.9%), degenerative valve disease (13.2%) and congenital valve disease (11.3%). All patients were submitted to conventional echocardiography, RV 2DS and 3DE. Most patients were in sinus rhythm; 14 patients (26.4%) with permanent AF were not excluded because we were able to analyze all echocardiographic parameters despite the presence of arrhythmia.

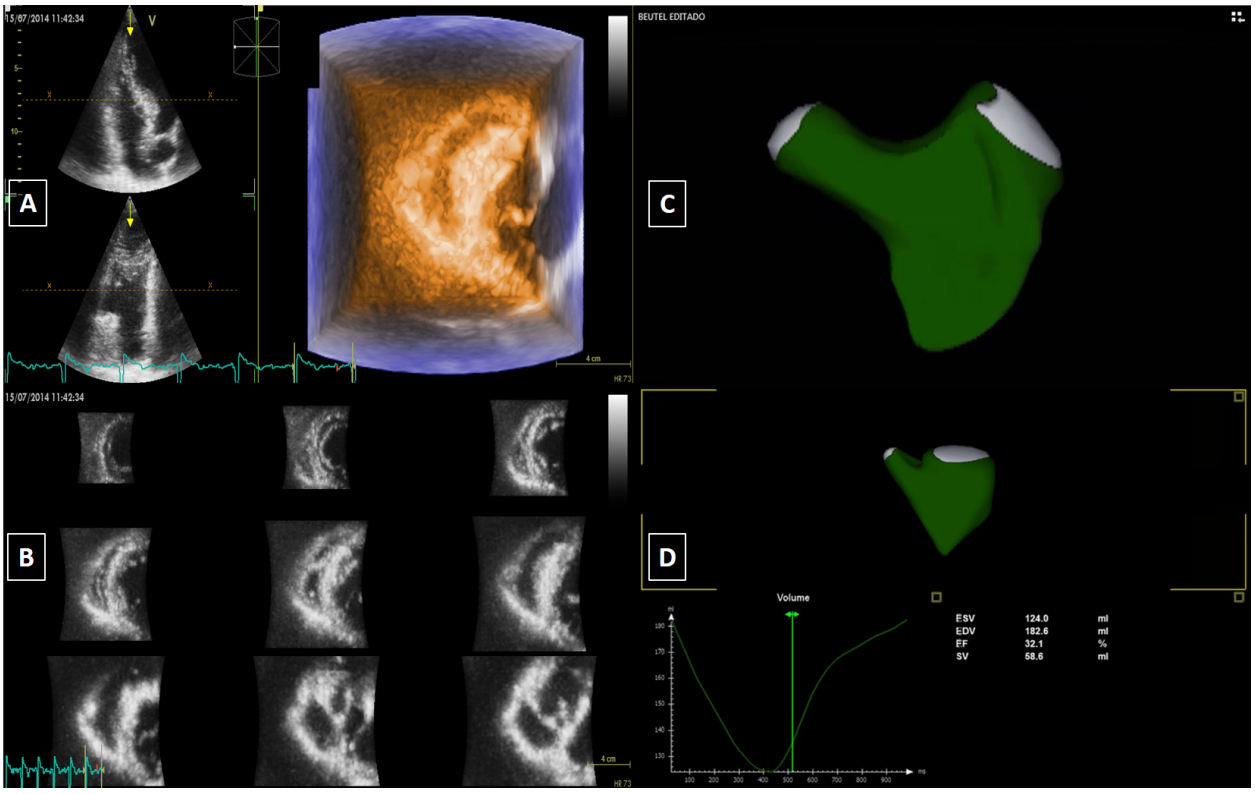

Figure 2 - (a,b) Right ventricular (RV) multi-beat, full-volume acquisition by three-dimensional echocardiography. (c,d) RV volumes and ejection fraction analysis using TomTec software. Rendering of RV chamber on the top (c), and volume-time curve and quantitative measurements on the bottom (d)

Table 1 - Clinical profile and comorbidities of the enrolled subjects

Clinical variable	Number of patients (% total)
Female	31 (58.5%)
NYHA I	3 (5.7%)
NYHA II	27 (50.9%)
NYHA III-IV	23 (43.4%)
Systemic arterial hypertension	23 (43.4%)
Atrial fibrilation	14 (26.4%)
Tabagism	14 (26.4%)
DM	5 (9.4%)
Obesity (BMI > 30 kg/m²)	6 (11.3%)

NYHA: New York Heart Association functional class; DM: diabetes mellitus.

Echocardiographic parameters

Technically adequate measurements of TAPSE, PSV, FAC and 2DS parameters were obtained in all patients.

Real-time 3DE images of the RV were successfully analyzed in 51 of the 53 patients evaluated (96.2%). Image quality was considered inadequate for analysis in two patients, due to unsatisfactory echocardiographic window (missing the anterior wall of the RV).

Considering the entire study population, mean values of LV chamber dimensions were increased, despite normal LV systolic function. Overall, RV dimensions and function were normal, as summarized in Table 2.

We compared conventional parameters of RV function and 2DS with RVEF measured by 3DE and found a significant correlation between RVFWS ($r = -0.578$; $p < 0.001$) and RVGS ($r = -0.596$; $p < 0.001$), very similar to FAC performance ($r = 0.635$; $p < 0.001$), and far better than TAPSE and PSV (Figure 3).

Table 2 - Two-dimensional, Doppler, 2D strain and three-dimensional parameters of the enrolled subjects

Parameters	Values (mean ± SD)
LA (mm)	48.81 ± 9.96*
RV (mm)	17 (16 - 20) **
LV EDD (mm)	57.34 ± 10.24*
LV ESD (m)	36.21 ± 8.65*
LVEF Teichholz (%)	67.0% (61.5 - 73.0%)**
LVEF Simpson (%)	66 (61 - 72%)**
RV basal (mm)	37 (31 - 41)**
RV mid-cavity (mm)	27 (22 - 34)**
RV apical-TV distance (mm)	60 (55 - 69)**
Tricuspid Annulus (mm)	30.19 ± 4.32*
PASP (mmHg)	40 (30 - 54)**
RVFWS (%)	-23.81 ± 6.77*
RVGS (%)	-21.42 ± 4.96*
PSV (cm/sec)	11.91 ± 3.73*
TAPSE (mm)	20.21 ± 5.92*
FAC (%)	44.46 ± 13.3*
RVEDF 3DE (ml)	80.4 (64.4 - 114.7)**
RVESV 3DE (ml)	34.1 ml (25.6 - 54.1)**
RVEF 3DE (%)	60 (42.5 - 63.4)**

**Data are mean ± SD. **Data are median with interquartile range. FAC: fractional area change; LA: left atrium; LV EDD: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; LV ESV: left ventricular end systolic dimension; PSV: peak systolic velocity of tricuspid annulus; RV: right ventricle; RVFWS: RV free wall longitudinal 2D strain; RVGS: RV global longitudinal 2D strain; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging; TV: tricuspid valve.*

The patients were classified into subgroups according to their predominant valve lesion as follows: (1) mitral stenosis (n = 11; 20.8%), (2) mitral regurgitation (n = 21; 39.6%), (3) aortic stenosis (n = 8; 15.1%), (4) aortic regurgitation (n = 9; 17%), and (5) combined lesions (n = 4; 7.5%). We defined combined lesions as the presence of two or more severe mitral and/or aortic valve lesions in the same patient. Of the four patients with combined lesions, two had severe mitral stenosis and regurgitation, one had severe aortic stenosis and regurgitation and the other one had severe mitral regurgitation and aortic regurgitation.

The echocardiographic variables were compared between these subgroups (ANOVA for multiple comparisons), and we found a significant difference between the groups in all the parameters, except for PSV (Figure 4). Patients with stenotic valve lesions had lower values of PSV compared with patients with regurgitant lesions. Patients with combined lesions had lower values of all conventional RV function parameters compared with the other groups. We observed lower absolute values of RVFWS, RVGS (less deformation) and higher PASP, and lower FAC and RVEF 3D in patients with mitral stenosis and patients with combined lesions.

Dividing the patients into two categories according to their RVEF by 3DE, considering patients with RVEF ≥ 44% as preserved function (A), and patients with RVEF < 44% as RV systolic dysfunction (B), we found a total of 14 patients with RV dysfunction (27.4%), with significant difference between the groups for all variables: PSV ($p = 0.005$), TAPSE ($p < 0.001$), FAC ($p < 0.001$), PASP ($p < 0.001$), RVFWS ($p < 0.001$), RFGS ($p < 0.001$) (Figure 5).

ROC curve analyses tested the clinical utility of all parameters for the diagnosis of RV dysfunction (determined by RVEF < 44% by 3DE), and established sensitivity (Se), specificity (Sp) and best cut-off values. The parameters with the largest areas under the curve (AUC) were: RVFWS (0.851), RVGS (0.872) and FAC (0.932), with best cut-off values of: -18.6% (Se: 86.5%, Sp: 79.6%), -20.1% (Se: 83.8%, Sp: 85.7%) and 41% (Se: 86,5%, Sp: 92,9%), respectively (Table 3).

Intra- and interobserver variability analysis

Reproducibility analysis showed excellent accordance between repeated measurements for the RV 2DS parameters by Bland-Altman analysis (Figure 6). Both RVFWS and RVGS showed high intraclass correlation coefficient (range, 0.97 - 0.98) with narrow confidence intervals (Table 4).

Discussion

There are few studies in literature focusing on RV function in left-sided VHD, most of which had limited number of patients and analyzed only conventional RV function parameters, without using 2DS parameters or 3DE. The great challenge in VHD is to detect early alterations in RV function, when subclinical disease may point to a worse clinical prognosis and contribute

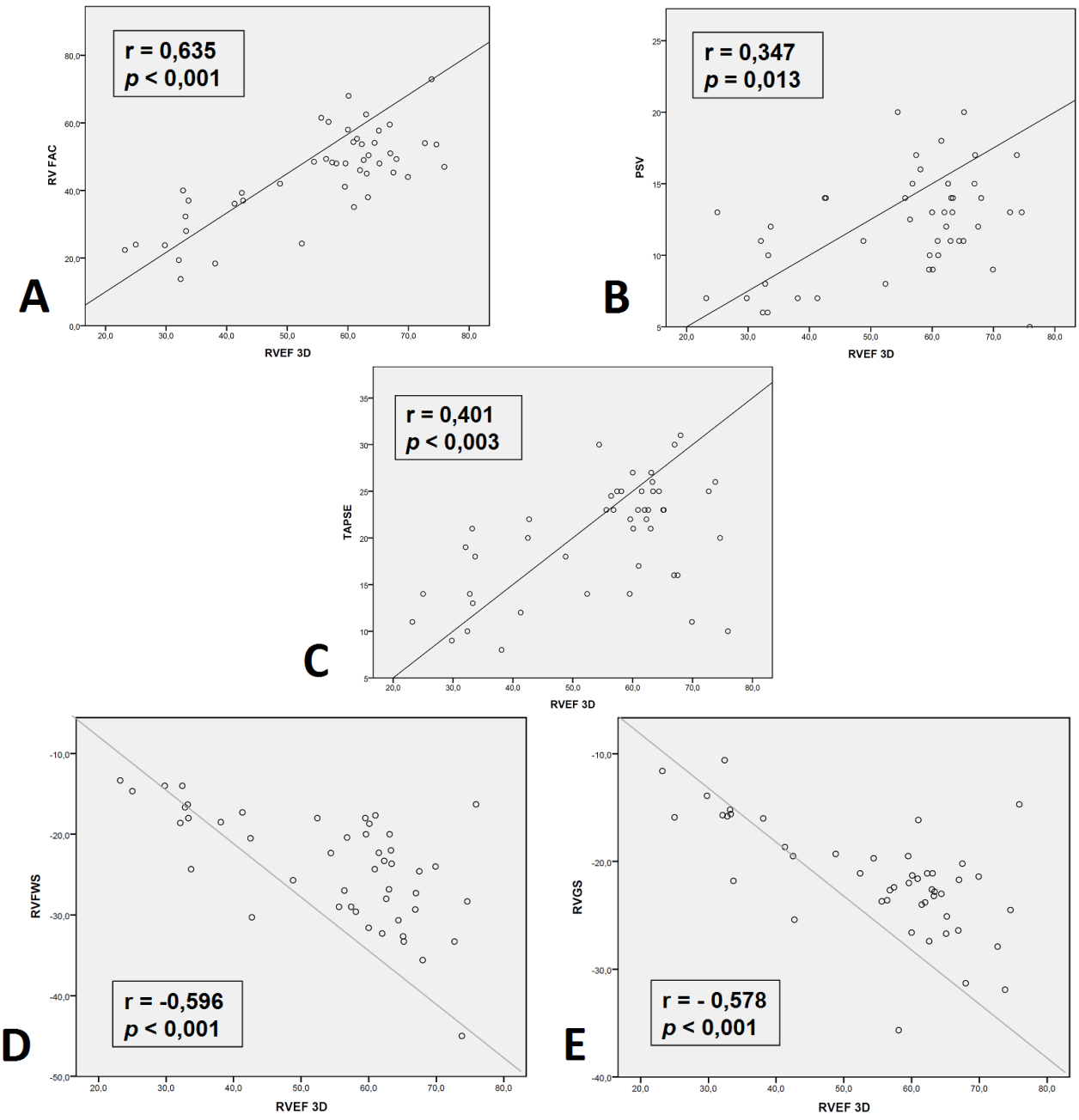

Figure 3 - Correlation between fractional area change (FAC) (a), peak systolic velocity (PSV) of tricuspid annulus by tissue Doppler (b), tricuspid annular plane systolic excursion (TAPSE) (c), right ventricular (RV) free wall longitudinal strain (RVFWS) (d), RV global longitudinal strain (RVGS) (e), and RV ejection fraction (RVEF), measured by three-dimensional echocardiography.

to surgery indication in appropriate timing. In this regard, STE based techniques as 2DS have shown good applicability and reproducibility for the evaluation of RV function, with great accuracy in detecting RV dysfunction when compared to gold standard methods.

A population of severe mitral and/or aortic valve disease patients was enrolled in this study, predominantly rheumatic in etiology, unlike other studies from Europe and North America that also evaluated RV function in VHD patients, in which the predominant etiology was degenerative valvular disease.[22,23] In Brazil, rheumatic fever is still a prevalent cause of VHD, and almost 60% of the patients that undergo cardiac surgery for valvular repair or replacement have rheumatic etiology.[24] These

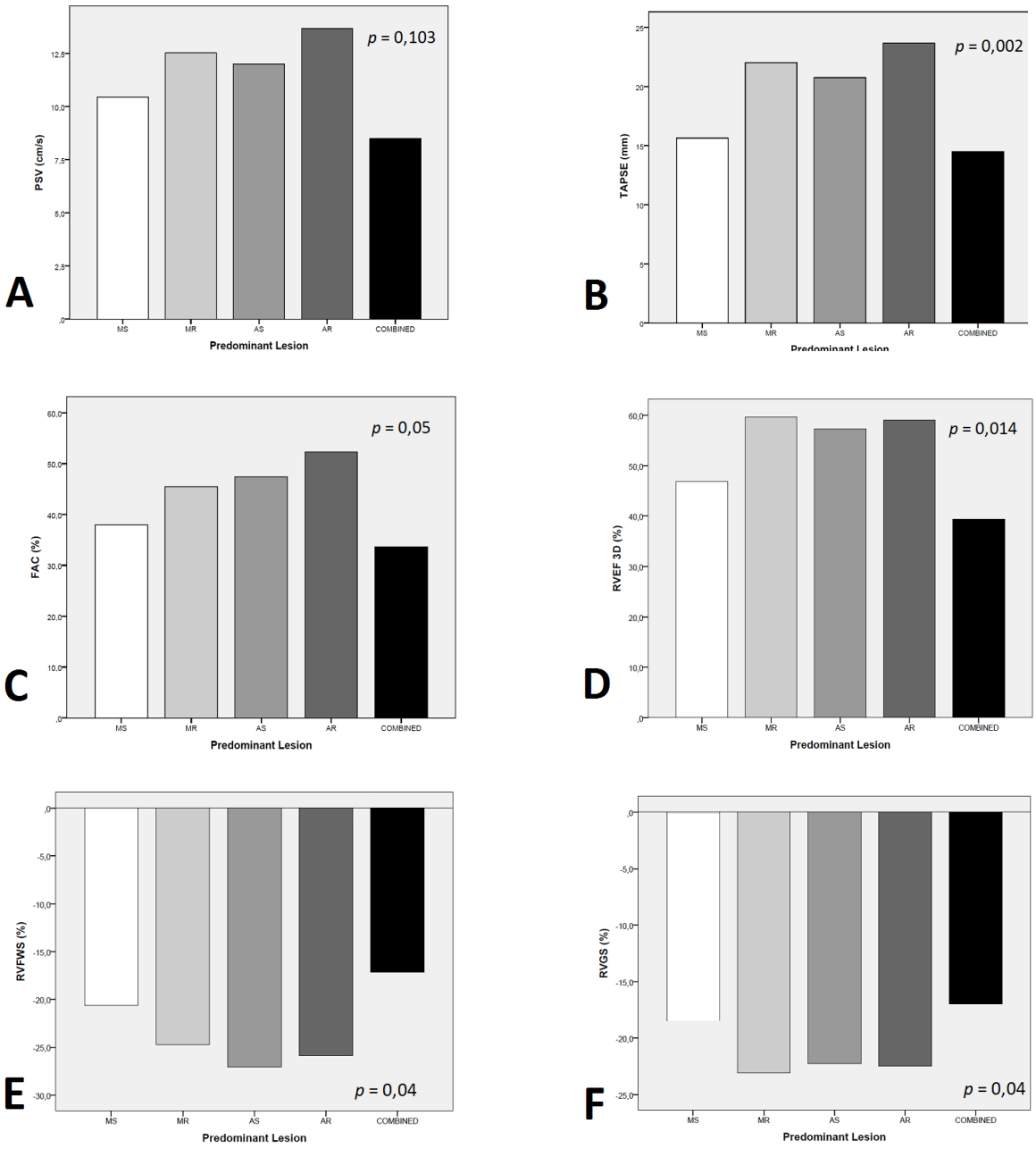

Figure 4 - Mean values of echocardiographic parameters by predominant valve lesion. P value refers to difference between all groups by multiple comparisons (ANOVA). MS: mitral stenosis, MR: mitral regurgitation, AS: aortic stenosis, AR: aortic regurgitation, PSV: peak systolic velocity of tricuspid annulus(a); TAPSE: tricuspid annular plane systolic excursion (b); FAC: fractional area change (c); RVEF 3D: right ventricular (RV) ejection fraction three-dimensional echocardiography (d); RVFWS: RV free wall longitudinal two-dimensional strain (e); RVGS: RV global longitudinal (two-dimensional) strain (f).

patients frequently present with disease in more than one valve, and therefore, we decided to include in the present study patients with combined mitral and/or aortic lesions, to better represent the entire clinical spectrum of the disease.

Considering RVEF measured by 3DE as an established reference standard for evaluation of RV function, most patients in our study had normal RV function (RVEF 3D ≥ 44%), although the number of patients with RV dysfunction was significant (n = 14; 27.4%). The mean

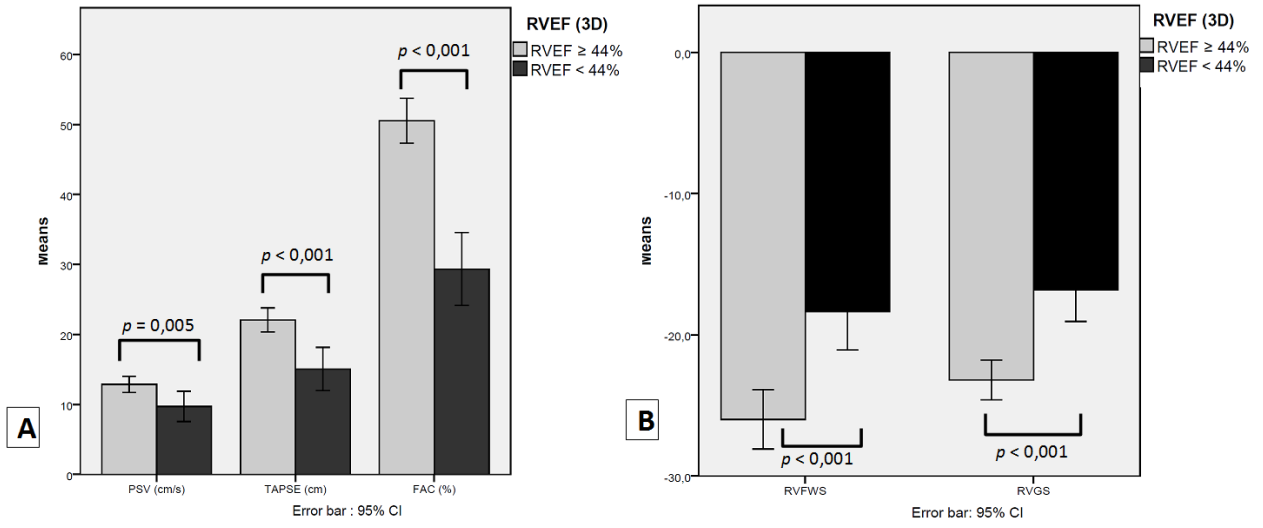

Figure 5 - Comparison of mean values of echocardiographic parameters between the groups: right ventricular (RV) preserved systolic function (RVEF = 44%; n = 37) and RV systolic dysfunction (RVEF < 44%; n = 14). (a) PSV: peak systolic velocity of tricuspid annulus; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; (b) RVFWS: RV free wall longitudinal (two-dimensional) strain; RVGS: RV global longitudinal (two-dimensional) strain.

Table 3 - Echocardiographic parameters. Performance for the detection of RV dysfunction (RVEF 3DE < 44%)

Parameter	Se	Sp	PPV	NPV	Cut-off	AUC	CI
RVFWS	86.5%	79.6%	72%	90%	-18.65%	0.851	0.726 - 0.956
RFGS	83.8%	85.7%	92%	89%	-20.1%	0.872	0.750 - 0.994
PSV	78.4%	64.3%	57%	83%	10.5 cm/s	0.756	0.593 - 0.919
TAPSE	84.2%	64.3%	60%	91%	15 mm	0.828	0.697 - 0.960
FAC	86.5%	92.9%	87%	90%	41%	0.932	0.867 - 0.998

RVFWS: right ventricular (RV) free wall longitudinal 2D strain; RVGS: RV global longitudinal 2D strain; PSV: peak systolic velocity of tricuspid annulus; TAPSE: tricuspid annular plane systolic excursion; FAC: RV fractional area change.

values of conventional RV function parameters (TAPSE, PSV, FAC) and 2DS parameters (RVFWS, RVGS) were normal considering the overall study population, despite an elevation of the median values of PASP (40 mmHg (30-54)), secondary to the advanced stage of the disease in these patients. We excluded patients with severe TR, a condition that may affect the accuracy of RV functional assessment by alterations in RV preload.[25]

We obtained acceptable 3DE images for RVEF analysis in 51 patients (96,2%), showing good feasibility of the technique, as previously shown by other authors (Kong et al.,[26] - 97%, Niemann et al.,[27] - 100%). The mean values of EDV, ESF and EF were normal in the overall population.

Analyzing the patients according to their predominant valve lesions using multivariate analysis, we observed significant differences between the groups for RVGS, RVFWS, TAPSE, FAC, and RVEF 3D, showing a tendency towards lower absolute values of RVGS, RVFWS (less deformation) and lower levels of FAC and RVEF 3D in patients with mitral stenosis and combined lesions. These findings are probably related to higher levels of pulmonary capillary pressure and RV pressure overload in mitral stenosis and combined lesions than in regurgitant lesions and isolated aortic stenosis. Furthermore, all patients with combined lesions were rheumatic, pointing to the possibility of a concurrent

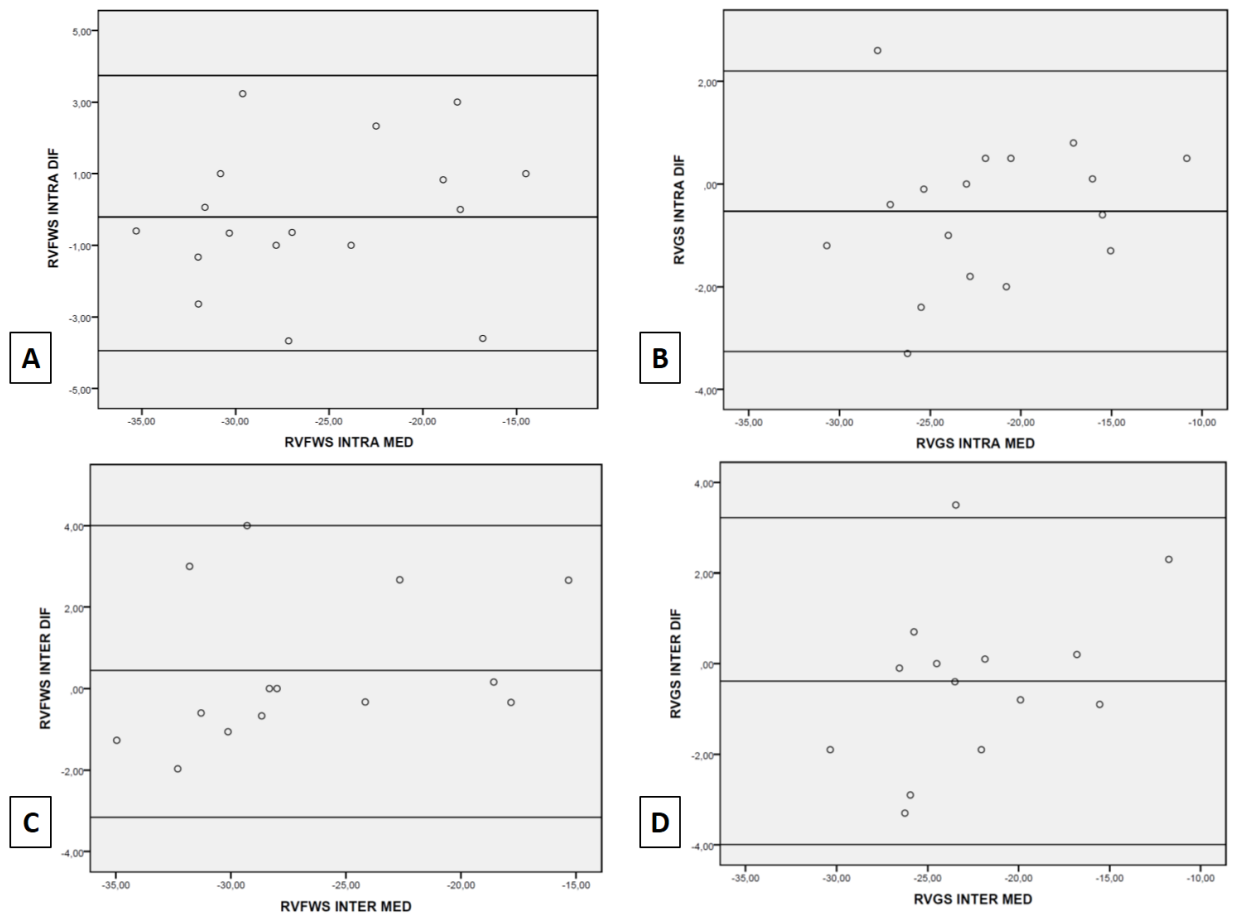

Figure 6 - Reproducibility analysis for repeated measurements of RV free wall longitudinal (two-dimensional) strain and RVGS: RV global longitudinal (two-dimensional) strain (Bland-Altman). (a) RVFWS intraobserver variability; (b) RVGS intraobserver variability; (c) RVFWS interobserver variability; (d) RVGS interobserver variability.

Table 4 - Reproducibility analysis for retest measurements of RVFWS and RVGS

Reproducibility analysis	ICC	CI(95%)
RVFWS intra-observer	0.975	0.932 - 0.991
RVFWS inter-observer	0.977	0.927 - 0.992
RVGS intra-observer	0.983	0.952 - 0.994
RVGS inter-observer	0.966	0.894 - 0.989

RVFWS: right ventricular (RV) free wall longitudinal 2Dstrain; RVGS: RV global longitudinal 2Dstrain; ICC: intra-class correlation coefficient; CI: confidence interval.

primary involvement of the myocardium, due to the inflammatory and fibrotic processes inherent to this disease. Using 2DS, Pirat et al.,[28] and Ikeda et al.,[29] demonstrated the occurrence of alterations in RV systolic function in patients with pulmonary artery hypertension, proportional to the severity of the disease, which could help explain some of our findings.

We compared the parameters of RV systolic function with RVEF 3D, and found a moderate, negative correlation between RVEF 3D and RVGS, RVEF 3D and RVFWS, and a moderate positive correlation between RFVE 3D and FAC, with weaker correlations for TAPSE and PSV. These findings are in accordance with previous studies, showing good correlation between RV 2DS parameters and RVEF measured by CMR[30] and FAC with RVEF measured by CMR.[31]

When the population was divided into two categories, according to the absence of RV dysfunction (group A, RVEF ≥ 44% by 3DE) and the presence of RV dysfunction (group B, RVEF < 44% by 3DE) we found a significant

difference in all parameters of RV function between the groups. ROC curve analysis was performed to test the diagnostic performance of these variables to detect RV dysfunction. The best AUC was obtained for FAC (0.932) followed by RVGS (0.872) and RVFWS (0.851), showing the clinical utility of these parameters in detecting RV dysfunction. Among all, FAC had the best performance, and this may be explained by the fact that this is the only parameter directly related to RV ejective function, while all others are closely related to longitudinal systolic function.

We performed intraobserver and interobserver analysis for RVGS and RVFWS and found good reproducibility for both parameters, making these measurements more robust and reliable, confirming previous data.[4,32,33]

Mittal et al.,[34] did not find any correlation between RV systolic parameters and PASP in 22 mitral stenosis patients, attributing RV myocardial dysfunction to inflammatory damage caused by the rheumatic disease. Ozdemir et al.,[35] demonstrated that patients with mild-to-moderate mitral stenosis had altered values of longitudinal RV 2DS compared to controls, probably unrelated to pulmonary hypertension, since they found only a mild elevation of PASP in these patients (39 ± 14 mmHg). Tanboga et al.,[32] studied patients with mild-to-moderate mitral stenosis and also found altered values of longitudinal RV 2DS compared to controls, but did not find any correlation of these values with PASP. Castro et al.,[36] studied 46 patients with isolated severe mitral stenosis, showing reduced longitudinal RV 2DS compared to controls, and a weak correlation between 2DS and PASP. Galli et al.,[37] studying 200 patients with degenerative aortic valve stenosis, demonstrated RV dysfunction in 24% of these patients, and established concomitant LV and RV dysfunction as the major predictor of mortality in 16 months. Le Tourneau et al.,[38] evaluating RV systolic function in 208 patients with severe organic mitral regurgitation found severe RV dysfunction (RVEF ≤ 35% measured by radionuclide angiography) in 63 patients (30%). The authors showed a weak correlation between PASP and RVEF and suggested a direct relation of RV dysfunction with septal function alteration and of LV enlargement with remodeling (ventricular interdependence). Mitral valve disease typically causes greater overload in the right chambers than aortic valve diseases,[39] probably due to an exceptional elevation of capillary pulmonary pressure, either by volume overload in mitral regurgitation or pressure overload in mitral stenosis.

Our findings suggest that RVGS and RVFWS may be reliable markers of RV dysfunction in VHD patients, with good accuracy and the potential advantage of early detection of alterations in myocardial function that precede alterations in the RV ejective function.

Limitations

Our findings must be validated in other studies involving a larger number of subjects. Our small sample size does not allow us to extrapolate these results to other populations. This was a clinical, uncontrolled study, which included consecutive patients with left-sided VHD from different etiologies and mechanisms of valvular dysfunction, reflecting the population of patients currently treated in our clinical practice.

Conclusion

In left-sided VHD patients, RVGS and RVFWS showed good correlation when compared with RVEF 3DE and good accuracy in detecting RV dysfunction. 2DS might be a useful tool for the early detection of changes in RV function in VHD patients.

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Author contributions

Conception and design of the research: Felix AS, Lorenzo AR, Azevedo Filho CF. Acquisition of data: Felix AS. Analysis and interpretation of the data: Felix AS, Siciliano APRV, Xavier SS. Statistical analysis: Felix AS, Xavier SS, Azevedo Filho CF. Obtaining financing: Felix AS. Writing of the manuscript: Felix AS, Lorenzo AR. Critical revision of the manuscript for intellectual content: Felix AS, Siciliano APRV, Belém LHJ, Azevedo FS, Xavier SS, Lorenzo AR, Azevedo Filho CF. Supervision / as the major investigador: Felix AS. Referral of Patients: Azevedo FS.

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 INC under the protocol number 20217813.1.0000.5272. 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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REVIEW ARTICLE

From Echocardiographic Evaluation to Biomarkers Measurement: The Role of Myocardial Dysfunction in Mortality Associated with Sepsis

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Abstract

Sepsis remains the leading cause of mortality and critical illness worldwide. Myocardial dysfunction is one of the most clinically relevant manifestations of sepsis and results from a complex interaction among genetic, molecular, metabolic, and structural changes. Despite the prominence given to the occurrence of systolic dysfunction during sepsis, the association between diastolic dysfunction and mortality is controversial, while diastolic dysfunction and right ventricular dysfunction are identified as independent predictors of mortality in the most recent studies. Elevation of biomarkers during sepsis may result from several mechanisms, and although the role of the B-type natriuretic peptide (BNP) and the N-terminal portion of its prohormone (NT-proBNP) as independent predictors of mortality is well defined, the same cannot be said about cardiac troponins due to conflicting results among currently available studies.

The objective of the present review is to discuss the pathophysiological mechanisms of myocardial dysfunction induced by sepsis in adults and the role of echocardiography and cardiac biomarkers as tools for prognostic evaluation in this clinical setting.

Introduction

Sepsis is a set of physiological, pathological, and biochemical abnormalities that can occur in response to infection caused by any pathological agent. Despite the advances in the treatment and support of critically ill patients, sepsis continues to be the main cause of mortality and severe disease throughout the world, with an estimated incidence of 17 million cases per year.[1]

Myocardial dysfunction is one of the manifestations of greater clinical relevance in sepsis and one of the organic dysfunctions that most early occurs in septic shock.[2] By definition, it consists of reversible systolic and/or diastolic dysfunction of the left ventricle (LV) and/or right ventricle (RV) (Figure 1).[3,4]

In recent years, myocardial dysfunction induced by sepsis became a focus of exhaustive investigation as an independent predictor of mortality in this clinical context, especially after the growing use of biomarkers of myocardial injury as indicators of poor prognosis in cardiovascular diseases.[5]

The objective of this review is to discuss the pathophysiological mechanisms of myocardial dysfunction induced by sepsis in adults and the role of echocardiography and cardiac biomarkers as tools for prognostic evaluation in this clinical scenario.

Keywords

Sepsis; Mortality; Biomarkers; Cardiac dysfunction.

Pathophysiology

Sepsis-induced myocardial dysfunction is believed to result from a complex interaction among genetic, molecular, metabolic, and structural alterations that may have unique and independent contributions or very confusing and intricate interrelationships (Figure 2).[6] The involved factors include:

- Action of myocardial depressants: the combined action of tumor necrosis factor-alpha (TNF-α) with interleukin 1-beta (IL-1 β) is cardiodepressant and can play an important role in the early reduction of myocardial contractility observed in the course of sepsis.[7] Furthermore, both induce the release of additional factors that may similarly affect the myocardial function, as for example, nitric oxide (NO), which in turn is also a cause of

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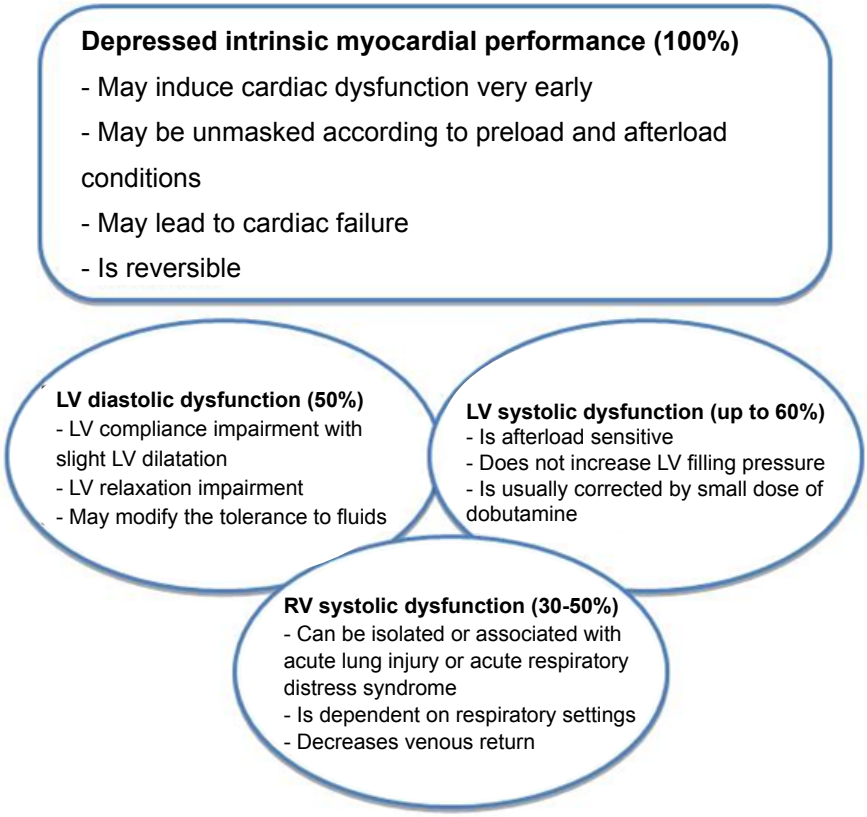

Figure 1 - Main mechanisms of cardiac dysfunction, along with its consequences and impact.
Adapted from Vieillard-Baron A, Cecconi M. Understanding cardiac failure in sepsis. Intensive Care Med 2014;40:1561.

reduced glutathione, oxidative stress, and mitochondrial dysfunction.[8,9] Although its exact role in the pathogenesis of myocardial dysfunction in sepsis is unknown, endothelin-1 has been demonstrated in animal models to directly affect the myocardial performance as well.[10]

- Alterations of calcium channels: the involvement of these channels with myocardial dysfunction can be explained by the relationship between intracellular calcium concentrations and cardiac contractility, but experimental models have shown that despite the reduction in L-type calcium channels observed in sepsis leading to a reduction in cardiac repolarization, there is no clear association between the resulting shortening of the duration of action potential and a possible reduction in myocardial contractility.[11]

- Toll-like receptors: toll-like receptors (TLRs) recognize specific pathogenic molecular patterns and play an important role in innate immunity. Experimental models have demonstrated that the activation of nuclear factor κB mediated by TLR4 plays an important role in the development of myocardial depression[12] and that TLR3 knockout mice maintain a normal cardiac function even during sepsis.[13]

- Adrenergic hyperstimulation: in the early stage of sepsis, there is a massive release of catecholamines from the autonomous nervous system, intestine, leukocytes, and macrophages, resulting in hyperstimulation of alpha and beta-adrenergic receptors, which finally leads to their downregulation and resistance to circulating catecholamines.[14,15]

- Mitochondrial dysfunction: an adequate supply of adenosine triphosphate (ATP) is fundamental to the maintenance of myocardial contractility, and several mechanisms of mitochondrial lesion can play an important role in the development of myocardial dysfunction during sepsis, such as edema of the mitochondrial matrix, oxidative stress, alteration of membrane permeability, imbalance between biogenesis processes (growth and division), and mitophagy (removal of dysfunctional mitochondria by autophagy).[16]

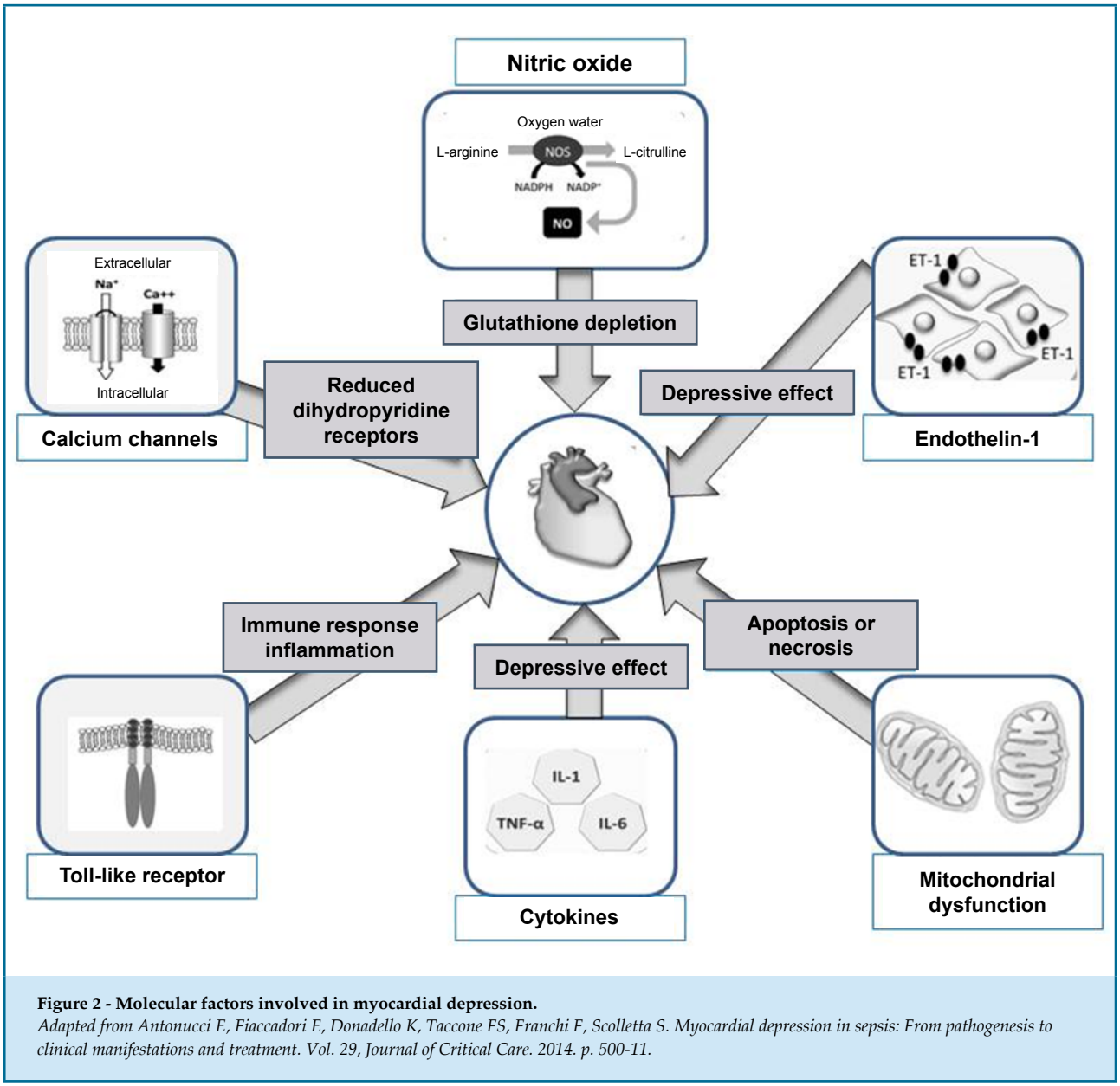

Figure 2 - Molecular factors involved in myocardial depression.
Adapted from Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: From pathogenesis to clinical manifestations and treatment. Vol. 29, Journal of Critical Care. 2014. p. 500-11.

Joseph et al.[17] demonstrated that the activation of the NADPH oxidase 2 – an enzyme complex found in the plasma membrane and involved in the maintenance of immune function, cell growth, and apoptosis – is one of the responsible factors for the oxidative stress induced by sepsis, and that its inhibition decreases not only the production of oxygen-derived reactive species, but also preserves the mitochondrial function and homeostasis of intracellular calcium, relieving the systolic dysfunction induced by sepsis in vivo.[17]

- Necrosis and apoptosis of cardiomyocytes: focal myocardial necrosis and subendocardial necrosis have been identified in experimental models of sepsis, while necrosis of the contractile bands was identified by Schmittinger et al.[18] in a prospective study involving the histological analysis of 20 biopsied human hearts.

- Myocardial infiltration: myocardial infiltration by neutrophils, monocytes, and macrophages is the main histological finding in septic cardiomyopathy. This inflammatory process is associated with interstitial edema, fibrosis, and formation of thrombi in the microcirculation.[18,19]

Left ventricular systolic dysfunction and mortality

LV systolic dysfunction has been the most studied and reported dysfunction in the literature, and despite

reduced myocardial contractility occurring in 100% of the cases of severe sepsis,[20] studies estimate that only 20 to 60% of the patients with septic shock have decreased LV ejection fraction (LVEF)[21-23] in the first 3 days of treatment, with a gradual return to the baseline value around the tenth day from the onset of sepsis among the survivors.[21]

Despite the importance given to the occurrence of systolic dysfunction during sepsis, its association with mortality is controversial. Ognibene et al.[24] observed that, paradoxically, patients with lower LVEF and greater LV end-diastolic volume (LVEDV) had a greater chance of surviving and recovering their myocardial function in the course of sepsis.[24] Additionally, Vieillard-Baron et al.[22] identified that acute and reversible left ventricular dysfunction was not associated with worse prognosis.

Narvaéz et al.[25] reported a 22.8% incidence of septic cardiomyopathy among patients with severe sepsis or septic shock, with no difference in mortality when compared with patients with LVEF ≥ 50% and normalization of LV function after recovery from the acute event.[25] De Geer et al.,[26] using speckle tracking, observed that the global longitudinal strain is often reduced in patients with septic shock, either alone or associated with a reduction in the LVEF or the average mitral annular motion velocity measured by tissue Doppler (e').[26] The authors also observed that the global longitudinal strain presents a strong correlation with NT-proBNP levels on the first day of hospitalization, but is not significantly different between survivors and nonsurvivors, therefore, is not a good predictor of mortality.[26]

In a recent meta-analysis that included seven prospective observational studies evaluating the relationship between systolic dysfunction associated with sepsis and mortality, the presence of a new-onset systolic dysfunction was not a sensitive or specific predictor of mortality due to the heterogeneity and low statistical power of the studies involved.[27]

The assessment of the systolic function during sepsis can be a complex and challenging task,[28] which may lead to the myocardial depression not being readily identified[29] or the LVEF to be even overestimated, depending on the moment it is assessed.[30] This occurs because the heart, despite being a central component of the cardiovascular system, is affected during sepsis by disorders of capillary permeability and peripheral vascular tonus, with fluid loss to the third space, absolute hypovolemia, and consequent decrease in preload, in addition to peripheral vasodilation with a direct reduction of the afterload and relative hypovolemia, leading to an additional decrease in preload.[28]

Since myocardial contractility is invariably reduced in sepsis, the LVEF ends up reflecting the balance between preload and afterload; in this way, despite the reduction of the intravascular volume directly affecting even more the myocardial function,[31] the arterial vasodilation, by reducing the afterload, may temporarily mask the myocardial depression and allow the LV systolic function to be preserved, i.e., overestimated despite a severely compromised intrinsic contractility, while the correction of the vasoplegia by volume resuscitation and the use of vasopressors unveil the contractile deficit.[30] In fact, Boissier et al.,[32] using tissue Doppler and speckle tracking, showed that most patients with septic shock have reduced LV strain, and observed an inverse correlation between most indices of contractility and afterload.[32] In addition, the diagnosis of systolic dysfunction in this clinical scenario can be hindered by the high prevalence of heart failure with reduced ejection fraction (HFREF) in the population, often done retrospectively by the observation of improvement in ventricular function through serial echocardiographic assessments.

Left ventricular diastolic dysfunction and mortality

Diastolic dysfunction is equally prevalent in the presence of sepsis, occurring in approximately 40% of the patients,[33,34] although this number may vary according to the criteria used to evaluate the diastolic function. This has been observed in a study conducted by Clancy et al.,[35] in which 60% of the patients evaluated on the first day of an episode of severe sepsis or septic shock presented diastolic dysfunction and 23% presented indeterminate diastolic function according to the guidelines published in 2016 by the American Society of Echocardiography along with the European Association of Cardiovascular Imaging, while 21% and 74% had diastolic dysfunction or indeterminate diastolic function, respectively, according to the 2009 guidelines of the American Society of Echocardiography.[35]

It is not yet clear whether diastolic dysfunction is induced by this condition or changed by its treatment (with volume expansion and use of vasopressors) or, even, if it is a preexisting condition aggravated by the infection.[31] The prevalence of diastolic dysfunction is known to increase significantly with age,[36] especially with the occurrence of comorbidities like hypertension and ischemic cardiopathy, characteristics often present

in the target populations of the studies. The isolated presence of diastolic dysfunction is already in itself a marker of poor prognosis. Redfield et al.[37] demonstrated by multivariate analysis that the isolated presence of any degree of diastolic dysfunction was strongly predictive of mortality, while Flu et al.[38] showed that isolated diastolic dysfunction was associated with a higher risk of cardiovascular events in 30 days and cardiovascular mortality in the long term in patients undergoing open vascular surgery.[38] Nevertheless, little is known about how the presence of diastolic dysfunction increases the risk of mortality in sepsis, but a very plausible hypothesis is that the abnormal relaxation of the LV potentiated by tachycardia induced by sepsis and/or decreased complacency could promote changes in cardiac hemodynamics in such a way that the normal cardiac output could only be maintained through increased LV filling pressures and greater atrial participation in ventricular filling.[39]

Once the left ventricular pressure rises disproportionately in response to a relatively small increase in volemia, such patients can progress with pulmonary venous congestion secondary to an overload of fluids required for volume resuscitation and enhanced by the widespread increase in capillary permeability secondary to endothelial dysfunction induced by sepsis.[40]

Regardless of the limitations presented, diastolic dysfunction has been singled out as an independent predictor of mortality by studies with tissue Doppler techniques for the evaluation of the properties of relaxation of the myocardium. Sturgess et al.,[41] in a prospective observational study with patients admitted to intensive care with septic shock, concluded that after adjustment for disease severity, presence of cardiac disease, volemic management, and degree of diastolic dysfunction, the ratio between the speed of early diastolic transmitral flow by pulsed Doppler (E) and e' – the E/e' ratio – was an important independent predictor of in-hospital survival that allowed a better discrimination of survivors and nonsurvivors than cardiac biomarkers.[41]

Landesberg et al., in a study including 262 patients with severe sepsis and septic shock, observed that diastolic dysfunction was not only common but also represented an important predictor of mortality in this context. The authors observed that patients with isolated systolic dysfunction (LVEF ≤ 50%; 9% of the patients) and diastolic dysfunction (e' < 8 cm/s; 40% of the patients) alone or associated with systolic dysfunction (14% of the patients) showed a significantly higher mortality than those without any type of dysfunction. In this study, a septal e' < 8 cm/s was considered an independent predictor of mortality.[42]

Mourad et al.[43] followed 72 patients with cancer admitted with septic shock to an intensive care unit and found that early diastolic dysfunction was a strong independent predictor of mortality in these patients and, once again, a lateral e' < 8 cm/s was an echocardiographic parameter independently associated with mortality.[43]

In 2014, Landesberg et al.[44] evaluated a new cohort of patients with severe sepsis and septic shock to investigate the manifestation of myocardial dysfunction that best correlates with troponin elevations and explain its association with mortality in sepsis. The authors concluded that diastolic dysfunction and RV dilation were the echocardiographic characteristics that best correlated with troponin levels and best independent predictors of in-hospital mortality than this biomarker, suggesting a potential contribution of these cardiac mechanical properties in the elevation of troponin levels and association with mortality in this clinical context. Once again, a septal e' < 8 cm/s was an important risk marker of mortality.[45]

More recently, Rolando et al., in a prospective observational study with 53 patients with a mean age of 74 years, observed that diastolic dysfunction was present in 83% of this population and that the E/e' ratio was the index of diastolic dysfunction that best correlated with decreased hospital survival on multivariate analysis.[45]

These findings have been corroborated by a meta-analysis comprising 16 studies and 1,507 patients with severe sepsis or septic shock, in which both a lower e' and a higher E/e' ratio had a significant association with mortality.[46]

Right ventricular dysfunction and mortality

Right ventricular systolic dysfunction, characterized by reduced contractility, increased right atrial pressure, and reduced venous return, has been reported in 30 to 50% of the patients during sepsis.[47] This complication may occur isolated or in association with left ventricular systolic dysfunction, justifying in the latter case the maintenance of filling pressures in the left side within the limits of normality, even in the presence of important contractility deficit.[20]

Similar to what occurs with the LV, the RV ejection fraction (RVEF) is directly dependent on the coupling between contractility and afterload, but different from the

systemic vascular resistance, which is initially reduced, pulmonary vascular resistance is increased since the early stages of sepsis by decreased production of NO[48,49] and increased circulating levels of vasoactive substances, such as thromboxane, endothelin, and serotonin.[50-53]

An RV with an intrinsic reduction in contractility induced by sepsis becomes more sensitive to the increase in afterload secondary to pulmonary vascular dysfunction[54] and only manages to maintain, at least initially, its systolic function through increased filling pressures provided by an adequate volume resuscitation; with fluid administration, there is an increase in cardiac index, central venous pressure, pulmonary capillary wedge pressure, and indices of end systolic and diastolic RV volumes, despite a progressive reduction in the ejection fraction of this ventricle.[55]

The failure of this compensatory mechanism becomes particularly more evident in patients on mechanical ventilation and in the presence of acute lung injury. In the first case, the effects of positive pressure on cardiac function lead to decreased venous return (hindering the increased filling pressures), elevation in pulmonary vascular resistance, and reduction in cardiac output due to increased intrathoracic pressure.[56] In the second, the hyperinflation resulting from recruitment maneuver and the pulmonary collapse due to alveolar filling and protective ventilation strategies using very low tidal volumes can also elevate the pulmonary vascular resistance by an increased autonomic tonus reflex and hypoxic pulmonary vasoconstriction, respectively.[57,58]

Regardless of this mechanism of adaptation, the literature has demonstrated an association between right ventricular systolic dysfunction and mortality in sepsis, with studies pointing to a lower RVEF[59,60] and, more recently, to a reduction in peak systolic velocity of the RV free wall on tissue Doppler in patients not surviving to sepsis compared with survivors.[61,62]

Vallabhajosyula et al.,[63] in a historical cohort study of patients with severe sepsis or septic shock admitted to all intensive care units at Mayo Clinic between January 2007 and December 2014, showed that 55% of the patients met the diagnostic criteria for right ventricular dysfunction and, after adjustment for age, comorbidities, disease severity, presence of septic shock, and mechanical ventilation, concluded that the presence of right ventricular dysfunction was associated with worse survival at 1 year (risk ratio of 1.6, 95% confidence interval [95%CI] 1.2 – 2.1, p = 0.002).[63] More recently, Orde et al.[64] showed that right ventricular dysfunction was present in 32% of the patients with severe sepsis or septic shock evaluated by conventional echocardiography, and that this number rose to 72% when the evaluation was performed with speckle tracking; this "unmasked" dysfunction, especially when severe, was associated with a high mortality rate.[64]

Biomarkers and sepsis

Cardiac troponins (I and T) are important independent predictors of mortality in acute coronary syndrome without ST-segment elevation[65] and other clinical conditions, such as end-stage renal disease,[66] stroke,[67] and pulmonary embolism.[68]

The elevation in troponin levels is relatively common in sepsis, occurring in approximately 60% of the patients;[69] even though it is unclear why this happens, the manifestations of myocardial dysfunction that most correlated to the elevation in troponin levels have been recently demonstrated to be diastolic dysfunction and right ventricular dilation.[44]

The role of the troponins as a prognostic factor in sepsis is still under debate, with some studies[70-72] having shown negative results in terms of increased mortality, and others concluded otherwise. John et al.[73] showed a higher mortality at 28 days in patients with positive troponin I (32% versus 14%, p < 0.0001),73 while Vallabhajosyula et al.,[74] in a retrospective cohort study, observed a relationship between troponin T elevation (≥ 0.01 ng/mL) on admission, in-hospital mortality (odds ratio [OR] 1.6, p = 0.003), and mortality at 1 year (OR 1.4, p = 0.04).[74]

BNP and NT-proBNP are two molecules secreted in response to atrial wall stretching and extensively used in the diagnosis and prognosis of heart failure. In the clinical context of sepsis, proinflammatory cytokines are believed to also exert an important role in the elevation of BNP levels. In vitro studies have shown the importance of interleukins 1 and 6 and TNF-α in inducing BNP secretion by cardiomyocytes,[75,76] explaining the higher plasma concentrations of this biomarker even in individuals without heart failure, and its correlation with the levels of C-reactive protein, a traditional marker of inflammatory activity.[77]

In sepsis, the interpretation of increased levels of BNP and NT-proBNP can be hampered by the inflammation and other factors like age and renal insufficiency, although studies have demonstrated their importance

as independent markers of mortality in this clinical scenario.[77,78] Brueckmann et al.,[79] for example, followed 57 patients diagnosed with severe sepsis and observed that patients with NT-proBNP levels > 1400 pmol/L showed a 3.9 times greater risk (relative risk [RR] 3.9, 95%CI 1.6 – 9.7) of dying from sepsis than patients with lower NT-proBNP values ($p < 0.001$).[79] Khoury et al.[80] studied 259 patients with sepsis and without cardiac failure and concluded using multivariate analysis that BNP is a strong predictor of in-hospital mortality at 90 days and 60 months, in addition to a better prognostic predictor than the Sepsis-related Organ Failure Assessment (SOFA) score for mortality at 90 days, and a better prognostic predictor of mortality at 60 months in low-risk groups.[80]

Final considerations

Evidence points to an association between myocardial dysfunction and sepsis as a relatively frequent event. The relationship between systolic dysfunction and mortality is still not defined, nor is the mechanism by which the diastolic dysfunction and the right ventricular dysfunction affect so adversely the evolution of patients with sepsis. There are no studies evaluating the effects of a differentiated strategy of treatment on the outcome of these patients. These gaps offer the opportunity for research and development of knowledge that can contribute to the treatment of such patients and, in the final analysis, improve their prognosis.

Author contributions

Conception and design of the research: Campista MS. Writing of the manuscript: Campista MS, Guedes MA. Critical revision of the manuscript for intellectual content: Jorge AJL, Campista MS, Martins WA. Supervision / as the major investigador: Jorge AJL.

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REVIEW ARTICLE

Phenotype Mapping of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFPEF) has become the main phenotypic model of heart failure (HF) in community and referral patients in Brazil and in the world. Despite advances in the development of new drugs for HF treatment, there has been no significant improvement in mortality of this condition.

According to many studies, this can be explained by the heterogeneous nature of HF physiopathology, whose basic mechanisms may result in different clinical presentations, culminating in the emerging of different phenogroups in this syndrome. In this context, phenotype mapping of HFPEF has emerged as a possible solution, since it enables the development of clinical trials that establish specific therapeutic strategies for each phenotypic profile.

New technologies in the field of artificial intelligence have enabled the assessment of a large volume of data and infer intrinsic patterns and different outcomes. Thereby, it is possible to obtain mutually exclusive categories of HFPEF, with a phenotype mapping of the syndrome and grouping of patients according to their phenotypic features. Besides, other diseases can have the same clinical phenotype but different pathophysiological basis, the so called "phenocopies".

These tools enable the analysis and categorization of the wide spectrum of heart failure, contributing to solve the dilemmas of the treatment of this syndrome.

Introduction

Heart failure with preserved ejection fraction (HFPEF) has become the main phenotypic model of heart failure (HF) in community and referral patients in Brazil and in the world.[1,2]

Only two forms of clinical presentations of HFPEF used to be recognized – first, in the outpatient setting, elderly women patients, intolerant to exercise, usually with no clinical evidence of congestion;[3,4] and second, patients admitted to emergency departments with hypertensive crisis, acute atrial fibrillation and acute pulmonary edema.[5]

Clinical profiles of HFPEF have been gradually identified. For example, HFPEF has been associated with pulmonary arterial hypertension and valve diseases – aortic stenosis, mitral stenosis – and deposition diseases, such as senile amyloidosis.[6,7]

In the last decades, progresses have been made in the understanding of pathophysiological mechanisms involved in HFPEF and the influence of comorbidities in the development and progression of the disease. In addition to diastolic dysfunction, abnormal chronotropic response, left atrial dysfunction, and altered physiology of coronary endothelium and systemic and pulmonary microcirculation have been reported. Molecular changes related to oxidative stress and a proinflammatory state have been also described, and seem to be associated with aging, hypertension, obesity and other cardiovascular and non-cardiovascular diseases.[8,9]

Despite advances in the study of HFPEF pathophysiology and development of new drugs, there has been no significant improvement in mortality or clinical outcome of this condition.[10]

A new discipline – phenomics – involving bioinformatics and artificial intelligence (machine learning) has been increasingly used for the study of phenotypes, including many areas of clinical medicine. More recently, it has been applied in cardiology for the study of HFPEF. Application of objective methods for identification of phenotypes goes in line with precision

Keywords

Heart Failure / physiopathology; Stroke Volume; Phenotype; Machine Learning; Artificial Intelligence.

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medicine, a new paradigm that has been successfully used in oncology. This approach considers genetic variability, environment, and lifestyle of each patient, allowing an individualized approach for the treatment and prevention of diseases.[11-13]

The aim of the present study was to present a narrative review of the literature to describe the clinical phenotypes of HFPEF and its potential impact on the management of patients and on clinical research.

Methods

Bibliographic review

We conducted a narrative review, from a clinical perspective, of studies published in MEDLINE using the PubMed search engine. The following MeSH (Medical Subject Heading) terms were used - (heart failure with preserved ejection fraction [tiab] OR diastolic heart failure [tiab] OR hfnef [tiab] OR hfpef [tiab]) AND (phenoc* [tiab] OR phenotype* [tiab]).

The search was carried out in February 2017, and 136 articles published in the period from 1990 and 2017 were identified. Thirty articles were independently selected by four investigators for detailed analysis. Additional articles were selected from the reference lists of the retrieved articles.

Pathophysiology of HFPEF

Heart failure (HF) is a complex clinical syndrome characterized by symptoms and signs caused by abnormal cardiac function and/or structure that leads to decreased cardiac output and/or increased intracardiac pressures.

HF patients can have different phenotypes according to morphofunctional characteristics of the disease, and receive different therapeutic approaches.[14,15] Based on this, patients are usually classified into patients with HF with reduced ejection fraction (HFrEF), marked by left ventricular ejection fraction (LVEF) lower than 40% - and HF with preserved ejection fraction (HFpEF), characterized by LVEF greater than 50%. Recently, the European Society of Cardiology has proposed a new phenotype – "HF with midrange ejection fraction" – with intermediate ejection fraction (LVEF between 40 and 49%) and a clinical profile different from HFeEF and HFpEF.[16]

The main diagnostic criteria of HFPEF – the focus of this study – are the clinical profile of LVEF equal to or greater than 50%, increased levels of brain natriuretic peptide (BNP) (greater than 35pg/mL or NT-proBNP greater than 125 pg/mL) and at least one of these two criteria – important structural cardiac disease (left ventricular hypertrophy and/or increased left atrium) and diastolic dysfunction.[16]

HFPEF is characterized by reduced end-diastolic volume, left ventricular hypertrophy, and increased left atrial volume and left ventricular filling pressure. These pathophysiological abnormalities are associated with increased left ventricular stiffness, decreased left ventricular relaxation, cardiomyocyte hypertrophy, myocardial interstitial fibrosis and reduced intramyocardial capillaries.[17-19] In addition, a proportion of patients with HFpEF present atrial fibrillation, which further aggravates cardiac function.[20]

The classical presentations - HFeEF and HFpEF – used to be distinguished only by the remodeling pattern of cardiac chambers and extension of myocardial dysfunction, culminating in different therapeutic responses. However, it is known today that morphofunctional changes are also based on molecular alterations, which are also different between these conditions.[10]

Left ventricular diastolic dysfunction, an important diagnostic criterion for HFPEF, may be explained by increased myocardial stiffness, resulting from changes in extracellular matrix and/or cardiomyocytes.[10] There are evidence that extracellular matrix stiffness results mainly from collagen metabolism. Excess deposition of type I collagen, the subtype with the highest stiffness property, is explained by increased synthesis and/or decreased degradation of this compound. Type I collagen synthesis can be measured by procollagen type I carboxy-terminal propeptide, which derives from type I procollagen and acts as a biomarker. Decreased degradation of type I collagen is caused by downregulation of matrix metalloproteinases (MMPs) and/or upregulation of tissue inhibitors of metalloproteinases (TIMPs). TIMP-1 plasma levels have also been suggested as promising biomarkers in HFPEF.[9,10]

Excess collagen is found in only one third of patients with HFPEF, even in the presence of ventricular stiffness, which usually results from an intrinsic cardiomyocyte condition, and may be related to the protein structure and/or to the disruption of the sarcomere structure.[9,10]

Cardiomyocyte structure depends directly on regulation of constituent proteins, and myocardial stiffness may indicate an unbalance in this process. One of the main proteins involved in this regulation is titin, an elastic constituent protein of cardiomyocytes, with two isoforms

- N2B (stiffer) and N2BA (more compliant). Changes in the ratio of one isoform to the other and phosphorylation of the fibers, as well as oxidative stress can have an impact on myocardial compliance, leading to stiffness.[9,18]

Disruption of sarcomere structure is the mechanical factor of ventricular relaxation. It is an energy-consuming reaction, and, for this reason, the lack of energy stores impairs a normal left ventricular relaxation. Recent studies have demonstrated a decreased phosphate creatinine/adenosine ratio in patients with HFPEF, which is consistent with a decline in myocardial energy store.[21-23]

In addition to interstitial (collagen-related changes) and structural (regulation of constituent proteins) changes, unbalanced levels of chemical mediators, especially of monophosphate cyclic guanine (cGMP), may also explain myocardial stiffness in HEPEF. Activation of protein kinase G (PKG) by cGMP results in phosphorylation cascade of proteins important for cardiomyocyte integrity – phosphorylation of titins inhibits cardiac hypertrophy and increases myocardial compliance, phosphorylation of potassium channels inhibits tissue ischemia, and phosphorylation of troponin I increases left ventricular relaxation. Also, PKG activation by cGMP increases calcium reuptake by sarcoplasmic reticulum.[9]

Low BNP, microvascular inflammation and oxidative stress, which are common in several conditions, such as obesity and insulin resistance, suppresses GMPc synthesis pathways. This, in turn, inhibits PKG phosphorylation cascade and culminates in myocardial stiffness, characteristic of HFPEF.[8,9]

Although HFPEF is commonly referred as diastolic HF, the disease is not limited to ventricular relaxation problems. A study[24] demonstrated that myocardial contractility may be decreased in HFPEF, even if the end-systolic elastance (ESE) – used to measure myocardial contractility – is increased.[24] This apparent contradiction may be explained by the influence of cardiac chamber geometry on ESE. Concentric hypertrophy, characteristic of HFPEF, independently increases ESE, even with reduced left ventricular contractility.[21]

In HFPEF, vascular stiffness is generalized, resulting in elevated pressure, which aggravates ventricular stiffness and attenuates vascular dilation in exercise, thereby decreasing blood supply to musculoskeletal system. Increased vessel stiffness, associated with elevated left heart pressure, increases pulmonary pressure and consequently the mortality of these patients.[21]

Defects in diastolic, systolic, vascular and chronothropic functions elucidate the heterogeneous nature and complexity of HFPEF. Its multiple pathophysiological factors indicate the need of phenotyping of these patients, and identification of specific causes of the worsening of each phenotype. This strategy has become increasingly possible with biomolecular advances in medicine and will possibly guide therapeutic decisions based on specific pathophysiological changes.

Modulation of HFPEF phenotypes by epigenetics – a new frontier

Epigenetics is an emerging science involving the study of changes in the regulation of genes and their expression, regardless of their sequences. Environmental factors can affect intracellular signaling pathways in a way that can affect chromatin structure, resulting in the passage of altered gene expression patterns to the offspring by epigenetic memory, affecting the phenotypes of the diseases.[25,26]

New evidence suggests the involvement of epigenetic regulation in target cells related to cardiovascular pathogenesis, including HF and its different phenotypes.[27] Cardiomyocytes, for example, can adapt to environmental stress by epigenetic regulation. This dysregulation in genetic expression provides information about the pathogenesis of cardiac and vascular remodeling, dysfunction of progenitor cells and endogenous repair system, inflammation, fibrosis and cardiac dysfunction.[28,29]

Four epigenetic mechanisms in cardiovascular diseases have been identified – DNA methylation, chromatin remodeling by adenosine triphosphate (ATP)-dependent enzymes, histone modification and microRNA-dependent mechanisms.[30-32] Recent findings have associated these mechanisms with HFPEF-related diseases; however, evidence on the role of epigenetics in changes in cardiac function and structure, and clinical trials corroborating theories involving both epigenetics and cardiovascular disease are still lacking. Advances in studies on this field should contribute to HF prevention and provide enough evidence for the stratification of HF phenotypes.

Clinical phenotypes and phenotypic mapping

Current phenotyping tools combined with advances in genetics and systems biology have the potential to improve the classification of complex, heterogeneous systems, such as HFPEF. Analysis of patients' data aiming to establish a pattern of these variables may be performed

by machine learning algorithms. Machine learning is a field of artificial intelligence, in which a computer is programmed to learn the relationship between the objects of study by data processing and accumulate experience with previous problem-solving approaches. Machine learning algorithms are classified into supervised and unsupervised. While supervised learning is focused on outcome prevention, unsupervised learning aims to infer intrinsic structures of the data.

Therefore, in this approach, a large volume of data can be analyzed and mutually exclusive categories of HFPEF can be obtained by phenotype mapping of the syndrome and grouping of patients in subgroups according to phenotypic characteristics. Phenotypic classification of patients with HFPEF would be helpful to the development of clinical trials on therapeutic strategies specific to each phenotypic profile.[12]

A recent study was the first to identify phenogroups of a heart disease, and the first to use the machine learning technique as an approach to solve the heterogeneity of a cardiovascular syndrome by phenotype analysis.[33]

The data analyzed for patients' classification using the machine learning approach included clinical variables, physical features, laboratory data and electrocardiogram and echocardiogram parameters.

Although the patients shared many clinical characteristics, they were classified in three subgroups with distinct characteristics and prognosis:[33]

• Group 1, composed of younger patients, with moderate diastolic function and relatively normal BNP levels. These patients have the mildest myocardial remodeling, electrical dysfunction and hemodynamic change, although 65% of them had moderate diastolic dysfunction and elevated pulmonary capillary pressure (PCP) and pulmonary artery systolic pressure.

• Group 2 involved obese, diabetic patients, with a high prevalence of sleep apnea and impaired left ventricular relaxation. This group showed the highest PCP and highest pulmonary vascular resistance.

• Group 3 was composed of older patients, with significant chronic kidney disease and pulmonary hypertension. In this phenogroup, a more severe myocardial remodeling and electric dysfunction was observed, with a longer QRS-T interval, higher relative thickness of cardiac walls, higher left ventricular mass index, higher E/e' ratio and worse right ventricular function.[33]

In addition, different phenogroups had different clinical course and outcomes, and distinct risk stratification. Prognosis was divided into the following categories: death, hospitalization for non-cardiac causes, hospitalization for cardiac causes, and hospitalization for HF. In group 1, the most frequent prognostic factors were hospitalization for cardiovascular and hospitalization for non-cardiovascular diseases; in group 2, hospitalization for non-cardiovascular causes and HF, and in group 3, the most prevalent outcome was death, followed by hospitalization for HF.[33]

However, although ideally the subgroups should be mutually excluding, some patients had overlapping clinical features, especially in the analysis of group 1 patients (Figure 1). Even so, this was a pioneer study in the phenotyping of complex cardiovascular syndromes.[33]

In light of the above, one may infer that the use of the machine learning tool in international centers would provide new, essential information on HFPEF epidemiology.

Considering that this study was conducted in a North American setting,[33] it is expected that results observed in the subgroups are different from those in South America. Therefore, application of the technique in Latin American prevalence studies is paramount for future phenotype mapping of HFPEF in Brazil.

Treatment

Classical therapeutic approach of HFPEF has not reduced mortality and morbidity rates of these patients. Thus, considerable differences between the phenogroups indicate the importance of a specific therapeutic approach, since advances in therapies have been so far hampered by such phenotypic complexity. To deal with that, new therapies that have a direct effect on signaling cascades involved in the pathophysiology of the HFPEF have been proposed.[34,35] Today, these therapies varied from signaling pathways of systemic inflammation to myocardial elasticity, and additional therapies to different comorbidities associated with the same pattern of phenotypic predisposition to the disease.

Aging, obesity, systemic hypertension, type 2 diabetes mellitus, kidney failure, and sleep apnea can trigger a chronic systemic inflammation that affects the myocardium and other organs. The patient may have pulmonary hypertension, sodium retention and impaired oxygen extraction by skeletal muscles.

For patients with pulmonary congestion or metabolic risk, it is recommended the use of diuretics, statins, organic nitrites /nitrates, energy-intake restriction, stimulants of PKG pathway, and extracellular matrix-stimulating agents, like spironolactone.

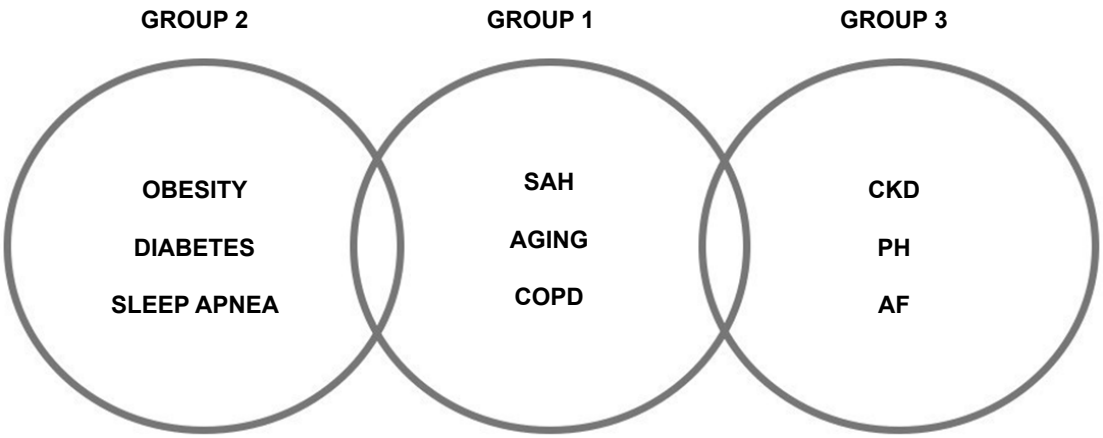

Figure 1 - Phenogroups of heart failure with preserved ejection fraction. SAH: systemic arterial hypertension; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PH: pulmonary hypertension; AF: atrial fibrillation.

For hypertension phenotype, anti-hypertensive are the most recommended treatment, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and calcium channel blockers, highlighting the importance of this treatment to HF prevention, to vascular conditions not related to HF (such as stroke and myocardial infarction) and to improve the quality of life of HFPEF patients. The CHARM-Preserved, PEP-CHF and TOPCAT studies demonstrated a reduction in hospitalization rates of patients with HFPEF by blockage of the renin-angiotensin-aldosterone system. These studies used, respectively, an angiotensin II receptor blocker, ACE inhibitors and an aldosterone antagonist (spironolactone).[36-38] Inhibition of the renin-angiotensin-aldosterone system would be of benefit to the patients due to the association of neurohormonal activation with hypertension and volume retention.[39,40]

Control of heart rate is mediated by activation of the sympathetic system, which has a direct effect on adverse outcomes in patients with HFPEF. A study derived from the I-Preserve study showed an association between increased heart rate and higher incidence of death for cardiovascular causes and hospitalizations in patients in sinus rhythm.[41] Therefore, heart rate control would be an effective treatment target.

In patients with pulmonary hypertension, the use of dobutamine improved pulmonary vascular function, and studies on new pulmonary vasodilators targeting GMPc, endothelin and nitric oxide (NO)[32] have also been developed (Table 1). In patients with kidney dysfunction, sildenafil had no significant effects in the RELAX clinical trial.[42] Due to the high prevalence of patients with HFPEF and pulmonary hypertension, and its intrinsic relationship with morbidity and mortality, pulmonary vasodilation is paramount in the treatment of these patients.[43]

Based on the studies reviewed, we conclude that phenotype mapping in HFPEF has enabled the development of a new generation of clinical trials aimed at new therapeutic approaches (Figure 2).

HFPEF accounts for nearly half of HF patients on treatment and its prevalence has increased. Cardiovascular disease phenotypes are complex, with many influencing factors. Systemic inflammatory reaction and microvascular endothelial dysfunction lead to ventricular remodeling and dysfunction. Specific therapeutic interventions should be multifaceted and focused on stages of these signaling cascades. New therapeutic approaches should encompass metabolic control, modulation of inflammatory response, control of pulmonary hypertension, prevention of muscle weakness, and reduction of sodium and water retention. Due to the wide range of interventions, phenotype mapping becomes an essential tool for future investigations and clinical trials (to confirm the results). Possibly, there will be more significant changes as new genetic, cellular, molecular and immunologic biomarkers are incorporated and used to discriminate treatment groups in a clear and objective manner.

Cardiac diseases that simulate HFPEF – Phenocopies

The term "phenocopies" was first used in the study of hypertrophic cardiomyopathies, in which a subgroup of

Table 1 - Example of therapeutic strategies for different phenotypes of heart failure with preserved ejection fraction

	Lung congestion	+ Chronotropic incompetence	+ Pulmonary hypertension	+ Skeletal muscle weakness	+ Atrial fibrillation
Overweight/ Obesity/ Metabolic syndrome/ Type 2 DM	. Diuretics (loop diuretics in DM) . Caloric restriction . Statin . Nitrate/Inorganic nitrite . Sacubitril . Spironolactone	+ Atrial pacemaker + Avoid betablockers and cardioselective calcium channel blockers	+ Pulmonary vasodilator + Anticoagulation (in PTE)	+ Exercise program	+ Cardioversion + Control of HR + Anticoagulation
+ SAH	+ ACEI/ARB + Calcium channel antagonist	+ ACEI/ARB + Atrial pacemaker	+ ACEI/ARB + Pulmonary vasodilator	+ ACEI/ARB + Exercise program	+ ACEI/ARB + Cardioversion + Control of HR + Anticoagulation
+ Kidney dysfunction	+ Ultrafiltration if necessary + nephroprotective drugs (ACEI/ARB)	+ Ultrafiltration if necessary + Atrial pacemaker	+ Ultrafiltration if necessary + Pulmonary vasodilator	+ Ultrafiltration if necessary + Exercise program	+ Ultrafiltration if necessary + Cardioversion + Control of HR + Anticoagulation
+ CAD	+ ACEI + Myocardial revascularization	+ ACEI + Revascularization + Atrial pacemaker	+ ACEI + Revascularization + Pulmonary vasodilator	+ ACEI + Revascularization + Exercise program	+ ACEI + Revascularization + Cardioversion + Control of HR + Anticoagulation

Adapted from: Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134(1):73-90. DM: diabetes mellitus; SAH: systemic arterial hypertension; CAD: chronic artery disease; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; PTE: pulmonary thromboembolism; HR: heart rate

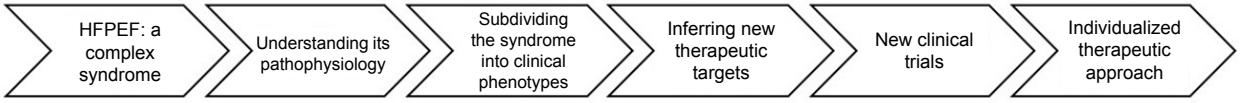

Figure 2 - The process towards effective therapies of heart failure with preserved ejection fraction: HFPEF: heart failure with preserved ejection fraction.

diseases was found to mimic their phenotypic features. We found that this concept may be extended to HFPEF. Due to the heterogeneity nature of HFPEF, other diseases may have the same clinical phenotype and thereby be considered their "phenocopies". Although both therapeutic intervention and prognosis of the diseases are different, their similar clinical presentation hampers the differential diagnosis. One pertinent example of a disease that mimics the clinical pattern of HFPEF is cardiac amyloidosis.[44,45]

Cardiac amyloidosis is a restrictive cardiomyopathy, regardless of its type, characterized by progressive diastolic dysfunction followed by systolic dysfunction and arrhythmia. It may be first identified as exercise intolerance or HF. The diagnosis of cardiac amyloidosis is usually established in the late stages of the disease, since the disease affects the same elderly population affected by HFPEF. However, the exact contribution of amyloidosis to HFPEF has not been elucidated. Protein accumulation leads to asymptomatic left ventricular

hypertrophy, with late diagnosis due to its gradual progression. Nevertheless, it is worth pointing out that individuals with HFPEF usually have other comorbidities that independently contribute to diastolic dysfunction.[46-48]

In addition to cardiac amyloidosis, "phenocopies" include other diseases such as hypertrophic cardiomyopathy, cirrhotic cardiomyopathy,[49] low-flow, low-gradient aortic stenosis, cardiac sarcoidosis and hemochromatosis (Figure 3).

The identification of "phenocopies" in HFPEF may enable an individualized approach to molecular targets and functional abnormalities, such as the use of certain drugs in senile amyloidosis, and betablockers and/or calcium channel antagonists in hypertrophic cardiomyopathy. Besides, the chance of diagnostic errors may decrease and that of early diagnosis of other diseases may increase when the presence of diseases that mimic HFPEF is considered.

The use of the machine learning technique for patients' grouping by phenotypes allows the analysis of a wide variety of variables and relationship between them, and to classify them in mutually exclusive phenogroups. In addition to allowing a phenotype categorization and to contribute to a therapeutic revolution, the identification of possible "phenocopies" is crucial for the differential diagnosis of a HFPEF model (Figure 4).

Conclusions

HFPEF is a common syndrome, whose prevalence will increase in the community. However, classification of phenogroups and results of therapeutic approaches are still incipient.

Today, the concept of adopting a phenotype network to explain HFPEF disrupts the Cartesian model in suggesting a complex approach of these patients, who may have many morphofunctional patterns. These distinct patterns may be related to abnormal signaling processes in the myocardium and associated with systemic inflammation, which is increased in patients with HFPEF and comorbidities.

Phenotype mapping of heterogeneous clinical syndromes, such as HFPEF, enables the categorization of patients, and can serve as a basis for the development of clinical trials and identification of new therapeutic approaches.

Author contributions

Conception and design of the research: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Acquisition of data: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Analysis and

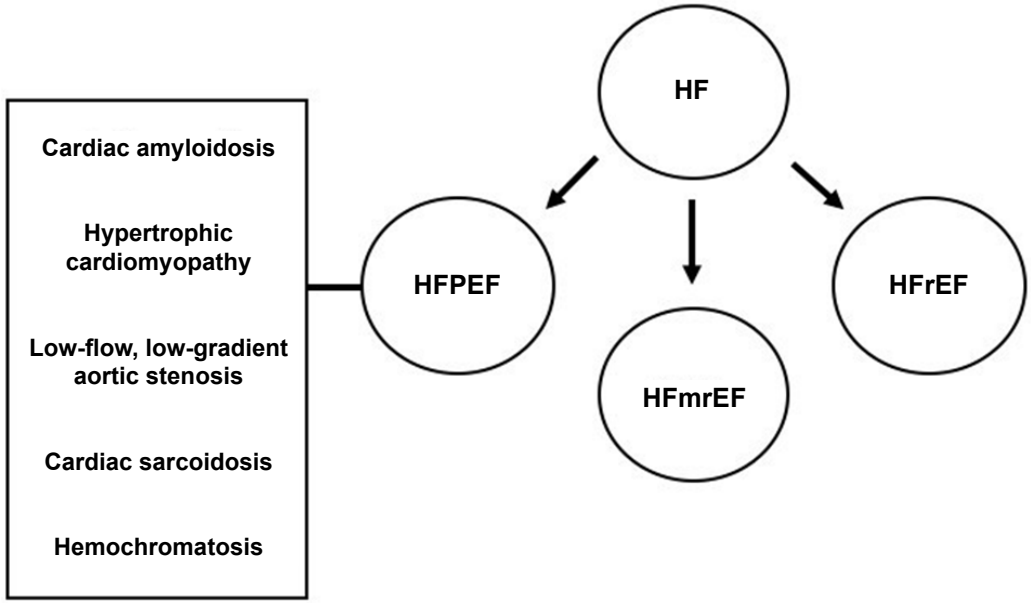

Figure 3 - Phenocopies of heart failure with preserved ejection fraction. HF: heart failure; HFPEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction.

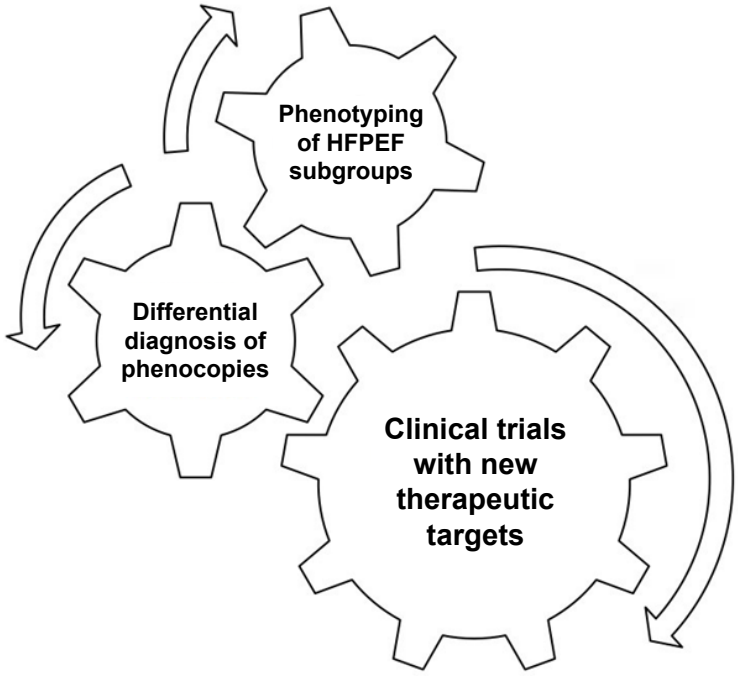

Figure 4 - Future management of heart failure with preserved ejection fraction. HFPEF: heart failure with preserved ejection fraction.

interpretation of the data: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Writing of the manuscript: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Critical revision of the manuscript for intellectual content: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR.

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VIEWPOINT

Remoras and Spontaneous Echocardiographic Contrast

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Abstract

The term "Remora" (hindrance) – re (again)/mora (delay) -originally designated a family of fishes – the suckerfishes. In ancient Greece and Rome and up to the early 19th century, these fishes were believed to slow down ships by attaching to them. Medicine adopted the term "remora" to describe fluid/blood stasis. Intracardiac blood stasis, or remora, especially in the left atrial appendage, is associated with thrombogenesis and responsible for cardioembolic phenomena. The slow and swirling movement of blood causes the appearance of spontaneous echocardiographic contrast (SEC). I briefly narrate the Naval Battle of Actium, whose result was mythically attributed to the remora fishes, and make a short review of remoras. I also describe Laennec's discussion about intracardiac blood stasis and give a short account of SEC, its original descriptions and importance.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of embolism to the brain and other sites. The risk is even greater in the presence of evident decrease in blood flow velocity in the left atrial appendage (LAA), a common feature of many conditions such as AF and mitral stenosis. Echocardiography can show the presence of blood stasis, or "remora", strongly correlated with an intracavitary smoky appearance, known as spontaneous echocardiographic contrast (SEC) (Figure 1).[1]

Keywords

Cypriniformes (remoras); Atrial Appendage; Embolism and Thrombosis; History, Ancient; Diagnostic Imaging; Ultrasonography/history; Echocardiography/history.

The term *remora* designates a family of fishes (shark suckers) known for their ability to adhere to large fishes and mammals using a specialized sucking structure. I describe why these fish were so-called "remora" in the first place, and why Cardiology has borrowed this term to describe the phenomenon of blood stasis.

The battle of Actium

Actium is a promontory in Acarnania, Greece. It occupies the southern side of a strait connecting the Ionian Sea to the Ambracian gulf. Octavian, later known as Augustus (27 B.C.), defeated Mark Antony and his allied Egyptian forces in a great naval battle there (September 2, 31 B.C.). The battle became the decisive confrontation of the Final War of the Roman Republic.

Antony's infantry was outnumbered (maybe 70,000 vs. 80,000 men) and Octavian had blocked Antony' s communication with Egypt via the Peloponnese. By following Cleopatra's advice, Antony moved his larger, heavily armed but less maneuverable fleet (500 vessels including the Egyptian forces). Cleopatra's fleet followed in the rear, but never entered in the battle. Octavian's fleet (250-400 warships) was mainly composed of lighter but well-equipped ships. Also, his crews were better trained and in better health, since Antony's soldiers had been struck by malaria before the confrontation.

The battle raged outside the gulf of Actium for many hours. Desertion of Cleopatra's lighter warships when the winds blew in the right direction decisively influenced the battle's result. Antony managed to catch up with Cleopatra but left the remaining of his fleet behind, which then surrendered to Octavian and his admiral Agrippa.[2]

Antony's land forces surrendered in the following week. Several battles followed during the following year and led to Octavian's final victory. Antony and Cleopatra VII committed suicide in 30 B.C. (July 31 and August 12,

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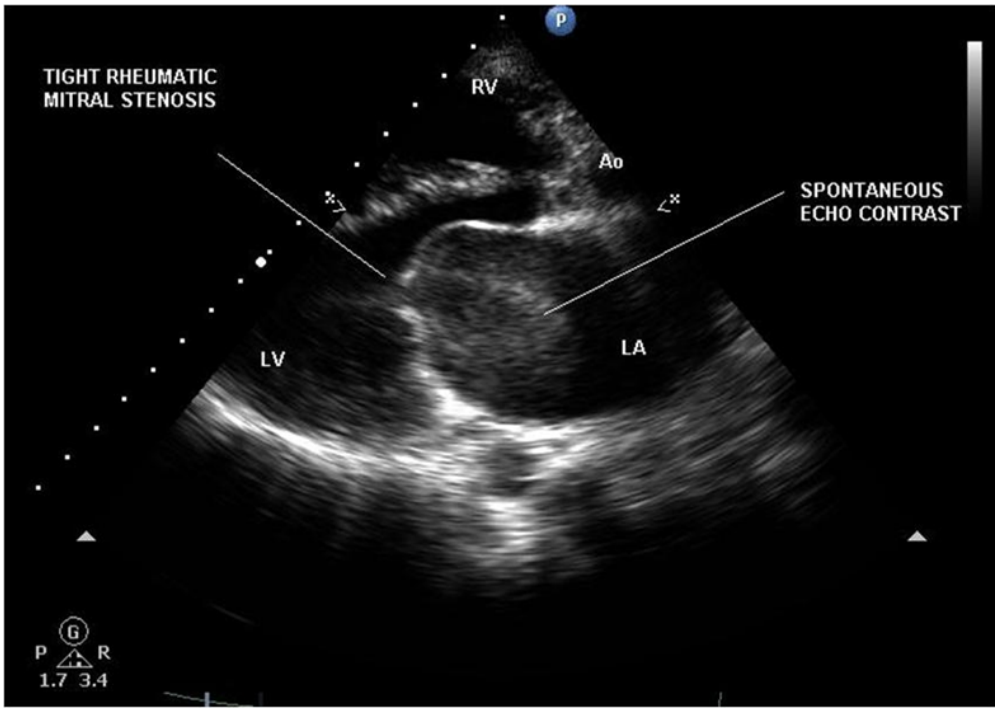


Figure 1 - Echocardiogram, parasternal axial view. Blood stasis (remora) appears as spontaneous echocardiographic contrast in a patient with tight mitral stenosis and atrial fibrillation. Also, note the "hockey stick deformity" of the anterior leaflet (upper part), and left atrial enlargement. Image posted by Jayachandran Thejus, MD, in http://www.heartpearls.com/category/interesting-echocardiographic-images/page/2

respectively). Octavian's power was then consolidated, and this opened the avenue to Rome's transition from Republic to Empire.

The myth

Antony's heavy and less maneuverable galleys behind the Egyptian fleet proved slow in the battle, and their defeat by Octavian substantiated the Remora myth. After describing the Actium battle and a similar episode involving the emperor Caligula, the naturalist and historian Pliny the Elder (23-79 CE) stated that all species of remora had the same property, adding an ancient Greek episode (Nat. Hist. 2, XXXII, 1).[3]

The false belief persisted for many centuries. In 1580 Michel de Montaigne (1533-1592) translated two episodes described by Pliny (author's translation from *Essais*, II, xii - pp.200-2): "Many believe that in that final and great battle in which Antony was defeated by August, Antony's galley was slowed by this tiny fish that the Romans call *Remora*, because of its property of slowing down every kind of ship to which it attaches. The Emperor Caligula, sailing with a large fleet by the Roman coast, was the only to have one of his ships slowed down by this same fish; once he detached the fish from the hull, the emperor got disappointed as he realized that such a tiny little animal could defy the sea, the winds and the strength of the oars by fixing its body to the ship only by its "beak" (in fact, it is a crustacean). He was also astonished, not without reason, by the fact that, inside the boat, the animal did not exhibit the same strength as it did outside the boat".[4]

The 1828 first edition of the Webster dictionary (http://webstersdictionary1828.com/) still defines remora as a fish "said to attach itself to the bottom or side of a ship and retard its motion". At the end of the 19th century, however, the mythic nature of their effect of slowing down ships was already well recognized. In 1893, for instance, the definition in the Larousse Dictionary was: "*poisson auquel on attribuait le pouvoir d'arreter les navires*".

Remora fish

Suckerfishes constitute a family (*Echeneidae*) of ray-finned fishes that measure up to 75 cm long. Their first

dorsal fins take the form of an oval slat-like structure with flexible membranes with thousands of spicules that increase friction forces (Figure 2a). This structure can generate suction and attach firmly on the smooth skin of large fishes – sharks, rays, tuna, swordfishes - and other animals such as dolphins, whales, dugongs and manatees, turtles etc. (Figure 2b). They can also attach themselves to boats and ships. Sliding backwards increases the negative pressure and suction and moving forward allows detachment from the surface and free swimming.

Remoras and their hosts live in commensality. Remoras eat the host's feces, leftovers, parasites and clean epidermal sloughing, whereas hosts confer protection, transport, promote fast passage of fluid through the gills and hence passive ventilation and energy sparing.

The term Remora is derived from the Latin (Hindrance; to defer, delay, linger) and is a composite of *re* (back, again) and *mora* (delay). The family name – *Echeneidae* (1810) – also refers to the mythic property of this fish (*Echein* – to hold, possess; and *Naus* - ship). Evidence of any deleterious hydrodynamic effects of the attachment of remoras to fishes or ships is, however, scarce or absent. Additional effort from hydrodynamic strain and metabolic demand for food imposed by the attachment of remoras to large fishes or dolphins are minimal (*circa* 1%), even at high speed (e.g., 500 cm/s). This, however, depends on the number of remoras attached and the size of the host.[5]

Remora as blood stasis

Cardiac blood stasis and its thrombogenic potential have been described for a long time. René Théophile Hyacynthe Laennec (1781-1826), who made extensive autopsy studies of his patients, does not refer to it in the first edition of his treatise on auscultation and lung and heart diseases (1819). However, he clearly mentions "*la stase du sang*" in Chapter XIX (*De l' inflammation de la Membrane Interne du Coeur et des Gros Vaisseux*, pp. 598-618) of the expanded and even more influential second edition of the *Traité* (1826).

The term *remora* was already in use in the 19th century to describe biological fluid stasis. As for intracardiac blood, the above text (the *Traité*, 1826) was translated into English by John Forbes (p. 663), as follows: "From all previous reports I believe we can draw the following conclusions – 1. Remora of the blood, in consequence of obstruction to its flow, is sufficient to produce coagulation, and to determine the formation of a coagulum of organizable fibrin. All causes capable of occasioning remora, particularly mechanical obstruction to circulation and repeated and prolonged episodes of syncope, seem to me sufficient to produce this effect".[6]

Spontaneous echocardiographic contrast

In 1975, Feigenbaum, using M-mode echocardiography, described left intracavitary echoes near dyskinetic segments of the left ventricle and thrombi in patients with coronary artery disease. Human and animal studies using real-time two-dimensional echocardiography confirmed that these variables – density and conformation echoes – moved in slow circles and were due to the sluggish blood flow caused by severe wall motion abnormalities,[7] which could be found even during anticoagulation treatment and were also detected within abdominal aortic aneurysms. These echoes "resembled smoke moving slowly through a light beam in a dark room".[7] Increasing layering and alignment of red blood cells (*rouleau*) in low-flow and whirling conditions are responsible for the increased echogenicity.[7]

Iliceto et al. first described dynamic intracavitary echoes – defined as a cloud of low-intensity echoes slowly moving in a circular or spiral shape – in the enlarged left atrium of 10 patients with severe mitral stenosis and AF.[8] At that time, correlation of SEC with thrombogenesis was already well established.

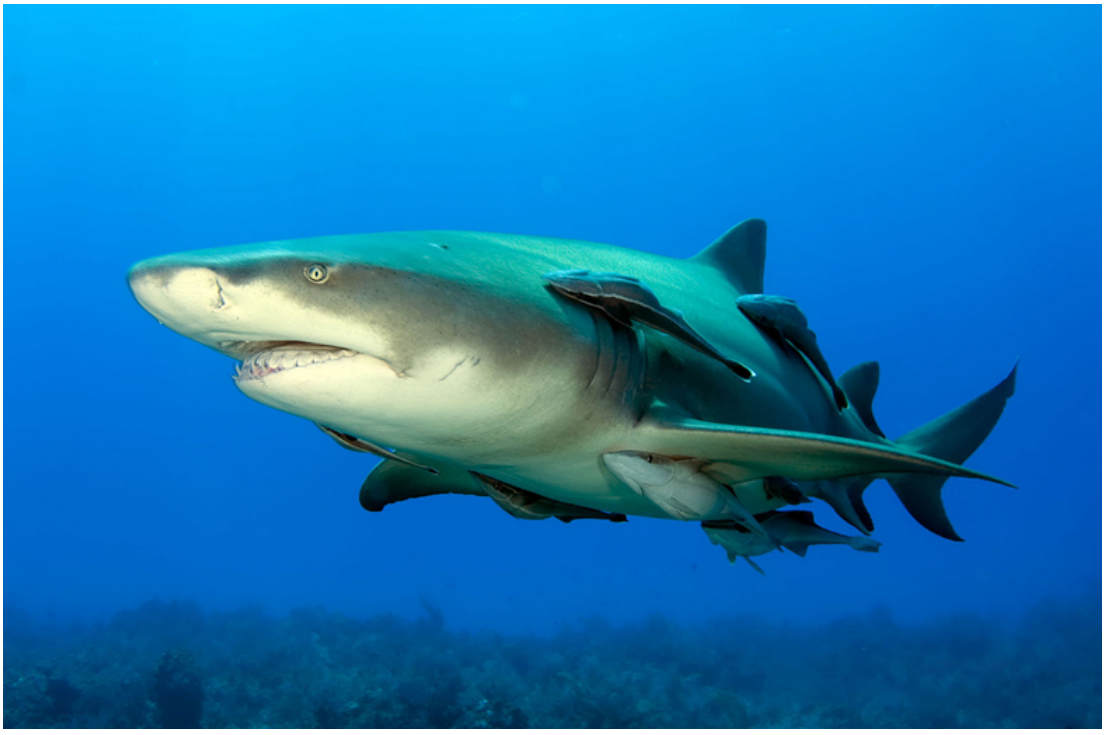
Most thrombi in patients with AF (90%) or mitral stenosis (60%) are detected in the LAA.[1] SEC is also most commonly seen in this structure. In the setting of stroke of unknown etiology, the presence of SEC in the LAA indicates a probable cardioembolic origin, even in the absence of thrombus.[9] LAA is an important contractile and multilobulated structure, whose dysfunction is the main cause of clot formation in AF, mitral stenosis, myocardial stunning after cardioversion, etc. SEC and thrombi are more frequently detected in patients with LAA contractile dysfunction.

A comprehensive study of the LAA is currently performed using transesophageal echocardiography including multiple imaging planes, pulsed wave-Doppler and tissue strain techniques.[1,10] These techniques provide an accurate analysis of LAA's contractile properties and demonstrate good correlation with the presence of SEC or thrombus and with thromboembolic risk.[1,11]

Conclusion

Thrombogenesis in FA and other conditions with slow atrial flow involves the complex interplay of

A



B

Figure 2 - The *Remora* (*Echeneidae*). A. *Echeneis naucrates*. The dorsal suction pad and the projecting lower jaw are shown. B. Remoras of varied size firmly attached to a large shark. http://www.realmonstrosities.com/2012/12/remora.html

blood stasis, increased extracellular matrix turnover, progressive morphological changes and endothelial lesion of the LAA, as well as changes in soluble blood components, such as fibrin D-dimer, and prothrombin fragments.[12] Mechanisms of these processes involve increased activity of the renin-angiotensin system and production of growth factors (especially VEGF), and impaired production of endothelial nitric oxide. Many other factors (age, hypertension, low cardiac index etc.) may additionally increase the risk of thrombogenesis and hence embolism.[12]

The word "remora" has been associated for centuries with the slow flow of many fluids, including blood. Intracardiac remora leads to the appearance of SEC in echocardiography and is strongly associated with thrombogenesis and an increased embolic risk. After all, remoras are not responsible for delaying battle ships; however, their connection to cardiology holds strong.

Author contributions

Conception and design of the research: Andre C. Acquisition of data: Andre C. Analysis and interpretation of the data: Andre C. Writing of the manuscript: Andre C. Critical revision of the manuscript for intellectual content: Andre C. Supervision / as the major investigador: Andre C.

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.

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CASE REPORT

Biventricular Arrhythmogenic Cardiomyopathy: A New Paradigm?

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Abstract

Arrhythmogenic right ventricular dysplasia is a classic form of chronic myocardial disease with a broad phenotypical spectrum. We report an atypical case of a patient with biventricular arrhythmogenic cardiomyopathy. Although the current diagnosis criteria are the most widely accepted ones, they focus solely on the right ventricular phenotype. The use of late gadolinium enhancement in cardiac magnetic resonance in this patient was essential for the diagnosis and assessment of the left ventricular involvement extent. This tool allows a broader use of current diagnosis criteria for this disease.

Introduction

Arrhythmogenic right ventricular dysplasia / cardiomyopathy (ARVD) consists of the classic form of a chronic, progressive and hereditary myocardial disease that has a broad phenotypic spectrum.[1] The use of the broader term "arrhythmogenic cardiomyopathy" (AC) is now accepted, which also encompasses the variants involving either mainly the left ventricle (LV) or the LV and the right ventricle (RV) - the latter, usually understood as a later form of the disease.[1] The incidence of this disease is 1:2,000 to 1:5,000, and the mean age at diagnosis is approximately 30 years old, constituting an important cause of sudden cardiac death.[2,3]

We report on a patient with ARVD and concomitant LV involvement.

Keywords

Cardiomyopathies; Arrhythmogenic Right Ventricular Dysplasia; Arrhythmias, Cardiac; Magnetic Resonance Imaging; Death, Sudden, Cardiac.

Case report

A 57-year-old male patient with irregular follow-up at a cardiology clinic for 15 years due to complaints of palpitations at exertion was assessed. He only had a history of systemic arterial hypertension, medicated and controlled with bisoprolol and lisinopril, with no other significant personal history or family history. The most recent electrocardiographic exams showed sinus rhythm, left anterior hemiblock pattern, premature ventricular contractions with complete left bundle branch block (LBBB) and superior axis, as well as periods of non-sustained ventricular tachycardia.

The previous complementary examinations included a 24-hour Holter monitoring with a non-sustained ventricular tachycardia (VT) episode with LBBB configuration, with very frequent polymorphic premature ventricular contractions (136/hr). The patient had been submitted to a transthoracic echocardiogram performed 3 years earlier, showing slight impairment of LV systolic function (ejection fraction of 47% according to the biplane Simpson's method) and diffuse hypokinesia; dilated RV also with slight systolic function impairment and apparent asymmetries in the segmental contractility of the inferior wall.

The patient was referred for cardiac magnetic resonance imaging (MRI) (Figure 1), which showed a slightly dilated LV (end-diastolic index volume of 107 mL/m^2), with ejection fraction of 44%; and a slightly dilated RV (end-diastolic index volume of 109 mL/m^2) with an ejection fraction of 39%, with evident dyskinetic areas on the free and diaphragmatic walls (in systole and diastole). There were also extensive areas of late enhancement (fibrosis) on the RV free wall (particularly at the third basal level), as well as on the LV interventricular septum and anterolateral wall, with a mid-myocardial distribution. No areas of adipocyte infiltration were observed in the fat suppression sequences.

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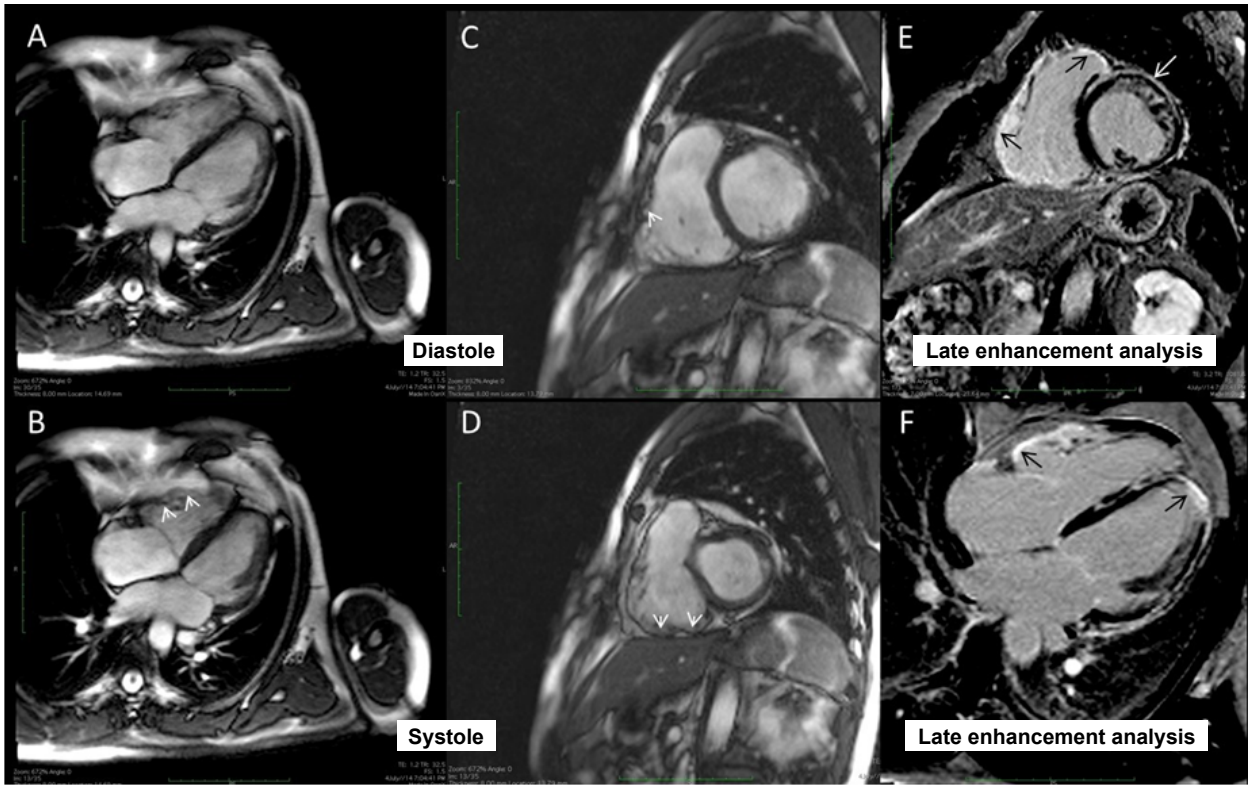

Figure 1 - Cardiac magnetic resonance imaging. (A to D) Cine-MRI, according to the steady-state free precession sequences. (A and B) long-axis, apical four-chamber view (A, diastole, and B, systole); (C and D) short axis (C, diastole and D, systole). Note marked dyskinesia of the free and diaphragmatic walls of the right ventricle in systole and diastole (arrowheads). (E and F) Gradient echo images - inversion recovery, 10 minutes after gadolinium injection: late enhancement areas (arrows) are visualized on the right ventricular free wall, interventricular septum and left ventricular anterolateral wall, with non-ischemic distribution (mid-myocardial).

The presence of arrhythmogenic cardiomyopathy with biventricular involvement was admitted as the definitive diagnosis. The documentation of several episodes of non-sustained ventricular tachycardia in this context, with biventricular dysfunction, was the reason the patient was referred to receive an implantable cardioverter defibrillator (ICD).

Discussion

Although most patients with ARVD are asymptomatic, palpitations and syncope are common presenting symptoms.[2] A high level of suspicion is essential in cases where these symptoms are related to frequent premature ventricular contractions or VT episodes (sometimes asymptomatic ones), usually with the LBBB configuration (right ventricular origin) and superior axis.[4,5]

The classical diagnosis requires the histological evidence of myocardial replacement by fibrous or fibroadipose tissue, predominantly in the RV;[3,6] however, in the clinical context, the revised diagnostic criteria of the 2010 Task Force are applied.[5]

The definitive diagnosis is based on the presence of two major criteria; one major criterion and two minor criteria; or four minor criteria from six different categories: global or regional structural changes, depolarization abnormalities, repolarization abnormalities, arrhythmias, histological findings, family history / genetic study (Chart 1).

Our case is noteworthy due to the presence of non-sustained VT, premature ventricular contractions with complete LBBB and superior axis pattern, as well as evidence of right ventricular dilatation and dysfunction associated with asymmetry / dyssynchrony of the RV free wall (Figure 1, arrow heads), with two major criteria being met - a definitive diagnosis according to the revised 2010 Task Force criteria. The presence of concomitant left ventricular dysfunction and late enhancement

Chart 1 - Revised 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD)

1. Global or regional dysfunction and structural alterations	
Major	At the two-dimensional echocardiogram: - Regional right ventricular akinesis, dyskinesis or aneurysm And one of the following (end-diastolic): - RVOT PLAX ≥ 32 mm (corrected for the body surface area – PLAX/BSA ≥ 19 mm/m²) - RVOT PSAX ≥ 36 mm (corrected for the body surface area – PLAX/BSA ≥ 21 mm/m²) - Or fractional alteration of the area ≤ 33% At the MRI: - Regional right ventricular akinesis, dyskinesis or dyssynchrony in right ventricular contractions And one of the following: Ratio of right ventricular end-diastolic volume and BSA ≥ 110 mL/m² (male) or BSA ≥ 100 mL / m² (female) -- Or right ventricular ejection fraction ≤ 40% At the right ventricular angiography: - Right ventricular regional akinesis, dyskinesis or aneurysm
Minor	At the two-dimensional echocardiogram: - Right ventricular regional akinesis or dyskinesis And one of the following (end-diastolic): - RVOT PLAX ≥ 29 mm and < 32 mm (corrected for the body surface area – PLAX/BSA ≥ 16 mm/m² and < 19 mm/m²) - RVOT PSAX ≥ 32 mm and < 36 mm (corrected for the body surface area – PLAX/BSA ≥ 18 mm/m² and < 21 mm/m²) - Or fractional alteration of the area > 33% and ≤ 40% At the MRI: - Regional right ventricular akinesis or dyskinesis or dyssynchrony in right ventricular contraction And one of the following: - Ratio of right ventricular end-diastolic volume and BSA ≥ 100 and < 110 mL/m² (man) or ≥ 90 and < 100 mL/m² (woman) - Or Right ventricular ejection fraction > 40% and ≤ 45%
2. Histological characterization of the ventricular wall	
Major	- Residual myocytes <60% in the morphometric analysis (or <50% by estimation) with fibrous replacement of the right ventricular free wall in more than one sample, with or without adipose replacement in myocardial biopsy
Minor	- 60-75% of residual myocytes in the morphometric analysis (or 50-65% by estimation) with fibrous replacement of right ventricular free wall in more than one sample, with or without adipose replacement in myocardial biopsy
3. Ventricular repolarization alterations	
Major	- Inverted T waves in V1, V2 or V3 in individuals aged > 14 years in the absence of complete RBBB with QRS ≥ 120 ms
Minor	- Inverted T waves in V1 and V2 in individuals aged > 14 years in the absence of complete RBBB with QRS ≥ 120 ms or in V4, V5 or V6 Inverted T waves in V1, V2, V3 and V4 in subjects aged > 14 years in the presence of complete RBBB with QRS ≥ 120 ms

Cont. chart 1 - Revised 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD)

4. Conduction/depolarization alterations	
Major	- Epsilon wave in leads V1 to V3
Minor	- Duration of QRS terminal activation ≥ 55 ms measured from the S wave nadir to the end of QRS, including R' at V1, V2, V3 in the absence of complete RBBB of the His bundle
	- High-resolution ECG late potentials in more than one of the following three parameters in the absence of QRS ≥ 110 ms on the standard 12-lead ECG:
	- Duration of filtered QRS (fQRS) ≥ 114 ms
	- QRS terminal duration < 40 μV (low amplitude signal duration) ≥ 38 ms
	- Root mean square of the potential in the 40 ms terminals of ventricular activation (MRIS40 - mV) ≤ 20 μV
5. Arrythmias	
Major	- Sustained or non-sustained ventricular tachycardia with complete LBBB morphology with superior axis (QRS negative or undetermined in II, III, aVF and positive in aVL)
Minor	- Sustained or non-sustained ventricular tachycardia with right ventricular outflow tract configuration, complete LBBB morphology with inferior axis (QRS positive in II, III and aVF and negative in aVL) or of indeterminate axis
	- > 500 ventricular extrasystoles in the 24-hr Holter monitoring
6. Family history	
Major	- Confirmed ARVD in a first-degree relative meeting the Task Force criteria
	- ARVD confirmed by histopathology at the autopsy or surgery in first-degree relative
	- Identification of pathogenic mutation categorized as associated or likely to be associated with ARVD* in a patient undergoing evaluation
Minor	- History of ARVD in a first-degree relative in whom it is not possible or the feasibility of confirming the presence of Task Force criteria is difficult
	- Sudden cardiac death (age < 35 years) due to suspected ARVD in first-degree relative
	- ARVD confirmed by histopathology or according to the current Task Force criteria in second-degree relative

** A pathogenic mutation is understood as a DNA change associated with ARVD, which alters or is expected to alter a coded protein, not being observed or being rare in a control population without ARVD, and which alters or is predicted to alter the protein function or structure, or that has shown an association with the phenotype of the pathology in a family tree. RVOT: right ventricular outflow tract; PLAX: parasternal long axis; MRI: magnetic resonance imaging; BSA: body surface area; PSAX: parasternal short axis; RBBB: right bundle branch block; ECG: electrocardiogram; LBBB: left bundle branch block. Source: adapted from Marcus et al.[5]*

not restricted to the RV (Figure 1, arrows) is a finding compatible with biventricular involvement in the context of this cardiomyopathy.

It is important to emphasize that these diagnostic criteria refer to the ARVD, with or without LV involvement. However, LV involvement has been increasingly described, because of the development of several complementary diagnostic means, such as the cardiac MRI.[7] It is worth mentioning that, in some series, biventricular involvement reaches 70%.[5]

This case is noteworthy not only for the presence of biventricular dilatation and dysfunction, but also for the obvious presence of late enhancement with a non-ischemic pattern in both ventricles; this last finding has a sensitivity of 66% and a specificity of 100% for the diagnosis of this entity.[8] Particularly relevant is the use of the late enhancement criterion for the supposed evaluation of the LV involvement extent in some published series and case reports, when it does not integrate the current Task Force diagnostic items.[9] In fact,

the current diagnostic criteria for this cardiomyopathy, although being the most unanimous and accepted ones, are based on data from a relatively small series of patients, in which the respective diagnostic sensitivities and specificities of each criterion were evaluated.

The main therapeutic goal in these patients is the prevention of malignant arrhythmias and, consequently, of sudden cardiac death, which is the most feared complication. The ICD plays a key role in the secondary prevention of sudden cardiac death, being associated with longer survival in these patients.[10] Patients with biventricular involvement and good functional status are potential candidates for ICD implantation, even in the absence of ventricular arrhythmias. However, how biventricular involvement in this setting may impact on the follow-up, the therapeutic approach, referral for ICD implantation, and patient prognosis should remain to be established.

Conclusions

Although the current diagnosis criteria are the most widely accepted ones, they focus mainly on the right ventricular phenotype. The use of late enhancement in cardiac magnetic resonance in this patient was essential for the diagnosis and assessment of the left ventricular involvement extent. This tool allows a broader use of the current diagnosis criteria for this disease.

Author contributions

Conception and design of the research: Augusto J, Abecasis J. Writing of the manuscript: Augusto J, Abecasis J. Critical revision of the manuscript for intellectual content: Abecasis J, Gil V.

Potential Conflict of Interest

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CASE REPORT

Spontaneous Dissection Of Left Anterior Descending Coronary Artery: Case Report

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Introduction

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome (ACS).[1-5] It usually affects young women with no risk factors for coronary disease.[3,5-8]

The real incidence of this disease in the population in general is unknown.[1,3-6] However, as has been observed in more recent studies, the prevalence of SCAD has increased due to the growth in the use of coronary angiography (from 0.2% to 4%).[5]

Because it is a poorly studied disease, its etiology remains little known and, therefore, the prognosis and therapeutic approach are still uncertain.[1,6,7] The percutaneous coronary intervention, surgical myocardial revascularization and clinical treatment are therapeutic options.[3,5,8]

Case Report

A 26-year-old female, with no cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, smoking and alcoholism) or other relevant pathological antecedents, under use of oral contraceptives only, woke up due to oppressive precordial pain associated with diaphoresis and dyspnea.

After seeking medical attention, she was admitted to an emergency care unit in her hometown 18 hours after the beginning of the clinical picture. The electrocardiogram showed ST elevation in leads V1 and V2 and ST-segment depression in leads DII, DIII and aVF.

Keywords

Acute Coronary Syndrome; Cardiac Catheterization; Coronary Artery Disease.

After administration of acetylsalicylic acid (ASA) 200 mg, she was referred to a referral hospital. Afterwards, the patient was hemodynamically stable, with sinus cardiac rhythm, eupneic, normotensive and with decreased pain. A coronary angiography was carried out 24 hours after the beginning of the symptoms and revealed dissection from the ostium to the proximal third of the ADA, with 90% obstruction and intramural thrombus (Figure 1), in addition to left ventricular anteroapical akinesia. The other coronary arteries showed no obstructive lesions.

Because the patient was hemodynamically stable and had no precordial pain, a non-interventionist strategy was chosen through clinical treatment of SCAD. A double antiplatelet therapy was started, with clopidogrel (loading dose of 300 mg followed by 75 mg/day maintenance dose) and ASA (loading dose of 200 mg and 100 mg/day maintenance dose), in adittion to full anticoagulation with enoxaparin (2mg/kg/day divided into 2 doses per day). After 8 days of treatment, an intravascular ultrasonography (IVUS) and a new coronary angiography were performed, confirming the finding of anterior descending CAD and significantly improved artery stenosis with 50% blockage in the proximal part. The exams did not evidentiate aortic arch disease.

The IVUS confirmed the finding of anterior descending coronary artery dissection and showed the presence of intramural hematoma with a thrombosed false lumen (Figure 2). Minimum lumen area of 5.5mm².

The patient was discharged after 12 days from the beginning of the symptoms. She was asymptomatic and the markers of myocardial necrosis were normal. She was instructed to maintain the use of ASA and clopidogrel and scheduled a new imaging examination (coronary angiography or coronary angiotomography) for six months after the acute event.

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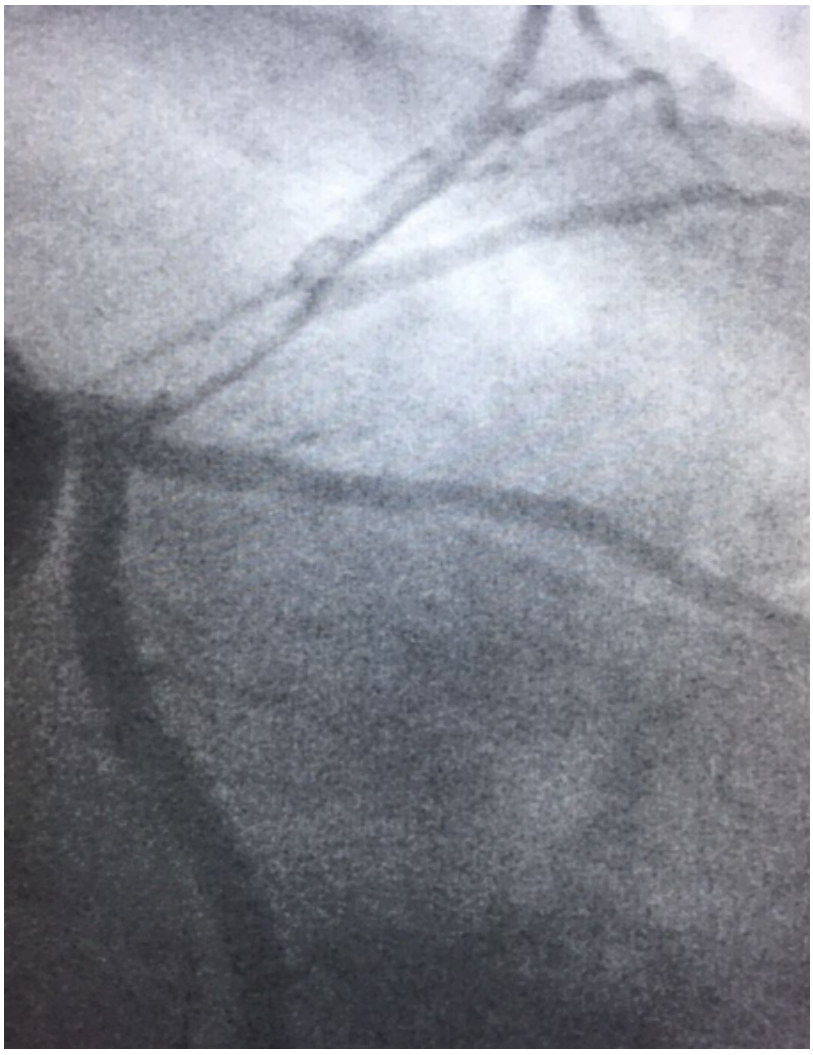

Figure 1 - Left coronary angiography in the right anterior oblique projection with caudal angulation demonstrates a 90% stenosis of the ostium and a negative image suggestive of a thrombus in the proximal third of the artery.

Discussion

The SCAD is a rare manifestation, which may present with all the clinical symptoms of ACS, including sudden death.[5-7] In patients with SCAD, in addition to the symptoms of ACS, in up to 50% of cases, the ECG shows ST elevation and significantly elevated troponin.[2] However, due to the rarity of this disease, it is usually forgotten as a differential diagnosis in ACS and, in most cases (70%), the diagnosis is made by necropsy, in such a way that its real incidence is underestimated.[1,3,4,9]

There is a marked predominance in women, with a proportion of 3 to 1 compared to men. About one-third of cases occur during pregnancy or in the puerperal period.[7] However, Yip and Saw1 suggest, in their study, these data might have been biased in older studies, since they present selective case reports of high morbidity and mortality.

In women, dissections usually occur when they are young, with a mean age of 40 years, with no risk factors for ACS, and mostly affect the left coronary artery.[3,5,7,9] In men, the impairment occurs at a higher age range, sometimes associated with the presence of risk factors for coronary artery disease, with a predominant involvement of the right coronary artery.[7] In general, the anterior descending artery is affected in up to 75% of cases.[3,5,7,9]

Because it is a rare disease, the best treatment approach for SCAD has not been defined yet, since

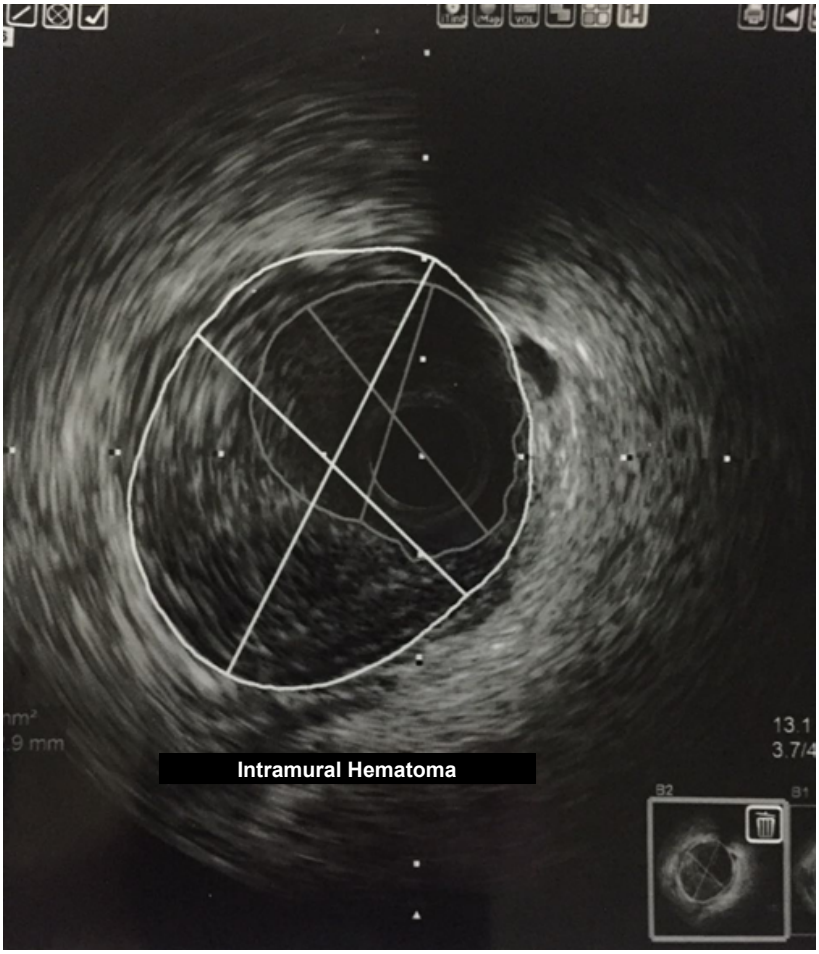

Figure 2 - Intravascular ultrasonography of the proximal third of the anterior descending artery, performed 8 days after the first coronary angiography, showing intramural hematoma with thrombi at 4-11h.

data on different therapeutic strategies are scarce and the decisions remain largely empirical.[6-8] Intracoronary imaging techniques, such as the IVUS and optical coherence tomography, are crucial to establish the diagnosis, therapeutic decisions and prognosis.[3,5,9] Through retrospective studies, it is possible to observe that adequate treatment varies depending on the clinical severity of the disease, considering the persistence or the relief of the symptoms of ischemia, the patient's hemodynamic condition, the myocardium area at risk, the extension of the dissection, the number of arteries involved and the distal coronary flow.[4,7,9]

Saw et al.,[3] in a revision study, designed an algorithm for the management of patients with SCAD, presenting the following basic concepts: 1) The conservative therapy is performed in stable patients, who are monitored in hospital from 3 to 5 days; 2) The revascularization, including coronary percutaneous intervention, if possible, should be considered for those with high-risk characteristics; 3) The use of intra-aortic balloon, oxygenation by extracorporeal membrane, left ventricular assist device or implantable cardioverter defibrillators should be considered in hemodynamically unstable patients.

In spite of its rarity, SCAD is an important cause of ACS and should always be considered in the differential diagnosis, particularly when it occurs in young healthy women. Intracoronary imaging can be used both to confirm the diagnosis and to guide the treatment decisions and, in combination with data provided by previous studies, help to define a more adequate therapeutic strategy, according to each type of disease presentation.

Author contributions

Conception and design of the research: Farnetano BS. Acquisition of data: Leão CN, Machareth MMV, Ribeiro PHDC, Damaceno RA. Analysis and interpretation of the data: Oliveira INF, Damaceno RA. Writing of the manuscript: Leão CN, Machareth MMV, Ribeiro PHDC, Oliveira INF. Critical revision of the manuscript for intellectual content: Leão CN, Ribeiro PHDC, Farnetano BS, Oliveira INF.

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