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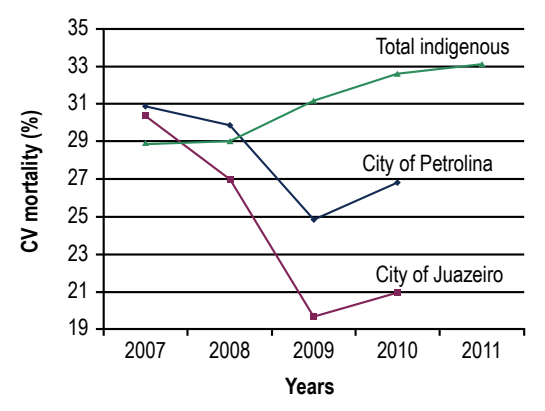

Figure – *Cardiovascular mortality (≥ 30 y/o) in indigenous and urban populations in the Sao Francisco Valley (Northeast Brazil). Total indigenous refers to total deaths among indigenous populations in the Sao Francisco Valley, Northeast Brazil. Page 242*

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Yellow Fever and Cardiovascular Disease: An Intersection of Epidemics

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Arboviral diseases are an important public health problem, especially in tropical and subtropical countries, such as Brazil, where viruses of the family *Flaviviridae,* responsible for dengue fever, zika and yellow fever (YF), and of the family *Togaviridae*, which cause chikungunya, predominate. In recent years, the number of cases has increased because of several factors, of which environmental changes, such as deforestation and climate changes, disorderly occupation of cities with low hygiene-sanitary conditions, in addition to the increased mobility of international travelers, stand out. Such factors have allowed the colonization of new areas by vectors, mainly *Aedes aegypti*, which can be found in 80% of the Brazilian territory.[1,2]

Dengue virus, which has four different serotypes, has accounted for isolated epidemics or for co-infections in 1984–1985, 1997–1999 and 2004–2007. Chikungunya, whose virus originated in Africa, succeeded the dengue fever in Brazil in 2014, with similar clinical and laboratory presentation, hindering the differential diagnosis. In 2015, the first cases of zika were reported in Brazil. Table 1 summarizes the clinical manifestations of those arboviral diseases.[2-4]

According to the World Health Organization, YF is endemic in Brazil since the year 1900, with sylvan and urban cycles, aggravated by the presence of *Aedes aegypti* in the cities. In the past decades, there has been a significant reduction in the number of cases because of the increase in vaccine coverage. However, the disease spread from endemic areas to the vicinities with similar ecological characteristics has enabled the emergence of the recent epidemic in the Brazilian states of Minas Gerais, Rio de Janeiro and São Paulo.[5] Table 2 shows the signs and symptoms of YF, highlighting hepatic and renal failures, in addition to bleedings that occur in the more severe forms.

Most monkeys in Africa are resistant to the YF virus, differently from the neotropical species of primates of the Americas, which are more susceptible to fatal infections, mainly the *Alouatta* ssp, which serves as a sentinel species for the YF virus. In those animal models, YF is characterized by a hemorrhagic viral disease with multiple organ failure and cardiovascular shock, similarly to that affecting human beings. In *Rhesus* monkeys, marked lymphopenia has been reported preceding the spleen, liver, kidney and lymphoid tissue damages. Those findings are probably due to viral replication, release of cytokines, IL-4, IL-5, IL-6, IL-8, IL-12/23p40, IL-15, IL-17, G-CSF, GM-CSF, sCD40, RANTES, MCP-1 and INFɣ, and gene expression associated with immune response, ionic metabolism and apoptosis.[6,7]

Cardiovascular involvement in arboviral diseases was described in 1822 in YF, with myocardial impairment characterized by bradycardia. Later, Lloyd[8] has reported prolongation of the atrioventricular conduction and ventricular repolarization changes. In 1965, bradycardia and hypotension were reported in chikungunya, and, in 1973, myocarditis, pericarditis and atrial fibrillation were reported in dengue fever.[9,10] A recent systematic review has reported that cardiovascular manifestations are common in chikungunya, mainly hypotension, shock, arrhythmias, myocarditis, dilated cardiomyopathy and congestive heart failure with troponin level elevation.[11] The histopathological assessment of the cardiac tissue of a fatal case of myocarditis and cardiogenic shock due to dengue fever in Brazil has shown muscular necrosis and interstitial edema with viral particles in cardiomyocytes and interstitial space, suggesting direct action of the virus in the myocardium.[12] Cases of myocarditis, heart failure, arrhythmia, atrial fibrillation and ventricular and supraventricular tachycardia have been reported in zika.[13]

The varied clinical presentation of YF, from asymptomatic to severe forms, affects directly the disease's therapeutic strategy. The malignant manifestations are associated with a mortality rate of up to 50%, requiring, thus, attention and differentiated care.[14] Although the disease has no effective specific treatment, respiratory, hemodynamic, metabolic and hemostatic supports, in addition to appropriate control of comorbidities, are fundamental to establish the patient's recovery. Moreover, the Ministry of Health criteria for outpatient clinic follow-up or hospitalization should be met in patients with heart diseases (Table 2).[14] However, some particularities of clinical management do apply to those patients.

There is no study in the literature about the safest way to treat patients with coronary artery disease (CAD) and manifestations of YF. The experience in treating epidemics of other arboviral diseases in Brazil, however, could be a reference. In 2013, the Brazilian National Institute of Cardiology (Instituto Nacional de Cardiologia) issued recommendations for the use of antiplatelet drugs in patients with CAD and dengue fever, which were incorporated into the Ministry of Health Manual of Diagnosis and Clinical Management of dengue fever.[15] In that document, the recommendations for suspension of antiplatelet drugs acknowledged the importance of different levels of platelet count essentially in patients with bare-metal or first-generation drug-eluting stents, who required at least 6 months of dual antiplatelet therapy to minimize the risk of thrombosis.[15] Since then, the most frequent use of second-generation

Keywords

Yellow Fever; Tropical Ecosystem, Arbovirus Infections; Aedes, Liver Failure; Kidney Failure, Chronic; Hemorrhage; Bradycardia; Drug-Eluting Stents / adverse effects.

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Table 1 – Clinical spectrum of dengue, chikungunya and zika

Arboviral disease	Clinical presentation	
	Mild forms	Severe forms
Dengue	High fever, myalgia, joint pain, nauseas, vomiting, skin rash, hemorrhagic manifestations, low platelet count	Organ failure (respiratory, heart, hepatic, hematologic, central nervous system), refractory shock and death
Chikungunya	The aforementioned manifestations + symmetrical pain in small and large joints, except for hemorrhagic syndrome	Nephritis, meningoencephalitis, Guillain–Barré syndrome and flaccid paralysis
Zika	Milder aforementioned manifestations, conjunctivitis	Neurological complications, such as microcephaly (newborn infants), Guillain–Barré syndrome, hearing loss

Table 2 – Clinical spectrum of yellow fever and respective treatment site[14]

Form	Signs and symptoms	Laboratory changes	Treatment site
Mild / Moderate	Fever, headache, myalgia, nauseas, absent/ mild jaundice	Low platelet count, moderate elevation of transaminases, normal or mildly elevated bilirubin levels	Outpatient clinic / hospital (ward)
Severe	All aforementioned, jaundice, severe hemorrhages, oliguria, reduced level of consciousness	Severe low platelet count, increased creatinine, significant elevation of transaminases	Hospital (ward / intensive care unit)
Malignant	All classic symptoms of the severe form intensified	All aforementioned, disseminated intravascular coagulation	Hospital (intensive care unit)

drug-eluting stents with everolimus or zotarolimus has allowed for shorter periods of dual antiplatelet therapy with the same safety level. Considering that low platelet count is one of the most important characteristics of all viral hemorrhagic fevers, those recommendations could also serve as a model for new recommendations for YF.[16]

Thus, the consideration of validated tools to assess the risks for hemorrhage and thrombosis after coronary stent implantation is a promising strategy. An example is the PRECISE-DAPT score, which uses hemoglobin, leukocyte count, age, creatinine clearance and history of bleeding as variables to estimate that risk. Scores < 25 are predictors of a low risk of bleeding and could identify patients who benefit from longer periods of dual antiplatelet therapy (6-12 months). However, scores ≥ 25 are associated with high rates of bleeding, indicating a shorter period of dual antiplatelet therapy (3-6 months).[17]

The 2017 European Society of Cardiology guideline considers that score in some of its recommendations and raises the possibility of only 1 month of dual antiplatelet therapy for patients at high risk for bleeding (PRECISE-DAPT ≥ 25), who might not tolerate 3 months of use. Those recommendations and that score application do not depend on the type of stent implanted.[17] Although the incorporation of that strategy into the management of patients with YF has been neither studied nor validated, it provides additional enhancement to isolated platelet count to estimate the risk for thrombosis and bleeding after percutaneous coronary interventions. Such assessment would be of fundamental importance to define the management, mainly because the modifiable variables used in the PRECISE-DAPT score can be affected by YF. Figure 1 shows an algorithm for the antiplatelet management of patients with coronary stents implanted within less than 12 months from the YF infection.

It is worth noting that in the presence of active bleeding or significant blood dyscrasia secondary to hepatic failure (INR > 1.5 or clotting time > 20 minutes), antiplatelet therapy should be suspended independently of any other criterion. Similarly, the suspension of antiplatelet drugs in patients with CAD without stents, or who had undergone percutaneous coronary interventions more than 12 months before, is recommended, even in moderate cases without significantly low platelet count, because the short-term thrombotic risk of those patients is lower. In addition, oral anticoagulants should be avoided in moderate severity cases, and in-hospital parenteral anticoagulation can be considered for patients with mechanical valve prostheses without active bleeding, evidence of liver dysfunction or other criteria of greater severity.

Patients with heart failure constitute another group whose management might require differentiated approaches in the context of YF. Support therapy in patients with moderate to severe forms of disease depends mainly on the maintenance of an appropriate hemodynamic status through oral or venous hydration, occasional transfusions of blood derivatives and even the use of vasoactive amines. In this scenario, the hemodynamic balance should be constantly reassessed and carefully adjusted, with eventual invasive monitoring in more extreme situations, because those patients are very sensitive to small variations in blood volume.

In addition, the maintenance of drugs often used in the chronic treatment of heart failure, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, might hinder the clinical management. Thus, in situations of moderate severity, with neither bleeding nor hemodynamic, renal or respiratory impairment, we suggest maintaining only beta-blockers, preferably at their usual dose. However, they should be avoided in severe cases, with a higher

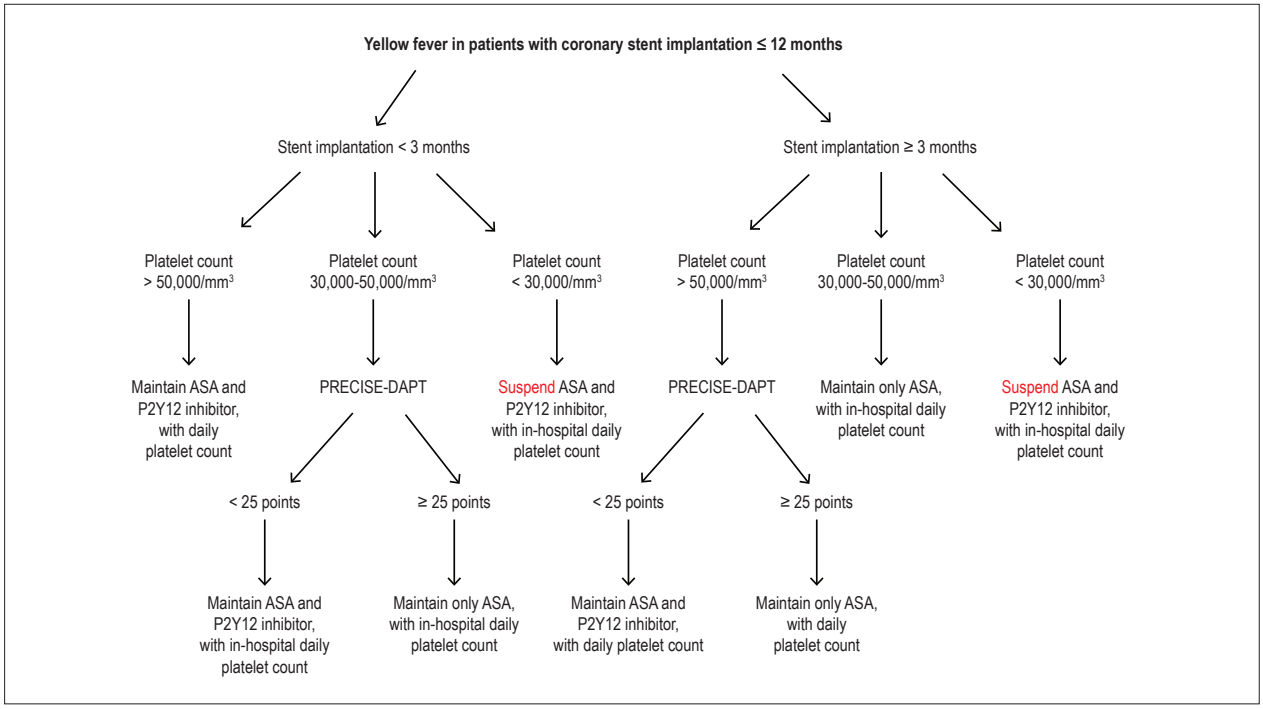

Figure 1 – *Algorithm for the management of antiplatelet drugs in patients with coronary stents implanted within less than 12 months and yellow fever with neither active bleeding nor blood dyscrasia signs. ASA: acetylsalicylic acid.*

likelihood of clinical deterioration. This recommendation is based on the previous demonstration that the suspension or reduction of those drugs in heart failure proved to be deleterious in other situations of clinical agudization.[18] Thus, similarly to diuretics and ACE inhibitors, statins should be avoided even in moderate severity cases, mainly because of their potential hepatotoxic effect.

Finally, the vaccine against YF should not be contraindicated based only on the presence of an underlying heart disease, even in patients with previous infarction and/or heart failure. For those patients, the criteria are the same already recommended by the Ministry of Health, with vaccination preferably indicated in the presence of high likelihood of exposure to the virus and low risk for adverse effects.[14] In the context of heart disease, only transplanted patients should not be vaccinated, because they are on chronic immunosuppressive therapy.

There is an increasing need for further and more detailed studies that assess how arboviral and cardiovascular diseases interact from both the individual and epidemiological viewpoints. In addition, the ineffective control of those epidemics is clearly related to socioeconomic deficiencies and failures in the environmental and urban planning processes, mainly in developing countries. The combination of such factors might be the intersection point, to where investments and research should be primarily directed.

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Association of Severity of Coronary Lesions with Bone Mineral Density in Postmenopausal Women

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Abstract

Background: **Coronary artery disease (CAD) and osteoporosis (OP) are common diseases in postmenopausal women. In both cross-sectional and longitudinal epidemiologic studies, low bone mass has been related to increased frequency of CAD. However, available data on the relationship between bone mineral density (BMD) and severity of coronary lesions is limited.**

Objective: **To investigate association between the BMD and severity of coronary lesions assessed by Gensini score in postmenopausal women.**

Methods: **This study included 122 postmenopausal women who were diagnosed with CAD. These patients were divided into two groups according to the severity of coronary lesions assessed by the Gensini score – patients with mild coronary lesions (Gensini score < 25) and patients with severe coronary lesions (Gensini score ≥ 25). Femoral neck mineral density was measured with dual energy X-ray absorptiometry (DXA).**

Results: **The study included postmenopausal women aged 64.31 ± 4.71 years, 85 of whom (69.7%) exhibited severe coronary lesions. Participants with severe coronary lesions had a significantly higher T score than did those with mild coronary lesions at the femoral neck ($p < 0.05$). The mean T-score was −0.84 ± 1.01 in mild coronary lesions group, −1.42 ± 1.39 in severe coronary lesions group ($p < 0.05$). Multivariable logistic regression analysis showed that osteopenia-osteoporosis at the Femoral neck (odds ratio 2.73; 95% confidence interval 1.06 to 6.13) was associated with an increased risk of developing severe coronary lesions. The multiple regression model showed that T-scores ($\beta = -0.407$, SE = 0.151, $p=0.007$) were the independent predictors of Gensini score.**

Conclusion: **The relationship between severity of coronary lesions and BMD was significant in postmenopausal women. BMD, a low-cost technique involving minimal radiation exposure, widely used for osteoporosis screening, is a promising marker of severity of coronary lesions. (Arq Bras Cardiol. 2018; 110(3):211-216)**

Keywords: **Coronary Artery Disease; Osteoporosis, Postmenopausal; Bone Density; Stroke; Morbidity; Bone Diseases, Metabolic.**

Introduction

Atherosclerosis (AS) is one of the most common diseases in elderly people, especially in postmenopausal women. The complications of AS, like coronary artery disease (CAD) and cerebrovascular diseases reduce quality of life and lead to excess morbidity.[1] Epidemiology studies found that the CAD morbidity and mortality rates were significantly higher in postmenopausal women compared with premenopausal women.[2] Unlike younger women, the risk of CAD in older women is higher when there is a decrease in estrogen production, marking the end of the protective effect of endogenous estrogens against CAD.[3-5] Therefore, identifying the risk factors associated with CAD in postmenopausal women is critical for improving patients' survival rate and life quality.

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Recently, increasing evidence has accumulated to support the correlation between low bone mineral density (BMD) and AS.[6-8] AS and osteopenia-osteoporosis syndrome share some risk factors, among which are parathyroid hormone, lack of estrogen, homocysteine, inflammatory process, vitamins D and K, lipid oxidation products, molecular pathways involved in bone and vascular mineralization, and calcification mechanisms that seem to be similar in vascular structure and bone.[9,10]

We have previously reported that coronary artery calcium scores, an earlier sign of coronary artery AS, were significantly higher in the osteopenia/osteoporosis groups compared to normal BMD groups, and that these values were negatively associated with T-scores. These findings indicate that decreased BMD may increase the risk of CAD.[11] However, little is known about the association between decreased BMD and severity of coronary lesions in postmenopausal woman.

Therefore, the aim of this cross-sectional study was to examine the associations between BMD and coronary lesions assessed by Gensini score in postmenopausal women who attended our Laboratory and who had their BMD measured and grouped by the severity of CAD.

Methods

Study population

A total of 122 female patients who were admitted to the cardiology clinic with chest pain between January 2014 and August 2016 were included in the study. Inclusion criteria were postmenopausal women aged ≥ 50 years, who were diagnosed with acute coronary syndrome or chronic CAD. This diagnosis was made by history of angina pectoris or myocardial infarction, electrocardiographic findings, cardiac enzymes, and coronary angiography results. These patients underwent a bone densitometry on a routine basis within the previous 12 months, and were not taking any medication with known effect on bone turnover. Exclusion criteria were patients with normal coronary angiography; patients who had moderate-to-severe heart valve disease and decompensated heart failure; patients with severe kidney or liver failure, malignancy, hematological diseases, or autoimmune disorder.

Clinical features and laboratory examination

The weight and height were measured at each of eligible patient. Body mass index (BMI) was calculated as body weight/height^2 (kg/m^2). Information concerning the history of diseases (diabetes, hypertension, and hyperlipidemia) was collected using a standard questionnaire.

Hypertension was defined as history of hypertension and/or an average systolic blood pressure (SBP) ≥ 140 mmHg and/or an average diastolic blood pressure (DBP) ≥ 90 mmHg on two separate occasions. Diabetes was defined as history or presence of diabetes and/or a fasting plasma glucose level > 126 mg/dL on 2 separate occasions, or a random glucose value of > 200 mg/dL on one or more occasion. Hypercholesterolemia was defined as a total serum cholesterol level of > 240 mg/dL; high triglyceride (TG) and high LDL-cholesterol (LDL-c) were defined as total serum TG > 200 mg/dL and LDL-C > 160 mg/dL, respectively.

BMD measurement

Participants had undergone a BMD test of the left femoral neck bone by dual-energy X-ray absorptiometry using a QDR 4500A fan beam bone densitometer (Bedford, MA, USA) according to the manufacturer's instructions within the previous 12 months. BMD results were reported as T-scores, which were also categorized into three groups according to the World Health Organization (WHO) criteria for diagnosing osteoporosis: normal BMD (T-score≥-1 SD); osteopenia (T < -1 SD and > -2.5 SD); and osteoporosis (T-score ≤ -2.5 SD).[11]

Gensini risk scoring

Coronary angiography was performed in all subjects. Gensini score: angiographic stenosis of a culprit artery in the range of 0% to 25% was scored as 1 point, stenosis in the range of 25% to 50% was scored as 2 points, 50% to 75% was scored as 4 points, 75% to 90% was scored as 8 points, 90% to 99% was scored as 16 points, and total occlusion was scored as 32 points. A multiplier was assigned to each vascular segment based on the functional significance of the myocardial area supplied by that segment: 5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending (LAD) coronary artery and the proximal segment of the circumflex artery, 1.5 for the mid-segment of the LAD, 1.0 for the right coronary artery, the distal segment of the LAD, the mid-distal region of the circumflex artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 for other segments.[12] Angiographic evaluations were reviewed by the consensus of two observers with more than two years of experience. Based on the Gensini score, patients were divided into two groups – 37 patients in the group of mild coronary lesions (Gensini score < 25 points) and 85 patients in the group of severe coronary lesions (Gensini score ≥ 25 points); this grouping was compatible with the literature.[13]

Statistical analyses

Analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL). Continuous variables with a Gaussian distribution are presented as mean ± standard deviation (SD), and those with a non-Gaussian distribution are presented as median values with corresponding 25th and 75th percentiles. The normal distribution of different parameters was verified with the Kolmogorov-Smirnov test. Differences between the groups were evaluated using unpaired t-test or the Mann-Whitney U-test. Categorical variables were compared with the chi-square test or Fisher's exact test (Fisher's exact test was used for frequencies of osteoporosis in Table 2). The association between BMD and risk for severe coronary lesions was evaluated by multiple logistic regression analysis. Multiple linear regression analysis was performed to assess whether BMD was the independent explanatory factor for the severity of coronary lesions (assessed by the Gensini score) in postmenopausal women. Statistical significance was set at $p < 0.05$ (2-tailed).

Results

A total of 122 postmenopausal women (mean age 64.31 ± 4.71) were included in the present study, 69.7% of whom exhibited severe coronary lesions. Clinical characteristics of all participants at baseline are summarized in Table 1. In all, 19.6% of the patients were found to have osteoporosis in the femoral neck and 41.8% osteopenia; 39.3% of the women suffered from high blood pressure, 38.5% have diabetes, and 31.1% have hyperlipidemia.

Table 2 shows the comparison between the groups with mild coronary lesions and severe coronary lesions in terms of some clinical parameters. Patients with severe coronary lesions patients were older, and had higher prevalence of diabetes and osteoporosis/osteopenia compared with those with mild coronary lesions ($p < 0.05$). There were no differences between the groups with respect to BMI, proportions of patients with hypertension and hyperlipidemia.

Univariate logistic regression analysis showed that osteoporosis/osteopenia was a risk factor for severe coronary lesions (OR = 2.51, 95% CI, 1.153–5.657, p = 0.003).

Corresponding to these findings, multivariate logistic regression analysis was used to detect the association between osteoporosis/osteopenia and risk of severe coronary lesions. After adjusting for confounding factors such as age, hypertension, diabetes, and hyperlipidemia, the osteoporosis /osteopenia remained the risk factors for severe coronary lesions (OR = 2.73, 95% CI, 1.06–6.13, p = 0.007, Table 3).

When Gensini score was considered as the dependent variable in a linear regression model, T-score (β = −0.407, *SE* = 0.151, p = 0.007) and age (β = 0.295, *SE* = 0.132, *P* = 0.023), but not diabetes, hypertension, BMI, and hyperlipidemia, were the independent predictors of Gensini score.

In a linear regression analysis with Gensini score as a dependent variable and age, T-score, diabetes, hypertension, BMI, and hyperlipidemia as independent variables (Table 4), only T-score (β = −0.407, *SE* = 0.151, p = 0.007) and age (β = 0.295, *SE* = 0.132, p = 0.023) correlated with Gensini score.

Table 1 – Characteristics of the study population (n = 122)

Age (years)	64.31 ± 4.71
Body mass index (kg/m^2)	26.19 ± 2.49
Hypertension, n (%)	48 (39.3%)
Diabetes, n (%)	47 (38.5%)
Hyperlipidemia, n (%)	38 (31.1%)
T-score	–1.24 ± 1.27
Gensini score	43.46 (17.5, 73)
osteoporosis, n (%)	24 (19.6%)
osteopenia, n (%)	51 (41.8%)
osteoporosis or osteopenia, n (%)	75 (61.5%)

Continuous variables with a Gaussian distribution are presented as mean ± SD, and those with a non-Gaussian distribution are presented as median values with corresponding 25th and 75th percentiles. Categorical data are expressed as absolute numbers with (percentages).

Discussion

In our study, postmenopausal women with severe coronary lesions are more likely to have osteopenia/osteoporosis compared with mild coronary lesions group, independent of other risk factors. This suggests that postmenopausal women with osteopenia/osteoporosis may have a higher risk of developing severe coronary lesions. Our findings are in accordance with previous studies demonstrating the relationship between BMD and CAD that concluded that BMD is a promising marker of severity of CAD.

Both osteopenia and AS are serious public health problems that can threaten people's health and quality of life.[14,15] Previous studies have proved a clear link between AS and BMD. In a retrospective study including 1,335 elderly patients, the incidence of CAD increased in low BMD patients, compared with patients with normal BMD. Multiple logistic regression analysis confirmed that low BMD is associated with CAD, after adjustment for diabetes mellitus, hypertension, smoking, and age.[16] Another study with 252 postmenopausal women showed that osteopenia/osteoporosis at the lumbar spine or femoral neck was associated with coronary AS assessed by 64-row multidetector computed tomography.[17] Our previous study showed that another measure of AS, coronary artery calcification, was associated with BMD of the lumbar spine in healthy postmenopausal women. The odds for coronary artery calcification in osteoporotic women were over three-fold higher compared with those in women with a normal BMD.[11]

Gensini score is an important angiographic scoring system used to assess the extent, severity, and complexity of CAD. CAD patients with high Gensini score are more likely to report major adverse cardiac events. Therefore, identifying CAD patients with high Gensini scores is critical for reducing CAD-related disability and death.[18,19] There are a few studies

Table 2 – Comparison of clinical parameters between the groups with mild coronary lesions and severe coronary lesions

Parameter	Mild coronary lesions group	Severe coronary lesions group	p value
	Gensini score < 25	Gensini score ≥ 25	
	n = 37	n = 85	
Age (years)	62.33 ± 5.65	65.17 ± 4.43	0.003
Body mass index (kg/m^2)	26.23 ± 2.53	26.17 ± 2.47	0.872
Hypertension, n (%)	13 (35.1%)	35(41.2%)	0.530
Diabetes, n (%)	9 (24.3%)	38 (44.7%)	0.034
Hyperlipidemia, n (%)	11 (29.7%)	27(31.8%)	0.824
T-score	−0.84 ± 1.01	−1.42 ± 1.39	0.024
osteoporosis, n (%)	3(8.1%)	21 (24.7%)	0.034
osteopenia, n (%)	10 (27.0%)	41 (48.2%)	0.029
osteoporosis or osteopenia, n (%)	13 (35.1%)	62 (72.9%)	0.000

Continuous variables with non-Gaussian distribution (except for those expressed as median) were compared using t-tests. For values expressed as median (25th and 75th percentiles), P values were determined by Mann-Whitney U test. Categorical variables were compared by chi-square test, except for osteoporosis, which were compared by Fisher's exact test (expected frequencies of ≤ 5).

Table 3 – Adjusted odds ratio of risk factors for severe coronary lesions

Independent variable	Odds ratio (95%CI)	p value
Osteopenia or osteoporosis	2.73(1.06–6.13)	0.007
Age	1.24(1.19–2.65)	< 0.001
BMI	1.37(0.73-3.57)	0.706
Hypertension	2.31(0.83–5.31)	0.313
Diabetes	3.13(0.96–7.37)	0.082
Hyperlipidemia	1.39(0.57–3.62)	0.431

BMI: body mass index; 95% CI: 95% confidence interval

Table 4 – Multiple regression analysis of Gensini score (dependent variable) versus age, diabetes, hypertension, body mass index, hyperlipidemia, and T-score (independent variables).

Independent variable	β	SE	p value
T-score	0.407	0.151	0.007
Age	0.295	0.132	0.023
Body mass index	0.183	0.203	0.136
Hypertension	0.147	0.134	0.254
Diabetes	0.113	0.179	0.572
Hyperlipidemia	0.053	0.121	0.697
R^2		0.31	

β: Values are standardized coefficient; SE: values are standard error of β. R^2: values are the total explained variance of the model.

about the relationship between BMD and severity of coronary lesions. A retrospective study carried out with 55 male patients with CAD, confirmed by coronary angiography, showed that decreased BMD was associated with severe coronary lesions assessed by Gensini score, independent of other cardiovascular risk factors.[13] Similarly, a study involving 74 male CAD patients revealed that the incidence of osteopenia/osteoporosis in severe coronary artery lesions group determined by SYNTAX score was significantly higher than mild coronary artery lesions group.[20] However, most of these studies have been based on male CAD patients while few studies have involved postmenopausal, CAD women patients. In our study, 186 postmenopausal women with CAD patients identified by coronary angiography were divided into two groups by Gensini scoring: mild coronary lesions patients (Gensini score < 25) and severe coronary lesions patients (Gensini score > 25). We found that there was an increase in the osteoporosis/osteopenia rate in the severe coronary lesions group. Multivariable logistic regression analysis showed that osteopenia/osteoporosis at the femoral neck was associated with an increased risk of developing severe coronary lesions. The multiple regression model showed that T-scores were the independent predictors of Gensini score. Most previous research, if not all, including our results indicate that low BMD not only were associated with increased risk of CAD, but also were an independent predictor of severity of coronary lesions in postmenopausal women.

Although many hypotheses have been proposed to explain the correlation between osteoporosis and CAD, it has not been thoroughly understood.[16,21,22] In spite of common risk factors of bone metabolism and cardiovascular risk (inflammation, dyslipidemia, menopause, hypertension, smoking, and diabetes mellitus), the possible influence of genetics and vascular calcification also exists.[23,24] Hydroxyapatite, an important part of the mineral phase of bone, is also found in the artery calcified plaque. Moreover, it has been reported that bone matrix proteins such as gla protein, bone morphogenetic protein-2, osteocalcin, and collagen were found in calcified plaques. Studies have suggested that some important gene mutations can lead to the early development of AS and osteoporosis, which indicate the evidence of common genetic basis.[25,26] It's worth noting that current evidence linking osteoporosis and CAD is far from conclusive. So, further study is needed to explore the relationship between the two common diseases.

Limitations

The main limitation of our study is that the sample size is relatively small. Further studies involving a larger number of menopausal patients are needed to establish and confirm the relationship between the severity of coronary lesions and osteopenia/osteoporosis. In addition, information on impaired vitamin K status, inflammatory cytokines, gla protein, and osteocalcin, which might be associated with both coronary lesions and osteoporosis, was not available for this study. Also, the fact that the BMD tests were not performed in the same service was another limitation of our study.

Conclusion

In this study, we investigated the association between BMD and severity of coronary lesions in postmenopausal women. Our results suggested postmenopausal women with low BMD are at high risk for severe coronary lesions. Future research should investigate common pathophysiological pathways between osteoporosis and severity of coronary lesions.

Author contributions

Conception and design of the research: Xu R, Xin-Chun C, Hong-Ni Y; Acquisition of data and Analysis and interpretation of the data: Xu R, Zhang Y, Hong-Mei L; Statistical analysis: Xu R; Writing of the manuscript: Xin-Chun C; Critical revision of the manuscript for intellectual content: Xu R, Hong-Ni Y.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uyghur Autonomous Region under the protocol number 678999009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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The Interface between Osteoporosis and Atherosclerosis in Postmenopausal Women

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In recent years, the association between osteoporosis and atherosclerotic disease has been described, regardless of patients' age, and highlighted epidemiologic and pathophysiologic similarities between arterial wall calcification and osteogenesis.[1,2] Cross-sectional, prospective studies have pointed out significant negative association between cardiovascular mortality and low bone mass, osteoporotic fractures, vascular calcification, extension of coronary artery disease and abdominal aortic injury.[3-5] Concomitant occurrence of both diseases seems to result from common pathophysiologic and molecular mechanisms between these conditions. However, it is still controversial whether a low bone mass is caused by arterial calcification or vice-versa, or whether these conditions only have the same pathophysiological mechanism.

Risk factors for osteoporosis and atherosclerotic disease include estrogen, parathyroid hormone, homocysteine and vitamin K deficiency, lipid oxidation products, inflammatory process, vitamin D excess, molecular pathways involved in both bone and vascular mineralization, and similar mechanisms of calcification involving vascular and bone structures.[6] Arterial calcification is found in more than 90% of atherosclerotic lesions. The process starts with formation of vesicles in the endothelial matrix, followed by proliferation and mineralization of the arterial intima-media wall, similarly to the bone tissue. Many bone remodeling regulators have been described in calcified atherosclerotic lesions, including osteocalcin, hydroxyapatite crystals, osteopontin, bone morphogenetic protein 2 osteoprotegerin, sclerostin, dickkopf factor (DKK), leptin, oxidized lipids and calcium sensor-related factor.[7]

Vascular atherosclerotic disease is more common in women with osteoporosis and osteopenia as compared with women without these conditions.[5,6] Increased mortality rates related to cardiovascular diseases have been reported at advanced ages in postmenopausal women with low bone mineral density (BMD). Despite a non-significant increase in myocardial infarction among women with low BMD, with a rate of 22%, a significant increase is observed among men with low BMD, with a rate of 39%.[2]

In the present issue, the study by Cheng et al.[8] adds to existing literature demonstrating an inverse association between BMD and coronary artery disease in postmenopausal women. The authors studied 122 postmenopausal women with diagnosis of coronary artery diseases (acute coronary syndrome or stable angina). All patients had undergone routine bone densitometry within one year prior to the assessment of atherosclerotic load by the Gensini score and invasive angiography. BMD of the femoral neck was measured by dual-energy X-ray absorptiometry. The presence of osteopenia/osteoporosis in femoral neck was associated with increased risk of severe coronary lesions. The multiple regression model revealed the T-scores as independent predictors of higher Gensini scores. This study corroborates previous data indicating an association between BMD and the severity of coronary atherosclerotic disease, suggesting that this parameter may be an independent marker of disease severity.

Prospective studies including a larger number of patients and serial test data of BMD are needed to establish the role of T-scores as risk predictors for the development of severe coronary artery disease in men and women. Evidence from clinical practice suggests that osteoporosis patients should also be assessed for the risk of severe coronary artery disease.

Keywords

Atherosclerosis / physiopathology; Osteoporosis / physiopathology; Bone Diseases, Metabolic; Women; Postmenopause.

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Subclinical Anthracycline-Induced Cardiotoxicity in the Long- Term Follow-Up of Lymphoma Survivors: A Multi-Layer Speckle Tracking Analysis

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Abstract

Background: **Anthracycline generates progressive left ventricular dysfunction associated with a poor prognosis.**

Objectives: **The purpose of this study was to evaluate whether layer-specific strain analysis could assess the subclinical left ventricular dysfunction after exposure to anthracycline.**

Methods: **Forty-two anthracycline-treated survivors of large B-cell non-Hodgkin lymphoma, aged 55.83 ± 17.92 years (chemotherapy group) and 27 healthy volunteers, aged 51.39 ± 13.40 years (control group) were enrolled. The cumulative dose of epirubicin in chemotherapy group was 319.67 ± 71.71mg/m². The time from last dose of epirubicin to the echocardiographic examination was 52.92 ± 22.32 months. Global longitudinal (GLS), circumferential (GCS) and radial strain (GRS), subendocardial, mid and subepicardial layer of longitudinal (LS-ENDO, LS-MID, LS-EPI) and circumferential strain (CS-ENDO, CS-MID, CS-EPI) values were analyzed. Transmural strain gradient was calculated as differences in peak systolic strain between the subendocardial and subepicardial layers. A value of $p < 0.05$ was considered significant.**

Results: **Conventional parameters of systolic and diastolic function showed no significant difference between two groups. Compared with controls, patients had significantly lower GCS and GLS. Multi-layer speckle tracking analysis showed significant reduction of circumferential strain of subendocardial layer, transmural CS gradient and longitudinal strain of all three layers. In contrast, the two groups did not differ in transmural longitudinal strain gradient and radial strains.**

Conclusions: **It proved the preferential impairment of subendocardial deformation in long-term survivors after exposure to anthracycline. Multi-layer speckle tracking echocardiography might facilitate the longitudinal follow-up of this at-risk patient cohort. (Arq Bras Cardiol. 2018; 110(3):219-228)**

Keywords: **Cardiotoxicity; Anthracyclines; Lymphoma, Non-Hodgkin; Hematologic Neoplasias/drug therapy; Echocardiography.**

Introduction

Anthracycline, a commonly used chemotherapeutic agent in the treatment of a wide spectrum of hematologic malignancies and solid tumors, is undermined by potential life-threatening cardiotoxicity.[1,2] Anthracycline-induced left ventricular dysfunction is believed to be refractory to conventional pharmacological therapy and to be associated with a poor prognosis. Therefore, detection of subclinical myocardial dysfunction is of vital importance to balance between the cardiac risk and the potential cancer treatment.

Two-dimensional speckle tracking echocardiography, based on tracking local image details from frame to frame throughout the cardiac cycle,[3-6] has allowed more accurate measurements of regional myocardial systolic performance.

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It has been proved that patients treated with epirubicin-based chemotherapy experienced significant decrease in strain values while LVEF remained stable and within normal limits.[7,8] Based on the 2D speckle tracking technology, a novel offline tool is recently introduced which has a potential of measuring strains in subendocardial and subepicardial layers comparatively.

Therefore, the objectives of this study were to evaluate whether layer-specified systolic strain analysis could differentiate the subclinical left ventricular function changes in patients after exposure to anthracycline-based chemotherapy.

Methods

Study population

A total of 45 anthracycline-treated survivors of histopathologically confirmed large B-cell non-Hodgkin lymphoma who have been off treatment for at least one year were enrolled in this study between March 2014 and Dec 2015 (chemotherapy group). Exclusion criteria were uncontrolled hypertension, significant valvular disease, congenital disease, a widened QRS complex on surface

ECG, arrhythmia, a previous history of heart failure and/or coronary artery disease. The following data were collected including date of completion of chemotherapy, duration of follow-up, cumulative doses of anthracyclines, symptoms and signs of heart failure, and cardiac medications. Twenty-eigh age-matched and gender-matched referred to our hospital for non-specific chest pain or palpitation, but with no history of cardiovascular disease patients and with completely normal electrocardiograms, echocardiograms, treadmill stress exercises and 24-hour, continuous ambulatory electrocardiograms were selected as controls (control group).

Echocardiographic imaging

Images were obtained in the left lateral decubitus position with Vivid E9 (GE Healthcare, Horton, Norway) ultrasound systems. Standard two-dimensional images were acquired according to recommendations of the American Society of Echocardiography.[9] Depth was minimized to optimize the frame rate. At least three beats were digitally stored for offline analysis. Left ventricular ejection fraction was calculated using the modified Simpson's biplane method. Left ventricular mass index, relative wall thickness, transmitral peak early (E) and peak late (A) diastolic filling velocities were also measured. Tissue Doppler echocardiography was performed with the sample volume positioned at the basal LV free wall and septum at the mitral annular junction to obtain lateral and septal mitral annular systolic (S') and early diastolic myocardial tissue velocities (E').

Multi-layer speckle tracking echocardiography

Gray scale images for offline speckle tracking analysis were acquired at frame rate of 53 to 84 MHz. Echopac version 11.1 (GE Healthcare, Horton, Norway) was used for multi-layer strain analysis. The automatic tracking analysis was performed in the apical 4-chamber, 2-chamber, long-axis apical view for longitudinal strain and in the parasternal short-axis view at basal, mid-papillary and apical level for circumferential and radial strain according to the vendor's instructions. The endocardial border was manually traced at end-diastole. The ROI (region of interest) for strain analysis was adjusted manually. The locations of the tracking points were adjusted when necessary so that the region of interest extended from endocardial to epicardial borders to approximate the myocardium, which was divided into subendocardial, middle and subepicardial myocardium layers of equal thickness.

Peak circumferential (CS) and radial strain (RS) measurements were obtained from the basal, mid-segments of the septal, lateral, inferior, anterior, anteroseptal, posterior walls, apical segments of anterior, inferior, septal, lateral walls, totally 18 segments. Peak longitudinal strain (LS) measurements were obtained from the basal, mid- and apical segments of the anterior, inferior, anteroseptal, anterolateral, inferoseptal, inferolateral walls, totally 16 segments. In each segment, the subendocardial, middle and subepicardial LS and CS were calculated automatically. Regional strain values were averaged to determine global longitudinal/circumferential/radial strain (GLS, GCS, GRS), global subendocardial, middle and subepicardial LS (LS-ENDO, LS-MID, LS-EPI) and CS (CS-ENDO, CS-MID, CS-EPI). Transmural strain gradient was calculated as differences of peak systolic strain between the subendocardial and subepicardial layers. Strain values of each level were calculated.

Reproducibility

Intra- and inter-observer reproducibility was assessed by calculating the difference between the values of 10 randomly selected patients measured by one observer twice and by a second observer.

Statistical analysis

Continuous variables with normal distribution were expressed as the mean ± standard deviation. Continuous variables with non-normal distribution were expressed as median and interquartile range. Differences between two groups were determined using independent samples t test for continuous variables with normal distribution and Kruskal Wallis test for with non-normal distribution. One sample K-S test was used in determining the normality of data. One way ANOVA test was used to compare the differences between strain values of different layers and different levels within each group. Relations between strain values and cumulative anthracycline dose were determined by Pearson correlation analysis. Interobserver and intraobserver reproducibility of strain values were assessed using intraclass correlation coefficients (ICCs) and Bland-Altman analysis. Data were analyzed by SPSS version 16.0 (SPSS, Inc, Chicago, IL, USA).

A value of $p < 0.05$ was considered significant.

Results

Three patients and one healthy volunteer were excluded from the analysis because of poor image quality (defined as > 2 non-visualized segments). Forty-two patients, 18 males, ranging in age from 22 to 77 years (mean age 55.83 ± 17.92 years), and 27 healthy volunteers, 14 males, ranging in age from 32 to 77 years (mean age 51.39 ± 13.40 years), were finally included in the statistical analysis. Table 1 shows the two groups clinical characteristics. In all patients, the cumulative dose of epirubicin was 319.67 ± 71.71 mg/m^2 (ranging from 150.94 mg/m^2 to 440.00 mg/m^2). Patients have not received radiotherapy or other cardiotoxic agents. No patient complained of cardiovascular related symptoms. EKG remained normal in all patients. The time from last dose of epirubicin to the echocardiographic examination was 52.92 ± 22.32 months (ranging from 24 months to 104 months).

Conventional echocardiographic parameters

Table 2 summarized the echocardiographic findings in the two groups. Conventional parameters of systolic and diastolic function, including body surface area indexed left ventricular end-diastolic volume (LVEDV/BSA), body surface area indexed left ventricular end-systolic volume (LVESV/BSA), left ventricular ejection fraction, E velocity, A velocity, E/A ratio, deceleration time, S' velocity, E/E', isovolumic relaxation time showed no significant difference between two groups.

Table 1 – Clinical characteristics of two groups

	Normal	Chemotherapy	p value
Number	27	42	
Male (n/%)	12 (44.44)	18 (42.86)	0.84
Age (y)	50.39 ± 13.40	55.83 ± 17.92	0.16
Hypertension (n/%)	0(0)	4(9.52)	
ACEI (n/%)	0(0)	1(2.38)	
ARB (n/%)	0 (0)	1(2.38)	
CCB (n/%)	0(0)	0(0)	
β-blocker (n/%)	0(0)	1(2.38)	
Smoker (n/%)	5(17.24)	9(21.42)	0.470
DM (n/%)	0(0)	1(2.38)	
SBP (mmHg)	124.8 ± 12.6	121.6 ± 12.5	0.627
DBP (mmHg)	70.7 ± 9.3	69.5 ± 7.9	0.233
HR (bpm)	78.0 ± 11.3	81.0 ± 14.5	0.099

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium-channel blocker; DBP: diastolic blood pressure; DM: diabetes mellitus; HR: heart rate; SBP: systolic blood pressure; p values were assessed by independent samples t test

Table 2 – Conventional echocardiographic parameters between two groups.

	Normal	Chemotherapy	p value
LVEDV/BSA (ml)	47.22 ± 13.97	46.99 ± 13.99	0.95
LVESV/BSA (ml)	16.31 ± 6.24	16.30 ± 6.47	0.99
LVMI (g/m^2)	79.32 ± 16.66	71.87 ± 13.68	0.13
RWT	0.36 ± 0.05	0.36 ± 0.05	0.93
LVEF (%)	66.46 ± 5.55	66.04 ± 6.52	0.78
E velocity (m/s)	80.38 ± 24.11	72.45 ± 16.99	0.11
A velocity (m/s)	76.62 ± 17.76	76.61 ± 19.07	0.95
E/A ratio	1.11 ± 0.44	1.01 ± 3.53	0.32
S' velocity (m/s)	9.50 ± 2.19	9.24 ± 2.08	0.60
E/E' ratio	6.95 ± 3.21	6.71 ± 2.31	0.71
DT (ms)	145.88 ± 27.81	149.95 ± 34.28	0.61
IVRT (ms)	85.36 ± 20.14	88.13 ± 24.77	0.62

BSA: body surface area; DT: deceleration time; FS: fraction shortening; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVMI: left ventricular mass index; IVRT: isovolumic relaxation time; RWT: relative wall thickness; p values were assessed by independent samples t test

Multi-layer speckle tracking echocardiography

In both groups, longitudinal and circumferential strains were highest in the apical region and decreased significantly from apical to basal level (Table 3,4). The left ventricular longitudinal and circumferential strains of different myocardial layers in patients and controls are shown in Table 5, Figure 1. Transmural strain gradients in LS and CS were demonstrated in both patients and controls, with strain values decreasing from the subendocardial to subepicardial layers. GCS was significantly decreased in chemotherapy group respect to control group (-27.73% ± 3.37% vs -24.94% ± 4.14%, p = 0.004). The reduction of GCS was attributable to significantly reduced CS-ENDO but preserved CS-EPI strain in patients compared with controls. The longitudinal strain values of global left ventricle and all three layers were significantly decreased in chemotherapy group. However, the two groups did not differ in transmural longitudinal strain gradient. In contrast, there was no statistic difference in radial strains between the two groups.

There was no correlation between anthracycline dose and layer specific strain values.

Table 3 – Three-layer circumferential strain values between two groups stratified by levels

	CS-Endo(%)			CS-Mid(%)			CS-Epi(%)		
	Control	Chemotherapy	P value	Control	Chemotherapy	P value	Control	Chemotherapy	p value
Basal level	-33.48 ± 5.10	-26.26 ± 4.34	0.000	-23.95 ± 4.26	-22.37 ± 4.28	0.149	-17.58 ± 4.03	-16.85 ± 3.93	0.453
Mid level	-34.29 ± 4.21	-31.25 ± 5.39	0.014	-24.45 ± 3.46	-22.57 ± 3.67	0.053	-17.54 ± 3.21	-16.85 ± 3.94	0.063
Apical level	-44.31 ± 6.14	-41.13 ± 9.47	0.038	-30.32 ± 4.46	-28.91 ± 6.34	0.316	-21.77 ± 3.95	-19.81 ± 5.39	0.105
P value	0.000	0.000		0.000	0.000		0.000	0.000	

CS-ENDO: subendocardial circumferential strain; CS-EPI: subepicardial circumferential strain; CS-MID: middle circumferential strain. P values were analyzed by one way ANOVA test.

Table 4 – Three-layer longitudinal strain values between two groups stratified by levels

	LS-Endo(%)			LS-Mid(%)			LS-Epi(%)		
	Control	Chemotherapy	P value	Control	Chemotherapy	P value	Control	Chemotherapy	p value
Basal level	-18.51 ± 2.55	-16.82 ± 2.36	0.006	-17.74 ± 2.50	-16.49 ± 2.11	0.027	-17.07 ± 2.50	-15.63 ± 2.00	0.009
Mid level	-22.76 ± 2.72	-21.04 ± 2.87	0.014	-20.82 ± 2.39	-19.45 ± 2.49	0.028	-19.23 ± 2.56	-16.87 ± 2.26	0.000
Apical level	-34.36 ± 3.23	-32.29 ± 5.69	0.101	-26.20 ± 3.06	-25.08 ± 4.23	0.623	-20.8 ± 2.55	-19.53 ± 5.12	0.538
P value	0.000	0.000		0.000	0.000		0.000	0.000	

LS-ENDO: subendocardial longitudinal strain; LS-EPI: subepicardial longitudinal strain; LS-MID: middle longitudinal strain. P values were analyzed by one way ANOVA test.

Table 5 – Strain values between two groups.

	Control	Chemotherapy	p value
GLS (%)	-21.86 ± 2.38	-20.36 ± 2.58	0.016*
GCS (%)	-27.73 ± 3.37	-24.94 ± 4.14	0.004*
GRS (%)	31.44 ± 12.98	26.89 ± 9.75	0.118
LS-ENDO(%)	-25.21 ± 2.72	-23.38 ± 3.11	0.014*
LS-MID(%)	-21.53 ± 2.36	-20.35 ± 2.58	0.029*
LS-EPI(%)	-18.83 ± 2.19	-17.35 ± 2.48	0.013*
LS gradient (%)	-6.38 ± 1.28	-6.03 ± 2.07	0.439
CS-ENDO(%)	-37.37 ± 3.79	-32.88 ± 5.23	0.000*
CS-MID(%)	-26.24 ± 2.98	-24.62 ± 4.13	0.073
CS-EPI(%)	-19.56 ± 4.45	-17.32 ± 4.13	0.066
CS gradient(%)	-17.80 ± 3.69	-15.55 ± 4.59	0.0*

*CS-ENDO: subendocardial circumferential strain; CS-EPI: subepicardial circumferential strain; CS-MID: middle circumferential strain; GCS: global circumferential strain; GLS: global longitudinal strain; GRS: global radial strain; LS-ENDO: subendocardial longitudinal strain; LS-EPI: subepicardial longitudinal strain; LS-MID: middle longitudinal strain. *: p < 0.05. p values were assessed by independent samples t test*

Inter and intra-observer variation

Inter-observer measurement showed ICC = 0.91 for CS-ENDO, 0.83 for CS-MID, 0.91 for CS-EPI, 0.95 for GCS, 0.61 for RS, 0.87 for LS-ENDO, 0.85 for LS-MID, 0.90 for LS-EPI, 0.91 for GLS. Similarly, intra-observer measurement showed ICC = 0.96 for CS-ENDO, 0.89 for CS-MID, 0.97 for CS-EPI, 0.97 for GCS, 0.73 for RS, 0.86 for LS-ENDO, 0.85 for LS-MID, 0.82 for LS-EPI, 0.94 for GLS, indicating satisfactory reproducibility by speckle-tracking-derived multilayer analysis of circumferential and longitudinal strain values. Bland-Altman curves of strain values were shown on Figure 2.

Discussion

Globally, cancer is diagnosed in 12.7 million people annually, with its incidence projected to increase by 40% in high-income countries from 2008 to 2030.[10]

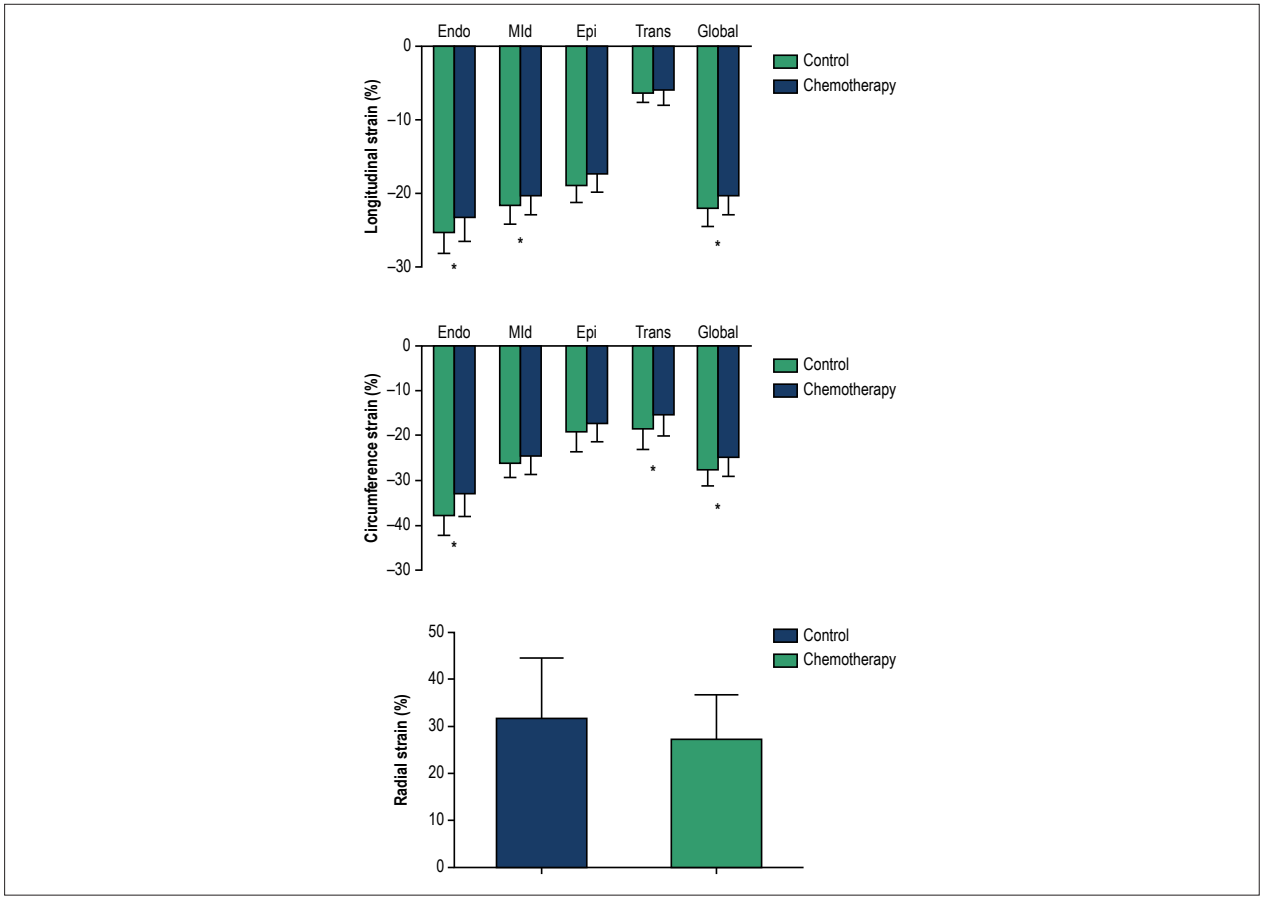

Figure 1 – *Strain values between two groups. *:p < 0.05.*

Anthracyclines are powerful cytotoxic agents, available to treat a wide spectrum of hematologic malignancies and solid tumors. However, life altering cardiac sequelae from anthracyclines remain a problem, with a range of 5-23% of patients developing late-onset heart failure secondary to anthracycline induced-cardiotoxicity.[11]

Reliable, sensitive and non-invasive methods in detecting cardiac function are of vital importance in these patients. The present study demonstrated that subclinical cardiotoxicity existed in long-survivors after receiving anthracycline therapy albeit normal conventional echocardiographic findings, implicating the more sensitive nature of these parameters in monitoring anthracycline cardiotoxicity.

Recently tagged magnetic resonance imaging provided a detailed quantitative analysis of left ventricular transmural differences in myocardial deformation.[12] Echocardiographic speckle-tracking strain analysis, which is angle-independent, provides a noninvasive method to assess left ventricular mechanics, thus translating clinically relevant aspects of cardiac performance from "bench to bedside". Furthermore, the echocardiographic speckle tracking derived transmural gradients has recently been validated against sonomicrometry crystal in a sheep model.[13] As proved by previous studies,[14-16] our observations showed great interobserver and intraobserver agreement, suggesting reasonable reproducibility of the speckle tracking-derived multi-layer strain parameters.

The present study confirmed the presence of transmural and translevel gradient in myocardial circumferential and longitudinal strains, with higher values in the subendocardial myocardial layer and in the apical level in both normal subjects and patients exposed to anthracycline, as is improved by Shi et al.[16] The difference in amplitude of myocardial contraction between the subendocardial and subepicardial regions was related to the orientation pattern of myocardial fiber in the heart. It has been described that in normal heart, contraction is greater in the subendocardial myocardium layer than in the subepicardial myocardium layer.[17] However, with greater contraction and higher energy requirements, subendocardial layer was more susceptible to injury, which can be detected by multi-layer speckle tracking strain analysis. Beck et al.[18] has demonstrated that a multi-layer analysis of myocardial deformation is highly accurate in the differentiation between different degrees of scar transmurality as assessed by MRI. In particular, multi-layer strain analysis provided higher accuracy to discriminate nontransmural versus noninfarction or trasmural versus nontransmural infarction compared with global strain. Altiok et al.[19] has also found that circumferential endocardial strain analysis allowed

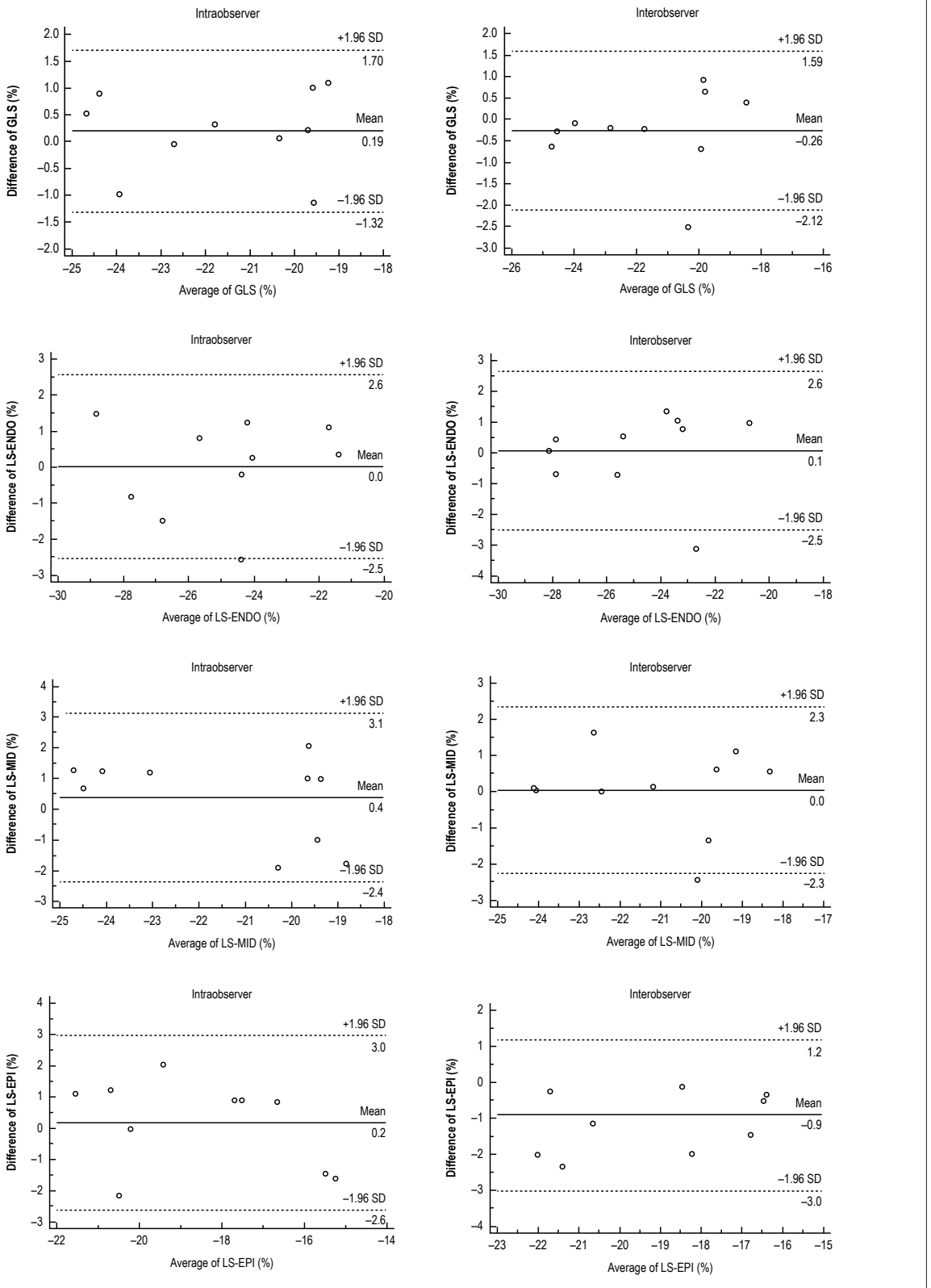

Figure 2 – *Bland-Altman analysis of inter-, intra-observation reproducibility.*

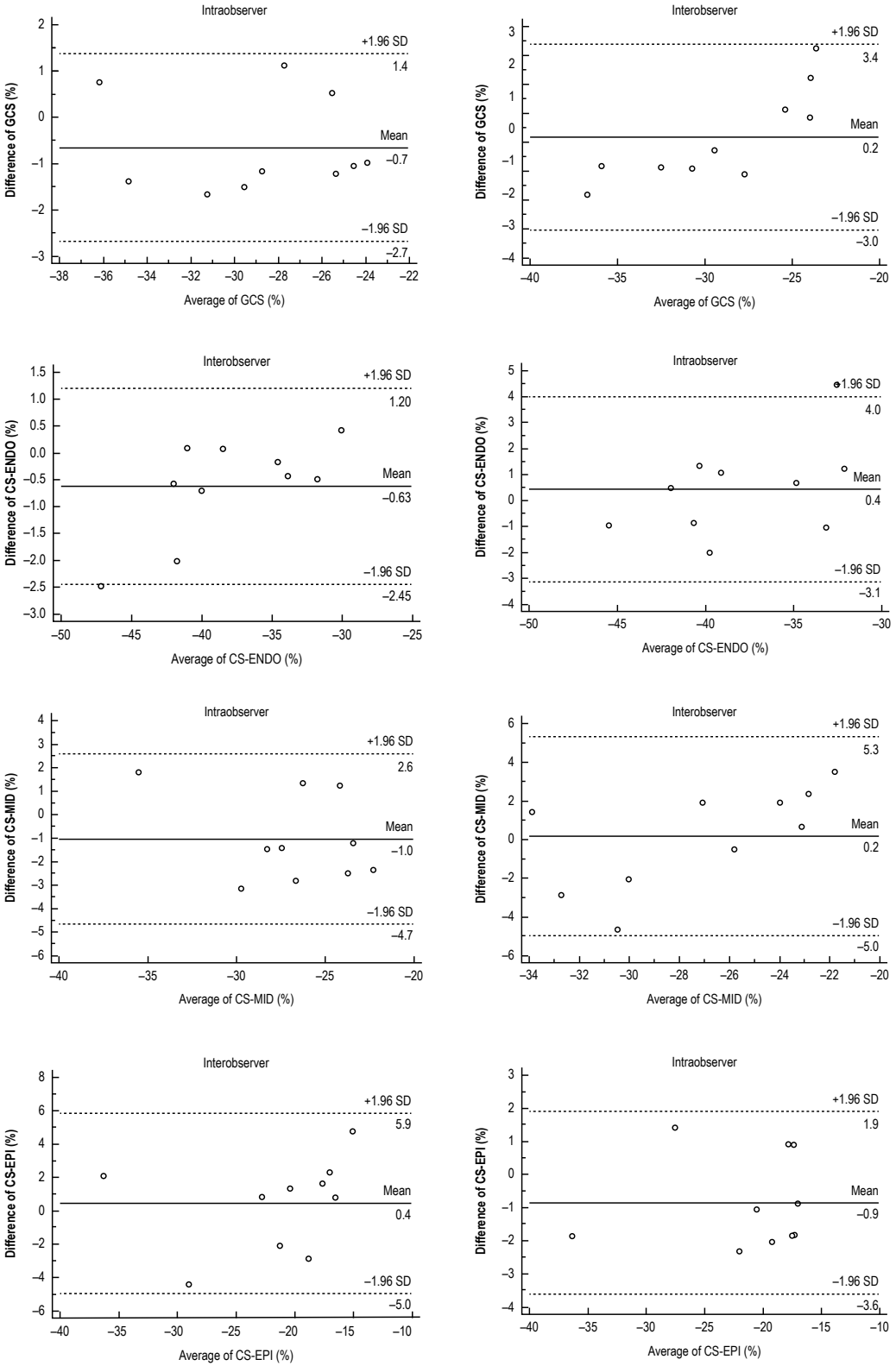

Figure 2 – *Bland-Altman analysis of inter-, intra-observation reproducibility.*

accurate distinction between segments with non-transmural infarction vs those with no infarction and between segments with transmural vs non-transmural infarction as defined by late gadolinium enhancement cardiovascular magnetic resonance. In the present study, we adopted a multi-layer strain approach in analyzing layer-specific ventricular deformation and observed the decrease of subendocardial circumferential strain values and transmural circumferential gradient in long-term survivors exposed to anthracycline. It has been proved in animal models of anthracycline cardiotoxicity that severe myocytolysis mainly involved the subendocardium of the ventricle.[20] Moreover, Perel et al.[21] observed a regional and diffuse pattern of subendocardial enhancement using cardiac magnetic resonance imaging in patients with anthracycline-induced cardiomyopathy. Hence, the findings in our study of reduction of subendocardial circumferential strain values and transmural circumferential gradient but preserved subepicardial circumferential strain was consistent with the same hypothesis of subendocardial injury induced by anthracycline. Moreover, it has been proved[22] that in patients with chronic ischemic cardiomyopathy, subendocardial circumferential strain was a powerful predictor of cardiac events and appeared to be a better parameter than LVEF and other strain variables analyzed by echocardiography. Therefore, we believed that further importance may need to be attached to the changes of subendocardial circumferential strains.

We observed that after anthracycline exposure, longitudinal strains of all the three layers decreased significantly. However, transmural longitudinal strain gradient did not show any difference compared to normal group. It is reported that the subendocardium is predominantly composed of longitudinal myocardial fiber. The subendocardial deformation is greatest in the longitudinal direction and verifies the endo-epicardial gradient in normal left ventricles on magnetic resonance imaging.[23,24] Hence, the longitudinal left ventricular mechanics are predominantly governed by the subendocardial region of the myocardium, which probably accounts for our findings of the reduction of all three layers of longitudinal strain values and the absence of difference in longitudinal transmural gradient.

The lack of difference in radial strain between two groups in our study was perhaps not surprising, which was concordance with some previous studies.[25,26] It was recently published that peak radial strain differed largely between different software and algorithms, and small changes in width can change large RS differences.[27] In the present study, the interobserver variation did not show satisfactory reproducibility of RS measurement. Hence, it may suggest that indices of radial deformation are not as sensitive as circumferential and longitudinal strains in detecting subclinical left ventricular dysfunction.

The absence of associations between strain parameters and cumulative anthracycline indicated lack of a safe dose that was free of cardiotoxicity. It has been proved that even children who have received a cumulative doxorubicin dose as low as 45mg/m^2 have reduced left ventricular mass[28] and anthracycline damage to all cardiac structures may begin with the first anthracycline dose.[29]

Limitation

Several limitations to this study warranted comment. This was a cross-sectional study of a relatively small patient cohort, which did not provide information on the value of myocardial deformation parameters in prognostication. Further out-come studies with hard clinical endpoints will be required to determine the clinical significance of our findings. Secondly, although speckle tracking echocardiography allows interrogation of global strain, these parameters are not entirely load dependent and need to be interpreted with caution when an alteration of cardiac status with acute changes in load is anticipated.

Conclusion

Despite normal left ventricular ejection fraction, subtle abnormalities in myocardial systolic function were present in long-term survivors after anthracycline exposure. It provided the evidence of preferential impairment of subendocardial deformation in long-term survivors after exposure to anthracycline. Multi-layer speckle tracking echocardiography, a potential non-invasive tool for the detection of subclinical anthracycline-induced myocardial abnormalities, might facilitate the longitudinal follow-up of this at-risk patient cohort.

Author contributions

Conception and design of the research: Kang Y, Shen X; Acquisition of data: Kang Y, Xiao F Xiao F, Chen H, Wang W, Zhao H; Analysis and interpretation of the data: Kang Y, Chen H, Wang W; Statistical analysis: Kang Y, Xiao F, Chen H, Shen L, Zhao H; Obtaining financing: Chen F, He B; Writing of the manuscript: Kang Y, Chen H, Shen L; Critical revision of the manuscript for intellectual content: Chen F, He B.

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 Renji Hospital under the protocol number 2014(N012). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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What is the Role of Two-Dimensional Speckle Tracking Echocardiography in the Diagnosis and Management of Anthracycline-Induced Cardiotoxicity?

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The increasing number of patients with neoplasms and survivors[1,2] has raised the interest of the scientific community in the diagnosis and early management of the effects of neoplasms and/or their treatments on patients. In that scenario, the injury caused to the cardiovascular system belongs to a spectrum and can impair all cardiovascular system structures in a clinically variable way, ranging from asymptomatic forms to cardiovascular death. Most studies on cardiotoxicity have focused on ventricular dysfunction because of its presentation severity and because it is the major cause of late non-oncologic mortality of neoplasm survivors.[3]

In oncologic patients, the drugs most commonly related to ventricular dysfunction are anthracyclines.[4] Recent studies have reported that the damage related to those drugs, if not identified and treated early, evolves continuously from cell injury to ventricular dysfunction. In the past decade, several studies showed that the subclinical detection of cardiotoxicity, by use of biomarkers, such as troponin and BNP, might be an opportunity to prevent cardiovascular injury, allowing for early treatment and more appropriate individualized follow-up.[5-8]

Another current challenge regarding cardiotoxicity is to understand the natural history of neoplasm survivors. Little is known about the prevalence of cardiovascular disease in those patients, and, thus, no long-term follow-up strategy has been defined for them.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Kang et al.[9] make a relevant contribution to the diagnosis of anthracycline-induced cardiotoxicity. In a cohort of survivors of non-Hodgkin's diffuse large B cell lymphoma treated with anthracyclines, those authors have shown that, as compared to healthy controls, those patients have lower values of circumferential and longitudinal strains on echocardiography in a population with normal ejection fraction. Such findings have been evidenced mainly by changes in the subendocardial segments. In accordance with previous studies,[10] those authors have emphasized the radial strain measure to be of little importance in that population. Inter- and intraobserver analyses reinforce that data obtained can be safely reproducible.

Kang et al.[9] have not observed a direct relationship between anthracycline doses and strain values, suggesting that the myocardial damage, reflected on impaired myocardial deformation, can occur even at doses considered non-cardiotoxic (lower than 240 mg/m^2), provided that the population studied used doses ranging from 150.94 mg/m^2 to 440.00 mg/m^2.

That was an observational study with a small sample, but its finding is clinically relevant and should be explored. It is yet to be defined whether that finding is only a marker of chemotherapeutic response or whether it represents the beginning of the pathophysiology of the clinically manifest cardiovascular lesion. Further studies are required to clarify whether the neoplasm itself, through its endothelial changes, could be related to changes in strain.

Even without definite responses, the study by Kang et al.[9] contributes to reinforce the importance of combining the clinical practice with a sensitive non-invasive method to aid the management of oncologic patients during and after chemotherapy.[10,11]

Keywords

Neoplasms; Cardiotoxicity; Anthracyclines / toxicity; Ventricular Dysfunction; Troponin; Natriuretic Peptides; Echocardiography; Speckle-Tracking.

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Echocardiographic Assessment of Ventricular Function in Young Patients with Asthma

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Abstract

Background: **Despite significant advances in understanding the pathophysiology and management of asthma, some of systemic effects of asthma are still not well defined.**

Objectives: **To compare heart function, baseline physical activity level, and functional exercise capacity in young patients with mild-to-moderate asthma and healthy controls.**

Methods: **Eighteen healthy (12.67 ± 0.39 years) and 20 asthmatics (12.0 ± 0.38 years) patients were enrolled in the study. Echocardiography parameters were evaluated using conventional and tissue Doppler imaging (TDI).**

Results: **Although pulmonary acceleration time (PAT) and pulmonary artery systolic pressure (PASP) were within normal limits, these parameters differed significantly between the control and asthmatic groups. PAT was lower ($p < 0.0001$) and PASP ($p < 0.0002$) was higher in the asthma group (114.3 ± 3.70 ms and 25.40 ± 0.54 mmHg) than the control group (135.30 ± 2.28 ms and 22.22 ± 0.40 mmHg). The asthmatic group had significantly lower early diastolic myocardial velocity (E', $p = 0.0047$) and lower E' to late (E'/A', $p = 0.0017$) (13.75 ± 0.53 cm/s and 1.70 ± 0.09, respectively) compared with control group (15.71 ± 0.34 cm/s and 2.12 ± 0.08, respectively) at tricuspid valve. In the lateral mitral valve tissue Doppler, the asthmatic group had lower E' compared with control group ($p = 0.0466$; 13.27 ± 0.43 cm/s and 14.32 ± 0.25 cm/s, respectively), but there was no statistic difference in the E'/A' ratio ($p = 0.1161$). Right isovolumetric relaxation time was higher ($p = 0.0007$) in asthmatic (57.15 ± 0.97 ms) than the control group (52.28 ± 0.87 ms), reflecting global myocardial dysfunction. The right and left myocardial performance indexes were significantly higher in the asthmatic (0.43 ± 0.01 and 0.37 ± 0.01, respectively) compared with control group (0.40 ± 0.01 and 0.34 ± 0.01, respectively) ($p = 0.0383$ and $p = 0.0059$, respectively). Physical activity level, and distance travelled on the six-minute walk test were similar in both groups.**

Conclusion: **Changes in echocardiographic parameters, evaluated by conventional and TDI, were observed in mild-to-moderate asthma patients even with normal functional exercise capacity and baseline physical activity level. Our results suggest that the echocardiogram may be useful for the early detection and evoluation of asthma-induced cardiac changes. (Arq Bras Cardiol. 2018; 110(3):231-239)**

Keywords: **Exertional Dyspnea / physiopathology; Echocardiography, Doppler; Asthma / physiopathology; Vascular Remodeling, Ventricular Dysfunction.**

Introduction

Asthma is characterized by chronic inflammation and remodeling of the airways.[1] This remodeling leads to structural changes in the walls of the airways induced by repeated injury and repair, which can cause an irreversible loss of lung function.[2] Moreover, asthma can lead to an increase in bronchial angiogenesis[3] and remodeling of the pulmonary vessels, culminating in changes in both bronchial and pulmonary circulation.[4]

The interaction between respiratory diseases and cardiovascular function is complex. Changes in the structure and function of the right ventricle are associated with pulmonary hypertension.[5] Recurring hypoxemia and hypercapnia associated with different mediators and cytokines related to chronic inflammation of the airways in patients with asthma cause pulmonary vasoconstriction and the development of pulmonary hypertension, with the consequent hypertrophy/dilatation of the right ventricle.[6] Diastolic dysfunction of the right ventricle is the earliest hemodynamic change found in patients with asthma due to the increase in the afterload imposed on the ventricle.[7] Pulmonary disease affects the size, shape and function of the right ventricle, but altered respiratory function can also affect the left ventricle.[5]

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Echocardiography is a non-invasive, relatively safe, cost effective and easily accessible method for the right ventricle assessment. Tissue Doppler imaging (TDI) has been demonstrated to furnish a quantitative measure of regional velocities in the myocardium as well as systolic and diastolic intervals.[8] TDI can detect subclinical abnormalities of the right ventricle in a phase when conventional echocardiographic findings are still within normal ranges,[8] thereby enabling the detection of right ventricular dysfunction in the early stage of a disease.[9-11]

Recent studies on young adults with asthma have employed TDI and found subclinical diastolic dysfunction directly related to the severity of the condition, suggesting that this imaging technique has greater predictive value than conventional echocardiography for the evaluation of right ventricular function[9]. Similar findings have been reported for children and adolescents in the stable phase of asthma. Shedeed et al.[11] evaluated children and adolescents aged 5 to 15 years with mild to severe asthma and found that TDI demonstrated right ventricular dysfunction that was positively correlated with the severity of the condition, despite the conventional echocardiogram being apparently normal. Likewise, Ozdenir et al.[10] found a negative correlation between right ventricular dysfunction and peak expiratory flow in children with asthma, suggesting that TDI has important diagnostic value for the early detection and monitoring of heart repercussions in children with asthma.

The clinical phenotype of asthma can differentially affect myocardial performance. Children with asthma and a predominance of shallow breathing exhibit more severe myocardial dysfunction than those with a predominance of wheezing as the manifestation of the condition.[12] The aim of the present study was to compare heart function, quality of life, physical activity level, functional exercise capacity and inspiratory muscle strength/endurance in young patients with mild-to-moderate asthma and healthy controls to determine the impact of this condition on echocardiographic variables.

Methods

Study population

Male and female children and adolescents from 10 to 16 years with mild to moderate asthma were enrolled in the present study. Asthma severity was established based on the guidelines of the Global Strategy for Asthma Management and Prevention.[13] The control group comprised of children and adolescents considered healthy. The groups were matched for sex and age.

Inclusion criteria

The group with asthma comprised children and adolescents with clinical and spirometric diagnosis of asthma, for more than 30 days with no history of acute upper or lower airway infection or exacerbation of the condition. The participants in the control group had a normal clinical history and normal lung function.

Exclusion criteria

Children and adolescents with acute or chronic lung disease, major thoracic deformities, neuromuscular, cardiovascular, digestive, rheumatic, osteoarticular or genital-urinary disorders, genetic syndromes or any adverse health conditions that limited the safe performance of the tests proposed in the protocol were excluded from the study.

Evaluation protocol

Height (meters) and weight (kilograms) were measured using an anthropometric scale (Filizola™, São Paulo, SP, Brazil). The tests were conducted in two steps. Step 1 – spirometric analysis was performed to confirm the diagnosis and classification of asthma. Next, the quality of life and baseline physical activity questionnaires were administered. The strength and endurance of the inspiratory muscles were then measured. Functional capacity was evaluated using the six-minute walk test (6MWT) 30 minutes after the evaluation of the inspiratory muscles. Step 2 – Echocardiography was performed. The order of the two steps was determined randomly and a maximum interval of 15 days was respected between steps.

Pulmonary function test

The spirometric variables analyzed were forced vital capacity (FVC), forced expiratory volume in the first second of FVC (FEV_1) and the Tiffeneau index (FEV_1/FVC). The group with asthma was also submitted to the bronchodilator test 20 minutes after the inhalation of salbutamol (400 μg/dose) distributed in four inhalations of 100 μg with a one-minute period between inhalations. Predicted values were analyzed and described using the equations proposed by Polgar and Promadhat.[14] An increase in FEV_1 equal to or greater than 12% of the predicted after the administration of salbutamol confirmed the variable limitation to airflow.

Evaluation of maximum inspiratory pressure

Maximum inspiratory pressure (MIP) was evaluated using an analog pressure gauge (MDI® model MVD300, Porto Alegre, Brazil) beginning from residual volume. At least five reproducible measurements were taken and the maneuvers were repeated until the two highest measurements did not differ by more than 5%.[15] The highest measurement was used to establish the load for the evaluation on inspiratory muscle endurance.

Evaluation of inspiratory muscle endurance

Inspiratory muscle endurance was evaluated after the determination of MIP, using a modified version of the protocol proposed by Sette et al.[16] Inspiratory muscle endurance was defined as the maximum time tolerated of spontaneous breathing with a load corresponding to 30% of MIP until exhaustion, which was defined as the inability to overcome inspiratory resistance in two consecutive attempts. The criteria for interrupting the test were intense weariness, dizziness, discomfort, cheek pain or peripheral oxygen saturation (SpO_2) less than 85%.

Evaluation of functional capacity using the 6MWT

The 6MWT was performed based on the guidelines of the American Thoracic Society. The participant was instructed

to walk as fast as possible along a 30-meter flat corridor marked every three meters and received standardized verbal encouragement every 30 seconds by the same evaluator. A second evaluator remained at one of the extremities of the track to assist in the data collection at the beginning and end of the test. Blood pressure (BP), respiratory rate (RR), heart rate (HR), SpO_2, and the Borg dyspnea score at rest and during exertion were the variables measured at the beginning and end of the test. The 6MWT was performed twice, with a 30-minute rest interval between tests. The test on which the participant travelled the longer distance was considered in the statistical analysis. The criteria for interrupting the test were extreme weariness, SpO_2 less than 85% or any other discomfort. The participant was told that the test could be interrupted at any type if he/she felt any discomfort. Dyspnea at rest and during exertion was evaluated using the modified Borg scale,[17] which is scored from 0 to 10 points based on verbal responses that correspond to no or maximum shortness of breath, respectively.

Evaluation of quality of life

Quality of life was evaluated using the Pediatric Quality of Life Inventory™ version 4.0 (PedsQL 4.0).[18,19] Self-assessments were available for the following age groups: 5 to 7, 8 to 12 and 13 to 18 years. The items on the forms for each age group are similar, differing only in terms of the use of language adequate to the level of development. The quality of life of the group with asthma was also evaluated using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ),[20] which has been translated and culturally adapted to Brazilian Portuguese for children and adolescents aged 7 to 17 years.[21]

Evaluation of baseline physical activity

Physical activity was evaluated using the Physical Activity Questionnaire – Child (PAQ-C),[22] which measures the level of physical activity of children and adolescents in the previous week.

Evaluation of echocardiographic variable

A single pediatric cardiologist who was blinded to the respiratory status of the participants performed the echocardiogram. The exam was performed with the participant positioned in left lateral and dorsal decubitus. The Toshiba echocardiograph was used with variable frequency transducers from 2.0 to 7.0 MHz. At least five consecutive beats were obtained from the parasternal window to determine the inner diameters of the ventricles. The exams were recorded and analyzed offline by two specialists in pediatric echocardiography.

The left and right ventricular functions were assessed by two-dimensional echocardiography: M-mode, color-flow imaging, standard pulsed-wave Doppler and TDI, according to guidelines of the American Society of Echocardiography. The following data were collected for statistical evaluation: measurements of aortic dimension, left atrium, right ventricle anterior wall, right ventricular end-diastolic dimension, interventricular septum, left ventricular end-diastolic dimension, left ventricular systolic dimension and left ventricle posterior wall obtained by the M mode paraesternal long and short axis view. There was no patient with congenital heart disease and all of them had symmetric left ventricular systolic function.

The apical four-chamber view enables studying blood inflow through the atrioventricular valves. The early (E) and late (A) diastolic velocities of mitral and tricuspid valves and E/A ratio were used to evaluate biventricular filling function. TDI was used to evaluate cardiac load and determine the myocardial performance index (MPI). The left ventricular TDI was achieved at the lateral wall through the mitral annulus, whereas the right ventricular TDI was achieved through the tricuspid lateral annulus. The recordings of peak early (E') and late (A') diastolic velocities, E´/A´ ratio, systolic (S´) annular velocity, isovolumetric relaxation time (IVRT) and isovolumetric contraction time (IVCT) were obtained in the apical four-chamber view. MPI is defined as the IVCT and IVRT divided by the ejection time (ET) (Figure 1).

The right ventricular systolic function was assessed by fractional area change (FAC), derived from tricuspid lateral annular systolic velocity wave (S') and tricuspid annular plane systolic excursion (TAPSE).

Pulmonary systolic arterial pressure (PSAP) was also estimated using two methods. Pulsed-wave Doppler tracing across the pulmonary valve was performed using the pulmonary acceleration time (PAT) by left parasternal short-axis view (Figure 2). The normal profile is symmetrical in shape. When pulmonary pressure and pulmonary vascular resistance are high, the peak occurs earlier. The other method was measuring maximal tricuspid regurgitation velocity, applying the modified Bernoulli equation to convert this value into pressure values and adding the estimated right atrial pressure (RAP). Normal RAP was considered 5 mmHg. PSAP = tricuspid regurgitation gradient + RAP. PSAP = ($Vmax^2$ x 4) + RAP. Normal systolic arterial pressure is up to 30 mmHg at rest and up to 40 mmHg during exercise.

Sample size

In order to calculate the sample size, we considered as objective to test the equality of the means of the mitral E-wave velocity among the groups of asthmatic patients and controls.[23] In order to detect a minimum difference of 4.7 cm/s between means, with a significance of 5%, minimum power of 80%, and variance based on a previous study,[9] it was necessary to obtain a ratio of 0.9 between controls/asthmatics, corresponding to 20 asthmatic children and 18 controls.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normality of the data. The variables were expressed as central tendency (mean and median) and variability (standard error of the mean or interquartile range-IQR). When appropriate, either the non-paired t-test or the Mann-Whitney test was used for the comparison of the different variables analyzed, and either Pearson's or Spearman's correlation coefficient were calculated to evaluate associations between the independent variables and response variable. All analyses were performed with the GraphPad Prism software (version 5.0, GraphPad Software, Inc.,

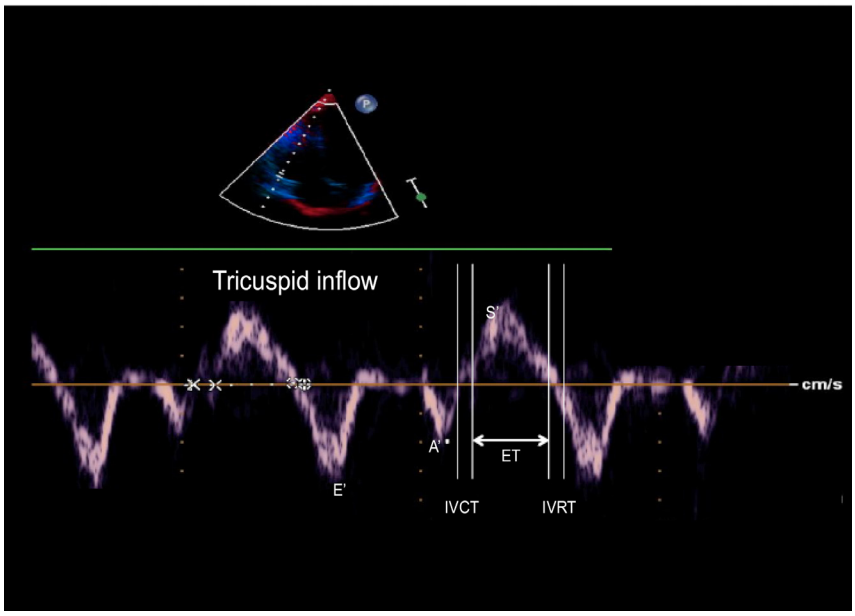

Figure 1 – *Tissue Doppler imaging performed at tricuspid annulus in apical 4-chamber view (E'- peak early diastolic annular tricuspid velocity; A': peak late diastolic annular tricuspid velocity; S´: systolic annular velocity; IVRT: isovolumetric relaxation time; IVCT: isovolumetric contraction time; ET: ejection time)*

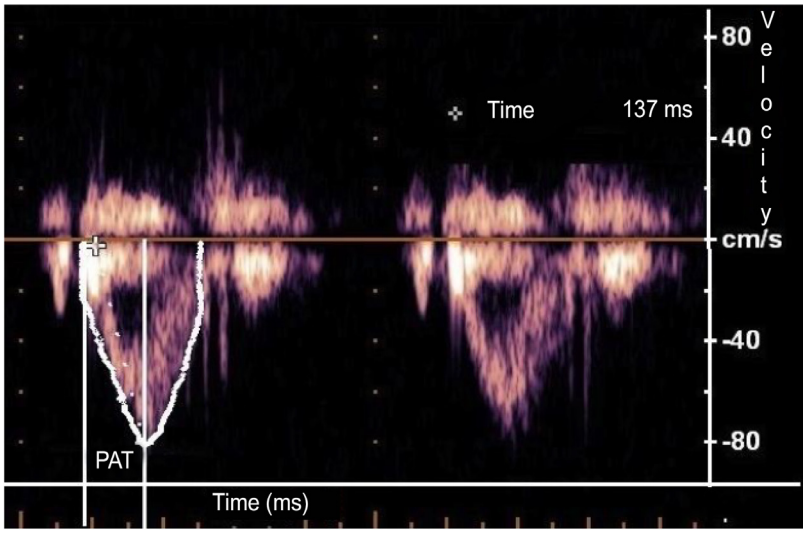

Figure 2 – *Pulsed-wave Doppler of pulmonary artery (PAT: pulmonary acceleration time = interval from onset of pulmonary flow to peak velocity; shorter acceleration time = higher pulmonary arterial pressure)*

La Jolla, CA, USA). A p-value < 0.05 was considered indicative of statistical significance.

Results

Anthropometric and pulmonary function test data

Control and asthmatic groups were similar with regard to age, weight, height, and body mass index (BMI). FEV_1 and the Tiffeneau index (FEV_1/FVC) were significantly lower in the group with asthma than the control group (Table 1). All asthmatic patients were clinically stable. Of the 20 patients, 86.95% presented mild asthma, 8.70% moderate asthma and 4.35% very severe asthma.

Echocardiographic characteristics

In the present study, conventional and tissue echocardiographic parameters in healthy and asthmatic children and adolescents free of any cardiovascular symptoms were assessed.

TAPSE, FAC% and S' were similar in both asthmatic and control groups. MPI was higher in asthmatic group. TDI of right diastolic function revealed that E', A' and the E'/A' ratio, evaluated in the tricuspid annulus, differed significantly between groups. Similarly, E and A diastolic annular tricuspid velocity and E/A differed significantly between groups (Table 2). Moreover, the IVRT was significantly ($p = 0.0007$) higher in asthmatic group (57.15 ± 0.97 ms) in relation to control (52.28 ± 0.87 ms) group.

Although PAT and PASP were within normal limits (> 130 ms and < 35 mmHg, respectively), these parameters differed significantly between the control and asthmatic groups. PAT was lower ($p < 0.0001$) and PASP ($p < 0.0002$) was higher in the asthma group (114.3 ± 3.70 ms and 25.40 ± 0.54 mmHg) than the control group (135.30 ± 2.28 ms and 22.22 ± 0.40 mmHg).

Table 3 shows that S' was lower and the MPI was higher in the group with asthma. TDI of left diastolic function revealed that both E' and A' differed significantly between groups. Peak E and A diastolic annular mitral velocity and E/A differed significantly between groups.

Among the 18 healthy children and adolescents submitted to echocardiograms, nine were submitted to an evaluation of inspiratory muscle endurance and functional capacity, along with the administration of the questionnaires on quality of life and level of physical activity. The group with asthma was submitted to all tests employed in the present study.

Inspiratory muscle endurance

No significant differences between control and asthma groups were found regarding MIP (109.4 ± 14.19 cmH_2O and 92.14 ± 5.62 cmH_2O, $p = 0.178$) or baseline dyspnea (0.14 ± 0.09 and 0.18 ± 0.10, $p = 0.871$). Despite the shorter respiratory muscle endurance time in the group with asthma (128.9 ± 14.08 s), the difference did not achieve statistical significance in comparison with control group (154.9 ± 46.69 s). Final Borg scale scores were significantly higher in comparison to the baseline evaluation in both groups. Moreover, the group with asthma (6.1 ± 0.39) had significantly ($p = 0.0129$) higher final Borg scores in comparison to the control group (3.67 ± 0.41).

Baseline physical activity and functional exercise capacity

Mean baseline physical activity, evaluated by PAQ-C, was similar ($p = 0.65$) in both control (2.2) and asthmatic (2.04) groups. The mean number of hours spent in front of the television per day was five hours in the control group and 5.71 hours in the group with asthma.

The functional exercise capacity was evaluated by 6MWT. All participants completed the test without interruption. No significant differences between groups were found regarding the cardiopulmonary variables (BP, HR, SpO_2, and dyspnea). The walked distance did not differ ($p = 0,239$) between control (327.3 ± 15.73 m) and asthma (328.8 ± 8.61 m) groups.

Evaluation of quality of life

The quality of life in control and asthmatic groups was measured using the PedsQL 4.0. No significant difference between groups was found regarding the mean total PedsQL 4.0 score ($p = 0.418$) or separately the scores on the emotional ($p = 0.698$), social ($p = 0.730$), school functioning ($p = 0.626$) and psychosocial ($p = 0.984$) domains. The score on the physical domain, however, was significantly lower ($p = 0.005$) in the group with asthma (74.06 ± 2.54) in comparison to the control group (92.86 ± 3.71). Regarding the PAQLQ, no significant differences between sexes were found on any of the domains. The "symptoms" domain had the greatest negative impact (5.22 ± 0.23).

Table 1 – Anthropometric data, and pulmonary function test in control and asthmatic groups

Variable	Control (n = 18)	Asthma (n = 20)	p
Age (years)	12.67 ± 0,39	12.0 ± 0.38	0.143[M]
Male sex	44. 44%	50%	-
Weight (Kg)	52.5 ± 5.0	50.3 ± 3.2	0.21[T]
Height (m)	1.57 ± 0.34	1.53 ± 0.22	0.44[T]
BMI	21.1 ± 1.4	21.0 ± 1.0	0.93[T]
Normal weight range	44.45%	47.6%	-
Overweight	33.33%	23.8%	-
Obese	22.22%	28.6%	-
Pulmonary function			
FVC (% predicted)	108.7% ± 4.7	95.8% ± 3.1	0.814[T]
FEV_1 (% predicted)	102.2% ± 4.9	84.4% ± 3.5	0.011[T]
FEV_1/FVC (%)	95.7% ± 1.6	86.4% ± 2.9	0.027[T]

Data expressed as mean ± SEM. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in first second of FVC; FEV_1/FVC: Tiffeneau index. Comparison between the two groups was made through the t-student or non-parametric statistical test Mann-Whitney test. [T] t-Student and [M] Mann-Whitney.

Table 2 – Doppler echocardiogram parameters of right ventricle systolic and diastolic function in control and asthmatic groups

Variable (normal value)	Systolic function		p
	Control (n = 18)	Asthma (n = 20)	
TAPSE cm (> 1.6)	1.9 ± 0.19	1.8 ± 0.11	0.184[M]
FAC % (> 35)	40 ± 3.21	38 ± 2.89	0.212[M]
S' cm/s (> 9.5)	12.29 ± 0.26	11.67 ± 0.34	0.3342[M]
MPI (< 0.55)	0.40 ± 0.01	0.43 ± 0.01	0.0383[M]
	Diastolic function		
Tricuspid E'/A' ratio (> 0.52)	2.12 ± 0.08	1.70 ± 0.09	0.0017[T]
Tricuspid E' cm/s (> 7.8)	15.71 ± 0.34	13.75 ± 0.53	0.0047[T]
Tricuspid E/A ratio (> 0.8)	2.34 ± 0.09	1.71 ± 0.06	< 0.0001[T]

Data expressed as mean ± SEM. TAPSE: tricuspid annular plane systolic excursion; FAC %: fractional area change; S': systolic myocardial velocity; MPI: myocardial performance index; E': early diastolic myocardial velocity; A': late diastolic myocardial velocity; E: peak early diastolic annular tricuspid velocity; A: peak late diastolic annular tricuspid velocity (atrial contraction). Data analysis for comparison between the two groups was made through the t-student or non-parametric statistical test Mann-Whitney test. [T]t-Student and [M]Mann-Whitney. In the tricuspid valve, the value of MPI is 0.39 (0.6) and 0.43 (0.6) for control and asthmatic groups.

Table 3 – Doppler echocardiogram parameters of left ventricle systolic and diastolic function in control and asthmatic groups

Variable (normal value)	Systolic function		p
	Control (n = 18)	Asthma (n = 20)	
Ejection fraction % (> 35)	69.0 ± 0.47	69.0 ± 0.80	0.4677[T]
Lateral mitral S' cm/s (> 6.7)	8.01 ± 0.20	7.30 ± 0.21	0.0170[M]
MPI (< 0.55)	0.34 ± 0.01	0.37 ± 0.01	0.0059[T]
	Diastolic function		
Lateral mitral E'/A' ratio (> 0.82)	2.89 ± 0.09	2.52 ± 0.20	0.1161[T]
Lateral mitral E' cm/s (> 10.0)	14.32 ± 0.25	13.27 ± 0.43	0.0466[T]
Mitral E/A ratio (> 0.8)	3.42 ± 0.17	2.25 ± 0.14	< 0.0001[T]

Data expressed as mean ± SEM. S': systolic myocardial velocity; MPI: myocardial performance index; E': early diastolic myocardial velocity; A': late diastolic myocardial velocity; E: peak early diastolic annular mitral velocity; A: peak late diastolic annular mitral velocity (atrial contraction). Data analysis for comparison between the two groups was made through the t-student or non-parametric statistical test Mann-Whitney test. [T]t-Student and [M]Mann-Whitney. In the mitral valve, the value S' is 7.93 (1.07) and 7.12 (1.08) for control and asthmatic groups.

Discussion

The present findings demonstrate for the first time that PAT was significantly lower and PSAP was significantly higher in the group with asthma compared to the controls. TDI has been used to evaluate quantitative measurements of regional velocities of the myocardium and both the systolic and diastolic intervals.[8] TDI enables the detection of right ventricular dysfunction in the early stages of respiratory disease.[9] In the current study, significant differences between groups were found regarding E' and A' evaluated in the tricuspid and mitral annuli. In addition, the MPI of the right and left ventricles was significantly higher in the group with asthma. Interestingly, respiratory muscle performance, baseline physical activity level and exercise capacity were similar in both groups. Taken together, these findings suggest that echocardiographic parameters, especially TDI parameters, can be useful as a complementary evaluation for patients with asthma, allowing the early detection of repercussions on the heart.

The interaction between respiratory diseases and cardiovascular function is complex. Changes in the structure and function of the right ventricle are associated with pulmonary hypertension.[5] In the present study, although the conventional echocardiogram demonstrated no evidence of changes in the structure of the right ventricle, the group with asthma exhibited a reduction in PAT and an increase in PSAP in relation to control group. Recent study has demonstrated that PAT inversely correlates with right heart catheterization-measured pulmonary hemodynamics and directly correlates with pulmonary arterial compliance in children.[24] Unlike findings described in studies by Shedeed et al.,[11] Ozdemir et al.[10] and Zedan et al.,[12] no right ventricular hypertrophy was found in the group with asthma in the present investigation. Moreover, in the current study the conventional Doppler echocardiogram revealed statistically significant difference between the controls and the group with asthma regarding peak velocities during the early diastole and atrial contraction (E, A and E/A) evaluated

in the annulus of the mitral and tricuspid valves. In contrast, Shedeed et al.[11] found no significant differences in these variables between controls and a group with asthma or between the different degrees of asthma severity.

A number of studies have demonstrated that patients with asthma exhibit diastolic dysfunction.[9,11,12] Indeed, in the current study significant differences between the controls and the group with asthma were found regarding myocardial diastolic velocities E' and A' as well as the E'/A' ratio evaluated in the tricuspid annulus. Similar results were found in the mitral valve annulus, with a reduction in myocardial velocity during early diastole and an increase in myocardial velocity during atrial contraction. A significant increase in the IVRT was also found in the group with asthma, contributing to a significant increase in the MPI. In contrast, the increase in the MPI of the left ventricle occurred at the cost of a reduction in systolic velocity in the ventricle.

The clinical phenotype of asthma may differentially affect myocardial performance. Zedan et al.[12] compared the MPI of children with asthma according to the phenotype (predominance of shallow breathing or wheezing as the clinical manifestation) and found that those with shallow breathing had a higher MPI. In the present study, the asthmatic children and adolescents were evaluated in a single group based only on the clinical and spirometric diagnosis of asthma.

In the current study, MIP was similar in both groups, despite the significant reductions in FEV_1 and Tiffeneau index in the asthmatic group. The results of studies involving inspiratory muscle strength in asthmatic children and adolescents are conflicting. Some studies show that there is no difference,[25,26] and other studies show that the strength of the inspiratory muscles of children and adolescents with asthma is reduced relative to their peers.[27] Similar results were observed in inspiratory muscle endurance. Endurance test was similar in the control and asthmatic groups. However, exertion dyspnea evaluated at the end of the endurance test was significantly more intense in the group with asthma, suggesting that this variable may have a discriminative value between healthy individuals and those with asthma when submitted to the same level of inspiratory muscle overload. There is a number of determinant factors of inspiratory muscle endurance, such as contraction strength and duration, shortening velocity, the relationship between baseline inspiratory pressure (IP) and MIP (IP/MIP) and the inspiratory flow pattern adopted by patients during the evaluation.[28] Further studies are needed to clarify the greater shortness of breath in the group with asthma.

The 6MWT is considered a safe, easy-to-administer method for the evaluation of sub-maximum exercise capacity in healthy children and adolescents,[29] as well as those with respiratory diseases.[30-32] Similar to the results of Basso et al.[31] and Soares et al.,[27] in the present study, no significant difference between groups was found regarding the distance walked or the cardiovascular variables analyzed before and after the 6MWT. In the same way, studies using other functional capacity assessment methods, such as the shuttle walking test[33] and cardiopulmonary exercise test[34] also did not observe a difference between asthmatic children and adolescents and control group.

Quality of life is one of the most important outcomes in the evaluation of patients with chronic disease. In the present study, this aspect was evaluated using a generic questionnaire as well as a specific questionnaire for children and adolescents with asthma. Regarding the generic questionnaire, quality of life was similar in both groups with regard to most domains, except the score on the physical domain, which was significantly lower in the group with asthma. In agreement with data described by Basaran et al.[35] and Andrade et al.,[30] the mean score on the asthma-specific questionnaire was 5.67 ± 0.23, which indicates a good quality of life among the children and adolescents studied in the present investigation.

Limitations of the study

The small sample size could be considered a limitation of the present study. However, even with the small number of participants, it was possible to demonstrate changes in conventional and tissue echocardiographic variables among the children and adolescents with asthma in comparison to the control group. Another limitation regards the evaluation of functional capacity. The 6MWT is considered a sub-maximal exercise test for measuring physical functional capacity. It is possible that the variables analyzed on a maximum cardiopulmonary stress test would be more sensitive in detecting differences in functional capacity between individuals considered healthy and those with asthma. A third limitation was the failure to evaluate the breathing pattern adopted during the respiratory muscle endurance test. The record of inspiratory flow allows the evaluation of inspiratory time, expiratory time, total cycle and the inspiratory time/total cycle ratio, as performance on the endurance test can vary depending on the breathing pattern adopted. The precise mechanism to clarify the difference in exertion dyspnea between healthy individuals and those with asthma during the inspiratory muscle endurance test needs to be determined.

Conclusion

Patients with asthma presented significant changes in diastolic velocities of the myocardium and the MPI of both ventricles, but with no repercussions regarding exercise capacity evaluated using the 6MWT. Further studies are needed to confirm these findings and to evaluate the clinical implications of these abnormalities.

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Author contributions

Conception and design of the research: Rodrigues-Machado MG; Acquisition of data: De-Paula CR, Magalhães GS,

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Potential Conflict of Interest

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

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Study Association

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

Ethical approval and informed consent

This study was approved by the Ethics Committee of the Faculdade Ciências Médicas-Minas Gerais under protocol number 14710413.0.0000.5134. All procedures involved in this study are in accordance with the Helsinki Declaration of 1975, updated in 2013. Informed consent was obtained from all participants included in the study.

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Urbanization is Associated with Increased Trends in Cardiovascular Mortality Among Indigenous Populations: the PAI Study

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Abstract

Background: The cardiovascular risk burden among diverse indigenous populations is not totally known and may be influenced by lifestyle changes related to the urbanization process.

Objectives: To investigate the cardiovascular (CV) mortality profile of indigenous populations during a rapid urbanization process largely influenced by governmental infrastructure interventions in Northeast Brazil.

Methods: We assessed the mortality of indigenous populations (≥ 30 y/o) from 2007 to 2011 in Northeast Brazil (Bahia and Pernambuco states). Cardiovascular mortality was considered if the cause of death was in the ICD-10 CV disease group or if registered as sudden death. The indigenous populations were then divided into two groups according to the degree of urbanization based on anthropological criteria:[9,10] Group 1 - less urbanized tribes (Funi-ô, Pankararu, Kiriri, and Pankararé); and Group 2 - more urbanized tribes (Tuxá, Truká, and Tumbalalá). Mortality rates of highly urbanized cities (Petrolina and Juazeiro) in the proximity of indigenous areas were also evaluated. The analysis explored trends in the percentage of CV mortality for each studied population. Statistical significance was established for p value < 0.05.

Results: There were 1,333 indigenous deaths in tribes of Bahia and Pernambuco (2007-2011): 281 in Group 1 (1.8% of the 2012 group population) and 73 in Group 2 (3.7% of the 2012 group population), CV mortality of 24% and 37%, respectively (p = 0.02). In 2007-2009, there were 133 deaths in Group 1 and 44 in Group 2, CV mortality of 23% and 34%, respectively. In 2009-2010, there were 148 deaths in Group 1 and 29 in Group 2, CV mortality of 25% and 41%, respectively.

Conclusions: Urbanization appears to influence increases in CV mortality of indigenous peoples living in traditional tribes. Lifestyle and environmental changes due to urbanization added to suboptimal health care may increase CV risk in this population. (Arq Bras Cardiol. 2018; 110(3):240-245)

Keywords: Indigenous Population; Cardiovascular Diseases / mortality; Urbanization / trends; Social Change.

Introduction

The urbanization process is a concern in developing countries, as it influences the prevalence of cardiovascular (CV) risk factors and coronary disease.[1] In fact, an early process of lifestyle changes appears to lead to increases in CV risk when rural migrants settle in metropolitan areas.[2] Moreover, traditional indigenous populations are recognized as in greater risk of CV complications.[3]

Diverse infectious diseases caused major health concerns when Europeans initially contacted Native American indigenous populations. Along the years, a shift in indigenous mortality rates has been shown toward chronic diseases affected by lifestyle changes, which varies highly across diverse native populations.[4-6] In recent years, isolated indigenous people in Brazil still showed low blood pressure that appears to be related to their traditional lifestyle.[7,8]

Major infrastructural projects may rapidly influence populations in the surrounding areas, often affecting indigenous communities. More recently, the Sao Francisco Valley in Northeast Brazil has been experiencing major changes in infrastructure – particularly regarding construction of large dams and canals – that appear to affect traditional indigenous lifestyle in the area.[9,10] It is unclear, however, how the urbanization process has been affecting CV mortality in native indigenous communities over the years.

The Project of Atherosclerosis Among Indigenous populations (PAI) was created to investigate the impact of urbanization on CV diseases among indigenous communities in the Sao Francisco Valley (Northeast Brazil). In this study, we

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investigate the CV mortality profile of indigenous populations during a rapid urbanization process that was largely influenced by governmental infrastructure interventions in the Sao Francisco Valley. For this purpose, we assessed longitudinal data on mortality rates of indigenous and non-indigenous populations in different degrees of urbanization.

Methods

Study population

We assessed data for indigenous mortality in the Sao Francisco Valley, Northeast Brazil (states of Bahia and Pernambuco) between 2007 and 2011, excluding deaths under the age of 30 years. We also assessed the total population in the Sao Francisco Valley according to the Brazilian Institute of Geography and Statistics.

The indigenous populations were then divided into two groups according to the degree of urbanization based on previous anthropological evaluations:[9,10] Group 1 - less urbanized tribes (Funi-ô, Pankararu, Kiriri, and Pankararé); and Group 2 - more urbanized tribes (Tuxá, Truká, and Tumbalalá).

We also assessed the mortality for the total population in two important and highly urbanized cities in the Sao Francisco Valley: Juazeiro and Petrolina. The Sao Francisco Valley University Ethics Committee approved this study.

Mortality data

The Brazilian Indigenous Healthcare Subsystem is currently the responsibility of the Special Secretariat of Indigenous Health, a section of the Ministry of Health, which, since 2007, has implemented a surveillance program regarding mortality.[11,12] Indigenous mortality was assessed from the official records of the Special Secretariat of Indigenous Health. Mortality in the largest cities of the Sao Francisco Valley used the Brazilian Health Ministry registry (DATASUS/TABNET: http://datasus.saude.gov.br/). Mortality was classified according to the ICD-10 groups. Cardiovascular mortality was considered if the cause of death was in the ICD-10 CV disease group or if registered as sudden death.

Statistical analysis

An exploratory analysis was performed to show trends of CV mortality in diverse indigenous populations over time. Trends over the years in CV mortality in adults (≥ 30 y/o) were shown as the percentage of the total deaths at the same age range for total indigenous communities in the Sao Francisco Valley and according to the urbanization group (less urbanized tribes in Group 1, more urbanized tribes in Group 2, and highly urbanized cities). Two Sample Test for Proportions assessed differences in CV mortality rates among indigenous populations. Statistical significance was established if p value < 0.05. STATA 10 was used for computing statistics.

Results

A total of 75,635 people was registered as indigenous in the Special Indigenous Health Districts of Bahia and Pernambuco. Of these, 25,560 were living in the assessed tribes of the Sao Francisco Valley, mostly in the less urbanized Group 1 tribes (Table 1).

There was a tendency for mortality at a younger age between 2010 and 2011 when compared to 2007-2009 (Figure 1).

The total of 1,333 deaths was registered for adult indigenous people in the Sao Francisco Valley, 281 deaths (1.8% of the population in 2012) in Group 1 (less urbanized) and 73 deaths (3.7% of the population in 2012) in Group 2 (more urbanized). Between 2007 and 2009, there were 133 deaths in Group 1 and 44 total deaths in Group 2. Between 2009 and 2010, there were 148 total deaths in Group 1 and 29 deaths in Group 2. Table 1 shows the absolute number of deaths in the indigenous people of the Sao Francisco Valley according to the study groups.

The proportion of CV mortality has shown consistent increases along time in the assessed populations. Conversely, CV mortality has shown consistent decreases for the largest cities in the Sao Francisco Valley (Figure 2).

When the degree of urbanization was considered for the entire period of observation, CV mortality rates were 24% and 37% in Group 1 and Group 2, respectively (p = 0.02). We also found a trend toward a steeper increase in Group 2 CV mortality along time, while Group 1 had nearly stable proportions of CV deaths (Figure 3).

Table 1 – Description of indigenous populations in the Sao Francisco River Basin, according to the study groups.

Groups	Ethnicity	Population¥	Villages	Total deaths*
Group 1	Funi-ô	4,564	7	58
	Pankararu	7,650	27	161
	Kiriri	2,185	15	36
	Pankararé	1,535	11	26
	TOTAL	15,934		281
Group 2	Tuxá	1,665	11	26
	Truká	6,741	36	39
	Tumbalalá	1,220	8	8
	TOTAL	9,626		73

*¥As registered by the Brazilian Institute of Geography and Statistics for 2012; *Deaths of indigenous people ≥ 30 years old, between 2007 and 2011.*

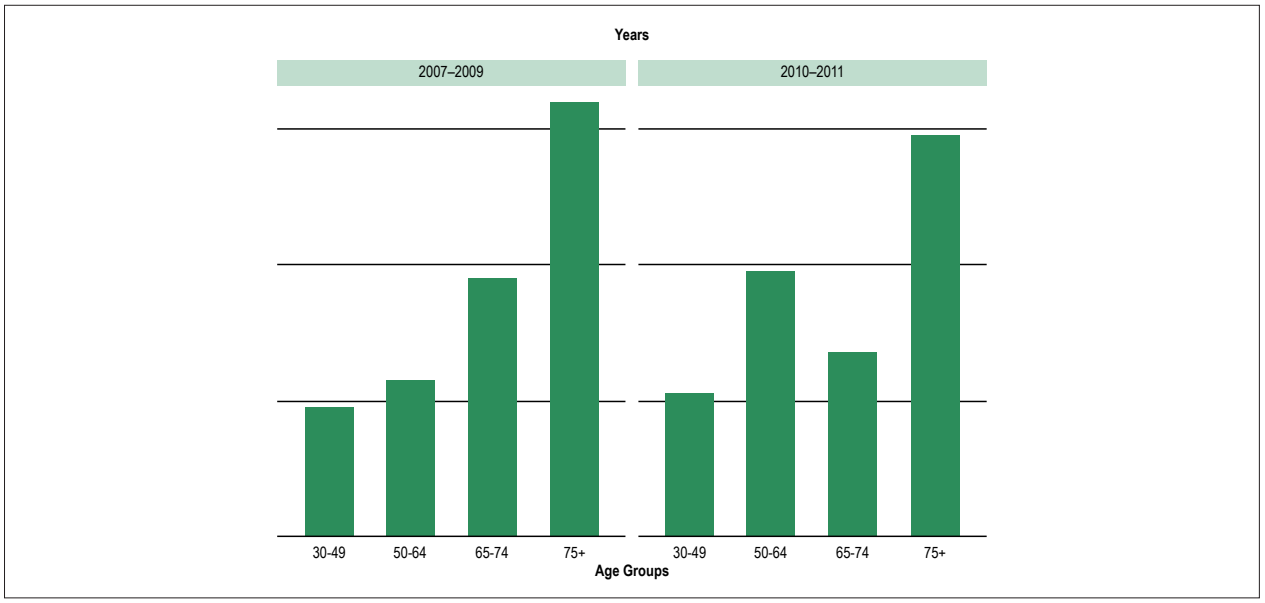

Figure 1 – *Mortality distribution for indigenous communities in the Sao Francisco Valley (Northeast Brazil) according to age groups.*

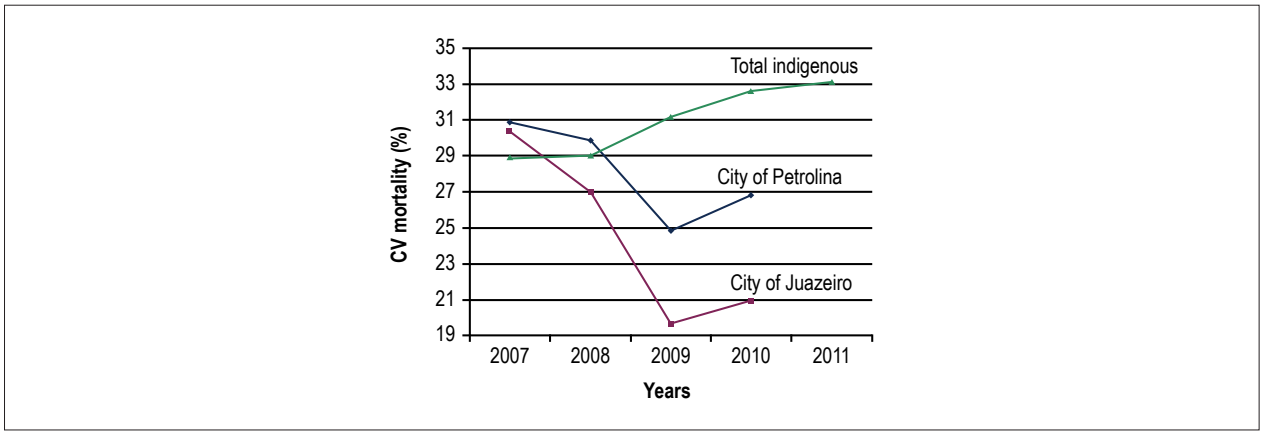

Figure 2 – *Cardiovascular mortality (≥ 30 y/o) in indigenous and urban populations in the Sao Francisco Valley (Northeast Brazil). Total indigenous refers to total deaths among indigenous populations in the Sao Francisco Valley, Northeast Brazil.*

Discussion

For the first time in the literature, we show indigenous mortality in the Sao Francisco Valley (Northeast Brazil) tending to a younger age over time, with increasing trends in the proportion of CV deaths. Increases in CV mortality rates in indigenous people living in an area of rapid infrastructural development may indicate that these populations are in harm's way due to changes related to the urbanization process. The knowledge of CV risk and mortality may aid in health policy planning for endangered traditional indigenous populations.

We assessed the available mortality rates – usually a reliable source of information – to explore the indigenous CV burden in Northeast Brazil's Sao Francisco Valley. This area has been through accelerated infrastructural development, such as construction of large canals and dams. Along recent year, hydroelectric power plants have been constructed along the Sao Francisco River, which now the highest concentration of power plants in Brazil.[9] Our findings indicate that the traditional indigenous populations affected by a rapid urbanization process are at increased risk of CV mortality.

Urbanization may be related to CV risk beyond ethnicity. In this regard, African Americans have shown higher coronary heart disease mortality rates than Whites, but apparently there are additional disparities according to the urbanization level of the population. The coronary disease-related mortality rates in large metropolitan areas showed a decline over the years in a higher magnitude compared to rural areas.[13] Similar findings have been reported in diverse countries.[14-16] There are few reports on indigenous health

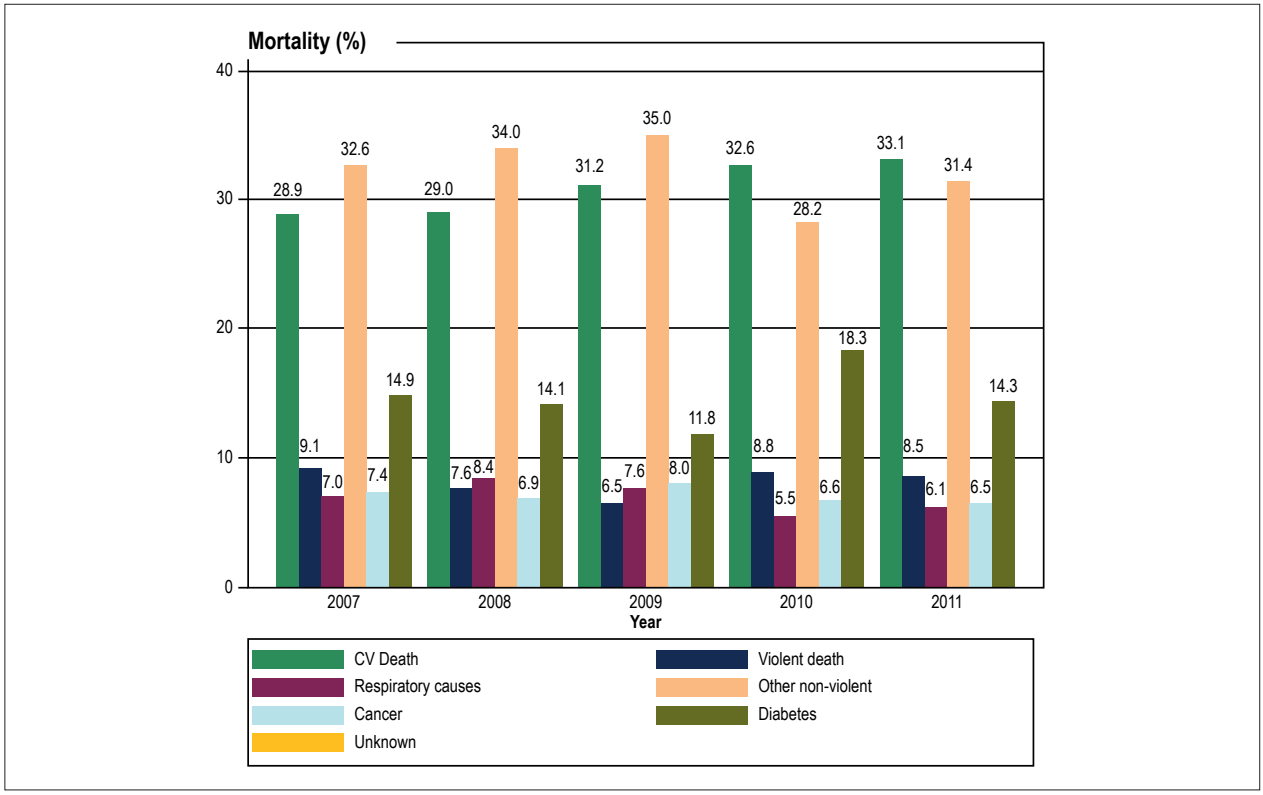

Figure 3 – *Mortality (≥ 30 y/o) in indigenous populations in the Sao Francisco Valley (Northeast Brazil), according to the degree of urbanization. Group 1 - less urbanized tribes; Group 2 - more urbanized tribes according to anthropological criteria.*

in Brazil, but surveys suggest that indigenous people have a less favorable CV risk profile than the general population.[17,18] Importantly, lifestyle differences related to CV risk are found in closely related traditional communities.[19] In fact, rapid changes in lifestyle affect indigenous populations differently from people in urban areas.[20]

Not only risk factors appear to be increasing among indigenous people; the complications related to health care quality are also alarming. In fact, there is evidence that urbanization directly affects the health care quality of a given area.[21] Additionally, socioeconomic disadvantages do not seem to completely explain the increasing CV risk trends in indigenous populations. Regions majorly populated by indigenous people show increased CV risk beyond the effects of socioeconomic disadvantage.[3,22] This may be related to difficulties for indigenous populations when interacting with other ethnicities regarding their traditional medicine.[23]

The classic expected dynamics of epidemiology for indigenous people in Brazil was based on two initial steps more closely related to infectious diseases, and a third step of epidemiologic transition and cultural losses. This third period would be characterized by an increase in chronic conditions such as CV disease and the emergence of an epidemiological profile similar to that of non-indigenous communities.[24] Our findings suggest that an epidemiological fourth step may be underway, in which the occurrence of CV diseases among indigenous people is not similar to that of the general population, but higher. These findings may be explained by rapid lifestyle and environmental modifications, added to a lower health care quality.

Our study had several limitations and should be interpreted in the context of an exploratory investigation. Furthermore, we were limited to assessing the increases in the profile of CV risk factors as we assessed secondary data for mortality. Thus, concerns regarding potential misclassification bias certainly apply. Although large infrastructural changes have historically affected indigenous lifestyles, the magnitude of the deleterious impact of urbanization on the CV risk profile of these groups is not totally clear. Increases in blood pressure, obesity, and glycemic abnormalities are examples of known CV risk factors that may lead to subclinical cardiac abnormalities over time, before a CV event is established.[25-27] Further studies in the context of the PAI project are planned to address early subclinical abnormalities in these populations.

Conclusions

In conclusion, we show increasing trends in CV mortality over time among indigenous populations in the Sao Francisco Valley (Northeast Brazil), which appear to be negatively affected by a higher degree of urbanization. Lifestyle and environmental changes due to urbanization added to suboptimal health care may be implicated in the increase in CV risk among indigenous people.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Armstrong AC, Ladeia AMT, Marques J, Armstrong DMFO, Silva AML, Morais Junior JC, Barral A, Correia LCL, Barral-Netto M, Lima JAC; Acquisition of data: Armstrong AC, Marques J, Armstrong DMFO, Silva AML, Morais Junior JC, Barral A, Correia LCL, Barral-Netto M, Lima JAC; Statistical analysis: Armstrong AC, Correia LCL, Barral-Netto M, Lima JAC; Obtaining financing: Armstrong AC, Ladeia AMT, Armstrong DMFO, Barral-Netto M, Lima JAC; Writing of the manuscript: Armstrong AC, Ladeia AMT, Marques J, Armstrong DMFO, Silva AML, Morais Junior JC.

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 UNIVASF and CONEP under the protocol number 48235615.9.0000.5196. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Cardiovascular Diseases in Indigenous Populations: An Indicator Of Inequality

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The number of articles on cardiovascular diseases in indigenous populations is not sufficient as a basis for the development of health policies. Although the most common conditions reported among indigenous people have been infectious and contagious diseases such as malaria, tuberculosis, respiratory infections, hepatitis, sexually transmitted diseases, among others, the prevalence of noncommunicable diseases (NCDs) have increased in this population as a result of urbanization process and their lifestyle. In addition, approaches of these conditions in indigenous people face logistic issues, as they require continuous medical care and development of health promotion programs in difficult areas.

The original, well-conducted study by Armstrong and colleagues contributes to fill this knowledge gap, as it highlights the impact of public investments that not only promote the development of the country, but also reveals the vulnerability and adverse effects of the changes in the lifestyle of indigenous people. Despite its methodological limitations, the study shows an association between mortality for cardiovascular diseases and rapid urbanization in this population.[1]

This phenomenon has not been described only in Brazil. A study conducted on indigenous people in the southeastern Asia described the influence of the urbanization process on epidemiological transition and increase in NCDs.[2]

Life expectancy and disease rates are variable and dependent on demographic and geographical characteristics of where people live.[3] The health system has a key role to reduce inequality; in this context, it is essential to implement intersectoral interventions at community level, particularly due to limited resources and need for effective interventions.

Community and family physician, together with other healthcare professionals, should foster indigenous traditional culture and integration of indigenous people to society as urbanization of their communities occurs. Primary health care should seek to identify and develop strategies in relation to social determinants, relevant to both communicable and NCDs.[4]

The context encountered by healthcare professionals in indigenous communities is a high prevalence of risk factors for NCDs, including overweight, smoking, alcohol consumption and unhealthy diet. This situation, which results from epidemiologic transition, is even more critical in these people, because of the occurrence of infectious diseases.

The classical study by Geoffrey Rose[5] is still current and points out the necessity to identify the cause of the causes, especially in case of a rapid urbanization without a careful planning, which leads to a worse quality of life associated with the stress of new challenges and exposure to risk factors for cardiovascular diseases.

Therefore, the present study shows the vulnerability of the indigenous people, whose health conditions require planning by health system managers. This should consider the difficulty of this population to integrate into society and have access to health services, which, in turn, should be prepared to meet their needs.

Health care services for indigenous communities should be aware of the high rates of unhealthy behavior and adverse social conditions related to an unhealthy environment – aspects that leads to inequality – as occurs in San Francisco Valley in the northeast of Brazil.

Increasing number of interventions on NCDs aimed at achieving Sustainable Development Goals have been described, and publication of their results in academic scientific literature should be highly encouraged to promote best practice.[6]

The role of journals like *Arquivos Brasileiros de Cardiologia* is to inform the frequency of cardiovascular diseases, to report etiologic, diagnostic, and prognostic approaches to these conditions, as well as the most effective interventions that should be encouraged by health managers. This is particularly relevant in the indigenous population, which is likely to experience an increase in the incidence of cardiovascular diseases as a reflection of urbanization. The actions developed by the government, especially in indigenous areas, should encompass intersectoral actions to reduce health problems and inequalities in this population.

Keywords

Cardiovascular Diseases / mortality; Indigenous Population; Urbanization / trends; Health Care (Public Health); Social Change; Risk Factors.

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Sports Practices and Cardiovascular Risk in Teenagers

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Abstract

Background: Cardiovascular diseases are the leading cause of deaths in the world, and many events could be prevented by healthy life habits.

Objectives: To compare the occurrence of cardiovascular risk factors in adolescents enrolled at public schools in the city of Rio de Janeiro, including a renowned school for sport practices.

Methods: Cross-sectional study, convenience sampling of 422 students enrolled at the Experimental Olympic Gymnasium (EOG) and at Figueiredo Pimentel School (FP). Using descriptive analyses, continuous variables were expressed as mean and standard deviation or median and interquartile ranges, and the Student's t-test or the chi-square test, respectively, was used for comparisons. The sports were classified according to the metabolic equivalent of task (MET) (below or above 5).

Results: We included 274 students enrolled at the EOG and 148 at FP. Mean age was similar between schools –12.5 ± 1.6 years at FP and 12.6 ± 0.9 at the EOG; 65.5% of the students at FP and 43.8% of the students at the EOG were female ($p < 0.01$). Significant differences in the prevalence of hypertension (20% vs. 6.3%, $p < 0.01$) and borderline cholesterol levels (27.7% vs. 17.3%, $p = 0.01$) were found between FP and EOG students, respectively.

Conclusion: High prevalence of hypertension, overweight/obesity and altered blood lipid profile was found in this group of adolescents. Regular sports training program combined with little influence of their eating habits outside school may contribute to a better metabolic profile and reduction in cardiovascular risk factors in students. Public health measures are also need. (Arq Bras Cardiol. 2018; 110(3):248-255)

Keywords: Cardiovascular Diseases / mortality; Risk Factors; Adolescent; Obesity; Hypertension; Exercise; Preventive Health Services.

Introduction

Cardiovascular diseases are the leading cause of death in the world.[1] It was estimated that 17.5 million people died for cardiovascular diseases in 2012, accounting for 31% of global deaths. More than three-fourths of these deaths were registered in low- and middle-income countries. In addition, 37% of deaths by non-communicable diseases in individuals younger than 70 years are caused by cardiovascular diseases, 3.2 million of them attributed to a sedentary lifestyle.[1] The majority of cardiovascular diseases may be prevented by strategies aimed at controlling behavioral risk factors, including smoking, unhealthy eating habits and alcohol abuse.[1]

Eating and physical exercise habits acquired during childhood and teenage years may be reflected in adulthood, since evidence indicates that atherosclerosis begins in the first years of life and slowly progresses to adulthood.[2] In an autopsy study of 100 young individuals who had died from causes unrelated to the cardiovascular system, intimal proliferations were observed in 95.3% of the coronary arterial segments in those aged between one and five years.[3] In addition, aortic atherosclerosis and lesions in the target organs may be found in hypertensive children.[4]

Studies involving children and adolescents have shown that disturbances of blood pressure and other morphological risk indicators, such as distribution of body fat, may begin during adolescence.[5] Eating habits and the routine of exercises of the adolescents, developed as they become independent, may potentiate or negatively affect their lifestyle and health in adult age.[6] It is worth pointing out that childhood is the ideal time to stimulate the practice of regular physical exercise, as this increases the likelihood that this practice will be maintained in adult life. Therefore, the adoption of measures aimed at early prevention of cardiovascular risk factors may enable the primary prevention of heart diseases.[7]

In 2012, the public school network of Rio de Janeiro started a project aimed at integrating academic and sports education – the Experimental Olympics Gymnasium (EOG) – a full-time school focused on sports. Students from the sixth to the ninth grade of elementary school practiced sports for 2 hours, 5 times a week. The exercise program was adequate to each age range group, and followed a long-term athletic development model,[8] which may contribute to the prevention of future cardiovascular diseases.

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The aim of the present study was to evaluate and compare cardiovascular risk factors between adolescent students enrolled in an EOG and students of a public school in which the sports program was not performed.

Methods

Observational, cross-sectional study conducted with students enrolled in two Rio de Janeiro City public schools. The EOG was located at the district of Santa Teresa. The students were selected for their sports potential to participate in a special training program of different sports, 10 hours weekly, and had five meals a day. The program was started one year before the study. At Fernando Pimentel (FP) School, the students participated in usual physical education activities, one hour per week, and had one meal a day at school.

Students at the sixth to ninth grade of elementary school of both schools were recruited. Students who had the informed consent form signed by their parents or guardians, and who met the criterion of a 12-hour fast before blood collection, were included in the study. The students underwent an interview, physical examination and capillary blood sampling by trained professionals. Blood pressure was measured (in mmHg) with the children comfortably seated, on the right arm, using a calibrated aneroid sphygmomanometer (Welch Allyn Tycos, modelo DS 58-MC). Waist circumference was measured using a measuring tape the midpoint between the iliac crest and the lowest rib. The Accutrend Plus System kit (Roche Diagnostics) was used for determination of glucose, total cholesterol (TC) and triglycerides (TG) levels in the samples of capillary blood. Echocardiography was performed using a Vscan portable ultrasound model 1.0 (GE Healthcare, series number (VH01688751) by a trained technician and all reports were written by a qualified physician. The test results were recorded on the data collection form immediately after the tests were performed.

Each sport was individually analyzed and classified into two categories according to their respective metabolic equivalent of task (MET) (2011 Compendium of Physical Activities) – MET < 5.0/low (table tennis, chess) and MET ≥ 5.0/high (swimming, soccer, judo, athletics, handball and volleyball).[9] Students who practiced at least one sport with MET ≥ 5.0 were included in the second group. Blood pressure (BP) measurements were categorized according to the percentile of systolic and/or diastolic blood pressure into normal (< 90th percentile), prehypertension (90th – 95th percentile) and hypertension (≥95th percentile).[10] Capillary blood glucose, and TC and TG levels were classified based on previously published guidelines.[7,11]

Statistical analysis

Statistical analysis was performed using the Stata software version 12. The Kolmogorov-Smirnov test was used to determine the distribution of continuous variables. Since all continuous variables had a normal distribution, data were expressed by descriptive analysis as mean and standard deviation (SD), and the unpaired t-test was used for comparisons. Categorical variables were expressed as proportion, and the chi-square test used for comparison. Logistic regression was used to assess the association between altered outcomes and exposure variables, with control of all possible confounding variables. Level of significance was set at $p < 0.05$.

Results

A total of 148 students enrolled at FP School and 274 enrolled at the EOG were included in the study. Students' mean age was not different between the schools – 12.5 years at FP School and 12.6 years at the EOG. At FP School and EOG, 65.5% and 43.3% of the students, respectively, were female ($p < 0.01$). Sports practiced at the EOG are described in Table 1. Only 20% of the students participated only in sports classified as MET < 5.0 (table tennis or chess). At FP School, 73.4% of the students did not practice sports regularly outside the school.

Mean weight and body mass index (BMI) were 52.3% kg and 21.2 kg/m^2 of the students of the FP School and 52.4% kg and 20.7 kg/m^2 of the students of the EOG ($p = 0.28$). Mean TC level was 164.3 mg/dL and 158.3 mg/dL at FP School and EOG, respectively, whereas median TG was 89 mg/dL in both schools (interquartile ranges, IQRs: 73-121 mg/dL at FP School and 65-114 mg/dL at the EOG). Mean BP was 110 x 66 mmHg at FP School and 101 x 65 mmHg at the EOG.

Table 2 describes metabolic characteristics of the students. Significant differences were found between the students enrolled at FP School and the EOG in the frequency of SAH (20% *vs*. 6.3%; $p < 0.01$) and borderline high-cholesterol (27.7% *vs*. 17.3%, $p = 0.01$). Students from the FP School had a 4.3 times higher chance to develop SAH (odds ratio, OR 4.4; 95% CI 2.1 – 8.6; $p < 0.01$) and a 1.7 times higher chance to have borderline high TC (OR 1.7; 95% CI 1.05 – 2.8; $p = 0.03$) than students from the EOG, when both age and sex were considered. Capillary glucose levels were at desirable levels (< 101 mg/dL) in all students from both schools, but 40% of them were overweight or obese. Besides, nearly 50% of the students had TG levels above desirable levels. No difference was found in nutritional status or altered TG between the groups (Table 2).

Considering the subgroups of EOG students divided by the sports they practiced and respective METs, no differences were found in age or sex between the subgroups. Mean weight in the low MET group was 48.5 ± 13 kg, and 53.3 ± 13.1 kg ($p = 0.02$); this difference may be ascribed to higher lean mass in the latter. No difference was found in BMI and TC, and the median TG was 89.5 mg/dL in both groups (IQRs: 65-134 mg/dL in low MET and 65-151 mg/dL in the high MET group). Borderline high TC was higher in low MET group than in high MET group (26.8% *vs*. 14.9%; $p = 0.04$) (Table 3). Considering age and sex, the low MET group had a two times higher chance to have borderline high TC (95% CI 0.98-0.41; $p = 0.056$).

Echocardiographic findings were not different between the FP School and the EOG students. Among the EOG students, hypertensive heart disease, interventricular communication and two cases of mitral valve prolapse were identified, whereas in the FP School group, two cases of interventricular communication were detected.

Table 1 – General characteristics of the students enrolled at Fernando Pimentel School (FP) and at the Experimental Olympics Gymnasium (EOG)

		FP (N = 148)		EOG (N = 274)		p value**
		Mean	SD	Mean	SD	
Age		12.5	0.9	12.6	1.6	0.591
		N	%	N	%	
Sex	Male	51		154	56.2	< 0.01
	Female	97		120	43.8	
Types of sports*	Low MET (< 5.0)					
	Table tennis	-	-	32	11.4	
	Chess	-	-	25	8.9	
	High MET (> 5.0)					
	Volleyball	-	-	44	15.7	N/A
	Soccer	-	-	41	14.6	
	Handball	-	-	39	13.9	
	Swimming	-	-	36	12.9	
	Athletics	-	-	33	11.8	
	Judo	-	-	29	10.4	
	Unknown	-	-	1	0.4	

*SD: standard deviation; MET: metabolic equivalent of task. *each activity is considered as 1 unit (260 students practiced 1 activity, 4 students practiced 2 activities, and 1 student practiced 3 activities); **chi-square test (for the categorical variable 'sex') or Student's t-test (for the continuous variable 'age'). N/A: not applicable*

Table 2 – Clinical and metabolic characteristics of the students enrolled at Fernando Pimentel School (FP) and at the Experimental Olympics Gymnasium (EOG)

		FP (N=148)		EOG (N=274)		p value*
		N	%	N	%	
Nutritional status (BMI)	Underweight	-	-	2	0.8	
	Normal weight	77	59.2	165	62.0	0.531
	Overweight	33	25.4	64	24.1	
	Obesity	20	15.4	35	13.2	0.567
	Unknown	18	12.2	8	2.9	
Blood pressure	Normal	93	71.5	235	87.0	
	Prehypertension	10	7.7	18	6.7	0.691
	Hypertension	26	20.0	17	6.3	< 0.01
	Unknown	19	12.8	4	1.5	
Capillary blood glucose	Desirable (< 101 mg/dL)	147	100	260	99.6	1.000
	Borderline (101-116 mg/dL)	-	-	1	0.4	
	Increased (≥ 117 mg/dL)	-	-	-	-	
	Unknown	1	0.7	13	4.7	
Total cholesterol	Desirable (< 170 mg/dL)	102	68.9	215	79.0	0.021
	Borderline (170-199 mg/dL)	41	27.7	47	17.3	0.012
	Increased (≥ 200 mg/dL)	5	3.4	10	3.7	0.875
	Unknown	-	-	2	0.7	
Triglycerides	Desirable (< 90 mg/dL)	76	51.4	89	50.3	0.848
	Borderline (90-129 mg/dL)	42	28.4	37	20.9	0.118
	Increased (≥ 130 mg/dL)	30	20.3	51	28.8	0.076
	Unknown	-	-	97	35.4	

*Data expressed as absolute values (percentage). BMI: body mass index; *chi-square test.*

Table 3 – Characteristics of the students enrolled at the Experimental Olympics Gymnasium (EOG) by type of sport

		Low MET (N = 56)		High MET (N = 217)		p value*
		Mean	SD	Mean	SD	
Weight (kg)/BMI		48.5	13.0	53.3	13.1	0.02
		20.0	4.8	20.9	4.4	0.20
		N	%	N	%	
Nutritional status /BMI	Underweight	-	-	2	0.9	
	Normal weight	37	68.5	127	60.2	0.44
	Overweight	9	16.7	55	26.1	0.15
	Obesity	8	14.8	27	12.8	0.72
	Unknown	2	3.6	6	2.8	
Blood pressure	Normal	48	85.7	186	87.3	0.28
	Prehypertension	6	10.7	12	5.6	0.22
	Hypertension	2	3.6	15	7.0	0.54
	Unknown	-	-	4	1.8	
Capillary blood glucose	Desirable (< 101 mg/dL)	54	98.2	205	100	0.21
	Borderline (101-116 mg/dL)	1	1.2	-	-	
	Increased (≥ 117 mg/dL)	-	-	-	-	
	Unknown	1	1.8	12	5.5	
Total cholesterol	Desirable (< 170 mg/dL)	39	69.6	175	81.4	0.11
	Borderline (170-199 mg/dL)	15	26.8	32	14.9	0.04
	Increased (≥ 200 mg/dL)	2	3.6	8	3.7	
	Unknown	-	-	2	0.9	
Triglycerides	Desirable (< 90 mg/dL)	20	50.0	68	50.0	0.98
	Borderline (90-129 mg/dL)	8	20.0	29	21.3	
	Increased (≥ 130 mg/dL)	12	30.0	39	28.7	
	Unknown	16	28.6	81	37.3	

*SD: standard deviation; MET: metabolic equivalent of task; BMI: body mass index. *chi-square test (for categorical variables) or Student's t-test (for continuous variables)*

Characteristics of parents/guardians that answered the questionnaire are described in Table 4. Mean age and sex were similar between the two schools – approximately 40 years of age and 85% women. Regular physical activity was more frequently reported by parents/guardians of the students enrolled at the EOG (48% *vs*. 16.5%; $p < 0.01$), which may have influenced the teenagers to engage in sports. With respect to comorbidities and cardiovascular risk factors, the number of individuals with SAH was 11.2% higher among parents/guardians of the students enrolled at the FP School than at the EOG (30.6% *vs*. 19.4%; $p = 0.03$).

Discussion

A high prevalence of cardiovascular risk factors was found in our study group, especially blood lipid levels, overweight / obesity and arterial hypertension. Approximately 50% and 25% of the adolescents had TG and CT concentrations, respectively, above desirable levels (borderline/high); 40% of them were overweight/obese and 17% had prehypertension/hypertension. These data corroborate the current evidence that, despite the importance of malnutrition, the rates of obesity and overweight have been significantly increasing. Previous studies have shown that approximately 23% of children aged between 6 and 12 years and 21% between 12 and 17 years are obese. This increase in obesity prevalence has been attributed to environmental and sociocultural factors.[12] In a cross-sectional study conducted at schools in Parana State, 154 students aged from 10 to 17 years were assessed for anthropometry, abdominal circumference and BP measurement. The authors reported an association between abdominal obesity and increased BP.[13]

Scherr et al.[14] reported a significant difference in TC levels between children (mean age 9 years) enrolled at public or philanthropic schools and those enrolled at private schools. In this study,[14] 23% of boys and girls from private schools and only 4% of boys and girls from public/philanthropic schools had TC levels above 190mg/dL. This may be explained by the intensity of physical exercise and nutritional surveillance in public/philanthropic schools.[14]

Table 4 – Characteristics of the parents/guardians of the students enrolled at Fernando Pimentel School (FP) and at the Experimental Olympics Gymnasium (EOG), who answered the questionnaire

		FP (N = 148)		EOG (N = 274)		p value*
		Mean	SD	Mean	SD	
Age		39,3	8,8	41,3	9,2	0,07
		N	%	N	%	
Sex	Male	13	13.1	40	15.9	0.519
	Female	86	86.9	212	84.1	
	Unknown	49	33.1	22	8.0	
Physical activity	No	71	83.5	131	52.0	< 0.01
	Yes	14	16.5	121	48.0	
	Unknown	63	42.6	22	8.0	
Smoking	No	66	77.6	208	82.9	0.26
	Yes	19	22.4	40	15.9	
	Ex-smokers	-	-	3	1.2	
	Unknown	63	42.6	23	8.4	
SAH	No	59	69.4	200	80.6	0.03
	Yes	26	30.6	48	19.4	
	Unknown	63	42.6	26	9.5	
Diabetes	No	79	92.9	240	95.6	0.39
	Yes	6	7.1	11	4.4	
	Unknown	63	42.6	23	8.4	
Previous AMI	No	83	96.5	247	98.4	0.38
	Yes	3	3.5	4	1.6	
	Unknown	62	41.9	23	8.4	
Previous stroke	No	86	100	250	99.6	1.00
	Yes	-	-	1	0.4	
	Unknown	62	41.9	23	8.4	
High cholesterol	No	71	86.6	228	91.6	0.19
	Yes	11	13.4	21	8.4	
	Unknown	66	44.6	25	9.1	

*SD: standard deviation; SAH: systemic arterial hypertension; AMI: acute myocardial infarction. *chi-square test (for categorical variables) or Student's t-test (for the continuous variable 'age')*

The control of cardiovascular risk factors in childhood and adolescence has been recommended worldwide, since several studies have strongly suggested that the presence of risk factors during childhood will affect cardiovascular health in adulthood.[15] Data of the Bogalusa Heart Study show that excessive adiposity and SAH in childhood and adolescence are associated with myocardial hypertrophy and consequently, higher cardiovascular risk.[16] In addition, during adolescence, low physical activity level may be associated with higher risk of stroke in the future, whereas participation in physical activity is associated with lower risk for cardiovascular disease, cancer and overall mortality in the future.[17,18]

These results are in agreement with those reported by Crump et al.[19] from a group of military conscripts at late adolescence, who were followed-up for 43 years. Comparison of the lowest and the highest tertile revealed that high BMI and low aerobic capacity were associated with increased risk of hypertension at adult age.[19] In the HELENA study, higher levels of cardiorespiratory fitness were associated with a higher number of ideal cardiovascular health components in both boys and girls, especially in boys. These findings in European adolescents indicate that cardiorespiratory fitness, as recommended by the American Heart Association, is positively associated with the ideal cardiovascular health index. Besides, the study identified a hypothetical cardiorespiratory fitness threshold associated with a more favorable cardiovascular health profile, which seems to be more characteristic in boys than girls. Therefore, a lifestyle change focusing on increasing physical activity and improving physical fitness may contribute to the improvement of cardiovascular health.[20]

It is worth mentioning that the association between diet, physical exercise and control of risk factors, with improvement of cardiovascular prognosis, has also been demonstrated in interventional studies. The STRIP (Special Turku Coronary Risk Factor Intervention Project) study followed approximately 530 children from 7 months of age until early adulthood. The intervention group participated in a nutritional counseling program, based on a low-cholesterol, low-saturated fat diet, whereas the control group followed a conventional diet. In the intervention group, there was a significant, favorable impact on the parameters of endothelial function and on reducing cholesterol serum levels.[21] A study on diabetic adolescents undergoing a physical exercise program showed a better glycemic control and greater reduction in serum lipid levels in those individuals with type 1 diabetes.[22] In the study by Högström et al.,[23] healthy Swedish boys at the age of 18 were followed-up for a median period of 34 years. After this time, higher incidence of myocardial infarction was observed in those adolescents with better aerobic fitness as compared with the low fifth of aerobic fitness.[23]

Interestingly, in our study, the practice of regular physical activity was more frequently reported by parents/guardians of the students enrolled at the EOG. These individuals also showed a lower rate of previously diagnosed SAH. It is possible that the attitude of these parents/guardians could have influenced the interest of the students in competitive sports, which corroborates the idea that support and encouragement of parents/guardians for their children to engage in regular physical activity is crucial. A previous study demonstrated that children's healthy behavior in terms of eating habits and physical activity is influenced by parents' behavior, as parents of athletic adolescents used to practice more exercises than those of sedentary adolescents.[24]

Study limitations

Limitations of the present study included the lack of data on nutritional aspects of these adolescents during periods outside school hours, and how long these students have been engaged in competitive sports (for at least one year). Even greater differences between the groups may have been mitigated by the limited period of competitive sports and the high percentage of missing data on TG in the EOG group. Besides, assessment of nutritional status only by BMI may not be conclusive. However, there is no current consensus on the best BMI classification system to diagnose overweight and obesity in adolescents.[25] Finally, with respect to our sample, in addition to being adherent to the program, the EOG students came from all parts of the city, and thereby composed a representative sample. On the other hand, the FP group came from a limited number of areas and was composed by convenience sampling, which may represent a limiting factor, since adherence of students who attended school in the afternoon was lower.

Conclusions

Altered blood pressure, BMI and blood lipid profile were frequent in adolescents enrolled at these public schools. Although more effective public health measures are still required, regular sports training program combined with little influence of their eating habits outside school seem to contribute to a better metabolic profile and reduction in cardiovascular risk factors in students.

Author contributions

Conception and design of the research, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Scherr C; Acquisition of data: Scherr C, Fabiano LCC, Guerra RL, Câmara ACG, Campos A; Analysis and interpretation of the data: Scherr C, Fabiano LCC, Guerra RL, Belém LHJ, Câmara ACG, Campos A.

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 Instituto Nacional de Cardiologia under the protocol number CAAE 14549513.1.0000.5272 and 248825 - 02/04/201. 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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Moderate Continuous Aerobic Exercise Training Improves Cardiomyocyte Contractility in B_1 Adrenergic Receptor Knockout Mice

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Abstract

Background: The lack of cardiac β_1-adrenergic receptors (β_1-AR) negatively affects the regulation of both cardiac inotropy and lusitropy, leading, in the long term, to heart failure (HF). Moderate-intensity aerobic exercise (MCAE) is recommended as an adjunctive therapy for patients with HF.

Objective: We tested the effects of MCAE on the contractile properties of left ventricular (LV) myocytes from β_1 adrenergic receptor knockout (β_1ARKO) mice.

Methods: Four- to five-month-old male wild type (WT) and β_1ARKO mice were divided into groups: WT control (WTc) and trained (WTt); and β_1ARKO control (β_1ARKOc) and trained (β_1ARKOt). Animals from trained groups were submitted to a MCAE regimen (60 min/day; 60% of maximal speed, 5 days/week) on a treadmill, for 8 weeks. $P \leq 0.05$ was considered significant in all comparisons.

Results: The β_1ARKO and exercised mice exhibited a higher ($p < 0.05$) running capacity than WT and sedentary ones, respectively. The β_1ARKO mice showed higher body (BW), heart (HW) and left ventricle (LVW) weights, as well as the HW/BW and LVW/BW than WT mice. However, the MCAE did not affect these parameters. Left ventricular myocytes from β_1ARKO mice showed increased ($p < 0.05$) amplitude and velocities of contraction and relaxation than those from WT. In addition, MCAE increased ($p < 0.05$) amplitude and velocities of contraction and relaxation in β_1ARKO mice.

Conclusion: MCAE improves myocyte contractility in the left ventricle of β_1ARKO mice. This is evidence to support the therapeutic value of this type of exercise training in the treatment of heart diseases involving β_1-AR desensitization or reduction. (Arq Bras Cardiol. 2018; 110(3):256-262)

Keywords: Heart Failure; Exercise; Myocardial Contraction; Myocytes, Cardiac; Adrenergic beta 1 Receptor Antagonists; Mice.

Introduction

Chronic sympathetic hyperactivity resulting from altered autonomic nervous system balance is common in many cardiovascular disease states, ending up in heart failure (HF), and is related to a higher incidence of morbidity and mortality.[1,2] Such hyperactivity is paralleled by a decrease in β-adrenergic receptors (β-AR) density and desensitization of the remaining β-AR, thus leading to a reduced cardiac contractile response to β-AR activation.[3] In this framework, β_1-AR, predominant in the heart, is selectively reduced, resulting in a modified ratio of β_1 to β_2 subtypes,[4] and β_2-AR are markedly coupled to inhibitory G protein. Consequently, inasmuch as the β_1-AR phosphorylates several Ca^{2+} regulatory proteins involved in cardiomyocyte excitation-contraction coupling,[5-7] cardiac chronotropism, inotropism and lusitropism are impaired under adrenergic stimulation.[8]

Exercise training in cardiac rehabilitation is very important in several cardiovascular diseases, including chronic HF.[9] Continuous moderate-intensity aerobic exercise (MCAE) is, at present, the best-established form of exercise for this population because of its efficacy and safety.[10] For example, aerobic exercise training recovers the resting autonomic balance in HF patients by reducing the resting sympathetic nerve activity,[11] and restoring the parasympathetic tone to the heart.[12,13] In the myocardium, aerobic exercise training increases stroke volume and, hence, cardiac output in patients[14,15] and in animal models of HF,[8] although some studies failed to confirm such benefits.[11,12] At the cellular level, studies on animal models for sympathetic hyperactivity have demonstrated aerobic exercise training improves the net balance of cardiac Ca^{2+} handling proteins either alone[8,16] or in combination with β-blockers.[17] Nevertheless, whether MCAE training affects mechanical properties of single myocytes in a heart lacking β_1-AR remains to be elucidated.

Therefore, the aim of this study was to test the effects of an MCAE program on mechanical properties of single

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left ventricular (LV) myocytes in β_1AR knockout (β_1ARKO) mice. We hypothesized that MCAE training positively affects mechanical properties of LV myocytes from β_1ARKO mice.

Methods

Experimental animals

A cohort of 4- to 5-month-old male wild type (WT) and congenic β_1ARKO mice in the C57Bl6/J genetic background were studied. Mice were maintained in cages under a 12:12-h light-dark cycle in a temperature-controlled room (22°C), with free access to water and standard rodent diet. WT and β_1ARKO mice were randomly assigned into one of the following groups by using the simple random sampling: WT control (WTc), WT trained (WTt), β_1ARKO control (β_1ARKOc) and β_1ARKO trained (β_1ARKOt). The sample size was defined by convenience. All groups initiated the experimental period with eight animals, however, during the cardiomyocyte isolation procedure, some animals/hearts were lost. Thus, the final number of animals in each group is specified in figures and table. Body weight (BW) was measured every week. The experimental protocols were approved by the Ethics Committee for Animal Use at the Viçosa Federal University (protocol #59/2012) in accordance with the Guide for the Care and Use of Laboratory Animals/2011.

Exercise training protocol and graded treadmill exercise test

MCAE was performed on a motor treadmill (Insight Equipamentos Científicos, Brazil) 5 days/week (Monday to Friday), 60 min/day, for 8 weeks. Over the first week, the duration and running speed of exercise were progressively increased from 10 minutes and 10% of the maximal speed until 60 minutes and 60% of the maximal speed, achieved during a graded treadmill exercise test. At the end of the fourth week of aerobic exercise training, graded treadmill exercise tests were repeated to readjust the running speed. This intensity was maintained during the rest of the training period. During the training period, animals from the untrained groups were handled every day and subjected to a short period of mild exercise (5 min, 0% grade, 5 m/min, 3 days/week). The exercise capacity estimated by total distance run was evaluated using a graded treadmill exercise protocol for mice (Panlab/Harvard Apparatus, Spain), as described previously.[18] Briefly, after being adapted to the treadmill for 1 week (10 min/day, 0% grade, 0.3 km/h), mice were placed in the exercise streak and allowed to acclimatize for at least 30 minutes. The graded treadmill exercise test began at 6 m/min with no grade and increased by 3 m/min every 3 minutes until fatigue, which was defined as when the test was interrupted because the animals could no longer keep pace with the treadmill speed. The graded treadmill exercise test was performed in WT and β1ARKO untrained and exercise-trained groups before and after the exercise training period.

Cardiomyocyte isolation

Forty-eight hours after the last exercise training session, mice were weighed and killed by decapitation, and their hearts were removed quickly. Left ventricular myocytes were enzymatically isolated as described previously.[19] Briefly, hearts were mounted onto a Langendorff system and perfused with calcium-free HEPES-Tyrode solution for 6 minutes with the following composition (in mM): 130 NaCl, 1.43 $MgCl_2$, 5.4 KCl, 0.4 NaH_2PO_4, 0.75 $CaCl_2$, 25 HEPES, 22 glucose, 0.01 μg/ml insulin, 0.1 EGTA, pH 7.4, at 37°C. Afterwards, the hearts were perfused for 7-10 minutes with a solution containing 1 mg/ml collagenase type II (Worthington, USA) and $CaCl_2$ (0.8 μM). The digested heart was then removed from the perfusion apparatus and the heart and left ventricle were carefully weighed. Left ventricle was cut into small pieces and placed into conical flasks with collagenase-containing solution. The cells were dispersed by agitating the flasks for periods of 3 minutes at 37°C. Single cells were separated from the non-dispersed tissue by filtration. The resulting cell suspension was centrifuged and resuspended in HEPES-Tyrode solution containing $CaCl_2$ (2.5 and 5 μM, subsequently). The isolated cells were stored in HEPES-Tyrode solution containing 10 μM $CaCl_2$ at room temperature until use. Only calcium-tolerant, quiescent, rod-shaped cardiomyocytes showing clear cross-striations were studied. The isolated cardiomyocytes were used within 2-3 hours of isolation.

Cell contractility measurement

Cell contractility was evaluated as described previously.[20] Briefly, the isolated cells were placed in a chamber with a glass coverslip base mounted onto the stage of an inverted microscope (Nikon Eclipse, TS100). The chamber was perfused with HEPES-Tyrode solution plus 10 μM $CaCl_2$ at 37°C. Steady-state 1-Hz contractions were elicited via platinum bath electrodes (Myopacer, Field Stimulator, IonOptix) with 5-ms voltage pulses and an intensity of 40 V. The cells were visualized on a personal computer monitor with a NTSC camera (MyoCam, IonOptix) in partial scanning mode. The image was used to measure cell shortening (our index of contractility) in response to electrical stimulation using a video motion edge detector (IonWizard, IonOptix). The cell image was sampled at 240 Hz. Cell shortening was calculated from the output of the edge detector using an A/D converter (IonOptix, Milton, MA). Cell shortening (expressed as percentage of resting cell length) and the velocities of shortening and relaxation were calculated.

Statistics

Data were subjected to Shapiro-Wilk or Kolmogorov-Smirnov normality tests as appropriate. Paired *t* test was used to compare initial and final BW in each group. The comparisons among groups of the values of BW, heart weight (HW), left ventricular weight (LVW) and ratios, as well as cell contraction were made using a two-way ANOVA followed by Tukey test using software SigmaPlot®, 12.5 version (Systat Software, San Jose, CA). Data are presented as means ± SD. A statistical significance level of 5% was adopted. Numbers of mice, hearts, and myocytes used are given in the relevant table and figure legends.

Results

Table 1 shows BW and LVW. The initial BW of β_1ARKO animals was higher as compared to their respective control

Table 1 – Body and left ventricular weights

	WTc (n = 7)	WTt (n = 6)	β_1ARKOc (n = 7)	β_1ARKOt (n = 6)
Initial BW, g	27.43 ± 2.46	26.50 ± 2.45	33.86 ± 2.46	32.67 ± 2.23
Final BW, g	29.86 ± 2.64*	28.67 ± 2.64*	37.14 ± 2.64*	34.33 ± 2.55*
HW, mg	231.00 ± 37.57	226.00 ± 37.48	302.00 ± 37.57	317.00 ± 37.48
LVW, mg	146.00 ± 20.82	141.00 ± 20.82	184.00 ± 20.82	194.00 ± 20.82
HW/BW, mg/g	7.73 ± 0.85	7.86 ± 0.86	8.12 ± 0.85	9.22 ± 0.86
LVW/BW, mg/g	4.89 ± 0.48	4.94 ± 0.49	4.96 ± 0.48	5.66 ± 0.49

*Values are means ± SD; WTc: wild-type control; WTt: wild-type trained; β_1ARKOc: knockout β_1-ARs control; β_1ARKOt: knockout β_1-ARs trained; BW: body weight; HW: heart weight; LVW: left ventricular weight; N: number of animals; *p < 0.05 vs. initial BW within the same group. Statistical differences were determined by paired t test.*

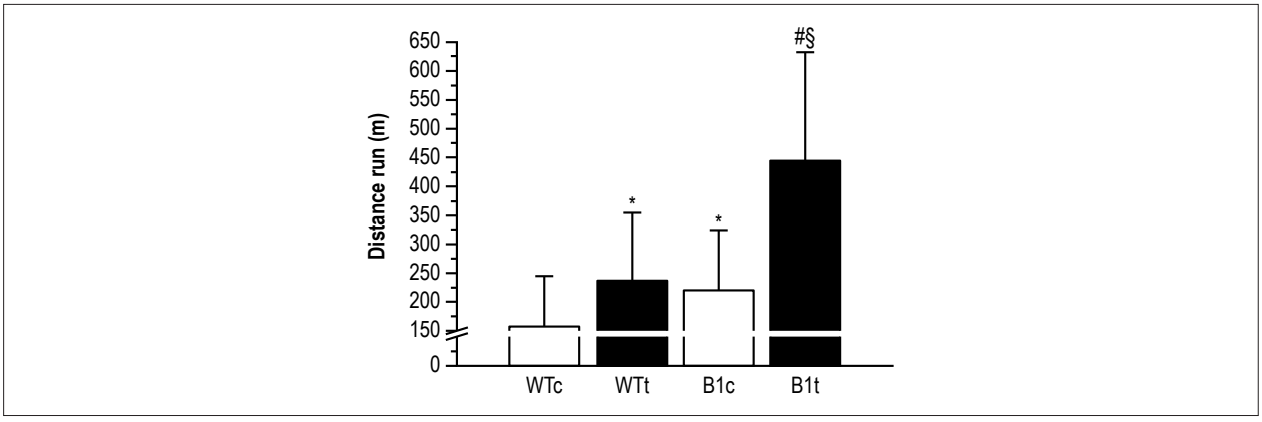

Figure 1 – *Total distance run. Values are means ± SD of 8 mice in each group. *p < 0.05 vs. WTc group; §p < 0.05 vs. WTt group; #p < 0.05 vs. β1ARKOc group.*

WT animals. As expected, the final BW of each group was higher, compared to their respective initial BW. The final BW was higher ($p < 0.05$) in β_1ARKO (β_1ARKOc + β_1ARKOt), compared to WT mice (WTc + WTt). However, the final BW was not affected ($p > 0.05$) by the MCAE. Likewise, HW was higher in β_1ARKO than in WT mice, but no effect of MCAE was observed ($p > 0.05$). Regarding LVW, β_1ARKO presented higher values than WT mice; nevertheless, no effect of MCAE was found ($p > 0.05$). As for the ratios, β_1ARKO mice presented higher HW to BW ratio than WT mice. However, it was not affected by MCAE ($p > 0.05$). The LVW to BW ratio was higher in β_1ARKO mice, compared to WT mice, but there was no effect of MCAE.

Figure 1 shows the physical capacity. β_1ARKO animals (β_1ARKOc + β_1ARKOt) exhibited a longer running distance, compared to WT animals (WTc + WTt). In addition, trained animals presented a longer running distance, compared to their respective controls.

The contractile properties of single LV myocytes are presented in Figure 2. β_1ARKO myocytes (β_1ARKOc + β_1ARKOt) had higher shortening amplitude that WT cells (WTc + WTt). The amplitude of shortening in β_1ARKOt myocytes was higher, compared to β_1ARKOc and WTt cells; and in WTc cells, compared to WTt cells (Figure 2A). Regarding the contractile time course, β_1ARKOc myocytes exhibited higher velocity of shortening than WTc cells. In addition, β_1ARKOt myocytes exhibited higher velocity of shortening than β_1ARKOc and WTt cells (Figure 2B). As for the velocity of relaxation, β_1ARKOc myocytes exhibited higher values than WTc cells. Moreover, β_1ARKOt myocytes exhibited higher velocity of relaxation than β_1ARKOc and WTt cells (Figure 2C).

Discussion

In this study, we tested the effects of MCAE on mechanical properties of LV myocytes from β_1ARKO mice. The main finding was that MCAE increased the amplitude of shortening and velocities of shortening and relaxation in β_1ARKO mice myocytes.

The initial and final BWs were higher in β_1ARKO than in WT mice. Similar results have been observed elsewhere.[21] β-AR activation in adipose tissue leads to cyclic adenosine monophosphate (cAMP) production, which activates protein kinase A (PKA) and stimulates lipolysis. Even though β_3-AR is the predominant receptor in rodent adipose tissue, mice overexpressing β_1-AR exhibit increased adipocyte lipolytic activity.[22] Therefore, β_1ARKO mice may have reduced lipolysis, which would influence the amount of body fat and, consequently, BW.[23] Nevertheless, our MCAE did not affect the final BW. Regarding HW, β_1ARKO mice exhibited heavier hearts and left ventricles than WT mice, as well as higher HW to BW and LVW to BW ratios. Our MCAE, nevertheless, did not modify these cardiac parameters. Exercise-induced cardiac hypertrophy in WT mice has been demonstrated elsewhere;[24-26] nevertheless in β_1ARKO mice, as far as we know, no data have been reported.

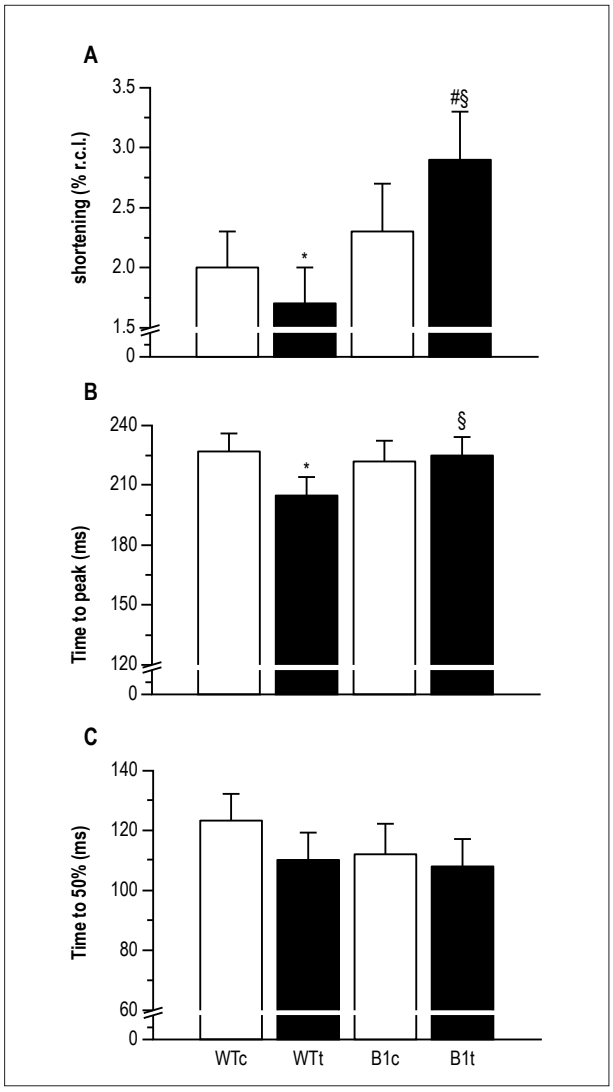

Figure 2 – *Cell contractility. A) Shortening. B) Velocity of shortening. C) Velocity of relaxation. WTc, wild-type control (n = 7; N = 14-39 cells from each mouse); WTt, wild-type trained (n = 6; N = 8-27 cells from each mouse); β1ARKOc, knockout β1-AR control (n = 7; N = 24-31 cells from each mouse); β1ARKOt, knockout β1-AR trained (n = 6; N = 17-29 cells from each mouse). Values are means ± SD.*p < 0.05 vs. WTc group; §p < 0.05 vs. WTt group; #p < 0.05 vs. β1ARKOc group.*

We observed that trained mice (WTt and β_1ARKOt) showed longer total running distance than their respective controls (WTc and β_1ARKOc). This MCAE-induced increase may be associated with cardiovascular adaptations, which are known features of aerobic exercise training.[27] Previous studies using the same aerobic exercise training protocol also observed increased exercise capacity in trained animals.[8,17] Specifically, the β_1ARKO groups showed longer total running distance than the WT groups. It is known that sympathetic activation during aerobic exercise promotes glycogenolysis by β-AR pathway.[28,29] Probably, the β_1ARKO mice have compensatory mechanisms in the skeletal muscle, such as modified β_2 and α_1 adrenergic signaling pathways, which could improve glycogenolysis, gluconeogenesis, insulin-independent glucose uptake and lipolysis in the skeletal muscles.[30] These compensatory mechanisms may have led to increased exercise performance in β_1ARKO mice. However, inasmuch as this issue is not the focus of this study, further investigations are needed to test the hypothesis that β_1ARKO mice increase exercise performance by altering β_2 and α_1 adrenergic signaling pathways.

Although myocytes from β_1ARKO mice had a higher amplitude of shortening than cells from WT mice, an independent factor effect, LV myocytes from β_1ARKOc and WTc groups had similar contractile properties. Although β_1AR is the predominant adrenergic receptor subtype expressed in the heart in terms of density and modulation of cardiac contraction,[31,32] its deletion had little impact on resting cardiac function, but had significant effects on cardiac function after β-agonist stimulation.[33] Other studies did not observe changes in cardiomyocyte contractility upon loss of β_1-AR[34] or $\beta_{1/2}$-AR under basal conditions.[35] Therefore, the similarity between β_1ARKOc and WTc groups suggests that β_1-AR has little impact on the contractile properties of cardiomyocytes under basal conditions.

More important, the MCAE program increased the amplitude of shortening of LV myocytes from β_1ARKO mice. The MCAE may have triggered two compensatory mechanisms in the heart of β_1ARKO mice. First, an increase in α_1-ARs signaling is common under situations of β_1-ARs desensitization when the reduction of β_1-adrenergic signaling is compensated by an increase in α_1-adrenergic signaling pathway, which could help preserve cardiac function.[36] Although not evaluated here, an increased inotropic responsiveness of rat cardiomyocytes via α_1-AR stimulation was found as an adaptation to aerobic exercise training.[37,38] Moreover, the potential therapeutic role of α_1-ARs to maintain normal cardiac function, especially in terms of commitment of the β_1-adrenergic signaling pathway, has been proposed in previous studies.[37-40] Second, MCAE may have reduced the responsiveness of β_2-AR in myocytes of β_1ARKO mice. When β_2-AR coupling to G_i protein is reduced, the inhibitory effect of the receptor to adenylate cyclase activation is also reduced,[5] which causes an increased cAMP production and phosphorylation of proteins involved in cardiomyocyte excitation-contraction coupling.[6]

The time courses of β_1ARKO LV myocyte contraction and relaxation were also improved by MCAE, indicating enhanced systolic and diastolic functions. The Ca^{2+} regulatory proteins modulate cardiomyocyte mechanical properties. While faster myocyte contraction is associated with increased density and or activity of L-type Ca^{2+} channels and RyR_2, quicker relaxation is dependent on the increased activity and or density of SERCA2a, PLB and NCX.[6] Although not measured in the present study, MCAE may have improved the net balance of cardiac Ca^{2+} handling proteins in β_1ARKO mice. Such adaptations have been demonstrated previously in a different model for sympathetic hyperactivity.[8,16] In addition, endurance-exercise training may have reduced the β/α-MHC ratio,[20] which would also help explain the increased velocities of LV myocyte contraction and relaxation.

In recent years, high-intensity interval training (HIIT) has emerged as the method that leads to significant benefits to cardiac function. For instance, mice submitted to HIIT

presented higher cardiomyocyte contractile function by increasing the expression and activity of calcium cycle regulatory proteins, as compared to those submitted to MCAE.[41-43] Thus, it is possible that cardiomyocytes from β_1ARKO mice might be more responsive to HIIT. However, in the present study, we chose the MCAE because the effects of such exercise protocol on the single cardiomyocyte contractility in β_1ARKO mice are not known. We believe that future studies using HIIT would provide interesting findings in this animal model.

This study has limitations. First, we used global KO mice and systemic alterations confounding the exercise effects may have occurred, thus these results have to be interpreted with caution. Second, although WTt animals had improved their exercise capacity, unexpectedly their LV myocytes presented lower cell shortening than WTc mice. This finding really intrigued us, and, unfortunately, we cannot explain it.

Conclusion

In conclusion, MCAE training improves myocyte contractility in the left ventricle of β_1ARKO mice. This finding has potential clinical implications and supports the therapeutic value of this type of exercise training in the treatment of heart diseases involving β_1-AR desensitization or reduction.

Author contributions

Conception and design of the research: Rodrigues AC, Natali AJ, Brum PC, Prímola-Gomes TN; Acquisition of data: Rodrigues AC, Cunha DNQ, Costa AJLD, Moura AG; Analysis and interpretation of the data: Rodrigues AC, Natali AJ, Carneiro-Júnior MA, Prímola-Gomes TN; Statistical analysis: Rodrigues AC, Félix LB; Writing of the manuscript: Rodrigues AC, Natali AJ, Prímola-Gomes TN; Critical revision of the manuscript for intellectual content: Natali AJ, Prímola-Gomes TN.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Universidade Federal de Viçosa under the protocol number #59/2012.

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Exercise Training Attenuates Sympathetic Activity and Improves Morphometry of Splenic Arterioles in Spontaneously Hipertensive Rats

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Abstract

Background: **Alterations in the structure of resistance vessels contribute to elevated systemic vascular resistance in hypertension and are linked to sympathetic hyperactivity and related lesions in target organs.**

Objective: **To assess the effects of exercise training on hemodynamic and autonomic parameters, as well as splenic arteriolar damages in male Wistar Kyoto (WKY) and Spontaneously Hypertensive Rats (SHR).**

Methods: **Normotensive sedentary (WKY_S) and trained (WKY_T) rats, and hypertensive sedentary (SHR_S) and trained (SHR_T) rats were included in this study. After 9 weeks of experimental protocol (swimming training or sedentary control), arterial pressure (AP) and heart rate (HR) were recorded in freely moving rats. We assessed the autonomic control of the heart by sympathetic and vagal autonomic blockade. Morphometric analyses of arterioles were performed in spleen tissues. The statistical significance level was set at $p < 0.05$.**

Results: **Resting bradycardia was observed in both trained groups (WKY_T: 328.0 ± 7.3 bpm; SHR_T: 337.0 ± 5.2 bpm) compared with their respective sedentary groups (WKY_S: 353.2 ± 8.5 bpm; SHR_S: 412.1 ± 10.4 bpm; $p < 0.001$). Exercise training attenuated mean AP only in SHR_T (125.9 ± 6.2 mmHg) vs. SHR_S (182.5 ± 4.2 mmHg, $p < 0.001$). The WKY_T showed a higher vagal effect (ΔHR: 79.0 ± 2.3 bpm) compared with WKY_S (ΔHR: 67.4 ± 1.7 bpm; $p < 0.05$). Chronic exercise decreased sympathetic effects on SHR_T (ΔHR: -62.8 ± 2.8 bpm) in comparison with SHR_S (ΔHR: -99.8 ± 9.2 bpm; $p = 0.005$). The wall thickness of splenic arterioles in SHR was reduced by training (332.1 ± 16.0 μm^2 in SHR_T vs. 502.7 ± 36.3 μm^2 in SHR_S; $p < 0.05$).**

Conclusions: **Exercise training attenuates sympathetic activity and AP in SHR, which may be contributing to the morphological improvement of the splenic arterioles. (Arq Bras Cardiol. 2018; 110(3):263-269)**

Keywords: **Exercise; Physical Exertion; Hypertension; Vascular Resistance; Arterioles; Rats.**

Introduction

Essential hypertension is inwardly connected to the blood vessels and is characterized by chronic increases in peripheral vascular resistance, mainly resulting from functional and structural alterations of the microcirculation. These lesions can be both the cause and the consequence of the elevation of arterial pressure (AP).[1] The major pathways that interact to develop morphological changes in arteriolar vessels in hypertension may compromise the splenic vessels (arteriolar hyalinosis, fibrinoid necrosis) and the interstitial space, causing fibrosis.[2-5] The arteriolar hyalinosis occurs by filtration of plasma proteins through the endothelium. It is not exclusive of any disease, being observed in arterioles of normal aging, especially in arterioles of the spleen. However, it occurs earlier and more intense in arterial hypertension.[6]

The autonomic nervous system plays a key role in the stabilization of AP control for maintaining homeostasis. In this respect, the literature data show that the sympathetic nervous system (SNS) can reciprocate incisively in the development of some forms of hypertension. Evidence of the participation of this system in the control of normal cardiovascular and metabolic functions and its role in the genesis and maintenance of several diseases is broad. The importance of understanding the workings of the SNS and systems related to it is essential not only to elucidate the path physiology of some diseases, but to understand how drugs that act on the adrenergic system interfere with the evolution of pathologies significantly altering the prognosis of patients.[7]

Experimental evidence has shown that chronic exercise produces beneficial effects on the cardiovascular system via alterations in neural control of the circulation. These effects include reductions in AP, sympathetic activity[8] and vascular resistance[9] concomitantly with attenuation in the target-organ damage.[10] If there is relation between exercise training and decrease of vascular resistance, the mechanisms by which chronic exercise training improves splenic arteriolar morphometry are

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not well established. Thus, the aim of this study was to assess the effects of exercise training on sympathetic activity and arteriolar damages in spleens of spontaneously hypertensive rats (SHR).

Methods

Animal model and exercise training protocol

Forty male SHR and Wistar Kyoto rats (WKY) aged 45-50 weeks were randomly assigned into four experimental groups of 10 rats each: SHR_T and WKY_T (that were submitted to exercise training protocol by swimming) or SHR_S and WKY_S (that were kept sedentary for a similar period of time). The sample size (n) was determined based on studies that evaluated the effects of exercise training on hypertension. These studies served as the basis for the present study that investigates the cardiovascular effects of the accumulated exercise.[11,12] All animals were kept in grouped cages (n = 3) at room temperature around 23°C, humidity of 40-70% and photoperiod of 12-hour light/dark cycle. Efforts were made to avoid any unnecessary distress to the rats, in accordance to the Brazilian Council for Animal Experimentation. All animal protocols were approved by the local Experimental Animal Use Committee (#271/2013), and were performed according to the regulations set forth by the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

The swimming exercise protocol was performed in a glass tank and ambient water temperature was kept at 30° ± 1°C. The trained animals received a 20-min adaptation period on the first day, with increases of 10 min each day until reaching 1 hour on the fifth day.[13] After this period, the rats trained 5 days/week with a gradual progression toward a 2-hour session during nine weeks. This protocol is defined as an aerobic endurance and low-intensity training, as the animals swam without additional work load, this method corresponds the intensity below the anaerobic threshold in rats.[14] Sedentary animals were placed in the swimming apparatus for 10 min twice a week to mimic the water stress associated with the experimental protocol.

Surgical procedures and hemodynamic parameters recording

Twenty-four hours after the last exercise training session, all animals were anesthetized with sodium pentobarbital (40 mg/kg ip) and cannulas of polyethylene (PE-10) were implanted into the femoral artery for cardiovascular recording and into the femoral vein for drug infusion. Then, the polyethylene catheters were exteriorized at the posterior neck region of the animal. Rats received food and water *ad libitum* and were studied 1 day after catheter placement. Prophylactic treatment with antibiotics and anti-inflammatory drugs were performed to prevent postsurgical infections and inflammation, respectively.[15] After 48 hours of recovery from the anesthesia and surgery, the arterial cannula was connected to an AP transducer and a signal amplifier (Model 8805A, Hewlett-Packard, USA) was converted by the analog-digital signal plate (sampling frequency - 1000 Hz) by a computerized system data acquisition (Aqdados, Tec Lynx. Eletron. SA, Sao Paulo, Brazil) and stored on computer. The animals were maintained in a peaceful environment for a period of 15 minutes and adaptive later pulsatile AP was continuously recorded at baseline for 30 minutes. During the experimental procedure, systolic AP (SAP), diastolic AP (DAP), mean AP (MAP) and heart rate (HR) were derived from pulsatile AP.

Cardiac autonomic tonus

To evaluate the exercise training influence on the tonic autonomic control of the heart, we also performed the sympathetic and vagal autonomic blockade after propranolol (5 mg/kg, i.v.) and atropine (4mg/kg, i.v.) injections, respectively, to calculate the sympathetic and vagal effects, as well as the intrinsic HR (iHR) and tonic sympathovagal index.[14] The autonomic blockers were administered in a random sequence with a 15-min interval between them. After double blockade, the cardiovascular recordings lasted for 15 min. Briefly, the sympathetic effect was considered as the difference between the HR after sympathetic blockade and resting HR. Vagal effect was calculated as the difference between HR after vagal blockade and resting HR. The tonic sympathovagal index was obtained as the ratio between resting HR and iHR, considering that the iHR was the HR obtained after double autonomic blockade.[16]

Analysis of splenic arteriolar morphometry

All animals were anesthetized with sodium pentobarbital and euthanatized with a lethal dose of potassium chloride. Their spleens were excised postmortem and immersed in saline (0.9%) to remove excess blood. Shortly after, the organs were placed on foil, previously treated and weighed in a semi-analytical Gehaka BG2000®. Subsequently, the material was cut and placed inside a sterilized glass with 10% formaldehyde. Thereupon, the material was dehydrated using ethanol at concentrations of 80%, 90% and 95%. Diaphanization was performed with xylol. The material was placed in containers containing liquid paraffin at 60°C. Then, the material was placed in blocks. Histological 2-μm cuts were performed using a microtome and then the material were mounted in glass slides and stained with Masson's Trichrome Blue. The area of the inner and outer layers of each arteriole was quantified by using common light microscope for capturing the images and the imageJ program to check the area of each layer. At the end of the procedures for quantification of the area of each layer, the thickness of each arteriole was obtained.

Statistical analysis

Shapiro-Wilks and Levene's tests were used to evaluate the normality and homogeneity of the sample. Results were expressed as mean ± SD (for normally distributed variables) or median with upper and lower quartiles (for non-normally distributed variables). For parametric data, we used two-way ANOVA (etiology vs. intervention), with the Tukey as a post hoc test. The nonparametric data were analyzed by the Mann-Whitney test. Pearson coefficient was used to test the correlation between sympathetic effect with area of outer wall thickness and total area thickness. Probability values of $P < 0.05$ were considered statistically significant. Analyses were performed using SigmaStat® v. 2.03 (SPSS, Chicago, IL, USA).

Results

The SHR_S showed higher resting HR in comparison to WKY_S ($p < 0.001$). As expected, both trained groups presented higher resting bradycardia compared with their respective sedentary groups ($p < 0.001$; Figure 1A).

Exercise training also was able to decrease baseline SAP ($p < 0.001$; Figure 1B), MAP ($p < 0.001$; Figure 1C) and DAP ($p < 0.001$; Figure 1D) in hypertensive animals compared with their respective sedentary group. The SHR_S presented higher pressure levels than WKY_S ($p < 0.001$) and WKY_T ($p < 0.001$) groups. After the 9-week training period, the AP was similar in WKY_T and WKY_S.

To evaluate the influence of chronic exercise on the tonic autonomic control of the heart, we performed the vagal and sympathetic autonomic blockade with atropine and propranolol injections, respectively, to calculate the vagal (Figure 2A) and sympathetic effects (Figure 2B), as well as the tonic sympathovagal index (Figure 2C) and iHR (Figure 2D). No difference on vagal effect was observed between the hypertensive groups. However, the WKY_T group evidenced a higher vagal effect than the WKY_S group ($p < 0.05$). Both hypertensive groups presented a lower vagal effect when compared with their respective normotensive groups ($p < 0.001$). In addition, no difference in the sympathetic effect was observed between the normotensive groups ($p = 0.563$). On the other hand, the SHR_T group showed a lower sympathetic effect as compared with SHR_S group ($p = 0.005$). Both normotensive groups had a lower sympathetic effect when compared with their respective hypertensive groups ($p < 0.001$). The sympathovagal index was lower in SHR_T than in SHR_S ($p < 0.05$). No difference was observed between the groups regarding iHR.

Morphometric analysis after histological processing revealed profound changes in microcirculatory profile of spleen circulation induced by training in hypertensive animals (Table 1). As expected, hypertensive splenic arterioles had a thicker wall than normotensive arterioles ($p < 0.001$). Despite this, exercise training was effective to normalize SHR arteriole wall/lumen ratio in spleen tissues analyzed when compared with that of SHR_S ($p < 0.001$). The SHR_S also presented a greater area of outer wall thickness when compared to WKY_S and WKY_T ($p < 0.001$). After exercise training protocol, the SHR_T obtained a reduction in the area of the outer wall thickness compared to SHR_S ($p < 0.001$). Similar results were observed in the total area thickness. The SHR_S had a higher total area thickness of the splenic arterioles than the normotensive groups ($p < 0.005$). In addition, the SHR_T evidenced an attenuation in total area thickness of splenic arterioles when compared with SHR_S ($p < 0.005$).

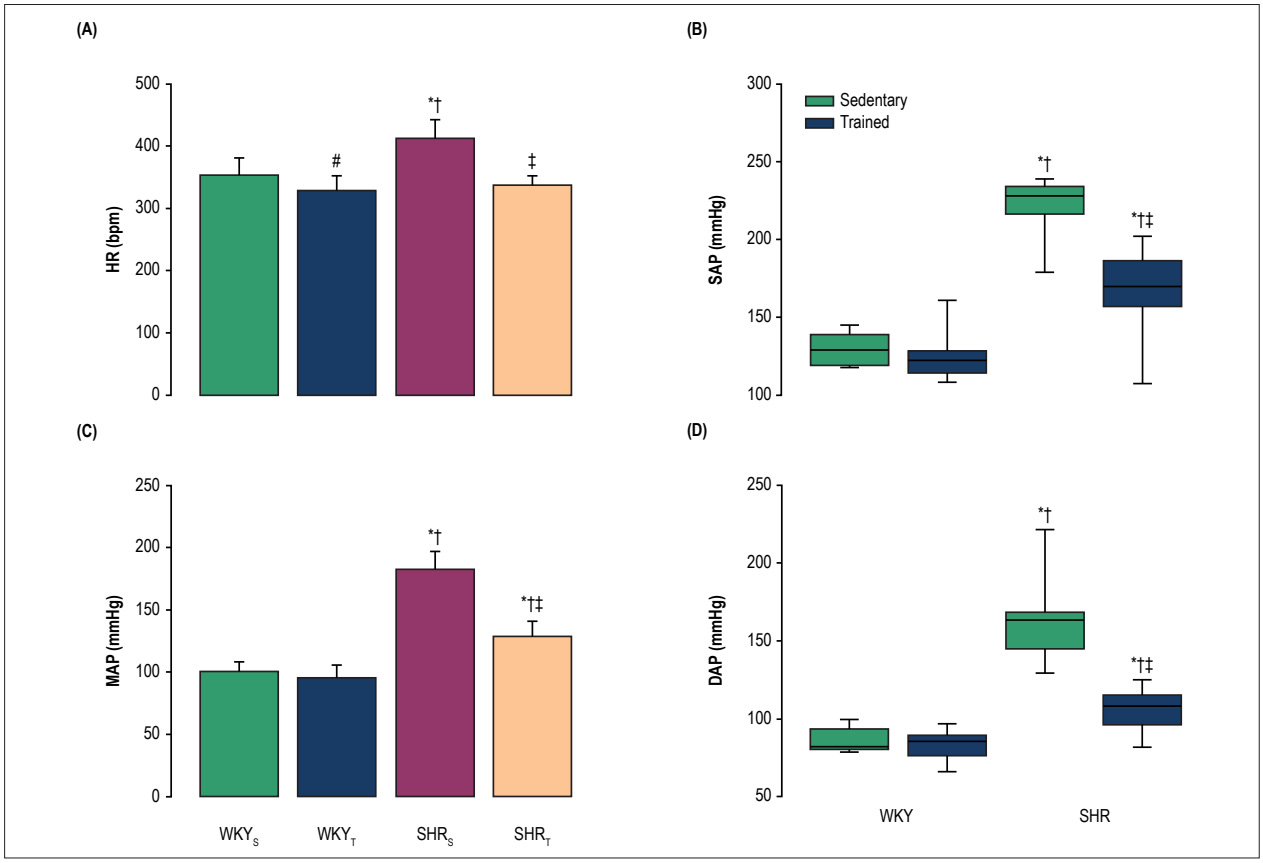

Figure 1 – *Baseline recording of heart rate (1A), systolic arterial pressure (1B), mean arterial pressure (1C) and diastolic arterial pressure (1D) in freely moving rats. WKY_S (sedentary normotensive rats); WKY_T (trained normotensive rats); SHR_S (sedentary hypertensive rats); SHR_T (trained hypertensive rats). Bars in figures 1A and 1C represent mean ± SD. Results in figures 1B and 1D are expressed as median (interquartile range). $^{\#}p < 0.05$ vs. WKY_S; $^{*}p < 0.001$ vs. WKY_S; $^{\dagger}p < 0.001$ vs. WKY_T and $^{\ddagger}p < 0.001$ vs. SHR_S.*

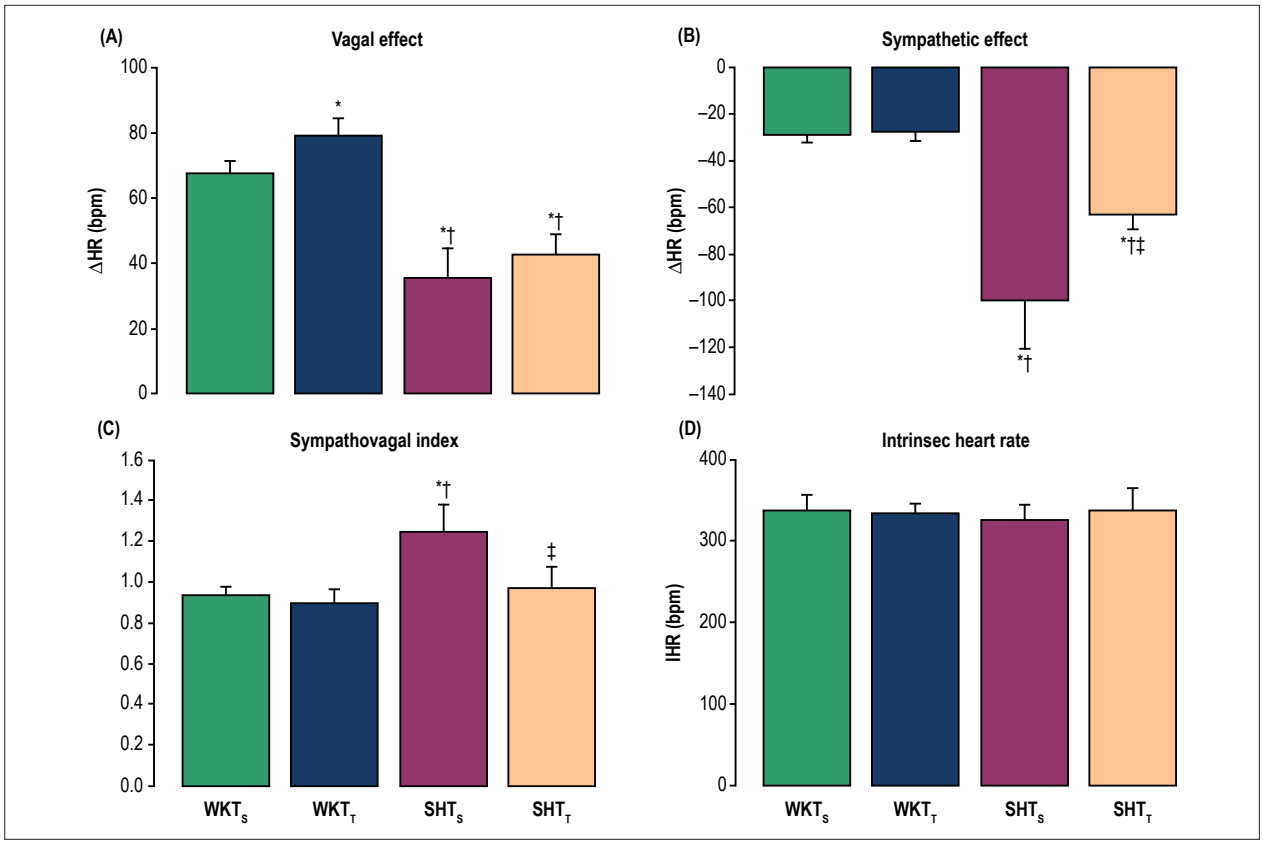

Figure 2 – *Effects of exercise training on the tonic autonomic control of the heart rate (HR) in non-anesthetized rats. (2A) vagal and (2B) sympathetic effects were obtained, respectively, by the difference between vagal blockade (by atropine) or sympathetic blockade (by propranolol) and resting HR. (2C) Sympathovagal balance was expressed by the tonic sympathovagal index, which is the ratio between resting and intrinsic HR (iHR). (2D) Intrinsic HR (bpm) obtained after autonomic double pharmacological blockade. Bars represent mean ± SD. *p < 0.05 vs. WKY_S; †p < 0.05 vs. WKY_T and ‡p < 0.05 vs. SHR_S.*

Table 1 – Values related to morphological analysis of the area of the wall thickness of splenic arterioles.

Thickness area	WKY_S (n = 10)	WKY_T (n = 10)	SHR_S (n = 10)	SHR_T (n = 10)
Inner wall (μm²)	60.5 ± 3.4	58.8 ± 2.3	87.3 ± 3.3*†	58.0 ± 2.6‡
Outer wall (μm²)	419.8 ± 29.3	405.6 ± 21.7	632.4 ± 29.1*†	418.8 ± 16.4‡
Total area (μm²)	335.6 ± 44.7	349.7 ± 35.8	502.7 ± 36.3*†	332.1 ± 16.0‡

*Data are expressed as mean ± SD. Abbreviations: WKY_S, sedentary normotensive rats; WKY_T, trained normotensive rats; SHR_S, sedentary hypertensive rats; SHR_T, trained hypertensive rats. Data expressed as mean ± SEM.*p < 0.05 vs. WKY_S; †p < 0.05 vs. WKY_T and ‡p < 0.05 vs. SHR_S.*

Further analysis showed a significant association between sympathetic effect and area of outer wall thickness ($r = 0.67$, $p < 0.005$; Figure 3A), sympathetic effect and total area thickness ($r = 0.52$, $p < 0.05$; Figure 3B), sympathovagal index and area of outer wall thickness ($r = 0.72$, $p < 0.001$; Figure 3C) and sympathovagal index and total area thickness ($r = 0.64$, $p < 0.005$; Figure 3D).

Discussion

Our main findings confirmed the efficacy of exercise training to attenuate sympathetic overactivity and to lower AP in hypertensive animals, showing, in addition, that the training-induced, sympathetic-lowering effect was associated with normalization of abnormal splenic artery diameter, decreasing the degree of vascular injury in spleen. The morphometric analysis of small vessels employed in the present study revealed that the splenic vascular adjustments are specific for the SHR_T. It is well documented that chronic physical exercise attenuates sympathetic hyperactivity[10] and arteriolar damage on hypertension.[17] To our knowledge, however, this is one of the first reports to evidence association between a reduction in splenic arteriole injury and sympathetic activity.

The cause-effect relation between hypertension and arteriolar damage (hypertrophy) is well established.[18-20] In this sense, the literature evidences that an effective

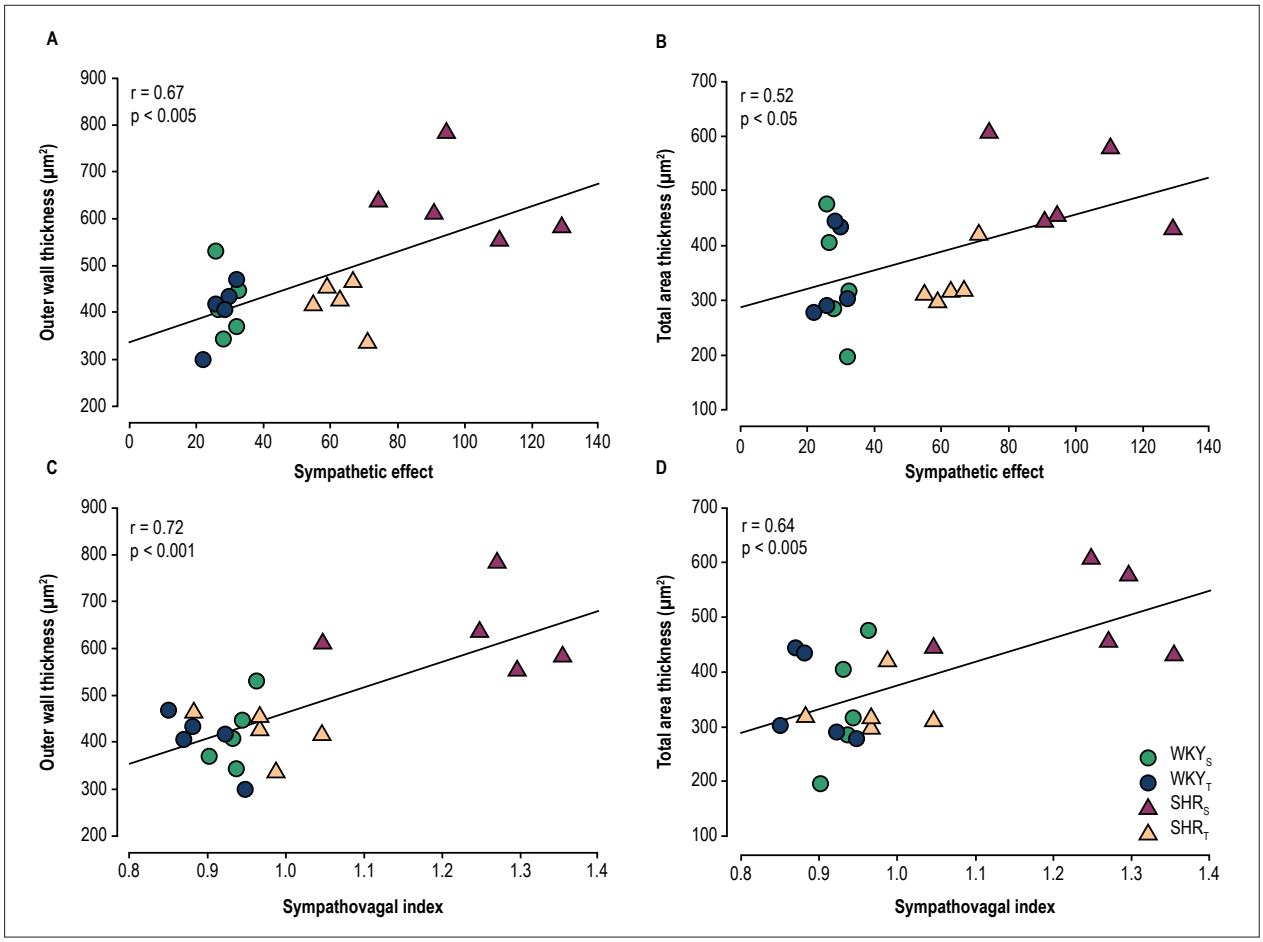

Figure 3 – *Correlation coefficient between sympathetic effect and outer wall thickness (A), sympathetic effect and total area thickness (B), sympathovagal index and outer wall thickness (C), sympathovagal index and total area thickness (D).*

antihypertensive treatment should aim not only to reduce AP but also to correct injuries associated with hypertension, such as the altered vascular structure. A previous study has shown the efficacy of training to normalize arteriole wall/lumen ratio, evidencing that arteriolar response as well as vascular resistance reduction after exercise training were significantly correlated with AP reduction.[21] Experimental study has found that arteriole wall/lumen ratios were reduced by increased internal and/or external diameter, which is a characteristic pattern for vascular remodeling.[21] Of importance is the demonstration that exercise training, by reversing lumen encroachment, normalizes enlarged wall/lumen ratio of small arterioles in hypertensive rats. These data are in accordance with the results found in our study.

Results from studies with animal models indicate that a sustained elevation of sympathetic tonus stimulates smooth muscle cell hypertrophy, suggesting that sympathetic overactivity may contribute to changes in arterial wall thickness.[22] In this way, an interesting finding in our study was a positive and significant correlation between sympathetic hyperactivity and splenic arterioles wall thickness in hypertensive rats, corroborating with results from other investigators who demonstrated that hypertension is associated with sympathetic overactivity that alters vasomotor control resulting in several abnormalities in tissue microcirculation, such as increased arteriolar wall-to-lumen ratio and decreased vessel density, which contribute to maintain an elevated total peripheral resistance.[23-28] Another important finding in our research was that exercise training was able to attenuate sympathetic activity in SHR and that this effect was associated with a reduction in splenic arteriole wall thickness. Exercise training produces beneficial effects on cardiovascular system in normal and sick people via alterations (or modifications) in the neural control of circulation.[29,30] These effects include reductions in AP, sympathetic outflow in humans,[31,32] as well as in animal models,[33,34] and vascular resistance.[35,36] In addition, there is evidence that exercise training improves the conditions of the small vessels in SHR subjected to swimming protocol.[37] Although this study did not address the mechanisms responsible for training-induced effects, one might speculate that arteriole adjustments are group-specific (hypertensive rats) and probably not dependent on paracrine, autocrine, metabolic, and/or myogenic factors, since similar alterations were observed in a previous study.[17]

It is well established that regular physical activity reduces AP in hypertensive individuals, without significant pressure changes in normotensive individuals.[38-40] In fact, several studies have suggested that exercise training intensity influences the pressure-lowering effect, with larger reductions being observed with lower exercise intensities.[40] We did not analyze the effect of training intensity, but our results clearly showed that the exercise protocol used caused an important AP decrease only in the SHR group. Pressure reduction was accompanied by both resting bradycardia and specific training-induced adjustment in splenic hypertensive arterioles. Resting bradycardia is considered to be an excellent hallmark for exercise training adaptation in humans and rats.[39-40] Thus, the bradycardia found in trained rats clearly demonstrates the effectiveness of the exercise protocol here used.

Conclusion

Considering our findings, we can conclude that exercise training was effective in reducing AP and improving splenic arteriolar morphometry in hypertensive rats. Briefly, these data strongly suggest that this improvement was associated with decreased sympathetic nerve activity. In addition, regression of hypertrophied splenic arteriole is the anatomic response to exercise training specific to the SHR group. These compensatory adjustments, by reducing local resistance and augmenting physical capacity, contribute to the training-induced, pressure-lowering effect observed in hypertensive individuals.

Author contributions

Conception and design of the research: Barbosa Neto O; Acquisition of data: Lemos MP, Sordi CC; Analysis and interpretation of the data: Lemos MP, Mota GR, Marocolo Júnior M, Sordi CC, Chriguer RS, Barbosa Neto O; Statistical analysis: Lemos MP, Barbosa Neto O; Writing of the manuscript: Lemos MP; Critical revision of the manuscript for intellectual content: Mota GR, Marocolo Júnior M, Sordi CC, Chriguer RS, Barbosa Neto O.

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 do Triângulo Mineiro under the protocol number #271/2013.

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Natriuretic Peptide and Clinical Evaluation in the Diagnosis of Heart Failure Hemodynamic Profile: Comparison with Tissue Doppler Echocardiography

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Abstract

Background: Physical examination and B-type natriuretic peptide (BNP) have been used to estimate hemodynamics and tailor therapy of acute decompensated heart failure (ADHF) patients. However, correlation between these parameters and left ventricular filling pressures is controversial.

Objective: This study was designed to evaluate the diagnostic accuracy of physical examination, chest radiography (CR) and BNP in estimating left atrial pressure (LAP) as assessed by tissue Doppler echocardiogram.

Methods: Patients admitted with ADHF were prospectively assessed. Diagnostic characteristics of physical signs of heart failure, CR and BNP in predicting elevation (> 15 mm Hg) of LAP, alone or combined, were calculated. Spearman test was used to analyze the correlation between non-normal distribution variables. The level of significance was 5%.

Results: Forty-three patients were included, with mean age of 69.9 ± 11.1years, left ventricular ejection fraction of 25 ± 8.0%, and BNP of 1057 ± 1024.21 pg/mL. Individually, all clinical, CR or BNP parameters had a poor performance in predicting LAP ≥ 15 mm Hg. A clinical score of congestion had the poorest performance [area under the receiver operating characteristic curve (AUC) 0.53], followed by clinical score + CR (AUC 0.60), clinical score + CR + BNP > 400 pg/mL (AUC 0.62), and clinical score + CR + BNP > 1000 pg/mL (AUC 0.66).

Conclusion: Physical examination, CR and BNP had a poor performance in predicting a LAP ≥ 15 mm Hg. Using these parameters alone or in combination may lead to inaccurate estimation of hemodynamics. (Arq Bras Cardiol. 2018; 110(3):270-277)

Keywords: Heart Failure; Natriuretic Peptide, Brain; Hemodynamics; Ventricular Function, Left; Echocardiography, Doppler.

Introduction

Clinical evaluation of patients with acute decompensated heart failure (ADHF) based only on physical examination has proved to be inadequate for both assessment of left ventricular (LV) function (systolic versus diastolic dysfunction)[1,2] and estimation of patient's hemodynamic status.[3] Precise determination of LV filling pressures is critical to the proper treatment of patients with ADHF, since congestion is the main determinant of symptoms, hospitalization, and prognosis.[4-7] Additional assessment using both invasive[8] and noninvasive tools may be useful, as it adds important information potentially contributing to tailored management.

Echocardiography has proven its usefulness in assessing the hemodynamic status of patients with ADHF, especially after the advent of new techniques, such as tissue Doppler imaging.[9] The so-called "hemodynamic echocardiogram" may help physicians to detect congestion.[10] Several studies have shown that echocardiographic-derived hemodynamic parameters correlate significantly with those obtained by right heart catheterization.[11]

Elevated levels of B-type natriuretic peptide (BNP) reflect increased LV filling pressures, secondary to myocyte stretch, due to volume or pressure overload.[12,13] Whether the association of BNP values adds diagnostic accuracy to the standard clinical assessment in estimating patient's hemodynamic status remains unknown. In this study we tested the hypothesis that BNP values add diagnostic accuracy to physical examination in detecting congestion in patients with ADHF, using echocardiogram-derived hemodynamic assessment as a reference method for comparison.

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Methods

Sample studied

A prospective convenience sample of patients admitted to the emergency department or coronary care unit of three hospitals (one university-affiliated and two tertiary hospitals) due to ADHF was studied. The study was conducted according to the Declaration of Helsinki standards for human research. Institutional review boards approved the research protocol, and all participants provided written informed consent before enrollment.

Inclusion criteria

Patients with ADHF due to LV systolic dysfunction, with LV ejection fraction (LVEF) <40% by Simpson's method, New York Heart Association (NYHA) functional class III or IV on admission and sinus rhythm were included within 24 hours of emergency care.

Exclusion criteria

The exclusion criteria were as follows: ADHF due to acute coronary syndrome; echocardiographic window precluding adequate analysis of hemodynamic parameters; primary valve disease; mechanical prosthetic valve; single mitral flow pattern; and presence of cardiac pacing.

Physical examination

The following physical findings were evaluated: jugular venous distension; hepatojugular reflux; hepatomegaly; ascites; lower extremity edema; third heart sound (S3); pulmonary rales; arterial blood pressure; and proportional pulse pressure. Patients were examined in a quiet emergency or critical care room. The jugular venous distension was evaluated with the patient sitting upright and the presence of a visible internal jugular vein above the clavicle was considered elevated. The hepatojugular reflux was tested in patients with no visible jugular vein, applying a firm right abdominal pressure. The liver was examined with the patient in recumbent position. Hepatomegaly was considered when the liver had more than 10cm of length, considering percussion technique initiating on the third intercostal space, along the midclavicular line. Liver palpation was the method of choice to assess the lower margin of the liver if it was palpable in the abdomen.

Patients with chest radiography showing any sign of congestion were considered to be congested. The radiological evaluation was done through the posterior-anterior and left lateral chest radiography. In cases of inability to take chest radiography in posterior-anterior and lateral positions, an anterior-posterior position with the patient sitting in bed was performed. The chest radiography was performed immediately prior to the echocardiogram.

B-type natriuretic peptide assay

Simultaneously to echocardiography, blood sample was drawn for measurement of BNP. Samples were drawn in EDTA tubes and BNP was measured in whole blood, by immunofluorescence technique, using a commercially available kit (Triage ® BNP test of Biosite Inc., San Diego, CA, USA). All measurements were performed within 30 minutes of blood sampling. Patients with levels of BNP > 400 pg/mL were considered congested,[14] and with levels of BNP < 200 pg/mL were considered "dry".[15]

Echocardiogram evaluation

All patients were submitted to a transthoracic echocardiography with tissue Doppler imaging (GE Vivid 7, Wauwatosa, WI, USA) within a maximum of 30 minutes after completion of the physical exam. In each center, only one examiner (the most experienced) performed all echocardiographic evaluations. Echocardiographic measurements were performed in a blinded manner: the examiner was unaware of the physical findings. Images were obtained from patients in the left lateral and recumbent position, and measurements followed the recommendations of the American Society of Echocardiography.[16] All Doppler profiles were recorded in an apical 4-chamber view.

The estimated left atrial pressure (LAP) was calculated as follows: calculation of the E/E' ratio by measuring the intra-myocardial flow velocity with tissue Doppler. The early diastolic mitral annular velocity (E') was obtained by tissue Doppler in the LV lateral wall and in case of technical impossibility of obtaining the velocity in this wall, as in ischemic involvement, it was measured in the interventricular septum. At least three consecutive cardiac cycles were used and an average was used as the final result. This measurement, when combined with the trans-mitral flow obtained with pulsed Doppler in early diastole (E) results in the relationship E/E'. The LAP was then estimated by the formula: LAP: 1.24 x (E/E') + 1.9. Indication of increased LV filling pressure was defined as LAP ≥ 15 mm Hg. Although patients with values below 15 mm Hg may have congestion, values ≥ 15 mm Hg have high specificity for increased LV filling pressure. Ejection fraction was evaluated through the Simpson's method.

Statistical analysis

Descriptive statistics were expressed as frequency (%) for categorical variables. For continuous variables data are presented as means ± standard deviation for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Measures of diagnostic performance (sensitivity, specificity, accuracy, positive and negative predictive values) were used to evaluate the diagnostic utility of physical exam signs of heart failure and/or BNP in predicting LAP ≥ 15 mm Hg (defined as indication of increased LV filling pressure).

The Spearman test was used to analyze the correlation between non-normal distribution variables. The level of significance was 5%.

To determine the best cut-off value for BNP to estimate elevation in LAP, a receiver operating characteristic (ROC) curve was constructed. A clinical score (CS) was built by giving 1 point to each positive sign of decompensated heart failure (elevated jugular venous distension, hepatojugular reflux, hepatomegaly, pulmonary rales or edema). Patients with

≥ 2 points were considered with a positive CS, according to analysis of ROC curve. To evaluate the capacity of physical exam and noninvasive diagnostic tests for the prediction of elevated LAP (LAP ≥ 15 mm Hg), separate models were built using combination of CS, CS + chest radiography, CS + chest radiography + BNP > 400 pg/mL, and finally CS + chest radiography + BNP > 1000 pg/mL (based on optimal cut-off point of BNP). Each of these diagnostic tests was dichotomized and compared to determine the incremental predictive value. Statistical analyses were performed using SPSS® (SPSS Inc, Chicago, IL, USA).

Results

Patients characteristics

Forty-three patients were included in the study. Patients were predominantly male (75%), elderly (69.9 ± 11.1 years) and had ADHF of ischemic etiology (65%). The mean serum creatinine was 1.3 ± 0.4 mg/dL, and the mean BNP was 1057 pg/mL ± 1024 pg/mL. Table 1 shows clinical and demographic characteristics of patients. All patients were in NYHA functional class III (10.7%) or IV (89.3%), with a mean LVEF of 25% ± 8.0%.

Nine patients had LAP < 15 mm Hg as assessed by echocardiogram. The most frequent sign of decompensation was the presence of rales (27 patients), followed by S3 (19 patients), edema, hepatomegaly and hepatojugular reflux (12 patients each). Prevalence of all clinical signs is show in Table 2.

Accuracy of clinical signs to predict increased LV filling pressures

Elevated jugular venous pressure was the most specific (88%) clinical sign to predict LAP ≥ 15 mm Hg, and rales were the least specific (33%). Accuracy of each sign to predict LAP ≥ 15 mm Hg is shown in Table 3. Combining any two signs of congestion has the best accuracy to predict elevation in LAP, according to the ROC curve.

Accuracy of chest radiography and BNP to predict increased LV filling pressures

Levels of BNP > 400 pg/mL had a suboptimal diagnostic capability to estimate congestion. Figure 1 illustrates the poor correlation between BNP and echocardiographically assessed LAP.

In fact, chest radiography showed a slightly better accuracy than BNP levels to predict congestion. Table 4 shows the performance of these variables to predict LAP ≥ 15 mm Hg. We constructed a ROC curve to estimate the best cut-off point of BNP to predict elevation of LA filling pressure. Levels of BNP > 1000 pg/mL showed a specificity of 88% and a positive predictive value of 93% to predict congestion, but this cut-off loses sensitivity (44% vs 73%) and accuracy (53% vs 67%) when compared with a value > 400 pg/mL (Table 4).

Combinations of clinical signs, chest radiography and BNP to predict increased LV filling pressures

Table 5 depicts the diagnostic characteristics of the CS alone, CS plus chest radiography and these two plus BNP > 400 pg/mL to predict LAP ≥15 mm Hg. Incremental accuracy was observed when progressively combining these parameters. The three parameters combined achieved a sensitivity of 91% and a positive predictive value of 81% to detect a LAP ≥ 15 mm Hg.

Table 1 – Clinical and demographic characteristics of the patients

Characteristics	
n	43
Age (years)	69.9 ± 11.1
Gender (male %)	76
Weight	75.3 ± 17.1
Body mass index (kg/m^2)	26.55.2
Etiology	
Ischemic	28 (65.1)
Idiopathic	7 (16.2)
Hypertensive	3 (6.9)
Valvular	4 (9.3)
Others	1 (2.3)
Left ventricular ejection fraction (%)	25.6 ± 8.0
B-type natriuretic peptide (pg/mL)	1057.39 ± 1024.21
Urea (mg/dL)	60.7 ± 23.4
Creatinine (mg/dL)	1.3 ± 0.4
Sodium (mEq/L)	135.9 ± 5.4
Potassium (mEq/L)	4.1 ± 0.5
Hemoglobin (g/dL)	11.8 ± 1.9

Table 2 – Frequency of physical signs of heart failure decompensation

Physical Sign	Frequency (n°)
S3	19
PJVD	8
HJR	12
Rales	27
Edema	12
Ascites	1
Hepatomegaly	12

S3: third heart sound; PJVD: pathologic jugular venous distension; HJR: hepatojugular reflux.

Diagnostic performances of combined clinical tools

Accuracy of CS and its combinations with chest radiography and BNP with cut-off values of 400 pg/mL or 1000 pg/mL are illustrated in Figure 2. Combinations of CS with chest radiography (AUC 0.60) and BNP > 400 pg/mL (AUC 0.62) did not improve the ability to discriminate between low or high LAP. Combination with levels of BNP > 1000 pg/mL improved only modestly (AUC 0.66).

Table 3 – Diagnostic characteristics of clinical signs to predict left atrial pressure ≥ 15 mm Hg

	Sensitivity	Specificity	PPV	NPV	Accuracy
S3	44	55	79	20	46
PJVD	20	88	87	22	34
HJR	29	77	83	22	39
Edema	29	77	83	22	39
Hepatomegaly	29	77	83	22	39
Rales	61	33	77	18	55

S3: third heart sound; PJVD: pathologic jugular venous distension; HJR: hepatojugular reflux, PPV: positive predictive value, NPV: negative predictive value.

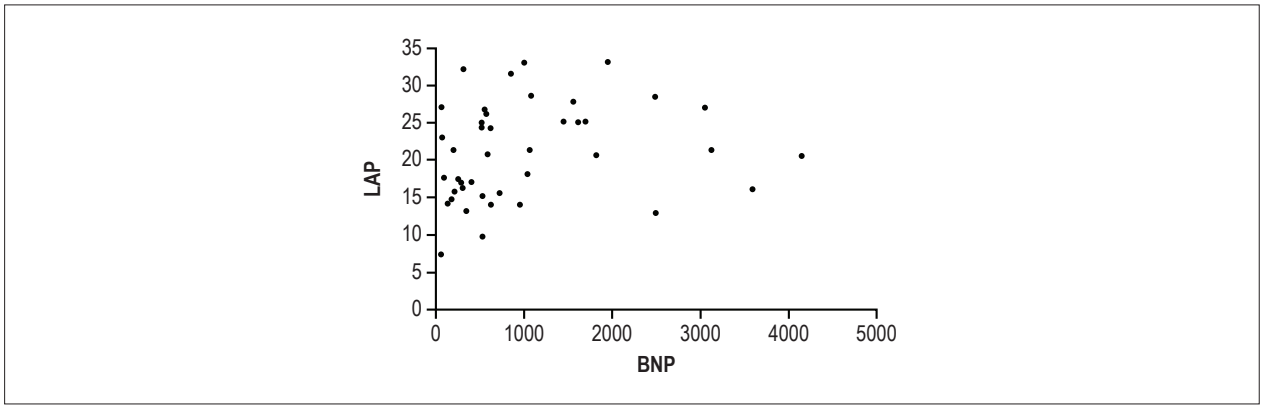

Figure 1 – *Correlation between left atrial pressure (LAP) and B-type natriuretic peptide (BNP). r = 0.3 (p = 0.046).*

Discussion

In this study, we have assessed the diagnostic accuracy of heart failure clinical signs to predict elevation of cardiac filling pressures as derived from echocardiogram-based parameters. Additionally, we have combined information from clinical signs and chest radiography regarding congestion and finally added the BNP value in order to augment the diagnostic accuracy in assessing congestion. This strategy reflects a "real world" practice to clinically evaluate the hemodynamics of ADHF patients, and we compared this clinical approach with objective measurements of hemodynamics derived from tissue Doppler echocardiogram. We have shown that a CS of congestion, chest radiography and BNP, alone or in combination do not accurately predict elevation of LAP.

Clinical findings in ADHF

Jugular venous pressure

The jugular venous pressure is the most important and probably the only physical examination sign that is relatively accurate in estimating ventricular filling pressures.[17] In a study with 35 patients in a critical care unit, the jugular venous pressure was accurate in estimating low or high filling pressures.[18] In another study, after evaluating a thousand patients referred for cardiac transplantation, the authors observed that estimated right atrial pressure below or above 10 was concordant with a pulmonary capillary wedge pressure (PCWP) below or above 22 mm Hg in 79% of patients.[19] Other studies also have shown prognostic information about elevated jugular venous pressure in patients with heart failure. Its presence was associated with adverse outcome, including progression of heart failure, even after adjustment for other prognostic factors.[20] But several factors limit its power in predicting filling pressures. There is not a universal method to estimate the jugular venous pressure. Controversy exists regarding the position (sitting upright or semirecumbent position of 30-45°), the jugular vein being used (internal x external), and the technique of measurement (vertically above clavicle, Louis angle or estimated right atrium position).[21,22] In patients with heart failure with preserved systolic function, the jugular vein pressure is far less studied.[23,24] In accordance with these observations, we have also found that elevated jugular venous pressure had the best specificity (88%) of all physical findings for elevated LAP. Additionally, in patients with no elevated jugular venous pressure, but with a positive hepatojugular reflux, we were able to identify an elevated LAP in 10 out of 12 patients. However, as expected, the absence of elevated jugular venous pressure was not able to exclude elevated LAP.

Third heart sound

Collins et al.[25] have studied patients with dyspnea in the emergency department and found that S3 did not improve diagnostic accuracy for ADHF, with a sensitivity of only 14.6%.

Table 4 – Diagnostic characteristics of the B-type natriuretic peptide (BNP) and chest radiography to predict left atrial pressure ≥ 15 mm Hg

	Sensitivity	Specificity	PPV	NPV	Accuracy
BNP > 400	73	44	83	30	67
BNP >1000	44	88	93	29	53
Chest radiography	79	44	84	36	72

PPV: positive predictive value; NPV: negative predictive value.

Table 5 – Diagnostic characteristics of clinical score, chest radiograph (CR), B-type natriuretic peptide (BNP) and all combined to predict left atrial pressure ≥ 15 mm Hg

	Sensitivity	Specificity	PPV	NPV	Accuracy
CS+	64	33	78	20	58
CS+ plus CR	82	33	82	33	72
CS+ plus CR plus BNP > 400	91	22	81	40	76

CS+: positive clinical score; PPV: positive predictive value; NPV: negative predictive value.

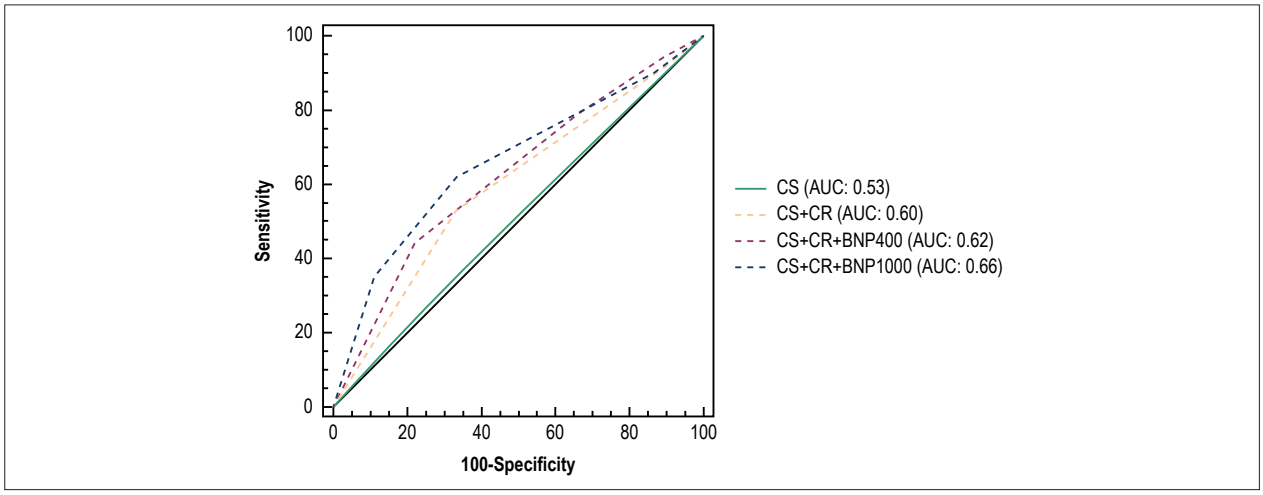

Figure 2 – *Receiver operator characteristics curves for estimating left atrial pressure ≥ 15 mm Hg. Estimates were based on dichotomized variables. CS: clinical score; CR: chest radiography; BNP: B-type natriuretic peptide.*

Moreover, in that study, a low diagnostic accuracy (58%) for the diagnosis of ADHF when utilizing all signs together was observed. In our study, S3 was present in less than half of patients and, when present, showed a positive predictive value of 79% for LAP > 15 mm Hg. When absent, an elevation of filling pressures could not be ruled out. In addition, S3 did not add any information regarding hemodynamic status. This is in accordance with other studies.[3,26] Of note, in our study, all physical examinations were done by a heart failure specialist. In the setting of a less experienced professional, the accuracy of physical exam (particularly S3) can be low, since studies suggest poor agreement between medical interns or residents and phonocardiographic findings.[27] On the other hand, reasonable agreement in S3 detection has been found among professionals of heart failure clinics.[28]

Levels of BNP

The strongest evidence for clinical use of BNP is to discriminate the cause of dyspnea in patients admitted in the emergency department[29] and to assess prognosis.[30,31] For other BNP purposes, data are less clear. In the Escape Trial,[32] the ROC curve for the performance of BNP in estimating an elevation in PCWP > 22 mm Hg showed a poor performance (AUC = 0.55). Another study with 40 critically ill patients utilizing invasive hemodynamic monitoring has shown a weak correlation between BNP and PCWP (r = 0.58).[33] Our data were consistent with these studies, showing a weak correlation between BNP and LAP (r = 0.29). BNP was also tested for guiding treatment, because, theoretically, lowering BNP is a consequence of lowering filling pressures,[34] but this strategy failed to show clinical benefit.[35] In contrast,

in the recent PROTECT trial,[36] a similar strategy of guiding treatment according to amino-terminal-Pro-BNP levels against standard of care resulted in decreased incidence of events, improvement in quality of life and in cardiac remodeling. However, that trial was conducted in an outpatient setting, involving very few heart failure patients in more advanced functional classes.

In the present study, we used a cut-off point of 400 pg/mL for BNP as a marker of congestion, since this value was employed in previous studies.[14,35] We have observed that BNP levels > 400 pg/mL had a poor prediction performance to identify elevation in LAP, similar to other physical findings or chest radiography performances when taken individually. No valuable information on filling pressures was observed when BNP levels were below 400 pg/mL. Using the AUC, we found that BNP levels of 1000 pg/mL had the best specificity to predict LAP ≥ 15 mm Hg. Therefore, we have also utilized this cut-off value in our subsequent combined analysis. Patients with moderate or severe renal impairment had higher BNP values, in our study the mean values of urea and creatinine were only slightly elevated and should not have influenced the results.

Although there is a time difference between the change in ventricular filling pressures and the corresponding change in BNP levels, this time lapse does not seem to have clinical significance. The half-life of BNP is short, about 20 minutes, and, in addition, the treatment-induced decrease in pulmonary capillary pressure leads to a rapid reduction in BNP levels (30 to 50 pg/mL/hour).

Combining tools to estimate congestion

In patients with intermediate BNP levels (100-500 pg/mL), adding the information about the presence of S3 increases the positive predictive value from 54% to 80%.[37] A recent study with 50 patients utilized a very similar strategy to our study, comparing a CS, BNP and a hand carried ultrasound in estimating elevation of ventricular filling pressures, but the gold standard in that study was right heart catheterization.[14] As in ours, that study used a cut-off value for BNP > 400 pg/mL and for PCWP ≥15 mm Hg as referencing parameters. The clinical symptom score had very little predictive utility for an elevated PCWP. Combining the information of jugular venous pressure, BNP and ultrasound, the best diagnostic characteristics for predicting elevated LV filling pressure was achieved (AUC 0.98). In our study, combining the findings of physical examination with chest radiography and BNP augmented progressively the sensitivity (64%, 82% and 91%, respectively) for detecting an elevated LAP, achieving a positive predictive value of 81%, although with a poor specificity. Still, combining these tools showed a modest power in predicting high filling pressures (AUC: 0.62). Thus, ours and the study by Goonewardena et al.[14] showed that clinical examination and BNP are not fully capable to precisely detect elevated filling pressures, and echocardiographically-derived hemodynamic assessment can reliably be incorporated into clinical practice of ADHF, avoiding the traditional invasive right heart catheterization method. The increasing utilization of hand carried ultrasound can be of great value in this area.

Study limitations

We have used the echocardiogram as the gold-standard method for defining filling pressures instead of right heart catheterization. Nonetheless, hemodynamic echocardiogram-derived parameters are well validated in the medical literature when correlated with invasive measurements.[38-40]

We primarily use the lateral annulus to measure E/e' ratio. Although the most recent recommendations suggest using the mean of the lateral and septal annulus values, this was mainly validated in normal subjects. The most recent 2016 guideline of the American Society of Echocardiography and the European Association of Cardiovascular Imaging recognizes that at times only the lateral e' or septal e' velocity is available, and it is clinically valid.

In addition, we did not follow patients during the hospitalization or in the post-discharge period to observe whether the initial hemodynamic profile was compatible with the clinical course.

Conclusions

In this study, we showed that in ADHF patients, clinical assessment alone or in conjunction with chest radiography and BNP may lead to inaccurate estimation of echocardiographically-derived hemodynamic profiling.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Almeida Junior GLG, Clausell N, Garcia MI, Esporcatte R, Rangel FOD, Rocha RM, Silva Neto LB, Silva FB, Gorgulho PCC, Xavier SS; Acquisition of data: Almeida Junior GLG, Garcia MI; Statistical analysis: Almeida Junior GLG, Clausell N, Silva FB, Xavier SS; Obtaining financing: Almeida Junior GLG; Writing of the manuscript: Almeida Junior GLG, Clausell N, Garcia MI, Xavier SS; Critical revision of the manuscript for intellectual content: Almeida Junior GLG, Clausell N, Garcia MI, Rangel FOD, Xavier SS.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Gustavo Luiz Gouvêa de Almeida Junior, from Universidade Federal do Rio Grande do Sul.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Pró-Cardíaco under the protocol number 021/10 (CAAE:0021.1.346.001-10). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Practical Implications of Myocardial Viability Studies

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Abstract

Many non-invasive methods, such as imaging tests, have been developed aiming to add a contribution to existing studies in estimating patients' prognosis after myocardial injury. This prognosis is proportional to myocardial viability, which is evaluated in coronary artery disease and left ventricular dysfunction patients only.

While myocardial viability represents the likelihood of a dysfunctional muscle (resulting from decreased oxygen supply for coronary artery obstruction), hibernation represents post-interventional functional recovery itself.

This article proposes a review of pathophysiological basis of viability, diagnostic methods, prognosis and future perspectives of myocardial viability. An electronic bibliographic search for articles was performed in PubMed, Lilacs, Cochrane and Scielo databases, according to pre-established criteria.

The studies showed the ability of many imaging techniques in detecting viable tissues in dysfunctional areas of left ventricle resulting from coronary artery injuries. These techniques can identify patients who may benefit from myocardial revascularization and indicate the most appropriate treatment.

Introduction

Assessment of myocardial viability using non-invasive imaging techniques has motivated several studies in search of the most promising and sensitive tests. These tests highlight the importance of a correct evaluation of this condition for an appropriate risk stratification and selection of patients considered eligible for myocardial revascularization. Since cardiac function is not a dichotomous variable, some of its aspects measured by imaging techniques may not be measurable by another method. Useful parameters to guide therapeutic strategies include ejection fraction, scar size, ischemia and remodeling extension, as well as duration of cardiac dysfunction.[1,2]

Using a multimodal approach of viability, a pilot study[3] showed higher values for these variables, which were analyzed in combination, providing a more reliable characterization of myocardial function. However, due to the lack of larger studies, imaging tests based on multimodal approach are not recommended yet. It is worth pointing out that even though the presence of a viable myocardium in a large heart area is important for revascularization, the decision for this procedure should be based on patient's clinical status, evidence of ischemia, coronary anatomy and left ventricular global and regional function.[4]

Determination of myocardial viability is a common and clinically relevant challenge, that may be necessary in post-infarction patients receiving thrombolytic therapy. Also, it may be helpful for surgeons and cardiologists in choosing the best therapy from interventionist strategy, angioplasty and myocardial revascularization.[5] This is particularly important in cases when myocardial revascularization is considered, due to high mortality rate and perioperative morbidity in these patients.[6]

In viability studies, while nuclear medicine techniques have high sensitivity, the techniques used to evaluate contractile reserve have higher specificity. Imaging methods, such as computed tomography (CT), positron-emission tomography (PET), myocardial scintigraphy, echocardiography with dobutamine and cardiac magnetic resonance (CMR) have been exhaustively investigated in attempt to establish the best method for myocardial study.[7]

Pathophysiology

Myocardial viability refers to myocardial cells that are alive after myocardial injury, according to cellular, metabolic and contractile functions. It describes ventricular dysfunction without tissue necrosis, which enables functional recovery after restoration of blood supply. In this context, although the definitions "stunned myocardium" and "hibernating" myocardium have distinct characteristics, the latter may represent the adaptation of repeated episodes of the former, as described by Chareonthaitawee et al.[8] (Figure 1).

"Stunned myocardium" results from a rapid, severe episode of coronary occlusion followed by recovery of coronary flow. An abrupt decrease in coronary flow causes contractile dysfunction, which persists even after its restoration. Despite minimal necrosis, ventricular dysfunction may be prolonged, from hours or even weeks. A group of researchers,[9] investigating ventricular function in patients with coronary heart disease, demonstrated that repeated episodes of ischemia may lead to cumulative stunning, which contributes to the development of chronic, post-ischemic, left ventricular dysfunction. Interestingly, similar degrees of left ventricular dysfunction in distinct patients may be associated with significant differences in the degree of myocardial viability. Besides, viability is not correlated with myocardial wall thickness, since ventricular wall thinning does not necessarily mean absence of myocardial viability.[10]

Keywords

Tissue Survival; Diagnostic Imaging; Myocardial Revascularization / surgery; Myocardium Stunning / physiopathology.

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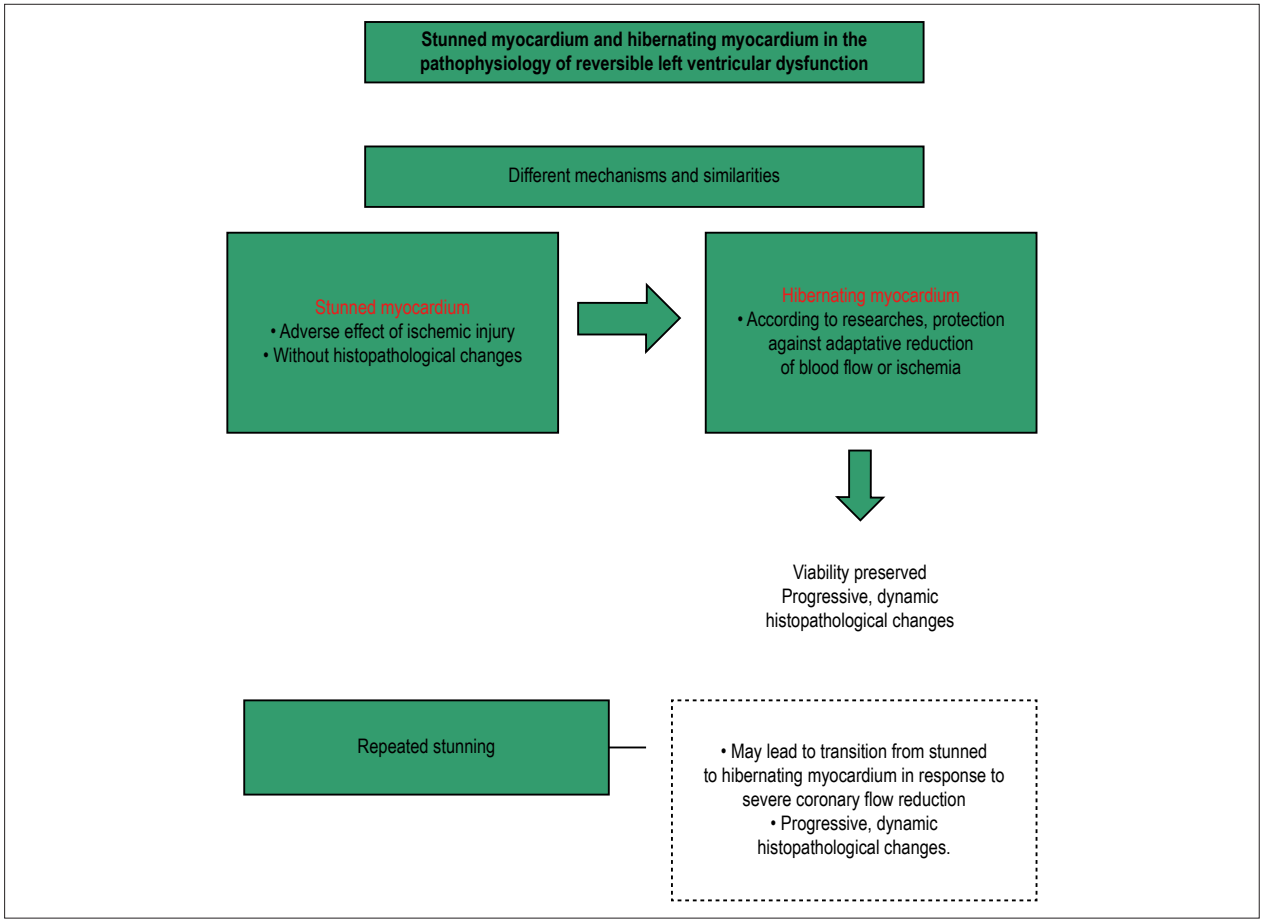

Figure 1 – *Main feature of the physiopathology of stunned myocardium and hibernating myocardium [adapted from Chareonthaitawee et al.[8]].*

"Hibernating myocardium" has been defined as the presence of severe systolic dysfunction with evidence of hypoperfusion at rest;[3] it refers to a myocardium with preserved cellularity, but reduced blood flow, leading to depressed ventricular function, even at rest.[11] The first theory of hibernating myocardium characterized it as an adaptation to chronic hypoperfusion whose intensity was not sufficiently significant to cause infarction.[12] This was supported by CMR and PET studies on dysfunctional myocardial areas with reduced blood flow.[13,14] However, pathogenesis of hibernating myocardium is still subject of studies and has not been elucidated yet,; it is believed, however, to be conditioned to a functional dysregulation related to mitochondrial impairment, in attempt to protect cardiac muscle cells from ischemia.[11,15] Hibernating is also known to have intrinsic cellular and extracellular changes, that may be associated with the time required for reversibility of the process,[12] which may vary from days to 14 months.[16,17]

Clinical implications

Assessment of viability may significantly contribute to the identification of patients who would benefit from revascularization, particularly by the improvement in ventricular function and survival. To demonstrate the clinical usefulness of viability, a meta-analysis was performed with 24 studies on different techniques on viability detection in patients with chronic coronary artery disease (CAD) and myocardial dysfunction. Annual mortality rate in the group of patients with myocardial viability and in drug treatment was 16%, in contrast with 3.2% in the group that underwent revascularization.[18,19]

In CAD patients, left ventricular dysfunction may be caused by areas of viable myocardium and fibrotic areas combined. Assessment of cardiac muscle using imaging methods enables the localization, quantification of viability in dysfunctional myocardium and possibility of anatomical revascularization, which is essential for treatment planning of these patients.[11]

This article proposes a review of pathophysiological bases of myocardial viability, diagnostic methods available, prognosis and risk for this condition. A bibliographic search was performed on the electronic databases PubMed, Lilacs, Cochrane and Scielo, based on pre-established criteria.

Methods

To achieve the objectives and results proposed, a descriptive review of scientific literature was conducted of studies on diagnostic accuracy of imaging tests used

for the measurement of myocardial viability. We included both studies showing the superiority of certain method and those comparing the efficacy of the methods from the perspective of other authors.

Inclusion criteria:

Types of study: as "review articles", we included studies aimed to demonstrate the efficacy of imaging tests in measuring myocardial viability after ischemia.

Population: heart disease patients with history of myocardial infarction.

Exclusion criteria:

Studies that did not provide a detailed description of the protocols of the diagnostic methods or of data statistical analysis, and studies that did not meet the inclusion criteria were excluded.

Search on the databases

The following databases were searched:

- PubMed/MEDLINE: North-American database, one of the largest in health, with no limits of date.

The following descriptors were used for the search on Pubmed: Myocardial viability; PET; CT; SPECT; Resonance Magnetic myocardial; Echocardiography.

- LILACS: database that integrates the BIREME system and includes several scientific journals, dissertations and books.

The following terms were used: Myocardial Viability ANS viability studies.

- COCHRANE: database focused on systemic reviews. The terms used in this database were: Myocardial viability.

Diagnostic methods

Assessment of myocardial viability by dobutamine stress echocardiography

The use of dobutamine stress echocardiography for detection of myocardial viability is an efficient and safe method in both acute and chronic phases of CAD,[20] with low incidence of significant events[21] (around 0,5%).[21,22] This method has favorable sensitivity (77-89%) and specificity (68-93%) not only in the post-infarction phase,[23,24] but also in the chronic phase (82% and 92%, respectively), as shown by Marzullo et al.[25]

Assessment of myocardial viability using baseline-nitrate ^{99m}Tc-Sestamibi scintigraphy

Myocardial perfusion scintigraphy using nitrate-augmented ^{99m}Tc-Sestamibi is a widely available method for assessment of myocardial viability. The use of nitrates enables the improvement of blood flow in narrowed and collateral vessels, responsible for irrigation of hypoperfused areas, which potentiates the ability of the method to detect viable tissues, especially when combined with ^{99m}Tc-Sestamibi.[11] This is assured by the fact that both absorption and retention of sestamibi depend on perfusion, cell membrane integrity and membrane potential (mitochondrial function), which hence constitute the markers of viable tissue.[25-27] Schinkel AF et al.[28] reported a 81% sensitivity and 69% specificity of nitrate-enhanced ^{99m}Tc-Sestamibi scintigraphy to detect viability, which is lower than those reported with the use of PET-^{18}F-FDG.[28] In Figure 1, we illustrate a case where rest perfusion defect, initially attributed to the infarction area, normalized after treatment of the coronary obstruction in the anterior descending artery, demonstrating a viable myocardium. These findings illustrate a practical limitation of imaging techniques using ^{99m}Tc-Sestamibi in the detection of myocardial fibrosis and viability.

In most studies on baseline-nitrate ^{99m}Tc-Sestamibi scintigraphy, two patterns of images are commonly obtained: rest images and nitrate-enhanced images. Reversibility of the lesion (by filling) is indicative of viability. Sciagra et al.[29] studied 105 patients with chronic CAD and left ventricular dysfunction who underwent baseline-nitrate sestamibi perfusion imaging and showed that the most powerful prognostic predictors of events were the number of nonrevascularized dysfunctional areas with viability in sestamibi imaging[28,29] (Figure 2).

Assessment of myocardial viability with ^{201}Tálio

^{201}Tálio has some limitations for routine use, due to its longer physical half-life, and relatively low photon energy and flow. This may yield images with low count-rates and possible attenuation artifacts and, consequently, suboptimal images.[4]

However, ^{201}Tálio has the advantage of entering myocardial cells by active transportation, which increases its accuracy for detecting viable myocardium. For this purpose, two protocols are usually used – stress-redistribution-reinjection and rest-redistribution imaging. While the first is focused on data about stress-induced ischemia and viability, the second focuses only on viability[26] (Figure 3).

^{201}Tálio perfusion scintigraphy may show different perfusion defects that vary within a range from totally reversible to irreversible, according to the degree of improvement in the activity of late images.[7]

In a meta-analysis, Schinkel et al. reported an 87% sensitivity and 54% specificity in predicting post-revascularization recovery.[28] Some studies have suggested that improvement in systolic function is not a *sine qua non* for clinical benefits, with a better prognosis but no improvement in the ejection fraction of some patients.[4,11,26,28]

Assessment of myocardial viability using positron emission tomography with fluorine-18-deoxyglucose (^{18}F-FDG PET)

Among the methods available for assessment of myocardial viability, ^{18}F-FDG PET is considered the gold standard method.[30,31] Because ^{18}F-FDG is a glucose analog, it is used to evaluate the metabolism of cardiac glucose, and thereby the uptake of this marker is similar to glucose utilization by myocytes.[4]

In fasting conditions, myocardium uses preferentially free fatty acids as energy source, whereas in post-prandial phase, its metabolism is shifted to glucose (with increased levels of circulating insulin).[5] As the metabolism of free fatty acids depends on oxygen, during myocardial ischemia, glucose is the preferred substrate (glycolytic pathway), which is the hallmark of myocardial viability.[35,32-35]

PET with ^{18}F-FDG has mean sensitivity of 92% and specificity of 63% in assessing the likelihood of functional improvement of the muscle in the after revascularization. Many studies have used comparative data of perfusion and ^{18}F-FDG uptake, defining myocardial viability as hypoperfused areas with preserved glucose metabolism.[26,28,32-34] (Figure 4).

Overall improvement of left ventricle may also be evaluated by ^{18}F-FDG. Left ventricular ejection fraction (LVEF) improves from 37% to 47% (mean values) in patients with myocardial viability detected by ^{18}F-FDG PET after revascularization. In patients without viable myocardium, LVEF remained almost unchanged (39% x 40%).[31,34-39]

Assessment of myocardial viability with computed tomography (CT)

CT is the most recent and widely used method for coronary angiography. Three techniques are currently used for cardiac CT – coronary angiography, CT with iodinated and non-contrast CT – and all of them can provide information on myocardial viability.[40-42]

CT coronary angiography has high negative predictive value (> 95%) in excluding epicardial CAD, with increasing role in the assessment of chest pain. It may also provide valuable information in the evaluation of patients with left ventricular systolic dysfunction, with suspected congenital heart disease or coronary anomaly.[42]

Delayed enhancement CT uses a similar principle to gadolinium-based magnetic resonance (MR) imaging for imaging studies of myocardial scarring. In CT, the use of iodinated contrast causes an increase in Hounsfield units in contrasted tissues, due to attenuation of X-rays, allowing the visualization of cardiac muscle in the early arterial phase, and discrimination of macro and microvascular obstruction. When evaluated 5-10 minutes after injection of iodinated contrast and increased enhancement, the obstruction is suggestive of infarction, due to extracellular contrast accumulation.[41,42]

Finally, non-contrast CT can reveal calcified aneurysms in the left ventricle, for showing similar images to those obtained during attenuation correction scans or calcium scoring.[41,42]

Some advantages of cardiac CT include the possibility of being performed in combination with coronary CT, requiring

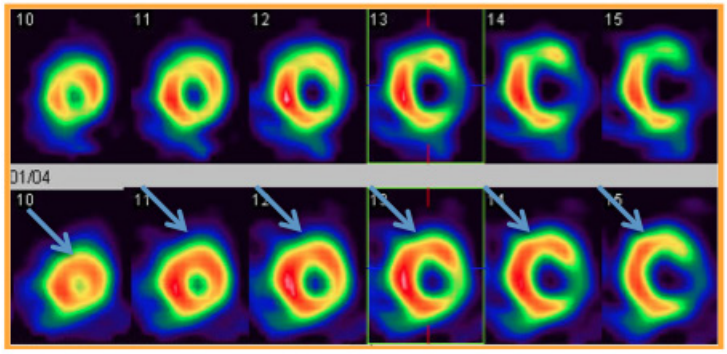

Figure 2 – *Images of rest (upper line) and nitrate-enhanced rest (lower line) myocardial perfusion scintigraphy, showing improvement of perfusion in anterior (apical, medial and basal) and anterolateral (medial and basal) segments.*

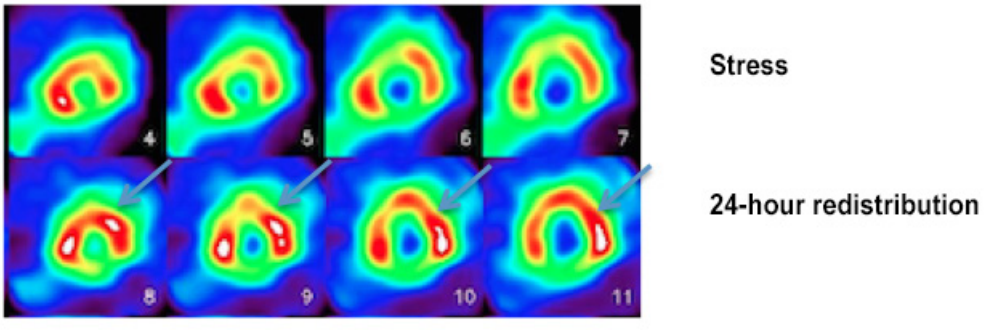

Figure 3 – *Myocardial perfusion scintigraphy with ^{201}Tálio for assessment of myocardial viability; stress imaging (upper line) and 24-hour redistribution imaging after injection of the radiotracer ^{201}Tálio (lower line), showing improvement of perfusion in anterior (apical, medial and basal) and anterolateral (medial and basal) segments.*

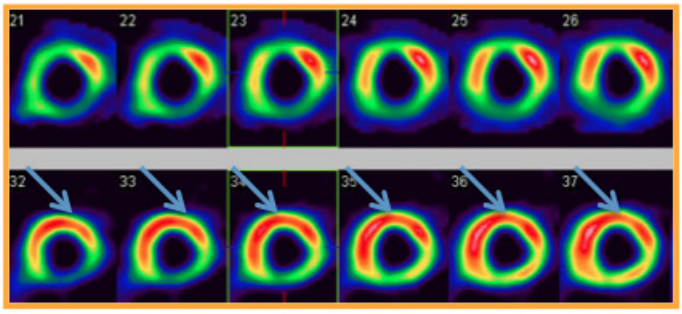

Figure 4 – *Myocardial perfusion scintigraphy with ^{99m}Tc-Sestamibi (upper line) and ^{18}F-FDG PET (lower line) for assessment of myocardial viability, showing improvement in perfusion/metabolism in anterior (apical, medial and basal), apical septal, anteroseptal (medial and basal) and inferoseptal (medial and basal) segments; "mismatch" pattern.*

only the addition of some minutes to the angiography protocol; its high spatial resolution, being of great importance in evaluation of small infarctions; near-isotropic resolution and reliable 3D data reconstruction for the small slide thickness; possibility of inclusion of patients with pacemakers and other metallic devices. As disadvantages, we can mention the necessity of higher radioactive emission for acquisition of additional images following coronary images, and poorer localization ability and transmurality as compared with CMR.[43]

Assessment of myocardial viability with MR imaging

MR is a highly efficient method for myocardial viability study[26] and has played an important role in the clinical practice. It has also been considered a gold standard method in the assessment of left ventricular function. MR allows assessment of left ventricular dysfunction associated with chronic ischemic disease by evaluation of contractile reserve using dobutamine at low dose and, most importantly, evaluation of fibrosis by late gadolinium enhancement. In a metanalysis, Romero et al.[44] concluded that MR with low-dose dobutamine has high sensitivity and specificity (81% and 91%, respectively), whereas late gadolinium enhancement MR has 95% sensitivity and 51% specificity, and high accuracy in determining some parameters, including ejection fraction, left ventricular volume, regional wall motion, and myocardial thickness.[45,46] Left ventricular wall thickness at end diastole is important to exclude viability.

The most notable characteristic of MR is its high spatial resolution, and, for this reason, the method stands out for its high imaging quality and capacity to diagnose ischemic areas that would not be detectable by other methods. MR may also be particularly useful in the assessment of myocardial blood flow at rest in hibernating areas of narrowed coronary artery and improvement of local myocardial contractility after coronary revascularization.[13,47]

The use of gadolinium as a contrast medium in MR allows the detection of the effects of perfusion, microvascular obstruction and differentiation between transmural and subendocardial necrosis.[48] Gadolinium has a low risk of nephrotoxicity, except for patients with end-stage renal disease, in which the risk of systemic toxicity is real. Although chelated-gadolinium compounds are distributed in the extracellular space, and do not penetrate in intact cells, they may accumulate in myocytes with ruptured cell membrane (e.g. acute myocardial infarction) and fibrotic areas[10] (Figure 5).

The likelihood of functional recovery after revascularization is proportional to the transmurality of acute myocardial infarction. A very important marker of improvement of myocardial function is the amount of delayed enhancement by MR imaging since there is a progressive improvement in myocardial function with the increase of transmurality of scar tissue. Kim et al.[46] evaluated the ability of contrast-enhanced MR imaging to predict functional recovery after revascularization. Approximately 80% of segments with less than 25% of transmural fibrosis had functional recovery after revascularization, whereas only 10% of the segments with transmurality higher than 50% recovered after revascularization. Selvanayagam et al.[47] showed that delayed-enhancement cardiovascular MR imaging is a strong predictor of myocardial viability after surgical revascularization.

Left ventricular wall thickness may reveal valuable information about viability. Schinkel et al.[26] showed that segments with an end-diastolic wall thickness of less than 5 mm was associated with higher likelihood of recovery after revascularization.

Taken together, these findings suggest that segments with an end-diastolic wall thickness of less than 5.5 mm never show recovery of function after revascularization, which may be related to the presence of nontransmural infarction. These segments contain subendocardial scar tissue, with residual viability in the epicardium. Therefore, significant wall thinning indicates scar tissue, with low likelihood of recovery after revascularization; nevertheless, evidence suggests that recovery of function may occur, but only when contrast-enhanced MR excludes scar tissue.[10]

Geber et al.[49] demonstrated that cardiac MR was important in identifying patients with ischemic cardiomyopathy and severe left ventricular dysfunction who would benefit from myocardial revascularization. CMR can be performed in ischemic cardiomyopathy with left ventricular dysfunction to characterize myocardial viability.[50] Limitations of this technique, however, include its high cost, difficulty of performing scans in patients with implanted devices, and limited availability.[10]

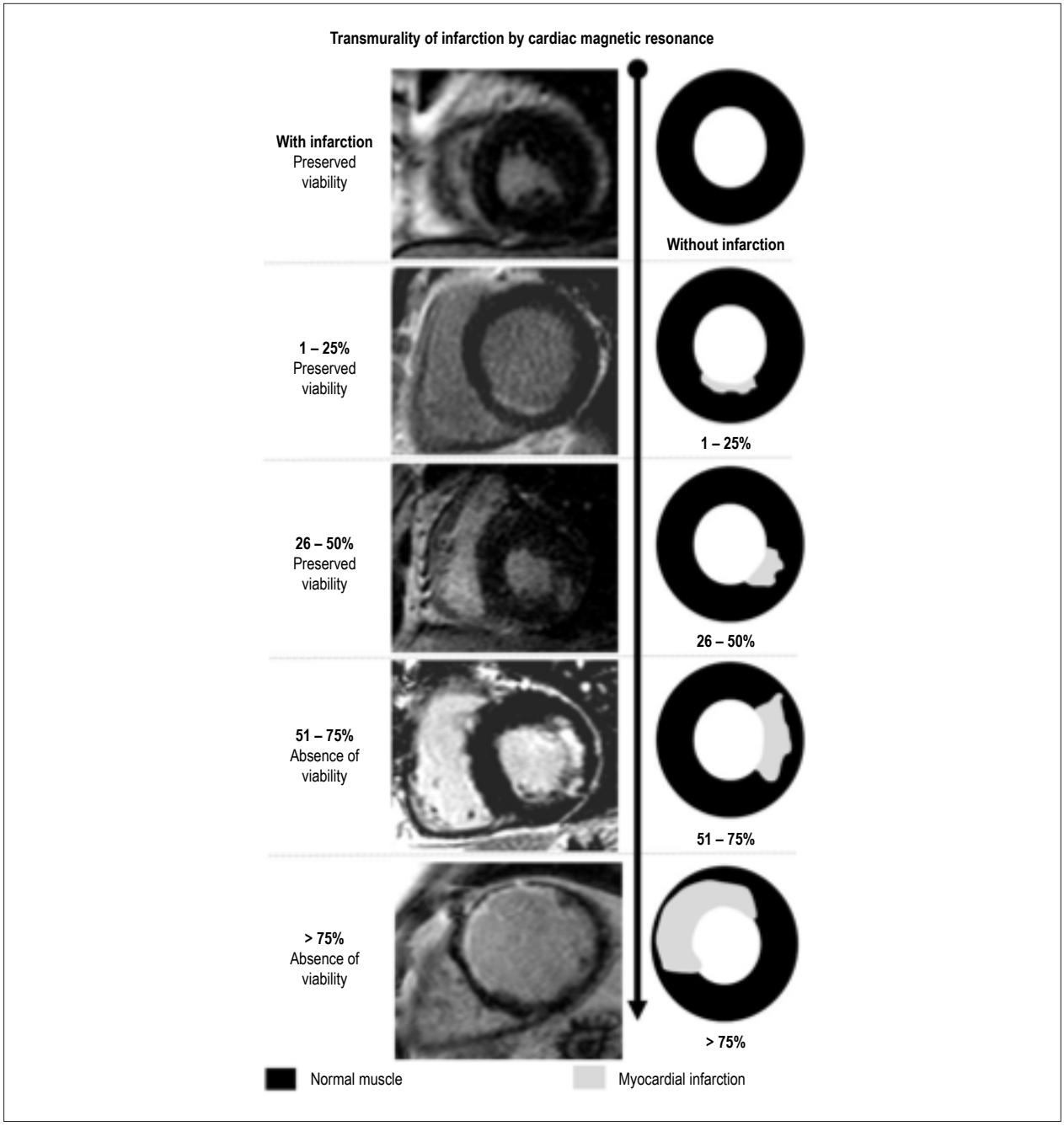

Figure 5 – *Patterns of transmurality of infarction in the presence and absence of viability by cardiac magnetic resonance*

PET-RM

A new technique – PET-MR started to be studied, but still has limited availability. The method has the advantage of combining the high spatial resolution of MR with the sensitivity of PET, without excessive ionizing radiation. In contrast to PET-CT, however, the synergism between PET and MR still need to be evaluated.

Comparison of left ventricular end-diastolic wall thickness on MRI with glucose use on ^{18}F-FDG PET demonstrated that regions with an end-diastolic wall thickness of less than 5.5 mm had reduced glucose use, whereas regions with a wall thickness of 5.5 mm did not use this carbohydrate.[51] Studies on usefulness of PET-MR in cardiology are still ongoing, but it includes specific localization of lesions, contributing to therapeutic intervention.[52] Preliminary data indicate the possibility of PET-MR to measure inflammatory response to myocardial infarction and neoangiogenesis.[52,53] While MR is helpful in the analysis of scar extension, PET provides characteristics of the subepicardium and likelihood of functional recovery of areas free of scars.[51]

Comparison between the techniques:

For practical purposes, the most appropriate methods for viability assessment are those in which the clinician or the institution have the highest experience. Echocardiography with dobutamine has, in general, high positive predictive value, and thus, is relatively more specific whereas nuclear medicine techniques are more sensitive to diagnosis, with a significative negative predictive value, as can be seen in the study by Panza et al.,[54] who compared the echocardiography and ^{201}Tálio myocardial scintigraphy methods. Hakimeh et al.[55] evaluated viable kinetic segments by resting ^{99m}Tc-Sestamibi, and observed that the number of these segments was significantly greater than those showing a contractile response to dobutamine. Hence, due to its greater accessibility, echocardiography may be the method of choice in the screening for the presence of viability, and in a second line of investigation, a nuclear method could be used.[56]

^{99m}Tc-Sestamibi has been used as an alternative to ^{201}Tálio for its higher quality combined with lower exposure to radiation. In cases when ^{99m}Tc-Sestamibi imaging are not conclusive, or when greater viability is still clinically possible, the use of ^{201}Tálio is indicated for its higher detection rate, especially in severe hypoperfusion areas.[25]

An excellent method for assessment of hibernating myocardium is ^{18}F-FDG PET, for its higher sensitivity in detecting dysfunctional, but viable, myocardium. Although a sensitivity of 93% was shown for this technique in a metanalysis,[35] other authors reported a lower specificity (58%).[57-59]

With respect to MR and nuclear medicine techniques, comparison of contrast MR imaging, with dobutamine echocardiography and ^{201}Tálio rest-redistribution showed an agreement of 83% and 75%, respectively.[60] Klein et al.[51] showed a good agreement between contrast MR and ^{18}F-FDG PET; in patients with CAD and severely reduced LVEF, MR imaging can identify fibrotic areas with results similar to those obtained by PET measurements, provided by comparison of flow and glucose metabolism. MR also provides other parameters of tissue viability, such as wall thickness, contractile reserve and delayed enhancement.[59-62]

In addition, in comparison with CT, MR has higher contrast resolution for soft tissues, without requiring radiation exposure. CT and PET[41] may be an alternative test to MR for patients with pacemakers, implantable cardioverter defibrillator or mechanical cardiac valve. Table 1 summarizes the comparison between these methods of assessment of myocardial viability.

Prognosis:

Observational studies have suggested that the presence of viable myocardium is directly associated with favorable progress of left ventricular function and good prognosis after revascularization. Patients who seem to benefit more from surgical revascularization are those with ischemic symptoms and severe left ventricular dysfunction. A significant perioperative risk should be considered in relation to long-term benefits on mortality.[62-66]

Comparison of randomized studies of miocardial viability

Today, there is little evidence of randomized studies on this theme, with conflicting results.

Stich trial

Randomized, multicenter study involving 1,212 patients, 601 assessed for myocardial viability by dobutamine echocardiography (130 patients), SPECT (321 patients) or both (150 patients).[67] In the myocardial viability study, 298 patients were randomly allocated to receive conservative treatment plus surgical revascularization, and 303 patients to receive pharmacological therapy alone. Median follow-up period was 56 months (12 months – 100 months).[67] No statistically significant benefit of surgical intervention on mortality, or of assessment of myocardial viability on surgical intervention, suggesting that investigation of a viable myocardium do not differentiate patients who would benefit from revascularization from those who would benefit from medical therapy alone.[67]

Table 1 – Comparison between myocardial viability assessment methods

	Radiation dose	Contrast/tracer redistribution	Protocol duration	Contrast phases *	Sensitivity	Specificity
Dobutamine echocardiography	n/a	n/a	30 min	n/a	77-89%	68-93%
^{99m}Tc-Sestamibi SPECT	Moderate	Absent	90 a 120 min	Two injections	81%	69%
^{201}Tálio SPECT	High	Present	3h with additional 24h imaging if necessary	One injection	87%	54%
^{18}F-FDG PET	Moderate	Absent	1h	One injection	92%	63%
Delayed enhancement / coronary computed tomography angiography	Moderate	Absent	25 minutes	Two injections	n/a	n/a
Cardiac magnetic resonance	n/a	Absent	35 minutes	Two injections	92-95%	51-89%

*n/a: non-applicable; DS: dobutamine-induced stress; Gad: gadolinium delayed enhancement. *Contrast phases are correlated with better evaluation when the contrast is injected in the stress phase only or in both phases, stress and rest phases. SPECT: single-photon emission computed tomography; ^{18}F-FDG: fluorodeoxyglucose F18; PET: positron-emission tomography*

Despite its limitations and biases, the STICH trial is, so far, the largest study on the influence of myocardial viability on clinical outcomes in patients with ischemic heart disease. Also, it is the first study to evaluate differential results of revascularization and pharmacological therapy.[67]

PARR-2 Trial

Study designed to evaluate the efficacy of ^{18}F-FDG PET in patients with left ventricular dysfunction, by risk stratification and identification of those who would benefit from myocardial revascularization. A total of 430 patients with LVEF < 35% and CAD were allocated into two groups – standard care (n = 212) and treatment assisted by ^{18}F-FDG PET (n = 218).[68]

At one year, the PARR-2 trial did not show a significant difference between the groups in the primary outcomes that included death for cardiac causes, acute myocardial infarction or hospital stays for cardiac cause (30% vs. 36% p = 0.15). In PET group, however, there was a significant decrease in primary outcome over the follow-up period (relative risk 0.62; 95% CI 0.42 – 0.93; p = 0.019).[68]

Perspectives

Myocardial viability is still a subject of clinical importance and a focus of clinical trials and translational science. Pathophysiological basis of left ventricular ischemic dysfunction seems to be correlated with myocardial stunning, hibernation or myocardial necrosis. Imaging methods used for assessment of viable muscular tissue have their own operational characteristics and should be appropriate to the patient's individual characteristics. The detection of myocardial viability may be a valuable predictor of the response to revascularization and long-term prognostic and, thereby, contribute to the decision-making in the medical practice.

^{18}F-FDG PET and CMR are considered first-choice methods for detection of viability due to their high sensitivity and specificity rates, whereas both echocardiography and myocardial scintigraphy considered acceptable methods for their wide availability and accessibility. With respect to the impact on medical practice, there are no definite studies showing the benefits of myocardial viability assessment on patients' prognosis, which reinforce the necessity of larger studies, considering the great relevance of the theme.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Ker WS, Nunes THP, Nacif MS, Mesquita CT; Obtaining financing: Ker WS, Nacif MS, Mesquita CT

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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Case 2 / 2018 – Coronary-Cavitary Fistula of Right Ventricular Coronary Artery 5 Years after its Occlusion by Interventional Catheterization

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Clinical data: Heart murmur detected in routine clinical examination at the age of 8 years, with no other manifestations. The patient was diagnosed as having coronary-cavitary fistula between right coronary artery and right ventricle, which was confirmed by echocardiography. The fistula was then occluded by interventional catheterization, and patient was asymptomatic, with full physical and mental health until the age of 13; in this period, the patient received no drug treatment.

Physical examination: good general condition, eupneic, acyanotic, with normal pulse rate at the four limbs. Weight: 36.95 Kg, Height: 154 cm, blood pressure (right arm): 100/60 mm Hg, HR: 76 bpm, oxygen saturation = 97%.

Precordium: apex beat was not palpable, absence of systolic impulses. Normal heart sounds with no heart murmurs. Liver was not palpable.

Before fistula occlusion, apex beat was located at the fifth left intercostal space, with mild systolic impulses at left sternal border and continuous murmurs at mid- and lower left sternal border, intensity grade ++/4, no radiation, and moderately loud heart sounds.

Complementary tests

Electrocardiography: sinus rhythm, with conduction defect in the right bundle branch in the period prior to fistula occlusion. In the late period, there was no evidence of such defect or volume overload.

Chest radiography: slightly increased heart size with cardiothoracic index of 0.47 before the coronary-cavitary fistula occlusion, which was clearly decreased 5 years later (cardiothoracic index 0.41) (Figure 1).

Echocardiography: in the period before the coronary-cavitary fistula occlusion, the test revealed dilation of left coronary artery ostium and trunk (8 mm), dilation of circumflex artery (4 mm), and normal anterior descending artery (2 mm). Right coronary artery emerged from the circumflex artery, which was also dilated. Aneurysm in the terminal segment (15 mm) of right coronary artery, before the coronary sinus ostium (4 mm), between the right ventricular outflow and inflow tracts. This chamber was slightly dilated, as well as the right atrium and pulmonary arteries. RV = 20, LV = 35, septum and posterior wall = 6, LA = 23, Ao = 20, RVSP = 20 mmHg, pulmonary arteries = 12 mm. Five years after fistula occlusion, cardiac chambers were normal, and coronary arteries were still dilated despite smaller diameters (left and right coronary trunks of 6 mm and 4 mm, respectively). There was a highly refractive area (10 mm) in the distal third of right coronary artery, corresponding to the arterial plug, and no flow through closed fistula.

Coronary computed tomography angiography: Coronary arteries were dilated, with left coronary artery main trunk of 7 mm-diameter, circumflex artery and right coronary artery of 6 mm with its distal end in the right ventricle.

Clinical diagnosis: coronary-cavitary fistula of right ventricular coronary artery, of little clinical repercussion, but with important dilation of the coronary circulation. Coronary dilation persisted even after fistula occlusion.

Clinical reasoning: There was clinical evidence of coronary-cavitary fistula, related to the presence of continuous murmurs at mid- and lower left sternal border. Due to this condition, the systemic fistula was supposed to occur in the right atrium or ventricle and was of minor clinical relevance, due to the modest increase in right cardiac chambers, revealed by echocardiography. The diagnosis was also established by coronary computed tomography angiography.

Differential diagnosis: In asymptomatic patients with continuous murmurs at lower left sternal border, differential diagnosis should include other types of communications between the systemic and pulmonary circulation, such as the aortopulmonary window between the ascending aorta and pulmonary trunk, and fistulas between the Valsalva aortic sinus and right cardiac chambers. When these communications are in the left ventricle, and anastomosis with the left atrium occurs, the murmur is diastolic and continuous, and heard in other regions, cardiac apex and axilla.

Management: The treatment of choice for coronary-cavitary fistula accompanied by dilation of coronary arteries was interventional catheterization. Coronary artery had a 6 mm-diameter, with aneurysm in its terminal segment of approximately 15 mm, and a 4-mm communication with the right ventricle. Occlusion of the aneurysm was successfully performed using a Amplatzer vascular plug II, with immediate resolution of the fistula. (Figure 2).

Comments: Rare congenital coronary artery fistulas are abnormal communications with cardiac cavities or the pulmonary arterial tree. Drainage is more commonly performed in the right cavities and occasionally in coronary sinus or left

Keywords

Fistula/congenital; Coronary Vessels; Percutaneous Coronary Intervention.

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Clinicoradiological Correlation

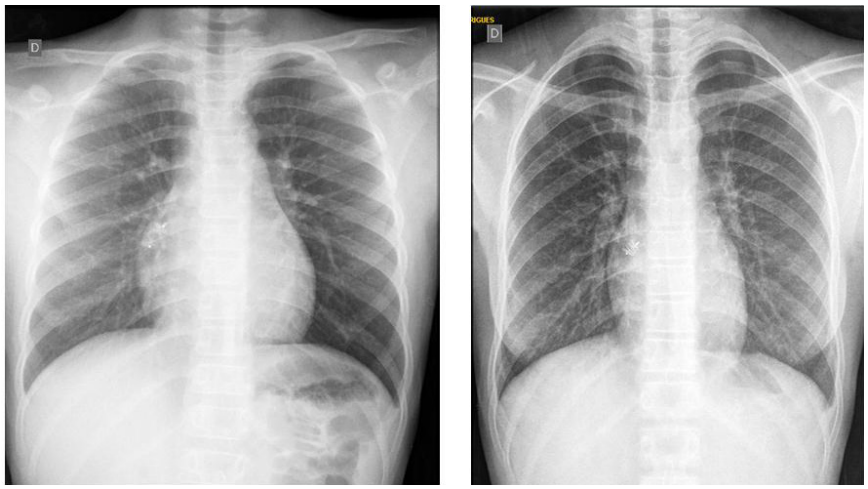

Figure1 – *Chest X-rays before (left) and 5 years after (right) coronary-cavitary fistula occlusion, highlighting the decrease in heart size (slightly enlarged before procedure).*

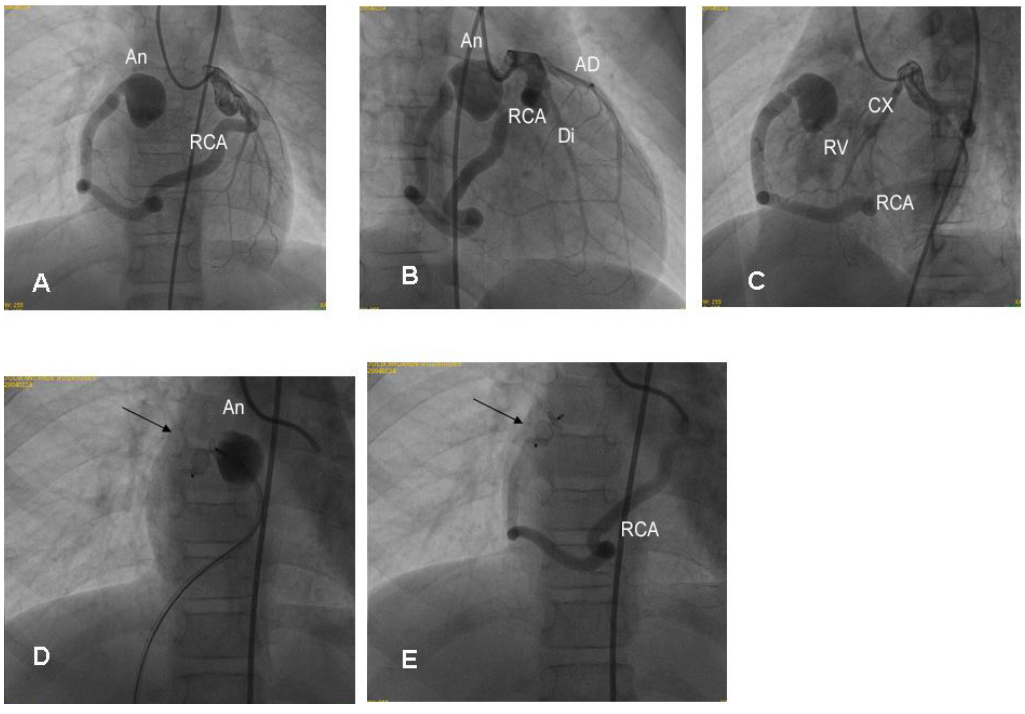

Figure 2 – *Coronary cineangiography showing important dilation of right coronary artery (RCA), emerging from the circumflex artery and terminating in the aneurysmal compartment (A and B). Drainage of aneurysm in the final segment of RCA was conducted in the right ventricle (RV). Insertion of the Amplatzer vascular plug II (arrow) from the RV can be seen in RCA, in the segment anterior to the coronary aneurysm (D) and interruption of the fistula drainage (E). Cx: circumflex; Di: diagonalis; AD: anterior descending artery.*

cavities. These fistulas may be simple or multiple, and cause a proportional volume overload, mimicking conditions including interatrial communication, interventricular communication and arterial channel persistence, depending on the drainage site. In addition, they cause myocardial ischemia, arrhythmias, vascular rupture, and endocarditis. Therefore, and effective treatment of these fistulas is paramount, and has been performed by surgery or by interventional catheterization since 1983.[1] Positive results of both procedures overcome complications which include infarction, prosthesis embolization, fistula dissection and arrhythmia. Indication for percutaneous intervention increases in face of a faster recovery, lower morbidity and lower cost. It is of note that coronary artery dilation is not reduced even after fistula resolution, which reflects the presence of concomitant lesion of elastic fibers of the vessel, that surpasses its limits of distensibility.

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Propafenone Overdose: From Cardiogenic Shock to Brugada Pattern

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Introduction

Propafenone is a class IC antiarrhythmic drug used in the treatment of ventricular and supraventricular arrhythmias.[1-7] It is primarily a potent sodium channel blocker, yet also exhibits beta-blocking and calcium channel blocking activity.[4,6,7] Propafenone is able to induce important ECG changes, namely prolongation of the PR interval, bundle branch block, wide QRS and QT intervals, as well as ventricular tachycardia or bradycardia.[3,4] It may be associated with significant proarrhythmogenic effects, even at therapeutic doses.[2] A fatal overdose on propafenone is usually attributed to conduction abnormalities, leading to asystole or electromechanical dissociation. The authors describe two clinical cases of propafenone intoxication with life-threatening ECG changes, but with a favorable final outcome.

Case Report

Case 1

Female patient, 44 years old, with no relevant medical history. The patient was brought to the Emergency Room (ER) following voluntary ingestion of 4500mg of propafenone. While being brought to the ER, the patient had a short-lasting seizure, later regaining consciousness. Upon arrival at the ER, she had a Glasgow Coma Scale (GCS) score of 10 (Eye-3, Motor-5, Verbal-2), bradycardic (55bpm) and hypotensive (Blood Pressure [BP] 85/30mmHg). Clinical examination was unremarkable. Gastric lavage was performed, with removal of what seemed to be pill residuals. Blood work revealed metabolic acidosis. The ECG at admission showed sinus arrhythmia, with right axis deviation, incomplete right bundle branch block (RBBB) and unspecific repolarization changes in DIII, V1 and V2. The PR, QRS and QT intervals were within normal range (Figure 1). BP did not respond to aggressive fluid therapy, thus a dopamine perfusion was started. After approximately an hour of beginning treatment, the patient suffered a tonic-clonic seizure accompanied by extreme bradycardia and widening of the QRS. Unfortunately, due to the urgency of the situation and the critical state of the patient, these electrical changes could not be recorded through standard 12-lead ECG. She was medicated with atropine and benzodiazepine. This resulted in a comatose state (Glasgow scale of 3), worsening of metabolic acidosis and respiratory failure. The patient was intubated, placed on continuous mechanical ventilation and admitted to the Intensive Care Unit (ICU).

Upon admission to the ICU, rhythm strip monitoring revealed atrial fibrillation with occasional sinus activity, along with a widening of the QRS (200 milliseconds) interval. Three hours later, sinus rhythm was restored and QRS interval returned to normal values, with an almost complete disappearance of the RBBB pattern. In the first 6 hours after admission, there was a progressive hemodynamic and clinical stabilization, allowing for a gradual weaning from aminergic and ventilator support. On day two, the patient was conscious and hemodynamically stable. She was discharged after a psychiatric consultation.

Case 2

Female patient, 56 years old, with a history of Atrial Fibrillation and major depressive disorder medicated with propafenone 150 mg twice daily and duloxetine 60 mg once daily. The patient was first observed in a small community hospital after voluntarily ingesting 3000mg of propafenone. At that institution, on arrival, the patient was initially fully awake and gastric lavage was begun. However, shortly afterwards, she developed a tonic-clonic seizure, followed by two episodes of cardiac arrest due to extreme bradycardia. Resuscitation was achieved after less than 2 minutes of advanced life support and atropine administration. After ensuring hemodynamic and electrical stability, the patient was transported to a centralized hospital. Upon admission, she was bradycardic (50 bpm), normotensive (BP 139/89 mmHg), and with a GCS score of 14 (Eye 4, Motor 6, Verbal 4). ECG revealed a junctional rhythm, with a type-1 Brugada pattern in V1 to V3 leads (Figure 2). The patient was admitted to the Cardiac Intensive Care Unit for monitoring. After 24 hours of clinical, hemodynamic and electrical stability, a new ECG was performed, revealing sinus rhythm and disappearance of the Brugada pattern.

Discussion

Propafenone is a Vaughan Williams Class IC antiarrhythmic agent, and thus a potent sodium channel blocker.[1,3,4,6,7] It also exhibits beta-blocking and calcium channel blocking activity.[4,6,7]Nearly 100% of propafenone is absorbed. However, because of a first-pass hepatic elimination effect, its bioavailability is unpredictable.[1,4] Propafenone is metabolized into two major metabolites: 5-hydroxypropafenone and norpropafenone, a process genetically determined by the CYP2D6 enzyme system.[1,4] The propafenone elimination half-time varies depending on whether the patient is a poor or an extensive metabolizer.[1,4] There are several infrequent adverse reactions, such as hematologic (agranulocytosis),

Keywords

Anti-Arrhythmia Agents; Propafenone; Arrhythmias, Cardiac; Calcium Channel Blockers; Toxicity.

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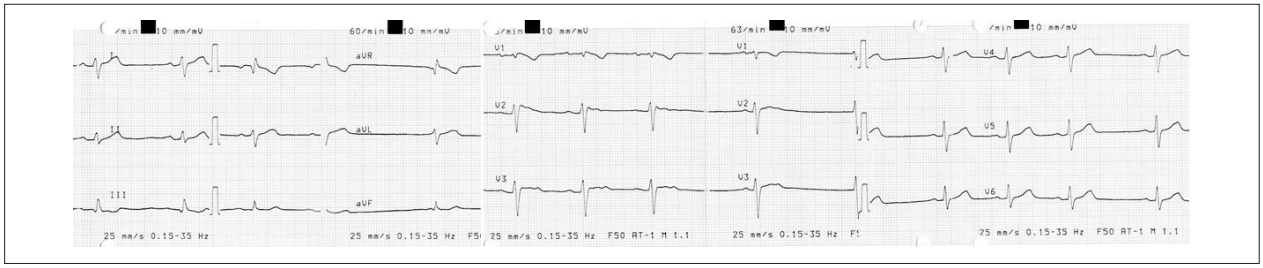

Figure 1 – *ECG on admission from case 1.*

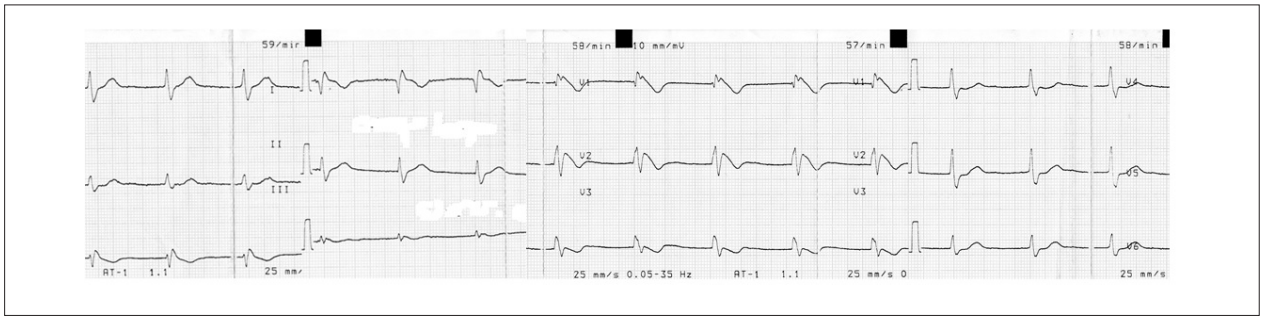

Figure 2 – *ECG from second clinical case revealing type-1 Brugada pattern.*

gastrointestinal, hepatic and neurological (convulsions, amnesia, peripheral neuropathy and exacerbation of myasthenia) reactions.[2] A number of clinical signs and symptoms have been associated with propafenone intoxication, ranging from nausea and vomiting to seizures, coma, respiratory depression and cardiovascular collapse (Table 1).[4] Propafenone may be responsible for several ECG changes, including sinus bradycardia, sinus arrest, atrial fibrillation, prolongation of the PR interval, intraventricular conduction abnormalities (QRS and QT widening and right bundle branch block), Brugada pattern,[8-11] ventricular tachycardia, ventricular flutter or fibrillation and cardiac arrest.[1,4]

The authors describe two cases of voluntary ingestion of excessive doses of propafenone, both with successful outcomes. There is no specific treatment. A timely gastric lavage was attempted in both cases. When performed promptly, gastric lavage is the only effective way of eliminating excessive doses of propafenone.[1,3]

In both cases, tonic-clonic seizures were observed. This is an important neurological manifestation of propafenone intoxication.[3,4] The reason for seizure occurrence is uncertain. Saz et al.[3] and Clarot et al.[4] suggest that it may be attributed either to a direct toxic effect of propafenone or to cerebral hypoperfusion caused by arrhythmia or conduction disturbance.

In the first case, all the major clinical warning signs were observed: cardiac failure, conduction disturbance, and seizures.[4] There was a progressive worsening of the neurological and respiratory status. The patient eventually became comatose, requiring mechanical ventilation. Cardiac failure was also observed, resulting in arterial hypotension, and requiring catecholaminergic support with positive inotropic and vasoconstrictive drugs. After progressive elimination of the drug, weaning from supportive measures was fairly straightforward. Another important aspect is the dynamic ECG changes. The patient underwent rhythm changes (going from sinus arrhythmia to atrial fibrillation and finally returning to normal sinus rhythm) and intraventricular conduction disorders (with widening of the QRS interval and enhancement of the RBBB pattern). These changes occurred only in the first 3 hours after admission, corresponding to peak serum concentration.[4] This highlights the importance of close monitoring and prompt treatment in the first hours following propafenone overdose.

In the second case, the ingestion of supratherapeutic levels of propafenone revealed a Brugada type 1 pattern on surface ECG. Concealed or intermittent forms of the Brugada Syndrome have been described in a few subset of patients, namely following hyperventilation, beta-adrenergic blockade and alpha-adrenergic stimulation, muscarinic receptors stimulation, and sodium channels blockade inducing or increasing ST elevation.[10,11] In this particular case, propafenone is able to unmask the concealed Brugada phenomenon due to its sodium channel and beta-adrenergic blocking activity.[10] The appearance of the Brugada pattern in response to type IC antiarrhythmic drugs does not seem to be associated with a great risk for polymorphic arrhythmias; however, further investigation is needed.[11] In this case, the Brugada pattern disappeared after drug elimination.

Both patients were closely monitored for 36 to 48 hours. The propafenone elimination half-time ranges from 17 ± 8 hours for poor metabolizers to 5 ± 2 hours for extensive metabolizers,[1,4] thus monitoring over that period of time is

Table 1 – Clinical Signs and Symptoms of Propafenone Intoxication, adapted from Clarot et al[4]

Nausea	Vomiting	Metabolic acidosis		
Blurred vision and sleepiness	Hypotonia	Seizure	Respiratory depression	Coma
Sinus Bradycardia	Sinus arrest	Atrial Fibrillation	AV Block	Intraventricular conduction disorders (QRS widening, Right Bundle Block)
Hypotension	Acute load of the right ventricle	Cardiac failure	Cardiovascular collapse	Cardiac arrest

required. Peak serum concentration occurs between 2 and 3 h after ingestion,[4] during which time the most life-threatening ECG changes may occur.

Both cases are paradigmatic in how unpredictable propafenone overdosing can be. It can range from an almost benign set of symptoms to a catastrophic presentation resulting in death. The first case presented the most important clinical warning signs, namely cardiac failure, conduction disturbance, and seizures. However, thanks to immediate treatment, the patient survived. The second case was critical as well, considering the seizing and extreme bradycardia requiring advanced life support; however, after the initial catastrophic presentation, clinical stability was maintained throughout the following hours. Another interesting aspect was the fact that a type-1 Brugada pattern was revealed. In both cases, no direct treatment for propafenone intoxication was available. Close monitoring and prompt supportive measures are crucial in assuring a good outcome

Author contributions

Conception and design of the research and Writing of the manuscript: Gil J; Acquisition of data and Analysis and interpretation of the data: Gil J, Marmelo B, Abreu L Antunes H; Critical revision of the manuscript for intellectual content: Santos LF, Cabral JC.

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Partial Prosthetic Mitral Valve Dehiscence: Transapical Percutaneous Closure

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An 80-year-old woman with a history of mitral and aortic prosthesis replacement with biological prostheses due to endocarditis presented worsening dyspnea. A transthoracic echocardiogram demonstrated a paravalvular regurgitation between the left ventricle and left atrial appendage. Given her high-risk surgery (EuroSCORE-II: 38%), a percutaneous approach was performed for definitive closure.

Transesophageal echocardiography (TEE) peri-procedure allowed the visualization of a partial dehiscence of the mitral prosthesis (Panel A, Figure 1). Through the 3D images, a tunneled defect with wall dissection measuring 12.5 mm of maximum diameter (Panel B, Figure 1) was observed. Using a transapical pathway and collecting three-dimensional (3D) images in real time, a 12 mm Amplatzer septal prosthesis was positioned, occluding the entire defect. The TEE 3D image demonstrated savings of adjacent structures and absence of pericardial effusion during closure. Coronary angiography demonstrated no arterial compromise. A slight residual flow was detected after device implantation (C-F Panels Figure 1).

Keywords

Endocarditis; Mitral Valve Insufficiency; Aortic Valve Insufficiency; Echocardiography,Transesophageal

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Paravalvular regurgitation may result from suture dehiscence of the mitral prosthesis. Symptoms of heart failure are an indication for closure. A transapical approach allows direct access to the defect, providing good technical support. The TEE 3D image is essential for guiding the guidewire through the defect, confirming the correct position of the device and relating it to critical structures. The anatomy of the defect and the surrounding structures make this case a challenge, on both imaging acquisition and percutaneous technique.

Author contributions

Conception and design of the research and Writing of the manuscript: Ruivo C; Acquisition of data: Ruivo C, Ribeiro J; Analysis and interpretation of the data: Ruivo C, Ribeiro J, Rodrigues A; Critical revision of the manuscript for intellectual content: Ribeiro J, Rodrigues A, Vouga L, Gama V.

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Image

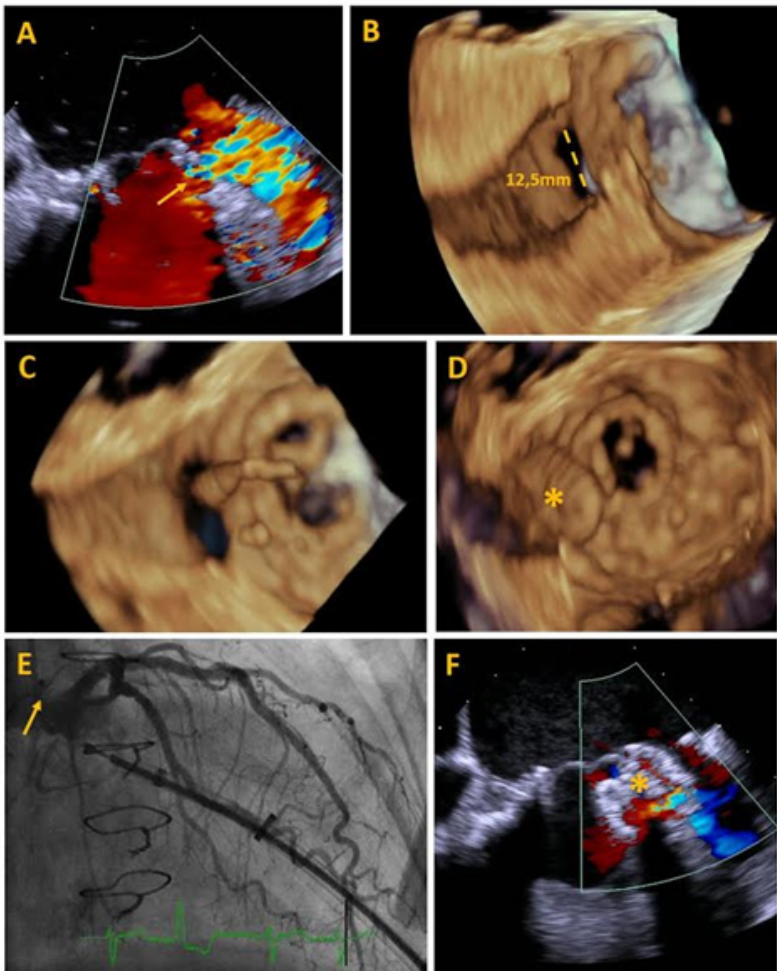

Figure 1 – *Panel A: 2D peri-processual transesophageal echocardiography (TEE) shows paravalvular regurgitation (yellow arrow) between left ventricle and left atrial appendage; Panel B: Defect 3D TEE with diameter measurement; Panel C: 3D TEE guiding the guidewire through the defect; Panel D: 3D TEE showing the device (asterisk) through the defect; Panel E: left coronary angiography without vascular involvement after occlusal implant (yellow arrow); Panel F: Light residual flux detected after device deployment (asterisk).*

Occurrence of Stroke and Reduced Ejection Fraction in Patients with Chagas Disease

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To the Editor

Chagas disease (CD) is a well-defined risk factor for stroke.[1] But the prognostic significance of stroke prevalence in left ventricular ejection fraction (LVEF) reduced compared to preserved LVEF in patients with heart failure and with CD, is still poorly known.[2]

There are studies that demonstrate the association of stroke with CD and reduced LVEF[3] and there are studies that refute this association.[4] In a cross-sectional study involving 85 chagasic patients with a mean age of 61.8 ± 9.3 years, 71.8% with heart failure and 96.5% of black race, patients were compared with LVEF ≤ 40% and LVEF > 40% to evaluate stroke occurrence in patients with CD and reduced LVEF. It was shown that LVEF ≤ 40% (OR 4.37: 1.65-11.63; p = 0.003) was an independent predictor for stroke compared to patients with preserved LVEF. There was also a high prevalence (50%) of CVA, which was obtained by cranial tomography, a number close to a cohort of 41.6% in the same town.[5] There were no hemorrhagic strokes and there was also no significant relationship between fibrillation atrial and stroke, this data can be explained by the use of oral anticoagulants in these patients. In addition, 54.8% of silent vascular accidents were detected in patients who had no history of stroke. The high prevalence of stroke in this study with chagasic patients may have occurred because all patients were evaluated with cranial tomography, contrary to other studies, which generally use clinical and/or radiological findings as diagnostic criteria for stroke[1,4] and do not usually evaluate silent cerebral infarction.[4] Data suggest that reduced LVEF is associated with stroke, confirmed by cranial tomography and may be an independent predictor of embolic events in this population.

Keywords

Chagas Disease; Chagas Cardiomyopathy; Stroke; Stroke Volume.

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