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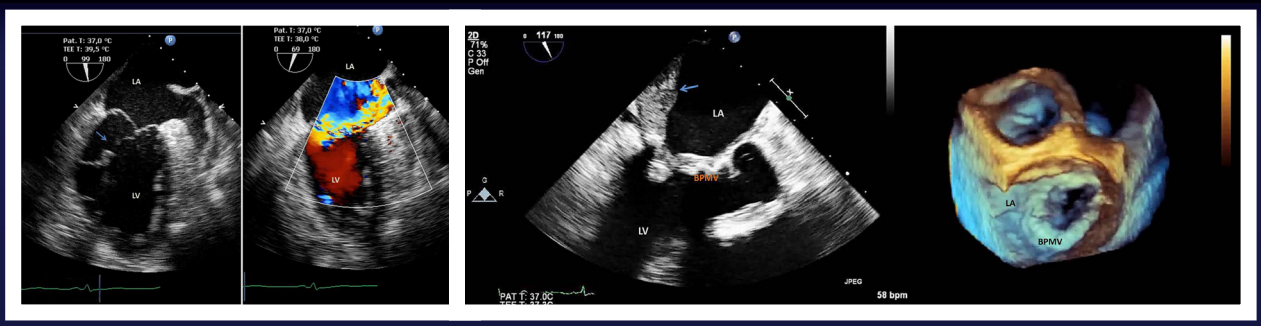

Figure 1 – *Transoesophageal echocardiogram two-chamber view showing a 9 mm disruption of the posteromedial papillary muscle (pointed with an arrow) consistent with a contained, but morphologically imminent rupture, leading to a broad posterior leaflet prolapse and a severe mitral regurgitation with an eccentric jet. LA: Left Atria; LV: Left Ventricle. Page 431* **Figure 2 –** *Transoesophageal echocardiogram long axis view and 3D zoom on face view of the mitral valve presenting a significant thickening of mitral bioprosthetic cusps due to thrombotic material deposition, leading to severe obstruction of the prosthetic valve and a large mural thrombus covering the left atrial posteroseptal wall (pointed with an arrow). BPMV: Bioprosthetic Mitral Valve; LA: Left Atria; LV: Left Ventricle. Page 431*

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REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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Editorial

The Brazilian Society of Cardiology and Hypertension: It's Time for Action

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The year is 2018 and the level of scientific knowledge is unquestionable.

In medicine in general, and in cardiology, in particular, advances in diagnoses are impressive, just as the therapeutic arsenal is extraordinary, either in clinical or surgical, conventional or alternative treatment.

Consequently, longevity increases and the average age, even in our weakened Brazil, exceeds 75 years.[1]

Nevertheless, regarding the circulatory system diseases, the national picture is discouraging. With an older population, there are more degenerative diseases, and a higher proportional mortality from this cause.[1]

Among cardiovascular diseases, arterial hypertension and its consequences (stroke, coronary disease, heart failure, renal disease and peripheral vascular disease) undoubtedly achieve a record in terms of morbidity and mortality.[1]

Over the years, we have attended and participated in numerous initiatives of international and national scientific societies, with the purpose of establishing norms and behaviors for health professionals regarding care of hypertensive patients. The starting point was the Joint National Committee, organized in the United States from 1977 onwards, which for years determined the action standards that are considered more appropriate for treating hypertensive patients. Throughout the world, there has been the mobilization of scientific societies for the same purpose, always seeking to establish more correct and effective strategies.[2-4]

In Brazil, the initial Consensus and current Guidelines were first implemented in 1990 with a document of only 16 pages. It was held in the city of Campos do Jordão, and was an excellent work of the Brazilian societies of cardiology and nephrology that even led to the creation of the Brazilian Society of Arterial Hypertension.[5]

From then on, every 4 years there is an articulated mobilization of the scientific societies that work in this field (cardiology, nephrology, internal medicine, geriatrics, and other scientific societies in the health area - nutrition, physical education, nursing) and, in a collective effort, the documents are updated, new directions and strategies established and, occasionally, the guidelines for the treatment are changed.[6]

The philosophy of this mobilization was its broad dissemination at all levels of the health system, so that the instructions emanated from it could become current practice for the benefit of the patients. There were some advances, but even if, on the plane of intentions, at any moment, there was a regulation of the Ministry of Health itself to adopt the official documents of the scientific societies as rules for general action, the practical implementation of this expressed will has always followed the current political system, the temporary managers, and the country's own economic situation.

A great frustration!

Where were we and where are we?

Focusing our attention on Brazil, we find that, in general, from 1990 to the present, that is, in an interval of more than 25 years, little progress has been made.

It is a fact that the knowledge of the presence of hypertension by the population increased. We went from values lower than 50% of knowledge to numbers above 75%, and the merit was everyone's. The dissemination of the importance of the disease, and its identification, took place at all levels and, currently, few are unaware of the risks caused by hypertension. In this case, there was collective responsibility, and our scientific societies had an active participation in the dissemination process, either through its proselytism with health professionals, or through its action with the media and, in a significant way, its actions with the public power.[6]

If we make a simple and objective analysis of these numbers, we will see that, even with this advance, in every 100 hypertensive patients, 25 do not know their situation, and therefore do not even think about seeking treatment.

The percentage of individuals who are aware of their high blood pressure status, and who are undergoing treatment, has also increased, but in a less marked way when compared to those who are aware of the disease.

This number is around 65%, that is, in absolute numbers, among the 75 who know they have hypertension, approximately 50 individuals are being treated. So far, we have seen that in the group of hypertensives, out of 100, only half started treatment.[6]

Then we come to those in treatment, who have controlled pressure. This number is disappointing all over the world, but in Brazil it is even worse. If we analyze the available epidemiological data of treated individuals who present with controlled pressure, we have a percentage of control that reaches a maximum of 40%. The practical meaning of this number is that, in absolute values, only 25 individuals out

Keywords

Hypertension/physiopathology; Hypertension/mortality; Hypertension/drug therapy; Cardiovascular Diseases/prevention & control; Indicators of Morbidity and Mortality; Practice Guidelines as Topic; Antihypertensive Agents/administration & dosage; Decision/policies.

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of 100 hypertensive patients in general have their pressure controlled, that is, the old rule of halves, that we thought was outdated, is still valid.[6]

A resounding failure!

It is interesting to think back that we have advanced a lot!

If this state of affairs is perpetuated, morbidity and mortality from cardiovascular diseases will continue to be the highest, and may even increase, as the epidemic of overweight has also arrived in our country, with evident signs that it came to stay.

Still focusing on Brazil, where did we go wrong? How can we improve?

In daily practice, we still have difficulties in knowing about the presence of hypertension, but in this case, universal dissemination strategies have worked and only need to be reinforced and continued.

Regarding treatment, if on the one hand we have a very satisfactory therapeutic arsenal, on the other we still have many difficulties with its correct use.

There are several equally important aspects that should be actively addressed by our scientific societies. These include: a) medical training; b) continuing medical education; c) access to health services; (d) access to essential drugs; e) compliance to treatment.

The Brazilian Society of Cardiology has a serious responsibility, and should be more incisive, seeking to actively participate in the policy to control the creation and operation of medical schools and, at the same time, further increasing its participation in continuing medical education.

There should be concern about the critical review of our Guidelines. To whom they are intended, the extent of their content, how to implement them, and how to disseminate them throughout the country.

It is upsetting, and it is part of the real world, to see patients receiving inadequate treatment, either due to the type of drug used or to inadequate doses, while our guidelines and various international guidelines are dealing with ultra-advanced concepts that are not even possible to be performed in our practice.[6-10]

We have to rethink some issues.

The issue of access to services and key drugs should also be a matter of honor.

It is the duty of the organized society and of each individual citizen to participate in the pressure mechanisms so that public policies in the health area are effectively and continuously implemented. Thus, we can continue with so many projects that have already provided some progress and were completely lost due only to the political will of leaders who are not committed to society.

Perhaps, following this path, we will, in fact, contribute to a change in the history of cardiovascular diseases in our country.

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Adiponectin in Relation to Coronary Plaque Characteristics on Radiofrequency Intravascular Ultrasound and Cardiovascular Outcome

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Abstract

Background: **Prospective data on the associations of adiponectin with in-vivo measurements of degree, phenotype and vulnerability of coronary atherosclerosis are currently lacking.**

Objective: **To investigate the association of plasma adiponectin with virtual histology intravascular ultrasound (VH-IVUS)-derived measures of atherosclerosis and with major adverse cardiac events (MACE) in patients with established coronary artery disease.**

Methods: **In 2008-2011, VH-IVUS of a non-culprit non-stenotic coronary segment was performed in 581 patients undergoing coronary angiography for acute coronary syndrome (ACS, n = 318) or stable angina pectoris (SAP, n = 263) from the atherosclerosis-intravascular ultrasound (ATHEROREMO-IVUS) study. Blood was sampled prior to coronary angiography. Coronary plaque burden, tissue composition, high-risk lesions, including VH-IVUS-derived thin-cap fibroatheroma (TCFA), were assessed. All-cause mortality, ACS, unplanned coronary revascularization were registered during a 1-year-follow-up. All statistical tests were two-tailed and p-values < 0.05 were considered statistically significant.**

Results: **In the full cohort, adiponectin levels were not associated with plaque burden, nor with the various VH-tissue types. In SAP patients, adiponectin levels (median[IQR]: 2.9(1.9-3.9) μg/mL) were positively associated with VH-IVUS derived TCFA lesions, (OR[95%CI]: 1.78[1.06-3.00], p = 0.030), and inversely associated with lesions with minimal luminal area (MLA) ≤ 4.0 mm² (OR[95%CI]: 0.55[0.32-0.92], p = 0.025). In ACS patients, adiponectin levels (median[IQR]: 2.9 [1.8-4.1] μg/mL)were not associated with plaque burden, nor with tissue components. Positive association of adiponectin with death was present in the full cohort (HR[95%CI]: 2.52[1.02–6.23], p = 0.045) and (borderline) in SAP patients (HR[95%CI]: 8.48[0.92–78.0], p = 0.058). In ACS patients, this association lost statistical significance after multivariable adjustment (HR[95%CI]: 1.87[0.67-5.19], p = 0.23).**

Conclusion: **In the full cohort, adiponectin levels were associated with death but not with VH-IVUS atherosclerosis measures. In SAP patients, adiponectin levels were associated with VH-IVUS-derived TCFA lesions. Altogether, substantial role for adiponectin in plaque vulnerability remains unconfirmed. (Arq Bras Cardiol. 2018; 111(3):345-353)**

Keywords: **Adiponectin; Atherosclerosis; Plaque, Atherosclerotic; Ultrasonography, Interventional; Coronary Artery Disease / complications.**

Introduction

Coronary plaque rupture has been described as the main mechanism through which mildly stenotic coronary atherosclerosis can lead to acute coronary thrombosis and myocardial infarction.[1] High-risk plaques that are vulnerable to such rupture demonstrate distinct morphological characteristics.[2] They can be differentiated from lesions responsible for stable coronary artery disease (CAD) by their large necrotic cores, thin inflamed fibrous caps, and positive remodeling.[2] Because plaque vulnerability is associated with inflammation, neovascularization, and necrotic core formation, circulating mediators of these processes may aid in detection of high-risk patients and therefore warrant investigation.[3] One important inflammatory mediator of CAD is adiponectin. Adiponectin is a protein mainly produced in white adipose tissue, involved in several antioxidant, anti-inflammatory, and anti-atherosclerotic processes.[4-6] Several studies have demonstrated associations of adiponectin with clinical adverse coronary events.[7-10] Yet, prospective data on the associations of adiponectin with *in-vivo* measurements of degree, phenotype and vulnerability of coronary atherosclerosis are currently lacking. To further elucidate the pathophysiology of adiponectin in patients

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with established CAD, we investigated the association of adiponectin with virtual histology intravascular ultrasound (VH-IVUS)-derived measures of degree and composition of coronary atherosclerosis, and with major adverse cardiac events (MACE), in patients undergoing coronary angiography.

Methods

The design of The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound (ATHEROREMO-IVUS) study has been described in detail elsewhere.[11,12] In brief, 581 patients who underwent diagnostic coronary angiography or percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS, n=318) or stable angina pectoris (SAP, n = 263) have been included between 2008 and 2011 in the Erasmus University Medical Center (Erasmus MC), Rotterdam, the Netherlands. The ATHEROREMO-IVUS study was approved by the medical ethics committee of Erasmus MC. The study was performed in accordance with the criteria described in the declaration of Helsinki. Written informed consent was obtained from all included patients. This study is registered in ClinicalTrials.gov, number NCT01789411.

Blood samples for biomarker measurements were drawn from the arterial sheath prior to coronary angiography and were available in 570 patients for the current study. The blood samples were stored at the clinical laboratory of Erasmus MC at a temperature of -80°C within 2 hours after blood collection. C-reactive protein (CRP) was measured in serum samples using an immunoturbidimetric high sensitivity assay (Roche Diagnostics Ltd., Rotkreuz, Switzerland) on the Roche Cobas 8000 modular analyzer platform. These analyses were performed in the clinical laboratory of Erasmus MC. Frozen EDTA plasma samples were transported under controlled conditions (at a temperature of -80°C) to Myriad RBM, Austin, Texas, USA, where adiponectin was measured using a validated multiplex assay (Custom Human Map, Myriad RBM).

Following the standard coronary angiography or PCI procedure, intravascular ultrasound (IVUS) imaging took place in a target segment of a non-culprit coronary artery which was required to be at least 40 mm in length and without significant luminal narrowing (< 50% stenosis) as assessed by on-line angiography. Selection of the non-culprit vessel was predefined in the study protocol. The order of preference for selection of the non-culprit vessel was: (1) left anterior descending (LAD) artery; (2) right coronary artery (RCA); (3) left circumflex (LCX) artery. All IVUS data were acquired with the Volcano s5/s5i Imaging System (Volcano Corp., San Diego, California) using a Volcano Eagle Eye Gold IVUS catheter (20 MHz). An automatic pullback system was used with a standard pullback speed of 0.5 mm per second. The IVUS images were analyzed offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) blinded for clinical and biomarker data. The IVUS gray-scale and IVUS radiofrequency analyses, also known as VH-IVUS, were performed using pcVH 2.1 and qVH (Volcano Corp., San Diego, California) software. The external elastic membrane and luminal borders were contoured for each frame (median inter-slice distance, 0.40 mm). Extent and phenotype of the atherosclerotic plaque were assessed. Plaque volume was defined as the total volume of the external elastic membrane occupied by atheroma.[13] Plaque burden was defined as plaque and media cross-sectional area divided by external elastic membrane cross-sectional area and is presented as a percentage. The composition of the atherosclerotic plaque was characterized into four different tissue types: fibrous, fibrofatty, dense calcium and necrotic core.[14] A coronary lesion was defined as a segment with a plaque burden of more than 40% in at least three consecutive frames. The following types of VH-IVUS high-risk lesions were identified:

(1) thin-cap fibroatheroma (TCFA) lesions: lesions with presence of >10% confluent necrotic core in direct contact with the lumen;[15,16]

(2) TCFA lesions with a plaque burden of at least 70%;

(3) lesions with a plaque burden of at least 70%;

(4) lesions with a minimal luminal area (MLA) of ≤4.0 mm^2.[11]

Follow-up started at inclusion and lasted 1 year. Post-discharge survival status was obtained from municipal civil registries. Post-discharge rehospitalizations were prospectively assessed during follow-up. Questionnaires focusing on the occurrence of MACE were sent to all living patients. Subsequently, hospital discharge letters were obtained, and treating physicians and institutions were contacted for additional information whenever necessary. ACS was defined as the clinical diagnosis of ST-segment elevation myocardial infarction (STEMI), non-STEMI or unstable angina pectoris in accordance with the guidelines of the European Society of Cardiology.[17-19] Unplanned coronary revascularization was defined as unplanned repeat PCI or coronary artery bypass grafting (CABG). The primary clinical endpoint was MACE, defined as all-cause mortality, ACS or unplanned coronary revascularization. Secondary endpoints included acute MACE (defined as the composite of all-cause mortality or ACS) and all-cause mortality. The endpoints were adjudicated by a clinical event committee blinded for biomarker and IVUS data.

Statistical analysis

The distributions of continuous variables, including adiponectin levels and IVUS parameters, were evaluated for normality by visual examination of the histogram. Normally distributed variables are presented as mean ± standard deviation (SD), while non-normally distributed variables are presented as median and interquartile range (IQR). Adiponectin concentration was not normally distributed and was therefore ln-transformed for further analysis. Categorical variables are presented in percentages. We examined associations of adiponectin concentrations with plaque burden, plaque volume, necrotic core fraction, dense calcium fraction, fibro-fatty fraction, and fibrous tissue fraction in the imaged coronary segment by linear regression, with continuous ln-transformed adiponectin concentration as the independent variable. Furthermore, we examined the relation between adiponectin concentrations and the presence of high-risk lesions using logistic regression analyses, with continuous ln-transformed adiponectin concentration as the independent variable. Cox proportional hazards regression analyses were performed to evaluate the relationship between adiponectin

concentration and MACE. Clinical variables age, gender, diabetes mellitus, hypertension, and indication for coronary angiography were considered as potential confounders and were entered into the full model. These covariates were a priori chosen based on existing literature, and taking into account the number of events available. CRP was also entered into the full model, as it is the most widely investigated inflammatory marker in CAD, and has been shown to be (inversely) associated with plasma adiponectin levels.[10] When analyzing the association of adiponectin with the secondary, composite endpoint of death and ACS, and death alone, we only adjusted for age and gender because of the limited number of endpoints.

First, statistical analyses were performed in the full cohort. Then, we included interaction terms (adiponectin multiplied by indication for angiography) into the models to investigate possible effect modification by indication. Subsequently, we repeated the analyses separately in patients with SAP and patients with ACS. All data were analyzed with SPSS software (SPSS 20.0, IBM corp., Armonk, New York). All statistical tests were two-tailed and p-values < 0.05 were considered statistically significant.

Results

Mean age of the patients was 61.5±11.4 years, 75.4% were men, 17.4% had diabetes mellitus, and median adiponectin concentration was 2.8 (1.9-4.0) μg/mL (Table 1). Coronary angiography or PCI was performed for ACS in 309 (54.2%) patients and for SAP in the remaining 261 (45.8%). Median adiponectin concentration was 2.9 (1.8-4.1) μg/mL in ACS patients and 2.9 (1.9-3.9) μg/mL in SAP patients. A total of 239 (41.9%) patients had at least 1 VH-IVUS-derived TCFA, including 69 (12.1%) patients with at least 1 VH-IVUS-derived TCFA with a plaque burden ≥ 70%.

In the full cohort, adiponectin levels were not associated with composition or burden of atherosclerosis on multivariable analysis (Tables 2 and 3). Adiponectin levels were not associated with MACE after adjustment for age, gender and indication for angiography (Table 4). After further multivariable adjustment, effect estimates remained non-significant (data not shown). Adiponectin levels tended to be univariably associated with acute MACE, (median [IQR] 1.16[0.82-1.62] μg/mL, *vs.* 1.02[0.64-1.38] μg/mL; HR [95%CI]: 1.77[0.96–3.23], p = 0.069), but after further adjustment this tendency disappeared. Adiponectin levels were independently associated with occurrence of death (median[IQR]1.48(1.03-1.79) μg/mL *vs.* 1.02(0.64-1.36) μg/mL, HR[95%CI]: 2.52[1.02–6.23], p = 0.045).

Signs of interactions between adiponectin and indication for angiography were present for associations with TCFA (p for interaction 0.050 (univariable) and 0.029 (multivariable)), with lesions with MLA ≤ 4.0 (p for interaction 0.058 (univariable) and 0.10 (multivariable)), and with fibrofatty tissue fraction (p for interaction 0.042 (univariable) and 0.082 (multivariable)). The remaining interaction terms were not significant (data not shown).

In patients with SAP, adiponectin levels were associated with the presence of VH-IVUS-derived TCFA lesions (median[IQR] 1.16[0.72-1.48] μg/mL *vs.* 0.95[0.62-1.30] μg/mL; OR[95%CI] per 1 unit increase in ln-transformed-adiponectin: 1.78[1.06-3.00], p = 0.030) (Table 3). Furthermore, adiponectin levels were inversely associated with presence of lesions with MLA ≤ 4.0 mm^2 (median[IQR] 0.95[0.49-1.30] μg/mL *vs.* 1.06[0.69-1.41] μg/mL; OR [95%CI]: 0.55[0.32-0.93], p = 0.025) (Table 3). Finally, adiponectin levels were associated with death (median[IQR] 1.62[1.32-1.84] μg/mL *vs.* 1.02[0.64-1.36] μg/mL; HR [95%CI]: 8.15[1.49-44.68]). After adjustment for age and gender, the HR remained similar in magnitude, although statistical significance was lost (HR [95%CI: 8.48[0.92 – 78.03], p = 0.058).

In patients with ACS, no associations were present between adiponectin and composition or burden of atherosclerosis. Although no associations were present with MACE or acute MACE, a tendency toward a univariable association with death was present (median[IQR] 1.39[0.90-1.86] μg/mL *vs.* 1.01[0.60-1.38] μg/mL; HR [95%CI]: 2.44[0.98-6.06], p = 0.055). After adjustment for age and gender, statistical significance was lost (HR [95%CI]: 1.87[0.67-5.19], p = 0.23).

Given the positive associations we found between adiponectin and death, we performed a post-hoc analysis to explore whether a synergistic effect of adiponectin and TCFA was present on death. For this purpose, we entered interaction terms into the models that consisted of adiponectin multiplied by presence of TCFA lesions. However, no effect modification could be demonstrated (interaction terms were not significant).

Discussion

To our best knowledge, this is the largest study that correlates circulating adiponectin with *in-vivo* measurements of coronary atherosclerosis using VH-IVUS in patients with known coronary disease. We found that in the full cohort, adiponectin levels were associated with death during 1-year follow-up, but not with VH-IVUS measures of atherosclerosis. In patients with SAP, adiponectin levels were positively associated with presence of VH-IVUS-derived TCFA lesions and were inversely associated with presence of lesions with MLA ≤ 4.0 mm^2; while the association with death was borderline significant. In ACS patients we only found a tendency toward an association with death during follow-up.

Fundamental experiments, animal models and human studies on vascular function in subjects free of symptomatic cardiovascular disease have all demonstrated associations of adiponectin with vasoprotective mechanisms, including insulin-sensitizing characteristics and anti-oxidative and anti-inflammatory properties.[4-6,8,10] In line with this, higher levels of adiponectin have been linked to decreased prevalence of CAD in healthy individuals and have demonstrated an inverse association with risk of myocardial infarction.[20,21] However, in patients with manifested CAD, adiponectin seems to play a different role. When elevated in patients with symptomatic CAD, this adipocytokine becomes associated with an increased risk of cardiovascular events; a phenomenon that has been described under the term "reverse epidemiology".[22-25] To explain these conflicting findings, it has been proposed that increased adiponectin levels reflect a compensatory and vasculoprotective mechanism.[25] Specifically, in conditions

Table 1 – Baseline characteristics

	Total (n = 570)	ACS patients (n = 309)	SAP patients (n = 261)
Patient characteristics			
Age, years (mean±SD)	61.5 ± 11.4	59.7 ± 11.9	63.6 ± 10.3
Men, n (%)	430 (75.4)	227 (73.5)	203 (77.8)
Diabetes Mellitus, n (%)	99 (17.4)	40 (12.9)	59 (22.6)
Hypertension, n (%)	295 (51.8)	134 (43.4)	161 (61.7)
Hypercholesterolemia, n (%)	317 (55.6)	137 (44.3)	180 (69.0)
Smoking, n (%)	164 (28.8)	115 (37.2)	49 (18.8)
Positive family history, n (%)	293 (51.5)	140 (45.3)	153 (58.6)
Previous MI, n (%)	184 (32.3)	80 (25.9)	104 (58.6)
Previous PCI, n (%)	185 (32.5)	57 (18.4)	128 (49.0)
Previous CABG, n (%)	18 (3.2)	7 (2.3)	11 (4.2)
Previous stroke, n (%)	23 (4.0)	10 (3.2)	13 (5.0)
Peripheral artery disease, n (%)	36 (6.3)	12 (3.9)	24 (9.2)
History of renal insufficiency (%)	32 (5.6)	13 (4.2)	19 (7.3)
History of heart failure, n (%)	19 (3.3)	6 (1.9)	13 (5.0)
Procedural characteristics			
Indication for coronary angiography			
Acute coronary syndrome, n (%)	309 (54.2)	309 (100)	0 (0)
Myocardial infarction, n (%)	159 (27.9)	159 (51.5)	0 (0)
Unstable angina pectoris, n (%)	150 (26.3)	150 (48.5)	0 (0)
Stable angina pectoris, n (%)	261 (45.8)	0 (0)	261 (100)
Coronary artery disease			
No significant stenosis, n (%)	42 (7.4)	18 (5.8)	24 (9.2)
1-vessel disease, n (%)	301 (52.8)	168 (54.4)	133 (51.0)
2-vessel disease, n (%)	166 (29.1)	88 (28.5)	78 (29.9)
3-vessel disease, n (%)	61 (10.7)	35 (11.3)	26 (10.0)
PCI performed, n (%)	501 (87.9)	287 (92.9)	214 (82.0)
IVUS characteristics			
Segment length (mm), median (IQR)	44.1 (33.7-55.4)	43.9 [32.9-54.1]	44.8 [34.2-57.2]
Plaque burden (%), median (IQR)	39.2 (30.0-46.4)	37.2 [28.0-45.5]	40.2 [31.8-47.8]
Presence lesion with MLA ≤ 4.0mm^2	176 (30.9)	88 (28.7)	88 (33.7)
Presence of VH-TCFA, n (%)	239 (41.9)	140 (45.5)	99 (37.9)
Presence of VH-TCFA with PB ≥ 70%, n (%)	69 (12.1)	32 (10.4)	37 (14.2)
Serum biomarker concentrations			
C-reactive protein (mg/L), median [IQR]	2.1 [0.8-5.3]	2.8 [1.1-7.0]	1.5[0.6-3.1]
Adiponectin (µg/mL) median [IQR]	2.8 [1.9-4.0]	2.9 [1.8-4.1]	2.9 [1.9-3.9]

ACS: acute coronary syndrome; SAP: stable angina pectoris; SD: standard deviation; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; IVUS: intravascular ultrasound; IQR: interquartile range; MLA: minimal luminal area; VH-TCFA: virtual histology thin-cap fibroatheroma; PB: plaque burden.

characterized by a marked systemic pro-inflammatory state and endothelial dysfunction, adiponectin levels increase as an attempt to counter-regulate or compensate for this systemic inflammation. Consequently, the protective effects of adiponectin are superseded by the underlying disease.[25]

In a cohort of 981 patients with stable ischemic heart disease, with average follow-up of 7.1 years, an association was found between higher adiponectin and adverse cardiovascular events (death, heart failure), but after adjustment for cardiac disease severity, the association was no longer statically significant.[24]

Table 2 – Association of adiponectin plasma levels with segment intravascular ultrasound characteristics in the total study cohort, acute coronary syndrome and stable angina patients

	IVUS characteristics	Unadjusted Model	p	Multivariable model*	p
		Beta ‡ (95% CI)		Beta ‡ (95% CI)	
All patients (n = 570)	Segment plaque Burden	-0.40 (-2.04 – 1.23)	0.62	-0.95 (-2.74 – 0.85)	0.30
	Dense calcium fraction %	1.35 (0.27 – 2.44)	0.001	0.36 (-0.86 – 1.58)	0.56
	Necrotic core fraction %	0.43 (-0.71 – 1.58)	0.46	0.39 (-0.92 – 1.70)	0.56
	Fibrofatty tissue fraction %	-0.62 (-1.51 – 0.27)	0.17	-0.46 (-1.46 – 0.55)	0.37
	Fibrous tissue fraction %	-1.17 (-2.81 – 0.48)	0.17	-0.29 (-2.16 – 1.58)	0.76
ACS patients (n = 309)	Segment plaque Burden	0.03 (-2.27 – 2.33)	0.98	-0.89 (-3.42 – 1.63)	0.49
	Dense calcium fraction %	2.53 (0.92 – 3.78)	0.001	1.10 (-0.50 – 2.70)	0.18
	Necrotic core fraction %	0.56 (-1.12 – 2.24)	0.51	0.23 (-1.69 – 2.16)	0.81
	Fibrofatty tissue fraction %	-1.47 (-2.78 – -0.15)	0.029	-0.99 (-2.49 – 0.50)	0.19
	Fibrous tissue fraction %	-1.45 (-3.78 – 0.89)	0.22	-0.35 (-3.00 – 2.30)	0.80
SAP patients (n = 261)	Segment plaque Burden	-0.71 (-3.00 – 1.58)	0.54	-0.87 (-3.46 – 1.73)	0.51
	Dense calcium fraction %	0.39 (-1.25 – 2.01)	0.64	-0.41 (-2.28 – 1.47)	0.67
	Necrotic core fraction %	0.24 (-1.29 – 1.77)	0.76	0.57 (-1.20 – 2.35)	0.52
	Fibrofatty tissue fraction %	0.38 (-0.80 – 1.57)	0.52	0.01 (-1.32 – 1.34)	0.99
	Fibrous tissue fraction %	-1.01 (-3.31 – 1.30)	0.39	-0.17 (-2.82 –2.48)	0.90

**Adjusted for age, gender, diabetes, hypertension, and C-reactive protein (CRP). Additionally adjusted for indication for coronary angiography in the total cohort. †Logarithmically transformed. ‡ Beta per unit increase in ln-transformed adiponectin concentration. IVUS: intravascular ultrasound; CI: confidence interval of 95%; ACS: acute coronary syndrome; SAP: stable angina pectoris; CRP: C-reactive protein.*

Table 3 – Association of adiponectin with presence of virtual histology intravascular ultrasound-derived high-risk lesions in the total cohort, acute coronary syndrome and stable angina patients

		Unadjusted Model	p	Multivariable model*	p
		OR† (95% CI)		OR† (95% CI)	
Total cohort (n = 570)	TCFA	1.11 (0.84 – 1.49)	0.44	1.23 (0.88 – 1.71)	0.23
	TCFA PB ≥70%	0.88 (0.57 – 1.37)	0.55	0.81 (0.50 – 1.33)	0.42
	Lesion with MLA ≤ 4.0 mm^2	0.84 (0.62 – 1.14)	0.25	0.70 (0.49 – 1.00)	0.052
	Lesion with PB ≥70%	1.02 (0.72 – 1.44)	0.93	0.93 (0.63– 1.39)	0.73
ACS patients (n = 309)	TCFA	0.85 (0.58 – 1.26)	0.42	0.90 (0.58 – 1.42)	0.66
	TCFA PB ≥70%	0.90 (0.57 – 1.42)	0.66	0.77 (0.37 – 1.58)	0.48
	Lesion with MLA ≤ 4.0 mm^2	1.13 (0.74 – 1.74)	0.57	0.87 (0.53 – 1.44)	0.59
	Lesion with PB ≥70%	1.25 (0.76 – 2.07)	0.38	1.08 (0.60 – 1.94)	0.80
SAP patients (n = 261)	TCFA	1.54 (0.99 – 2.38)	0.057	1.78 (1.06 – 3.00)	0.030
	TCFA PB ≥70%	0.86 (0.48 – 1.52)	0.60	0.87 (0.45 – 1.69)	0.68
	Lesion with MLA ≤ 4.0 mm^2	0.62 (0.40 – 0.97)	0.035	0.55 (0.32 – 0.93)	0.025
	Lesion with PB ≥70%	0.86 (0.54 – 1.39)	0.54	0.85 (0.49 – 1.47)	0.56

**Adjusted for age, gender, diabetes, hypertension, and C-reactive protein (CRP). Additionally adjusted for indication for coronary angiography in the total cohort. OR: odds ratio; CI: confidence interval of 95%; TCFA: thin-cap fibroatheroma; PB: plaque burden; MLA: minimal luminal area; ACS: acute coronary syndrome; SAP: stable angina pectoris. †Odds ratio per unit increase in ln-transformed biomarker concentration*

Another cohort with median follow-up of 2.5 years found that higher adiponectin levels were associated with future cardiovascular death or nonfatal myocardial infarction in SAP patients (n = 1130), but found no association in ACS patients (n = 760).[22] Our results, demonstrating an association of adiponectin with death in SAP patients, comply with these findings. The lack of statistical significance for this association in ACS patients in our study may, in part, have been caused by a limited number of clinical events. Moreover, pathophysiological differences may possibly have contributed to the difference

Table 4 – Association of adiponectin with major adverse cardiac events, secondary endpoints and death

		Univariable	p	Adjusted for age and gender†	p
		HR* (95% CI)		HR* (95% CI)	
Total (n = 570)	MACE (n = 56)	1.28 (0.81 – 2.02)	0.29	1.19 (0.71 – 1.99)	0.52
	Acute MACE (n = 32)	1.77 (0.96 – 3.23)	0.069	1.36 (0.68 – 2.72)	0.38
	Death (n = 19)	3.36 (1.49 – 7.59)	0.004	2.52 (1.02 – 6.23)	0.045
ACS (n = 309)	MACE (n = 26)	1.29 (0.66 – 2.50)	0.46	1.02 (0.48 – 2.19)	0.95
	Acute MACE (n = 20)	1.75 (0.81 – 3.72)	0.14	1.40 (0.59 – 3.29)	0.44
	Death (n = 14)	2.44 (0.98 – 6.06)	0.055	1.87 (0.67 – 5.19)	0.23
SAP (n = 261)	MACE (n = 30)	1.30 (0.69 – 2.46)	0.42	1.43 (0.69 – 2.98)	0.34
	Acute MACE (n = 12)	1.75 (0.61 – 4.94)	0.29	1.33 (0.41 – 4.28)	0.64
	Death (n = 5)	8.15 (1.49 – 44.68)	0.016	8.48 (0.92 – 78.03)	0.058

*HR: hazard ratio; CI: confidence interval of 95%; MACE: major adverse cardiac events; ACS: acute coronary syndrome; SAP: stable angina pectoris; Acute MACE: composite of death or acute coronary syndrome (secondary endpoints). †Additionally adjusted for indication for coronary angiography in the total cohort. * Hazard ratio per unit increase in ln-transformed biomarker concentration*

we found between SAP and ACS. While in SAP patients, atherosclerosis appears to be a slowly progressing disorder, in ACS patients, coronary plaque rupture may be present, and the latter is accompanied by the production of tissue factor and other homeostatic factors that increase the risk of thrombosis.[3] Plasma adiponectin levels have been inversely correlated with markers of platelet activation.[26,27] This might have possibly influenced the association between adiponectin and clinical outcome in these patients.

Adipose tissue produces both pro- and anti-inflammatory adipocytokines,[10] and adiponectin has shown *in vitro* and *in vivo* anti-inflammatory effects.[28] However, little is known about the clinical significance of adiponectin for coronary plaque stability *in vivo*. Only a few studies have been performed on this topic, all of which at the University of Kobe, Japan. Sample size of these studies was modest. In a randomized trial of 54 patients with type 2 diabetes and stable angina, treated with pioglitazone, adiponectin was found to be associated with a reduction of necrotic core components as assessed by VH-IVUS.[29] A case control study of 63 ACS and 43 non-ACS patients showed that serum adiponectin was inversely associated with necrotic core evaluated by VH-IVUS in both culprit and non-culprit lesions in patients with ACS, but not in those with stable angina.[30] In 50 men with stable CAD, low plasma adiponectin was associated with presence of TCFA.[31] Altogether, these studies point toward an inverse association of adiponectin with plaque vulnerability. In contrast, in our study, we found a positive association of adiponectin with VH-IVUS TCFA in SAP patients. This finding is in line with the association of adiponectin with death, as well as the association of VH-IVUS TCFA with adverse outcome which we demonstrated earlier.[12] However, the exact mechanism behind the positive association between adiponectin and VH-IVUS-derived TCFA lesions warrants further investigation. With regard to the discrepancy between our study and the Japanese ones, differences in study population and sample size could have played a part. Ethnic differences in adiponectin levels are of particular interest in this context. The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study and the Multi-Ethnic Study of Atherosclerosis (MESA) have shown that adiponectin levels are lowest in persons from South Asian or Chinese descent compared to other ethnic groups.[32] Moreover, polymorphisms in the adiponectin gene have been found to be associated with adiponectin levels.[33] Some of these polymorphisms have also shown associations with insulin resistance, metabolic syndrome and the onset of CAD.[32-34] Finally, while we found a positive association of adiponectin with VH-IVUS TCFA, we could not demonstrate such an association with necrotic core fraction. This seeming discrepancy may be explained by the fact that these measures reflect somewhat different aspects of atherosclerosis. Size of necrotic core fraction alone may not be able to fully capture the properties of rupture-prone plaques; the definition of VH-IVUS TCFA on its part incorporates additional plaque properties, such as confluence of the necrotic core and direct contact of the necrotic core with the lumen.

Some limitations of this study need to be acknowledged. The spatial resolution of VH-IVUS (200 μm) is insufficient to exactly replicate histopathological definitions of a thin fibrous cap (<65 μm).[13] Therefore, VH-IVUS tends to over-estimate the number of TCFA lesions. Nevertheless, the presence of VH-IVUS-detected TCFA lesions carries prognostic information[12] and is therefore clinically relevant. Furthermore, VH-IVUS imaging was performed in a prespecified single target segment of a single non-culprit coronary artery.[35] This approach was chosen because previous studies have demonstrated that such segments reflect larger coronary disease burden and are associated with subsequent cardiac events.[12,36] Finally, adiponectin was associated with mortality, but the number of deaths in our dataset was small.

Conclusion

In conclusion, in the full cohort, adiponectin levels were associated with death but not with VH-IVUS measures of atherosclerosis. In SAP patients, adiponectin levels were

associated with VH-IVUS derived TCFA lesions, while the association with death was borderline significant. Altogether, a substantial role for adiponectin in plaque vulnerability remains unconfirmed and warrants investigation by other, large studies.

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Conception and design of the research: Akkerhuis M, Garcia-Garcia HM, Serruys PW, Boersma E, Kardys I; Acquisition of data: Buljubasic N, Cheng JM, Garcia-Garcia HM, Regar E, Robert-Jan VG, Serruys PW, Kardys I; Analysis and interpretation of the data: Marino BCA, Buljubasic N, Akkerhuis M, Cheng JM, Garcia-Garcia HM, Regar E, Robert-Jan VG, Serruys PW, Boersma E, Kardys I; Statistical analysis: Marino BCA; Obtaining financing: Serruys PW, Boersma E, Kardys I; Writing of the manuscript: Marino BCA; Critical revision of the manuscript for intellectual content: Buljubasic N, Akkerhuis M, Cheng JM, Garcia-Garcia HM, Regar E, Robert-Jan VG, Serruys PW, Boersma E, Kardys I.

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

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Original Article

Adiponectin in Relation to Coronary Plaque Characteristics on Radiofrequency Intravascular Ultrasound and Cardiovascular Outcome

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Short Editorial regarding the article: Adiponectin in Relation to Coronary Plaque Characteristics on Radiofrequency Intravascular Ultrasound and Cardiovascular Outcome

Inflammation is a complex and necessary component of the response to biological, chemical, or physical stimuli, and the cellular and molecular events that initiate and regulate the interactions between the various players in the inflammatory process of the atherosclerotic lesions remain a source of ongoing investigation.[1]

The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound (ATHEROREMO-IVUS) study aimed to investigate the relations of genetic profile and novel circulating and inflammatory biomarkers with coronary plaque phenotype and vulnerability as determined by intravascular ultrasound (IVUS).[2] Results from this trial have been helping us to improve our knowledge on the role of genetic profile and circulating inflammatory biomarkers in relation to the development of atherosclerosis and vulnerable plaques.

Keywords

Inflammation/physiopathology; Atherosclerosis; Biomarkers/blood; Plaque, Atherosclerotic/diagnostic imaging; Plaque, Atherosclerotic/genetics; Ultrasonography, Interventional; Adiponectin

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As an endocrine organ, adipose tissue is recognized as a rich source of pro-inflammatory mediators that may directly contribute to vascular injury, insulin resistance, and atherogenesis.[3] Therefore, this kind of tissue may modulate inflammatory response by releasing a wide range of mediators, known as adipocytokines. Adiponectin, a kind of adipocytokines, has antiatherogenic and anti-inflammatory properties and acts as a factor increasing insulin sensitivity, and its protective effect may result from its ability to suppress production of proinflammatory cytokines.[3] Due to the complex balance between pro- and anti-inflammatory activity, their pathophysiological and prognostic role in cardiovascular diseases still remains debated.[4]

Adiponectin, tested in this trial, was presented herein by Marino BCA et al.[5] Although the median of its serum value in the complete cohort is not associated to the composition of the atherosclerotic plaque nor to the plaque burden assessed by Virtual Histology IVUS (VH-IVUS), it may be considered as an independent variable of death in this sample. Differently, in the sub-group of patients with stable symptoms, adiponectin median value was associated to a thin-cap fibroatheroma identified by VH-IVUS, but not to death.

These discrepancies reveal the difficulty in this elegant way in attempting to identify any biomarker for the recognition of patients with vulnerable atherosclerotic plaques and therefore at high risk for hard outcomes such as death. But it also shows that this is a long way, but one that must be pursued and validated, and then, try to find out what else, besides the measures already known, can be added to this so special group of patients and with a such high risk.

Short Editorial

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Secondary Dyslipidemia In Obese Children – Is There Evidence For Pharmacological Treatment?

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Abstract

Background: Long-term safety, effectiveness and criteria for treatment with statins in children are still unclear in clinical practice. There is very limited evidence for the use of medication to treat children with dyslipidemia secondary to obesity who do not respond well to lifestyle modification.

Objective: Systematic review of randomized clinical trials of statin use to treat children and adolescents with dyslipidemia secondary to obesity.

Methods: We performed a search in PubMed, EMBASE, Bireme, Web of Science, Cochrane Library, SciELO, and LILACS for data to evaluate the effect of statins on: improvement of surrogate markers of coronary artery disease in clinical outcomes of adulthood; increased serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and apolipropotein B (APOB); and decreased serum levels of high-density lipoprotein cholesterol (HDL-C) from inception to February 2016. Participants were children and adolescents.

Results: Of the 16793 potentially relevant citations recovered from the electronic databases, no randomized clinical trials fulfilled the inclusion criteria for children with dyslipidemia secondary to obesity.

Conclusions: We found no specific evidence to consider statins in the treatment of hypercholesterolemia secondary to obesity in children. The usual practice of extrapolating findings from studies in genetic dyslipidemia ignores the differences in long-term cardiovascular risks and the long-term drug treatment risks, when compared to recommendation of lifestyle changes. Randomized clinical trials are needed to understand drug treatment in dyslipidemia secondary to obesity. (Arq Bras Cardiol. 2018; 111(3):356-361)

Keywords: Dyslipidemias; Child; Obesity; Adolescents; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Cholesterol.

Introduction

According to the National Survey on Health and Nutrition Examination, 11.7% of adults aged 20-39 years and 41.2% of adults aged 40-64 years had elevated low-density lipoprotein cholesterol (LDL-C) levels.[1] Recent data shows that the estimated number of adults who have total cholesterol (TC) levels ≥ 240 mg/dL reaches 30.9 million and 32.6% of the adults have hypertension.[2] In 2011-2012, of 5 boys and girls, 1 had abnormal concentration of TC, high-density lipoprotein cholesterol (HDL-C) or non-high density lipoprotein cholesterol (non-HDL-C). The prevalence of high TC, HDL-C, non-HDL-C is 7.8%, 12.8% and 8.4%, respectively, and 20.2% had abnormal concentration of at least 1 of the 3 measurements.[3] Dyslipidemia causes have changed in epidemiological studies; previously, genetic disturbances were the most common conditions causing dyslipidemia in children. In the last few decades, dyslipidemia secondary to obesity (DSO) has been increasing.[4]

Drug therapy for high-risk lipid abnormalities resulted in great advances in the prevention and treatment of atherosclerotic diseases in adults.[5] However, the use of pharmacological therapy in children with secondary dyslipidemia is a subject of controversy. Safety, effectiveness and criteria for statin treatment in children are unclear in clinical practice.[6] There is limited evidence for medication use in children with DSO that do not respond well to lifestyle modification. The majority of studies with statins refer to children and adolescents with genetic dyslipidemia and higher levels of LDL-C.

The objective of this study is to discuss critically the evidence about the effectiveness, safety and effects of the use of statins in children and adolescents with DSO, based on a systematic review of the literature.

Methods

This systematic review was performed in accordance with the PRISMA Statement and registered at the PROSPERO under identification CRD42015020530.

The search was conducted in MEDLINE (via PubMed), EMBASE, Bireme, Web of Science, Cochrane Library, SciELO,

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and LILACS. The search strategy included the terms: "Child", "Adolescent", "Hypercholesterolemia", "Dyslipidemias", "Cholesterol", "Hydroxymethylglutaryl-Coa reductase inhibitors", "Statin", "HDL-C" and "Triglycerides". Two reviewers (G.R. and G.S.) performed the literature search and study selection independently. Disagreements were solved by consensus or by a third reviewer (L.C.P.).

Selection criteria

Types of study: Randomized clinical trials describing statin therapy for children and adolescents. Participants: children and adolescents (up to 18 years old). Interventions: statins for at least 8 weeks. Target condition: DSO. Outcomes: reduction in the risk factors, TC, LDL-C, apolipropotein B (APOB) and HDL-C, improvement in the coronary artery disease indirect markers and/or clinical outcomes in adult life.

Search limits: Language: no language restriction. Time period: from inception to February 2016. Design: Randomized clinical trials. Main outcome: risk factors reduction in the infancy, improvement of coronary artery disease indirect markers in clinical outcomes of adult life. Secondary outcomes: statin effects - elevated plasmatic levels of TC, LDL-C and APOB, decrease in the HDL-C levels.

Inclusion criteria: Randomized clinical trial reporting children with statin treatment for at least 8 weeks.

Exclusion criteria: Non-blinded treatment duplicated data or absent reporting of considered outcomes.

Data extraction and quality evaluation: The CONSORT analysis instrument was used to evaluate methodological quality of the included studies performed by two independent reviewers.

Results

We identified 16793 citations from the electronic search of the databases from inception to February 2016. After duplicate studies were removed, 15820 studies were subjected to title and abstract screening. We excluded 15740 studies and 80 studies were subjected to full-text review. We did not include any randomized clical trial about DSO in children, and all 80 articles of full-texts were excluded for the reasons: 39 studies on non-pediatric population (subjects aged 18 to 80 years), 15 studies did not use treatment with statins, 12 studies did not have the design of a randomized clinical trial, and 14 randomized clinical trials evaluated children and adolescents with familial hypercholesterolemia (FH), involving a total of 2347 individuals (Figure 1).

Discussion

Dyslipidemia secondary to obesity in children and adolescents is increasingly prevalent in clinical practice. However, the present review did not retrieve specific evidence about drug therapy in this group.

In this type of dyslipidemia, the most common lipid alterations are low HDL-C and elevated triglycerides (TG) secondary to insulin resistance syndrome.[7] High TC levels may be associated with these conditions, but cannot be considered the most important factor. Steinberg et al.[8] showed that the degree of insulin resistance explains a significant proportion of variation in the levels of TG, LDL-C, and HDL-C, and Stan et al.[9] estimated a 10% prevalence of small dense LDL (sdLDL) particles in children showing insulin resistance compared to 1% in those without insulin resistance. As recommended by the Expert Panel,[5] low saturated-fat and cholesterol diet is the first approach to lower TC and LDL-C levels, to reduce obesity and insulin resistance, and to prevent the development of atherosclerosis. These recommendations[8] confirm that primary prevention in children with dyslipidemia involves lifestyle modification. In childhood, the construction of healthy eating habits must be emphasized, since early preference patterns have a long-term influence on dietary intake later in life.[10,11] To provide information about nutrition is, therefore, an important part of the routine visits.[12,13] However, neither assessment of the patient's nutritional status nor discussion of dietary habits seem to be performed systematically.[14] Physicians often point to the lack of knowledge in this area as one of the main limitations to this practice.[15-17]

On the other hand, obese children may also suffer from FH, that is phenotypically diagnosed by the presence of high levels of LDL-C and a family history of premature cardiovascular disease and/or high cholesterol at baseline in one of the parents and/or a mutation that causes FH.[18-20] After dietary intervention, any child with LDL-C ≥ 5 mmol/L (190 mg/dL) has high probability of having genetic FH. A family history of premature cardiovascular disease in close relatives and/or high cholesterol levels at baseline in a parent, LDL-C ≥ 4 mmol/L (160 mg/dL) are also indicative of a high probability of genetic FH. The detection of a pathogenic mutation, usually in the LDLR gene, is the gold-standard diagnosis test for FH. The LDL-C levels must be measured at least twice in 3 months to confirm the diagnosis of FH.[21]

The maintenance of a healthy lifestyle and statin treatment (age 8 to 10 years) are proposed as the main interventions to control heterozygous FH (HeFH). The target of LDL-C for children is 3.5 mmol/L (130 mg/dL) if > 10 years old, or, ideally, to reduce 50% of the baseline level among children aged 8 to 10 years, especially with an extremely high LDL-C, high levels of lipoprotein(a), family history of premature cardiovascular disease or others cardiovascular risk factors, balanced against the risk of long-term adverse effect of treatment.[18,21-23] Statins have shown better effects on major cardiovascular outcomes, justifying their use despite their still unknown side effects when used for more than 2 years in children.[24]

The inhibitors of HMG-CoA reductase have shown repeatedly in random controlled studies to effectively reduce coronary morbidity and mortality in adults at high risk. As a result, statins have become one of the most prescribed drugs for adults in the world.[25] In adults, statins have proved to effectively reduce both LDL-C levels and vascular events.[26,27]

At usual doses, statins are a remarkably safe drug group. Few reports exist about serious adverse gastrointestinal events, and hepatic transaminases and creatine-phosphokinase elevation. However, evidence for their use in children still lacks.[28] Children with serious lipid abnormalities due to genetic disorders may meet the criteria for drug therapy with the statins commonly used in adults. In the last few years, reports about the short-term safety of some of these drugs in this group have been published.[29-31]

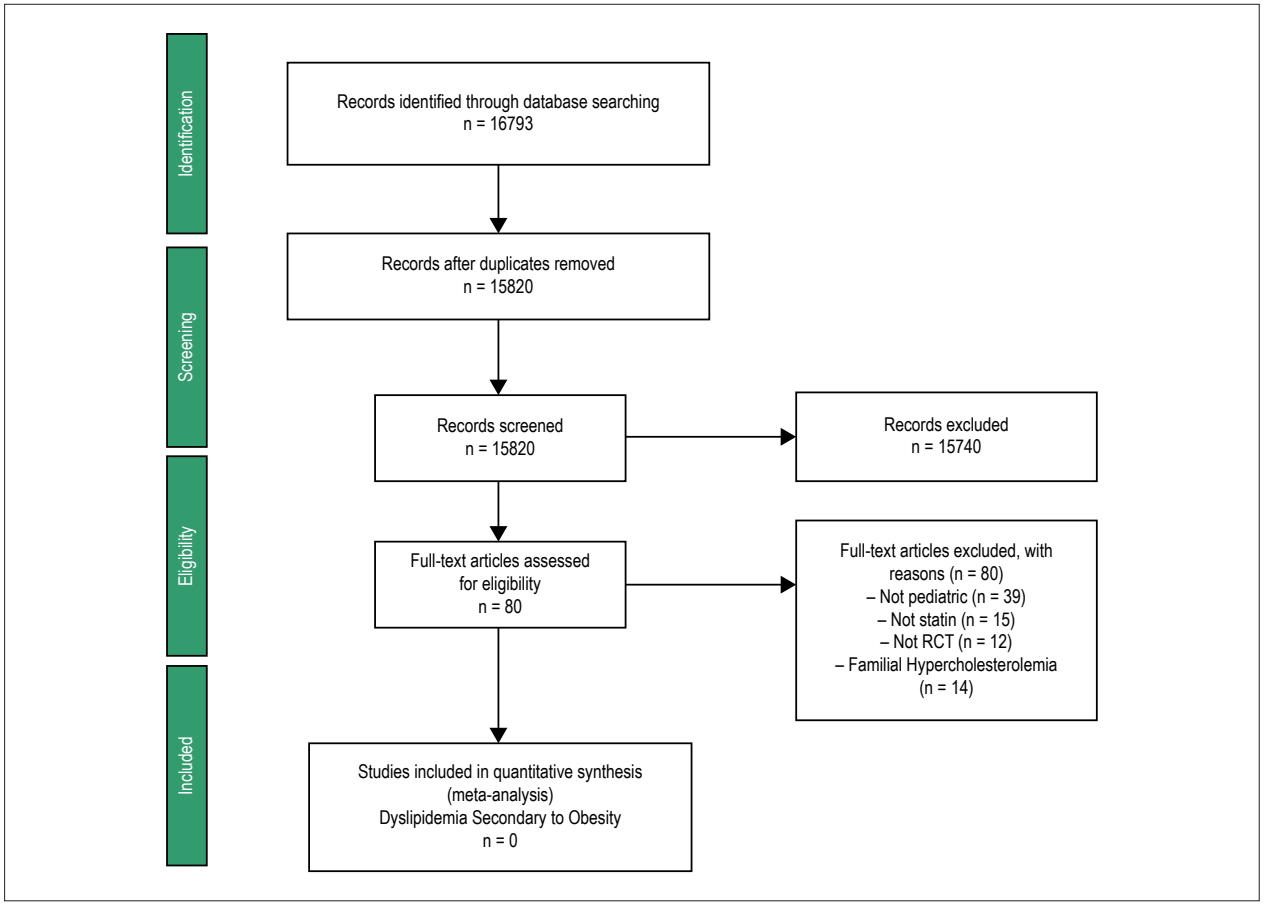

Figure 1 – *Flow diagram of the studies included. RCT: randomized clinical trial.*

All statins recommended by the US Food and Drug Administration (FDA)[23] have been approved for children with FH and some other primary or genetic dyslipidemia causes. Data about cholesterol reduction in other groups of children were insufficient.[32] The statins used to treat children with HeFH are approved by the FDA or used in treatments based on cholesterol-lowering studies in children with HeFH.[33] For other dyslipidemia causes in children, the focus should be on the diet and treating subjacent metabolic disorders.[34] Treatment may be started earlier in severe cases.[35]

Effectiveness and safety are similar in both children with genetic disorders and children with DSO in the short term. However, concerns about long-term safety still remain.[36,37] None of these studies cited above had a long-term follow up, and none of them described potential late collateral effects of early therapy for cholesterol reduction or delay in cardiovascular outcomes.[38] Kusters et al.[39] have reported the longest follow-up in children with FH treated with statins. Long-term treatment with statins started during childhood in patients with FH was associated with the normalization of the ntima-media thickness progression. No serious adverse event was reported during the 10-year follow-up. Braamskamp et al.[40] have published the first study that evaluated the long-term effect of statin treatment started in childhood on the plasma of gonadal steroid hormones, gonadotropins and dehydroepiandrosterone in young adults with FH. After 10 years of statin treatment, the concentrations of testosterone, estradiol, luteinizing hormone and follicle stimulating hormone in those patients with FH were within the reference range when compared with non-affected siblings.

Before starting the widespread use of statins in children with secondary dyslipidemias, ideally studies should establish that statins can reduce total morbidity and mortality in the long-term. There must also be a logical progression of studies addressing primary prevention, from the oldest to the youngest. The use of statins for primary prevention in adults with secondary hyperlipidemia is currently under debate. The introduction of statins at an earlier age may offer the possibility of greater risk reduction than the one currently observed in studies with adults, but to this date this hypothesis remains highly speculative.

Conclusions

In our search, we found no randomized clinical trial addressing the use of statin therapy in children and adolescents with DSO. All studies retrieved had been performed in patients with FH.

The usual practice of extrapolating findings from studies in genetic dyslipidemia ignores the differences in long-term cardiovascular risks and long-term drug treatment risks, when compared to recommendation of lifestyle changes. Randomized clinical trials are needed to understand drug treatment in secondary dyslipidemia.

Author contributions

Conception and design of the research: Radaelli G, Pellanda LC; Acquisition of data: Radaelli G, Sausen G; Analysis and interpretation of the data and Writing of the manuscript: Radaelli G, Cesa CC; Obtaining financing: Radaelli G; Critical revision of the manuscript for intellectual content: Radaelli G, Sausen G, Cesa CC, Portal VL, Pellanda LC.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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Original Article

Secondary Dyslipidemia In Obese Children – Is There Evidence For Pharmacological Treatment?

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Short Editorial regarding the article: Secondary Dyslipidemia In Obese Children – Is There Evidence For Pharmacological Treatment?

Obesity is a condition that has progressively increased throughout the world, also affecting children and adolescents, leading to high costs for health systems. Pediatric obesity is associated with dyslipidemia, oxidative stress, insulin resistance, and endothelial dysfunction, cardiovascular risk factors and components of the metabolic syndrome,[1] and leads to adverse consequences such as early mortality and physical morbidity in adulthood in the short and long term.

Obesity-related dyslipidemia consists of increased triglycerides and free fatty acids, and decreased HDL-c (high-density cholesterol), normal or slightly increased LDL-c (low-density cholesterol), and increased VLDL-c (cholesterol of very low density). Plasma apolipoprotein B (apo B) concentrations are also frequently increased, in part due to increased hepatic production of apo B-containing lipoproteins.[2,3]

In most cases, dyslipidemia is a consequence of bad lifestyle habits, such as a diet rich in saturated or trans fats, and sedentarism. To plan monitoring and treatment, a cardiovascular risk stratification should be done since childhood, and not only the child, but especially the entire family living with him/her, should be educated. Longitudinal studies have shown that interventions in children are effective in the prevention of cardiovascular disease in adults.

The treatment of obesity-related dyslipidemia should be directed to weight loss through increased physical exercise and better eating habits, with a reduction in total calorie intake and reduced intake of essential fatty acids. Lifestyle changes synergistically improve insulin resistance and dyslipidemia.[4] The child and the adolescent should be ideally followed by a nutritionist or nutrologist, because of the risk of growth and development impairment.

Interaction among genes, obesity and lipid levels, but also with the type of fat taken in the diet, was recently described.[5,6] Studies suggest the potential utility of a nutrigenomic approach to dietary interventions to prevent or treat obesity and its associated dyslipidemia.[5,6]

Further studies should be conducted on the behavior of coronary artery disease markers, and of serum levels of total cholesterol, low-density lipoprotein, apolipoprotein B, and high-density lipoprotein in children and adolescents compared to adults,[2] both in the pre- and post-treatment of obesity-related dyslipidemia, and in the short and long term, considering the cardiovascular risks, and the adverse effects resulting from pharmacological treatment, especially of statins.[3,7-11]

Lipid-lowering therapy should be started after at least six months of intensive lifestyle modification. The drugs used are statins, cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants, phytosterol supplements, omega-3s, and fibrates.

Statins are the drugs of choice among all pharmacological agents to reduce LDL-c, non-HDL-c and/or apoB. However, statins do not lower triglycerides well, and do not completely correct the characteristic dyslipidemia observed in obesity, keeping a residual risk after therapy initiation.[11] Recently, strategies for therapies combined with statins and other drugs to achieve even lower cholesterol levels have been reviewed.[11-15]

Children and adolescents with dyslipidemias who do not adequately respond to changes in lifestyle and habitual doses of lipid-lowering medications should be referred to specialist centers.

The work presented in this issue on secondary dyslipidemia in obese children demonstrates the scarcity of randomized clinical trials in the literature on the use of statins for the treatment of children and adolescents with obesity-related dyslipidemia.

Undoubtedly, this is a topic that should be investigated in depth and in details, with well-defined studies, to prove the efficacy of the several treatments already consecrated for the adult population in the pediatric and adolescent age.

Keywords

Heart Defects, Congenital; Dyslipidemias; Oxidative Stress; Metabolic Syndrome; Indicators of Morbidity and Mortality.

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Obstructive Sleep Apnea is Common and Associated with Heart Remodeling in Patients with Chagas Disease

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Abstract

Background: **Chagas Disease (CD) is an important cause of morbimortality due to heart failure and malignant arrhythmias worldwide, especially in Latin America.**

Objective: **To investigate the association of obstructive sleep apnea (OSA) with heart remodeling and cardiac arrhythmias in patients CD.**

Methods: **Consecutive patients with CD, aged between 30 to 65 years old were enrolled. Participants underwent clinical evaluation, sleep study, 24-hour Holter monitoring, echocardiogram and ambulatory blood pressure monitoring.**

Results: **We evaluated 135 patients [age: 56 (45-62) years; 30% men; BMI: 26 ± 4 kg/m², Chagas cardiomyopathy: 70%]. Moderate to severe OSA (apnea-hypopnea index, AHI, ≥ 15 events/h) was present in 21% of the patients. OSA was not associated with arrhythmias in this population. As compared to patients with mild or no OSA, patients with moderate to severe OSA had higher frequency of hypertension (79% vs. 72% vs. 44%, p < 0.01) higher nocturnal systolic blood pressure: 119 ± 17 vs. 113 ± 13 vs. 110 ± 11 mmHg, p = 0.01; larger left atrial diameter [37 (33-42) vs. 35 (33-39) vs. 33 (30-36) mm, p < 0.01]; and a greater proportion of left ventricular dysfunction [LVEF < 50% (39% vs. 28% vs. 11%), p < 0.01], respectively. Predictor of left atrial dimension was Log_{10} (AHI) (β = 3.86, 95% CI: 1.91 to 5.81; p < 0.01). Predictors of ventricular dysfunction were AHI > 15 events/h (OR = 3.61, 95% CI: 1.31 - 9.98; p = 0.01), systolic blood pressure (OR = 1.06, 95% CI: 1.02 - 1.10; p < 0.01) and male gender (OR = 3.24, 95% CI: 1.31 - 8.01; p = 0.01).**

Conclusions: **OSA is independently associated with atrial and ventricular remodeling in patients with CD. (Arq Bras Cardiol. 2018; 111(3):364-372)**

Keywords: **Chagas Disease; Sleep Apnea, Obstructive; Ventricular Remodeling; Arrhythmias, Cardiac.**

Introduction

Chagas disease (CD) is the third most common parasitic infection, after malaria and schistosomiasis, affecting about 7 to 8 million people worldwide.[1] CD is caused by the protozoan *Trypanosoma cruzi*, transmitted to humans by insects (*Triatominae*), blood transfusion, organ and tissue transplantation, oral contamination or congenital transmission.[2]The epidemiological profile of the disease has been modified in recent decades, due to migratory flows,[2] thus also generating attention in non-endemic countries such as the United States, Canada, Spain, Italy and Japan.[3,4]

Chagas cardiomyopathy is the most common form of nonischemic cardiomyopathy and one of the leading causes of complications and death in Latin America.[5] Approximately one third of patients with CD develop Chagas cardiomyopathy[3] characterized by ventricular arrhythmias, cardiac blockages, alterations in cardiac proteins with heart remodeling, heart failure and sudden death. Heart failure due to CD worsens patient prognosis, when compared with other cardiomyopathies.[6] In addition to the myriad of characteristics involved in CD, it is important to consider potential comorbidities that may have a negative impact on patients' health.

Obstructive sleep apnea (OSA) is the most frequent respiratory disturbance in the overall population and is associated with heart remodeling and arrhythmias in patients without[7,8] and with comorbidities, including heart failure.[6] However, whether this association exists in patients with CD is unknown. We hypothesized that OSA is independently associated with cardiac arrhythmias and heart remodeling in patients with CD.

Methods

Subjects

Consecutive patients with CD (with two positive blood tests-immunofluorescence and ELISA), aged between 30 and 65 years old were recruited from a specialized outpatient service

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from August 2013 to August 2014. Chagas cardiomyopathy was diagnosed in patients with serological evidence of antibodies to *T. cruzi* and evidence of Chagas heart disease who may or may not have cardiac symptoms (such as dyspnea, edema, and chest pain). The indeterminate form of CD was diagnosed in patients with serological and/or parasitological evidence of *T. cruzi* infection who lacked symptoms, physical signs, electrocardiographic abnormalities and any radiographic evidence (on chest radiography, barium-contrast esophageal, or colon radiography) of cardiac or gastrointestinal involvement.[9] Patients with cardiac pacemakers, manifest or suspected coronary disease; decompensated heart failure requiring hospital admission, predominant central sleep apnea (>50% of events scored as central), or renal disease (serum creatinine >2mg/dL), as well as those with a previous stroke were excluded.

Patients were invited to undergo the sleep study in the week after they underwent all examinations, including echocardiography, Ambulatory Blood Pressure Monitoring (ABPM) and 24-hour Holter monitoring as described below.

Sleep Study

All patients underwent portable sleep monitoring in the sleep laboratory using a validated device (Embletta Gold, PDS; Medcare, Reykjavik, Iceland)[10] to evaluate oxygen saturation, body position, nasal flow measurements (pressure cannula), and respiratory effort measurements using two respiratory inductance plethysmography belts. All exams were scored by an experienced physician. Apnea was defined as total absence (>90%) and hypopneas as a decrease (>30%) in nasal flow for ≥ 10 seconds, followed by a 4% desaturation (in hypopneas), respectively.[11] The apnea-hypopnea index (AHI) was calculated by dividing the total number of apnea and hypopnea events by the total hours in bed.[11,12]

Mild OSA was defined by an AHI between 5 and 14.9 events/h and moderate to severe OSA was considered when the AHI was ≥ 15 events/h. The oxygen desaturation index (ODI) was calculated as the total number of desaturations, divided by the total time in bed.

Excessive daytime sleepiness was evaluated using the Epworth Sleepiness Scale. A total score > 10 was considered excessive daytime somnolence.[13]

Office blood pressure

Blood pressure (BP) was measured after 5 min of rest using standard protocols.[14] The average of two readings was obtained at 5 min intervals with an automatic digital sphygmomanometer (Omron BP742).

Ambulatory Blood Pressure Monitoring (ABPM)

All participants underwent blood pressure monitoring for 24 hours, using SpaceLabs equipment (model 90207; SpaceLabs, Redmond, WA). The BP reading was taken every 10 minutes during the day and every 20 minutes at night, using an appropriate cuff placed on the non-dominant arm. Participants were instructed to perform their ordinary daily activities and not to move their arm during the ongoing measurement. Activity, bedtime, and time on awakening from sleep were recorded by participants in diaries.[15] The normal BP dip was defined separately for systolic and diastolic BP as a ≥ 10% reduction in BP during sleep compared with the awake period. Nondipping was defined as a decrease of < 10%.

Holter monitoring

Holter monitoring (Cardios®, Cardio Systems, São Paulo, Brazil) was performed in all patients for 24 hours. The following characteristics of the ECG were analyzed: baseline heart rhythm, heart rate, ventricular and atrial arrhythmias, and breaks. The complexities of the arrhythmias were described as follows: isolated, paired, or tachycardia.[16] Patients were instructed to keep a diary with their symptoms during the exam. The Holter analysis was performed by an experienced observer, who was blinded to the presence or absence of OSA.

Echocardiogram

A transthoracic echocardiogram was performed using a Philips IE33 S5-1 device. Conventional M-mode echocardiography was used to measure cavity dimensions (diastolic and systolic diameters, wall thickness, and aorta and left atrial size).[17] Left atrial volumes were indexed by body surface area according to the American Society of Echocardiography.[18] Using two-dimensional echocardiography, segmental and global contractility were assessed, and the left ventricular ejection fraction (LVEF) was calculated using Simpson's formula. Ventricular dysfunction was considered when LVEF <50%.[18] **Le**ft ventricular longitudinal strain with speckle-tracking was calculated and values below –16% were considered abnormal.[19] The Echocardiographic evaluation was performed by the same experienced observer, who was blinded to the presence or absence of OSA.

Statistical analysis

Normality distribution was evaluated with the Kolmogorov-Smirnov test.

For the categorical variables, the Chi-square test of Pearson was used. Quantitative variables with a normal distribution were presented as mean and standard deviation and the ANOVA test was used, whereas the variables without normal distribution were presented as median and percentiles (P25; P75) and the Kruskal-Wallis was used, with Bonferroni post-hoc test, when appropriate.

A multiple linear regression analysis was performed to evaluate independent predictors of left atrial dimensions. The independent variables of the left atrial dimensions were age, 24-hour systolic BP, body mass index (BMI), and AIH. Due to the non-normality of the AHI, a log-transformed version of this variable was used in the multivariate model. To analyze the predictors of ventricular dysfunction, a multiple logistic regression analysis was performed with the following variables: age, BMI, male gender, 24-hour systolic BP, diabetes mellitus diagnosis, AHI ≥15 events/h, ODI, and saturation < 90%. The data were analyzed with SPSS 21.0 statistical software (IBM Corporation) and a value of $p < 0.05$ was considered significant.

Results

We consecutively evaluated 287 patients with CD (41 [30%] with the indeterminate form of the disease and 94 [70%] with Chagas cardiomyopathy). Most of the exclusions were due to the presence of cardiac pacemakers (Figure 1). One patient had a predominance of central sleep apnea and was also excluded, resulting in a final sample of 135 patients (Figure 1).

The frequency of OSA in patients with CD was 58%. Mild OSA was diagnosed in 50 patients (37%) and moderate-to-severe OSA (IAH ≥ 15 events/h) in 28 patients (21%). None of the participants had a previous OSA diagnosis. Patients with moderate-to-severe OSA had larger neck and waist circumferences, a higher frequency of high blood pressure and a higher percentage of them were on diuretics, b-blockers and ACE inhibitors, as well as AT1 inhibitors compared to patients with mild and no OSA, respectively (Table 1).There was no difference in the degree of sleepiness (Epworth Sleepiness Scale) between the groups (Table 1). The demographics and clinical characteristics according with the absence or presence of OSA are described in Table 1.

Overall, there were no clinically significant differences in supraventricular and ventricular arrhythmia frequencies across the three groups. However, there was a greater proportion of supraventricular paired in patients with moderate-to-severe OSA, compared with patients with mild and no OSA (50% vs 40% and 23%; p = 0.03), respectively. (Table 2)

Patients with moderate-to-severe OSA had increased nocturnal blood pressure (119 ± 17 vs. 113 ± 13 and 110 ± 11 mmHg; p = 0.01) compared to patients with mild and no OSA, respectively (Table 3). The aorta size, left ventricular systolic and diastolic diameters, septum and posterior wall thickness were similar between groups. Left atrial diameter [37 (33-42) vs. 35 (33-39) and 33 (30-36) mm, p < 0.01(Figure 2) and volume [66(54-95)vs. 46(39-65) and 42(35-56) mL/m^2, p < 0.001] were larger in patients with moderate-to-severe OSA, compared with mild and no OSA groups, respectively(Table 3).

These findings were significant when the whole study population was analyzed, as well as in the subgroup of patients with Chagas cardiomyopathy, but not in patients from the indeterminate group. Left ventricular longitudinal strain was

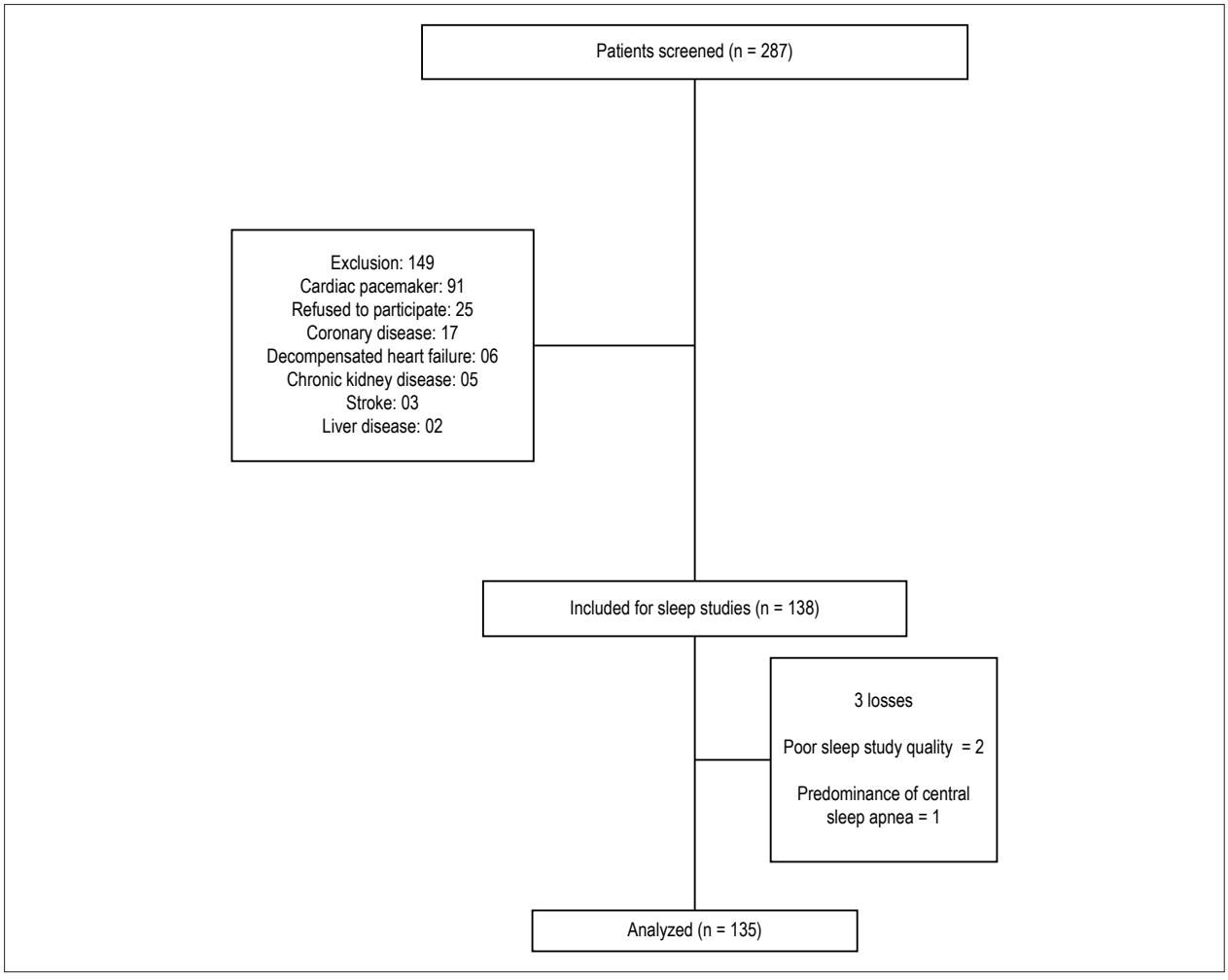

Figura 1 – *Diagrama de fluxo do paciente.*

Table 1 – Anthropometrics and clinical characteristics

	Total n = 135	No OSA n = 57	Mild OSA n = 50	Mod/Severe OSA n = 28	p
Age, years	56 (45–62)	48 (42–58)	59 (55–63)	61 (51–63)	< 0.001*
Male, n (%)	40 (30)	15 (26)	15 (30)	10 (36)	0.67†
BMI, kg/m^2	26.3 ± 4.2	24.7 ± 3.9	27.4 ± 3.9	27.6 ± 4.5	0.001¥
Neck circumference, cm	35 (33–38)	34 (32–36)	36 (33–39)	38 (34–39)	0.02†
Waist, cm	92 (83–96)	87 (79-92)	96 (89–102)	96 (91–104)	< 0.001*
Caucasians, n (%)	43 (32)	19 (33)	16 (32%)	8 (29%)	0.86†
Diabetes mellitus, n (%)	17 (13)	5 (9)	7 (14)	5 (18)	0.46†
Hypertension, n (%)	83 (62)	25 (44)	36 (72)	22 (79)	0.001†
Office Systolic BP, mmHg	131 ± 22	128 ± 20	135 ± 22	133 ± 26	0.27¥
Office Diastolic BP, mmHg	81 ± 11	83 ± 11	81 ± 12	78 ± 11	0.14¥
Use of antihypertensive drugs, n	1 (0–2)	1 (0–2)	2 (1–2)	2 (0–3)	0.001†
Diuretics, n (%)	54 (40)	13 (23%)	26 (52%)	15 (54%)	< 0.001†
ACE inhibitors / AT1 inhibitors n (%)	76 (56)	23 (30%)	35 (46%)	14 (24%)	< 0.001†
B-blockers, n (%)	57 (42)	17 (30%)	25 (50%)	13 (54%)	0.04†
Spironolactone, n (%)	14 (10)	5 (9%)	5 (10%)	4 (14%)	0.73†
Epworth sleepiness scale, Score, n (%)	9.8 ± 4.9	9.3 ± 5.2	10.2 ± 5.2	10.1 ± 3.8	0.57¥

*Values are mean (±SD). Variables with skewed distribution presented as median (interquartile range). OSA: obstructive sleep apnea; BMI body mass index; BP: blood pressure. *: Test of Kruskal-Wallis; †: Chi-square test of Pearson; ¥: Anova test.*

Table 2 – Holter evaluation – Distribution of atrial and ventricular arrhythmias

Variable	Total n = 135	No OSA n = 57	Mild OSA n = 50	Mod/Severe OSA n = 28	p
HR Minimum (b.p.m)	50 (45–55)	50 (45–56)	50 (45–56)	52 (46–54)	0.97*
HR Average (b.p.m)	71 (65–77)	71 (66–79)	71 (65–74)	71 (62–75)	0.82*
HR Maximum (b.p.m)	113 (105–25)	118 (109–132)	112 (103–121)	109 (98–121)	0.045*
Total awake ventricular (%)	94 (70)	39 (68)	37 (74)	18 (64)	0.65†
Total sleep ventricular (%)	95 (70)	36 (63)	40 (80)	19 (68)	0.16†
Isolated ventricular arrhythmias (%)	107 (79)	44 (77)	40 (80)	23 (82)	0.86†
Ventricular bigeminy (%)	38 (79)	14 (25)	14 (28)	10 (36)	0.56†
Ventricular paired (%)	50 (37)	18 (32)	19 (38)	13 (46)	0.41†
Non-sustained ventricular tachycardia	27 (20)	10 (18)	10 (20)	7 (25)	0.72†
Total awake supraventricular	115 (85)	47 (83)	42 (84)	26 (93)	0.43†
Total sleep supraventricular	118 (87)	48 (84)	44 (88)	26 (93)	0.52†
Isolated supraventricular tachycardia (%)	124 (92)	51 (90)	48 (96)	25 (89)	0.40†
Supraventricular paired (%)	47 (35)	13 (23)	20 (40)	14 (50)	0.03†
Non-sustained supraventricular tachycardia (%)	27 (20)	10 (18)	10 (20)	7 (25)	0.26†
Chronic atrial fibrillation (%)	1 (0.7)	0	1 (2)	0	0.43†
Paroxysmal atrial fibrillation (%)	1 (0.7)	0	0	1 (3.6)	0.15†
Right bundle-branch block (%)	62 (46)	23 (46)	23 (54)	9 (41)	0.59†

*OSA: obstructive sleep apnea; HR: Heart Rate; *: Test of Kruskal-Wallis; †: Chi-square test of Pearson.*

lower in patients with moderate-to-severe OSA compared with patients with mild and no OSA -16(-19/-13)% vs. -17(-20/-12)% and -19 (-21/-15)%, p = 0.04. The prevalence of ventricular dysfunction [LVEF < 50% (39% vs 28% and 11%), p < 0.01] was also higher in the group with moderate-to-severe OSA than in participants with mild or no OSA (Figure 3). This higher prevalence was also observed in the subgroup of patients with Chagas cardiomyopathy.

Table 3 – Echocardiography, Ambulatory Blood Pressure Monitoring and sleep study characteristics

Variable	Total n = 135	No OSA n = 57	Mild OSA n = 50	Mod/Severe OSA n = 28	p
Echocardiography					
LVFE (%)	60 (51–65)	61 (57–66)	59 (47–65)	57 (43–63)	0.09*
LA volume index (mL/m^2)*	29 (23–38)	27 (21–33)	30 (23–38)	37 (51–55)	< 0.001*
Aorta (mm)	30 (28–33)	30 (28–32)	30 (29–34)	30 (27–34)	0.21*
LV diastolic dimension (mm)	52 (49–58)	51 (48–55)	53 (49–58)	56 (50–61)	0.24*
LV systolic dimension (mm)	34 (30–41)	32 (30–37)	34 (30–40)	39 (30–48)	0.14*
Septum (mm)	8.0 (8.0–9.0)	8.0 (7.5–9.0)	8.0 (8.0–9.0)	8.0 (8.0–9.8)	0.10*
Posterior wall thickness (mm)	8.0 (7.0–9.0)	8.0 (7.0–9.0)	8.0 (8.0–9.0)	8.0 (8.0–9.0)	0.27*
LV longitudinal strain (%)**	–17 (–20/–13)	–19 (–21/–15)	–17 (–20/–12)	–16 (–19/–13)	0.04*
ABPM					
Systolic BP awake, mmHg	121 ± 12	118 ± 12	121 ± 12	123 ± 14	0.22¥
Diastolic BP awake, mmHg	74 ± 8	76 ± 8	73 ± 8	73 ± 9	0.34¥
Systolic BP Sleep, mmHg	113 ± 14	110 ± 11	113 ± 13	119 ± 17	0.01¥
Diastolic BP sleep, mmHg	67 ± 9	67 ± 8	66 ± 9	69 ± 9	0.41¥
Systolic non-dipping, %	78	75	79	89	0.29†
Diastolic non-dipping, %	48	40	41	75	< 0.01†
Sleep variables					
AHI. Events/hour	5.8 (2.7–11.9)	2.4 (1.6–3.3)	7.2 (5.8–10.0)	20.3 (16.7–29.1)	< 0.001¥
Mean SaO_2, %	96 (95–97)	97 (94–97)	96 (94–97)	95 (94–97)	< 0.001*
Lowest SaO_2, %	88 (83–92)	92 (89–94)	86 (83–89)	83 (79–87)	< 0.001*
Desaturation index. Number/hour	5.5 (2.2–12.8)	2.1 (0.9–3.4)	7.5 (4.9–10.4)	19.0 (5.9–26.5)	< 0.001*
SaO_2 < 90. % of night time	0 (0–3)	0 (0–0)	1 (0–4)	2 (1–5)	< 0.001*

*Values are mean (±SD). Variables with skewed distribution presented as median (interquartile range). OSA: obstructive sleep apnea; LVFE: left ventricular ejection fraction; LA: left atrial; LV: left ventricular; ABPM: ambulatory blood pressure measurement; BP: blood pressure; AHI: apnoea-hypopnoea index; SaO_2: arterial oxyhemoglobin saturation. **Data from 103 patients. *: Test of Kruskal-Wallis; †: Chi-square test of Pearson; ¥: Anova test.*

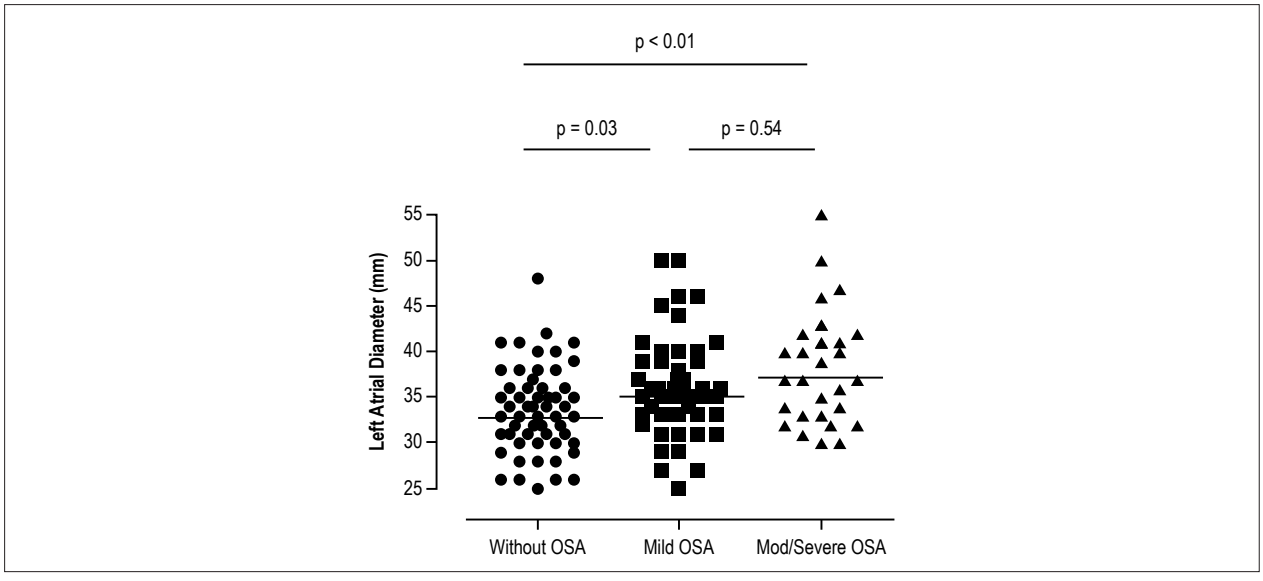

Figure 2 – *Left atrial diameter in patients with Chagas disease. OSA: obstructive sleep apnea. Kruskal-Wallis test, with Bonferroni post-hoc.*

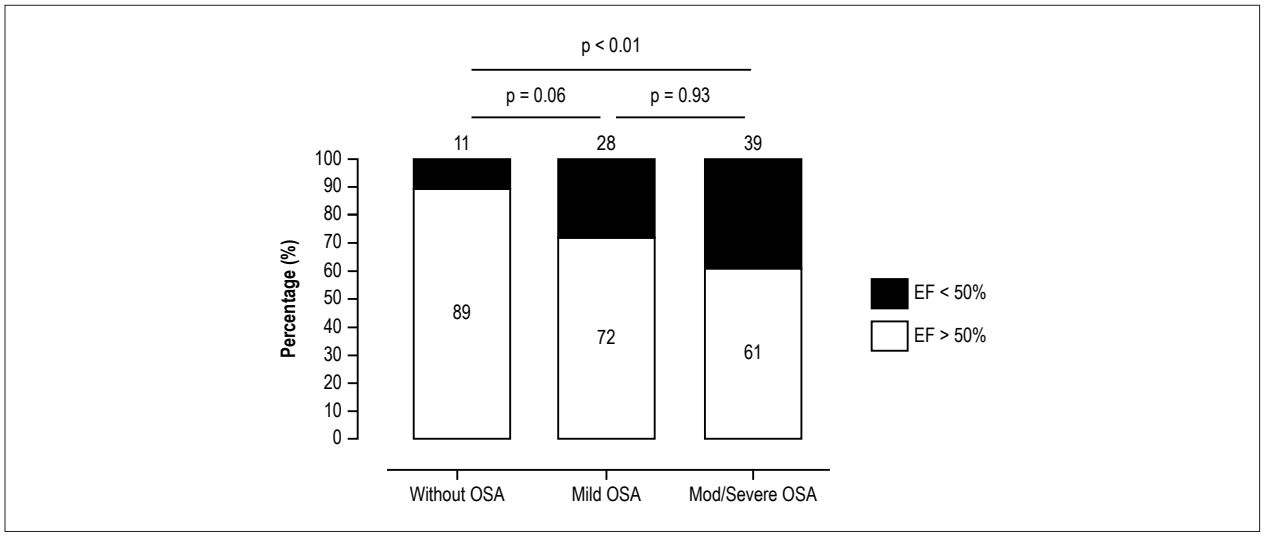

Figure 3 – *Frequency of Obstructive Sleep Apnea in patients with Chagas disease OSA: obstructive sleep apnea; Kruskal-Wallis test.*

Table 4 – Univariate and multiple linear regression predictors of left atrial dimension

Univariate			Multivariate		
Variable	(β)	p	(β)	CI	p
Age (Years)	0.05	0.36			
24h Systolic BP (mmHg)	–0.03	0.46			
BMI. kg/m^2	0.32	0.01	0.16	–0.01 to 0.44	0.06
Log_{10}AHI (events/hour)	3.86	< 0.001	3.86	1.91 to 5.81	< 0.01

BP: blood pressure; BMI: body mass index; AHI: Apnoea-hypopnoea; CI: Confidence interval

Table 5 – Logistic regression to assess predictors of ventricular dysfunction

	Univariate		Multivariate	
Variable	p	OR	CI	p
Age (years)	0.49			
BMI. kg/m^2	0.09			
Male %	0.01	3.24	1.31 – 8.01	0.01
24h Systolic BP (mmHg)	0.01	1.06	1.02 – 1.10	< 0.01
DM	0.95			
AHI (≥ 15 events per hour)	0.02	3.61	1.31 – 9.98	0.01
Desaturation index. number/hour	0.25			
SaO_2 < 90%. % of night time	0.21			

BMI: body mass index; BP: blood pressure; DM: Diabetes mellitus; AHI: apnoea-hypopnoea; OR: odds ratio; CI: Confidence interval.

The only predictor of left atrial dimension in the multivariate analysis was Log_{10} (AHI) (β = 3.86, 95% CI: 1.91 to 5.81; p < 0.01) in the whole population (Table 4), as well as in the subgroup with Chagas cardiomyopathy.

The independent predictors of the presence of ventricular dysfunction were AHI (≥ 15 events/h) (OR = 3.61, 95% C.I.:1.31 to 9.98; p = 0.01), systolic blood pressure (OR = 1.06, 95% C.I.: 1.02 – 1.10; p =< 0.01) and male gender (OR = 3.24, 95% C.I.: 1.31 – 8.01; p = 0.01) (Table 5).

Discussion

To the best of our knowledge, this is the first study that evaluated OSA in consecutive patients with CD. We found a high frequency of moderate to severe OSA in patients with CD (21%). None of the participants had a previous diagnosis of OSA, which suggests a low awareness of the disease in this population. Patients with moderate to severe OSA were more hypertensive, used more antihypertensive drugs and had increased nocturnal blood pressure. In addition, moderate

to severe OSA was independently associated with cardiac remodeling parameters, including larger left atrium dimension and a higher prevalence of ventricular dysfunction, especially in the subgroup of patients with Chagas cardiomyopathy. Taken together, our study emphasizes the concept that OSA may contribute to a poor prognosis in patients with CD.

OSA is a prevalent condition in patients with cardiovascular disease,[20] and our study confirms its high frequency in patients with CD. Particular characteristics of studied OSA patients deserves some comments: First, the presence of higher BMI and neck circumference in patients with moderate to severe OSA as compared to patients with mild or no OSA denotes a typical phenotype of the disease (Table1). However, the lack of excessive daytime sleepiness, a characteristic of OSA patients from the overall population referred to sleep laboratories may explain the low awareness of OSA in patients with cardiovascular disease.[21] This finding is in line with other populations with cardiovascular diseases, including heart failure[22] and hypertrophic cardiomyopathy.[23] The low prevalence of central sleep apnea in our sample is in contrast with a previous study that evaluated sleep disorders in patients with heart failure (LVEF < 45%), including CD. Silva et al.[24] included 24 patients with CD, of which only 12% had OSA, but 44% of whom had Cheyne-Stokes respiration. The median LVEF of our sample was within the normal range (60%) and the majority of our sample did not have heart failure. Moreover, we excluded patients with decompensated heart failure from our study, which may explain the different frequencies.

OSA is recognized as being a cause of hypertension.[25] In our sample, hypertension was more frequent in the group with moderate to severe OSA and this group used more antihypertensive drugs. However, only systolic BP during sleep was higher in patients with moderate-to-severe OSA. This finding may be related to the fact that the study took place in a reference center for cardiology, where most patients are being properly treated for hypertension. The relatively low frequency of atrial and ventricular arrhythmias in our study may be also explained by the exclusion of more severe cases of CD cardiomyopathy.

Our study demonstrated that in patients with CD, OSA is independently associated with left atrial enlargement. This finding is consistent with other OSA populations[7,23,26] Rossi et al.[27] conducted a meta-analysis of 1,157 patients who took part in 18 heart failure studies, and concluded that left atrial enlargement was associated with a worse prognosis, regardless of age, functional class, ejection fraction or diastolic function pattern,[28] reinforcing the importance of our findings. In our study, moderate to severe OSA was also associated with a lower left ventricular longitudinal strain and a four-fold higher proportion of ventricular dysfunction than patients with no OSA. This finding is consonant with an earlier study that evaluated patients referred to a sleep laboratory and may impact negatively on mortality.[6,29]

There are several mechanisms that can contribute to cardiac remodeling in OSA patients[30] One possible explanation for the heart remodeling in our study may be partially explained by the increased frequency of hypertension and higher nocturnal systolic blood pressure, as well as increased frequency of abnormal blood pressure dip in the moderate to severe OSA group. Taken together, the increased hypertension burden may increase arterial stiffness and left ventricular afterload, contributing to these abnormalities.[7] Moreover, inspiratory efforts during the apneas generate negative intrathoracic pressure, which leads to an increase in the left ventricular afterload and a decrease in the left ventricular preload, which in turn cause a reduction in the ejection volume and may induce left atrial enlargement, as demonstrated in our study. Intermittent hypoxia may also influence cardiac contractility, directly or indirectly, thereby reducing cardiac output.[22] OSA induces hypoxia, hypercapnia and sleep arousals, thus promoting an increase in sympathetic activity and hence, in blood pressure.[31] Long-term exposure to high sympathetic nerve activity can induce hypertrophy and apoptosis of the cardiac myocytes[32] and thereby cause left ventricular dysfunction. These adverse hemodynamic effects may be more pronounced in individuals with heart failure,[33] as shown in our subgroup with Chagas cardiomyopathy compared with patients with the indeterminate form.

The major strength of the present study is that it is the largest and one of the only cohorts evaluating the association between sleep apnea in patients with CD. The recruitment of consecutive patients with well-characterized CD not referred to a sleep laboratory may generalizes the findings of our study, as does the use of gold-standard techniques to assess blood pressure (ABPM) and respiratory effort (inductance plethysmography belts).[11] The study has some potential limitations. A portable sleep monitor that does not measure sleep duration was used. Thus, measurements of the AHI were taken based on the total recording time and not on the total length of sleep, although this device has already been validated against full polysomnography.[34] Furthermore, our findings are derived from a cross-sectional study and we cannot infer causality, but only an independent association between OSA and heart remodeling. The fact that we could not demonstrate the same atrial and ventricular remodeling findings in the subgroup of patients with the indeterminate form of CD could be due to the small number of patients in this category. Moreover, the absence of increased incidence of arrhythmias in OSA patients in this study should be analyzed with caution, as 24 h Holter monitoring could not detect intermittent arrhythmias. New studies with technologies that analyze long periods of time are warranted.

Conclusion

OSA is common and independently associated with atrial and ventricular remodeling in patients with CD. The improvement in OSA recognition and treatment may contribute to reducing the morbidity attributed to CD.

Author contributions

Conception and design of the research: Medeiros CA, Oliveira Júnior W, Pedrosa RP; Acquisition of data: Medeiros CA, Secundo IV, Martins SM, Pedrosa RP; Analysis and interpretation of the data: Medeiros CA, Secundo IV, Silveira CAM, del Castilho JM, Albuquerque ALT, Martins SM, Pedrosa RP; Statistical analysis: Pedrosa RP; Writing of the manuscript: Medeiros CA, Martins SM, Lorenzi-Filho G, Pedrosa RP; Critical revision of the manuscript for intellectual content: Oliveira Júnior W.

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 Complexo Hospitalar - Hospital Universitário Oswaldo Cruz - PROCAPE - Universidade de Pernambuco/UPE under approval the protocol ZAAE - 16127213.7.0000.5192, report number: 358162. 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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Obstructive Sleep Apnea: A Marker of Cardiac Remodeling in Patients with Chronic Chagas Disease

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Short Editorial regarding the article: Obstructive Sleep Apnea is Common and Associated with Heart Remodeling in Patients with Chagas Disease

Chronic Chagas disease (CCD) continues to be a major scourge for people living in South America and an emergent medical problem outside the American Continent because of world globalization. Chronic Chagas heart disease (CCHD) affects about 30% of patients with CCD, appearing 20-30 years after infection with *Trypanosoma cruzi*.[1] Prognosis of CCD patients is relentless, with a 5-year mortality approaching 35%.[2] CCHD patients have an outcome even worse,[2] particularly those with ventricular and atrial remodeling, which manifests by chronic systolic heart failure and atrial fibrillation.[3,4]

It is, therefore, important to recognize predictors of ventricular and atrial remodeling in patients with CCHD to offer the proper available treatment for patients with this condition. Systolic blood pressure, male sex, and New York Heart Association Functional Class appear to predict ventricular remodeling in patients with CCD.[5] Conversely, as far as I know, predictors of atrial remodeling have not yet been established for patients with this condition.

In this issue of the Journal, Medeiros et al.[6] report on an original study of 135 Chagas disease patients (30% of them in the indeterminate form and the remaining with CCHD) who have undergone overnight polysomnography to assess the relationship of sleep-disordered breathing and cardiac remodeling. Importantly, 62% of patients also had concomitant systemic arterial hypertension (SAH). Moderate to severe obstructive sleep apnea (OSA) was found in 21% of patients. Medeiros et al.[6] confirm that male sex and SAH are predictors of ventricular remodeling, and also discovered that the apnea-hypopnea index, a diagnostic marker of the severity of OAS, was a predictor of both atrial and ventricular remodeling.

Keywords

Chagas Disease; Trypanosoma Cruzi; Chagas Cardiomyopathy; Sleep Apnea, Obstructive; Polisomnography/methods; Atrial Remodeling.

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The prevalence of OSA is 21% in a general population. It is moderate to severe in 9% of affected individuals,[7] and increases morbidity and mortality.[8] OSA has independently been associated with SAH[9] and with several different types of cardiovascular disorders, including chronic heart failure,[10] a condition usually associated with cardiac remodeling. It is noteworthy that OSA by itself has also been independently associated with left ventricular remodeling and left atrial diameter.[11]

How can the exciting findings reported by Medeiros et al.[6] be incorporated in clinical practice? I think that it would be necessary to test the usefulness of polysomnography in patients with CCD without concomitant SAH. By doing that, we could rule out the additive effect of OSA and SAH[11] on the genesis of cardiac remodeling, as well as to establish the real effect of OSA on the induction of cardiac abnormalities in patients with this condition.

On the other hand, it is important to recognize that a substantial proportion of patients with CCD do not have concomitant SAH in the study by Medeiros et al.[6] Therefore, it is reasonable to admit that OSA by itself could have induced, at least in part, the atrial and ventricular remodeling observed in that study. The appearance of OSA by itself might represent an additional burden to myocardial function to patients with CCD/CCHD because OSA activates sympathetic activity[12] and is proinflammatory.[8]

The histological findings observed in catecholamine cardiomyopathy are similar to those found in CCHD,[13] thus suggesting a role for autonomic dysfunction in the pathogenesis of this disease. Furthermore, proinflammatory cytokines are more increased in patients with CCHD and SAH in comparison with patients with CCHD alone,[14] suggesting a role for cytokines in the pathogenesis of patients with this condition as well. Clearly, the presence of OSA might represent a potential curable threat for patients with CCHD.

I congratulate Medeiros et al.[6] for this important study, and I do hope that they continue to pursue this research line not only because its potential contribution to the understanding of the pathogenesis of CCHD, but also for its potential impact on the clinical course of this scourge to our people.

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Original Article

Right Ventricular Functional Improvement after Pulmonary Rehabilitation Program in Patients with COPD Determined by Speckle Tracking Echocardiography

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Abstract

Background: Although right ventricular (RV) dysfunction in pulmonary diseases has been associated with increased morbidity, tools for RV dysfunction identification are not well defined.

Objective: The aim of this study was to evaluate the magnitude of RV dysfunction by means of speckle tracking echocardiography (STE) in patients with chronic obstructive pulmonary disease (COPD) and to investigate whether STE could be used as an index of RV improvement after a pulmonary rehabilitation (PR) program.

Methods: Forty-six patients with COPD undergoing PR program and 32 age-sex matched healthy subjects were enrolled. RV function was evaluated at admission and after PR program by conventional two-dimensional echocardiography (2DE) and STE. In addition, exercise tolerance of subjects was evaluated using the six-minute walk test (6MWT).

Results: COPD patients had worse RV function according to STE and 2DE as well. STE was more sensitive than conventional 2DE in determining RV improvement after PR program – RV global longitudinal strain (LS): 20.4 ± 2.4% vs. 21.9 ± 2.9% $p < 0.001$ and RV free wall LS: 18.1 ± 3.4% vs. 22.9 ± 3.7%, $p < 0.001$). RV free wall LS was directly related to distance walked at baseline 6MWT ($r = 0.58$, $p < 0.001$) and to the change in the 6MWT distance (6MWTD Δ) ($r = 0.41$, $p = 0.04$).

Conclusions: We conclude that STE might be as effective as 2DE for evaluation of global and regional RV functions. STE may become an important tool for assessment and follow-up of COPD patients undergoing PR program to determine the relationship between RV function and exercise tolerance. (Arq Bras Cardiol. 2018; 111(3):375-381)

Keywords: Ventricular Dysfunction, Right / rehabilitation; Pulmonary Disease, Chronic Obstructive / rehabilitation; Echocardiography / methods; Strain, Speckle Tracking.

Introduction

The right ventricle plays an important role in the morbidity and mortality of patients with signs and symptoms of cardiopulmonary disease.[1] Although transthoracic two-dimensional echocardiography (2DE) provides important information about the right ventricular (RV) anatomy and function, the RV complex geometry and crescent-shaped structure wrapped around the left ventricle (LV) make accurate assessment difficult.[2] Moreover, conventional 2DE measures, including velocity and displacement-based analyses, can be affected by translational motion of the heart and respiratory variation. The new echocardiographic method of speckle tracking echocardiography (STE) assesses myocardial deformation on grayscale (B-mode) images and can be used to evaluate both global and regional myocardial strain without being limited by the Doppler beam angle.[3,4]

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Patients with advanced chronic respiratory disease regularly experience distressing symptoms despite optimal pharmacological treatment. Pulmonary rehabilitation (PR) complements conventional medical therapy, and has been clearly demonstrated to reduce dyspnea, increase exercise performance, and improve RV functions.[5] Today, is well known that chronic obstructive pulmonary disease (COPD) patients experience substantial mortality and morbidity from RV function impairment.[6,7]

A number of studies have used conventional 2DE to evaluate the RV in patients with cardiopulmonary diseases, but there is relatively limited information concerning the assessment of RV performance by means of speckle tracking-derived strain.[8,9] Therefore, we sought to analyze the use of STE in the assessment of global and regional RV function and impact of PR program on it.

Methods

Study design and participants

Subjects were recruited from Sureyyapasa Chest Medicine and Thoracic Surgery Research and Training Hospital, Istanbul, Turkey. Fifty-seven patients with moderate-to-very severe COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD classes 2-4) were enrolled in the study. Six patients

were excluded from the analyses due to the poor quality of their echocardiographic records. In the remaining patients, the apical segment of the RV free wall and the apical septum could not be analyzed in 3 and in 2 patients, respectively.

All patients had a previous diagnosis of symptomatic COPD. The control group included 32 healthy volunteers. Patients with impairment of LV systolic function (ejection fraction < 55%), significant valvular heart disease, cardiomyopathy, history of coronary artery disease, and malignancy were excluded. The investigation complies with the principles outlined in the Declaration of Helsinki. The study was approved by the local Ethics Committee and written informed consent was obtained from all participants.

Adult patients with COPD with medically optimized symptomatic lung disease, admitted to the outpatient PR program, were referred by respiratory physicians after an initial multidisciplinary assessment clinic with a respiratory or rehabilitation physician, cardiology physician, nurse, and physiotherapist. Before starting the PR program, we obtained medical histories and performed physical examination of all patients. Specific measurements recorded at the beginning and end of PR program included 6-minute walk test (6MWT), mMRC (modified Medical Research Council) dyspnea scale, the BODE index – body mass index (BMI), degree of obstruction (FEV_1), dyspnea (mMRC scale), exercise capacity. The PR program consisted of 2 sessions each day for 6 days per week for a total of 4 weeks. Each session lasted 30 minutes and included symptom-limited exercise training (walking or cycling).

All 6MWTs were performed on a flat surface, enclosed, temperature-controlled corridor using standardized instructions.[10,11] Two 6MWTs and echocardiographic examinations were performed at the beginning of the pre-rehabilitation and post-rehabilitation assessments at the end of PR program due to possible learning effect. The best 6MWT was recorded and used for analysis. The 6MWTDΔ (delta) was determined by the difference between pre- and post-rehabilitation of 6MWTs. The effect of the 6MWT after the PR program was evaluated by BODE index and the mMRC score.

Conventional and speckle-tracking echocardiography

All echocardiographic examinations of patients and healthy controls were performed in accordance with the American Society of Echocardiography guidelines using an ultrasound system (IE33, Philips Medical Systems, Andover, MA, US).[12] Estimation of systolic pulmonary artery pressure (sPAB) was based on tricuspid regurgitation peak velocity using the simplified Bernoulli equation: 4x(tricuspid regurgitation peak velocity)^2+ right atrial pressure (RAP). Estimation of RAP was done on the basis of the inferior vena cava diameter and collapse index.[2] Tricuspid annular plane systolic excursion (TAPSE) is defined as the total excursion of the tricuspid annulus from end-diastole to end-systole, and it is measured typically at the lateral annulus using M-mode Isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), myocardial performance index (MPI) (calculated as [IVRT + IVCT]/ejection time), and ejection time intervals were measured using either pulsed-wave Doppler (PWD) or Doppler tissue imaging (DTI) at the lateral tricuspid annulus. RV and LV ejection fractions from 2D methods were calculated as (end-diastolic volume - end-systolic volume)/end-diastolic volume.

The general principles that underlie 2D speckle-tracking modalities have been previously described.[13,14] 2D echocardiographic grayscale apical 4-chamber images and a frame rate of 70 to 80 frames/s were obtained, which seems to be the best compromise between appropriate temporal resolution and acceptable spatial definition of the LV lateral wall and RV free wall. In postprocessing analysis, the region of interest was obtained by tracing the RV endocardial borders at the level of the septum and the free wall in a still frame at end-systole. An automated software program calculated the frame-to-frame displacements of speckle pattern within the region of interest throughout the cardiac cycle. Longitudinal strain (LS) curves were obtained from six RV segments (basal, mid, and apical segments of the RV free wall and septum); the global RV strain curve was based on the average of the six regional strain curves, and longitudinal strain curves of the lateral LV wall were obtained by repeating the same analysis (Fig. 1). The extent of myocardial deformation (defined as global or regional longitudinal strain) was expressed as a percentage of the longitudinal systolic shortening compared with diastolic shortening for each segment of interest. All analyses were repeated twice one day later by the same observer in order to assess intraobserver variability, which was calculated as the average difference between the 10 measurements taken. A second independent observer repeated the analyses for the assessment of interobserver variability, which was calculated as the absolute difference divided by the average of the two observations of all parameters. The intraobserver and interobserver variability were 5% and 7 %, respectively.

Statistical analysis

All statistical tests were performed with a commercially available software program (SPSS 16.0 for Windows; SPSS, Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. In sample size calculation, 46 COPD patients and 32 healthy subjects in each group would be needed to detect a 2-point difference in DAN scale, with a power of 80% and 1% of significance level. Categorical variables are presented as numbers and percentages and continuous data expressed as mean ± standard deviation. Since all variables were normally distributed, correlation coefficients and their significance were calculated using the Pearson test, and comparisons of quantitative data performed by a paired sample t-test. A p-value of less than 0.05 was set as statistically significant.

Results

In our study, 46 patients (mean age: 60.8 ± 10.2 years; gender: 28 male, 18 female) with moderate to very severe COPD undergoing PR and 32 healthy subjects (mean age: 58.5 ± 8.9 years; gender: 13 male, 19 female) were enrolled. Baseline characteristics are shown in Table 1. Age and sex distributions were similar between the two groups.

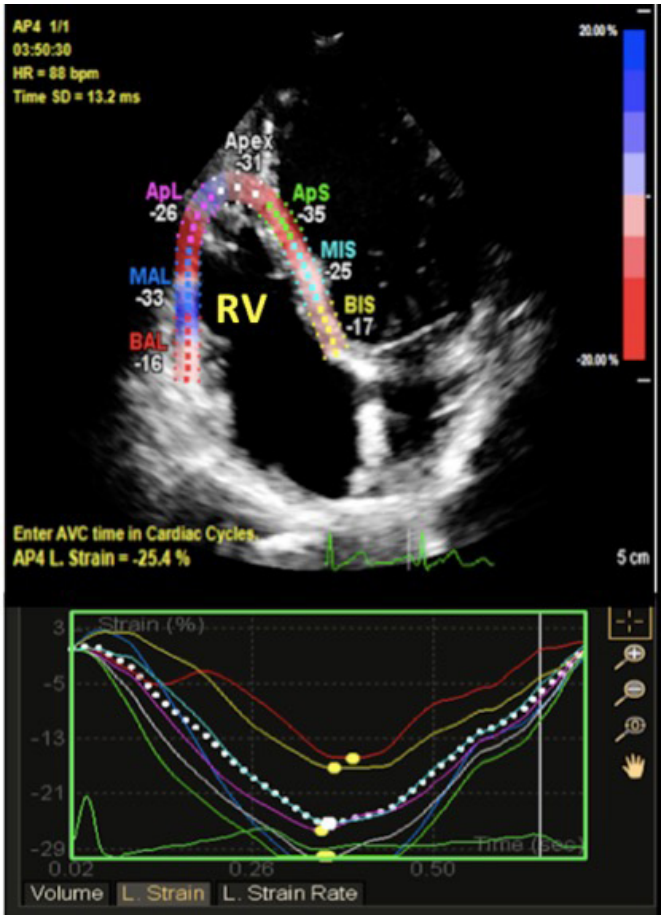

Figure 1 – *Representative two-dimensional right ventricular strain images. Speckle-tracking apical four chamber view showing global and regional right ventricular longitudinal strain. L. Strain: Longitudinal strain.*

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification; there were 22 class-II, 18 class-III, and 7 class-IV COPD patients. COPD patients had higher RV basal diameter, right atrial (RA) end-systolic area, sPAP, and MPI, as well as lower tricuspid annular plane systolic excursion (TAPSE) values compared to healthy control subjects in conventional echocardiographic measurements. In addition, there were significant differences in RV global LS and RV free wall LS between the two groups.

In post-rehabilitation echocardiography and 6MWT assessments, there were significant improvements in RV speckle-tracking measurements (Table 2) and increase in 6MWT. In 2DE measurements, there were differences among sPAP, TAPSE, and MPI. However, sPAP was only statistically significant.

RV free wall LS was directly related to distance walked at baseline 6MWT ($r = 0.58$, $p < 0.001$) and to 6MWTDΔ ($r = 0.41$, $p = 0.04$) (Figura 2). There were improvements of both BODE index and MRC parameters, but only the BODE index was statistically different. There was a statistically significant correlation between RV free wall LS and BODE index (r: 0.52, $p < 0.001$).

Discussion

In our study, we evaluated RV dysfunction in patients with moderate-to-very severe COPD in comparison with healthy subjects and also its improvement after PR program. In determination of both global and regional RV function improvement, STE was shown to be as effective as conventional 2DE. Moreover, RV global longitudinal strain was directly related to exercise tolerance determined by means of 6MWT and BODE index.

Although the current available prognostic models for COPD do not include RV function, it might serve as a surrogate endpoint for determining mortality and morbidity rates in a variety of cardiopulmonary diseases.[15,16] On the other hand, RV assessment can be challenging. STE overcomes most of the limitations inherent in conventional 2DE, given that it is independent of cardiac translation, and it is angle- and load-independent, thus allowing accurate quantification of myocardial function.[17] STE also demonstrates whether reduced RV performance is due to a global failure or to localized impaired contraction. Moreover, it identifies discrete and localized losses in

Table 1 – Clinical, conventional echocardiographic, and ventricular strain data in patients undergoing pulmonary rehabilitation and in healthy control subjects

	Patients undergoing pulmonary rehabilitation (n: 46)	Healthy control subjects (n: 32)	p value
Age (years)	60.8 ± 10.2	58.5 ± 8.9	0.15
Gender (male,%)	28(61%)	13(41%)	
Body mass index (kg/m^2)	28.2 ± 8.4	27.9 ± 7.2	0.67
Heart rate (beats/min)	78 ± 12	80 ± 10	0.77
GOLD classes 2/3/4, n	22/18/7		
RV end-diastolic basal diameter (mm)	38.1 ± 4.1	27.6 ± 3.5	< 0.001
RV end-diastolic longitudinal diameter (mm)	74.2 ± 9.4	60.4 ± 6.4	< 0.001
RV anterior wall thickness (mm)	4.35 ± 0.21	4.19 ± 0.31	0.82
RA end-systolic area (mm^2)	17.2 ± 2.9	12.9 ± 1.8	< 0.001
sPAB (mmHg)	46.7 ± 15.4	24.8 ± 10.5	< 0.001
TAPSE (mm)	16.6 ± 2.6	20.4 ± 3.1	< 0.001
Tissue Doppler MPI	0.58 ± 0.08	0.35 ± 0.05	< 0.001
RV ejection fraction (%)	54.8 ± 4.9	56.3 ± 5.5	0.41
LV ejection fraction (%)	57.7 ± 5.5	59.4 ± 4.4	0.34
RV-TDI s'	12.9 ± 2.93	13.6 ± 3.06	0.38
RV free wall longitudinal strain (%)	18.1 ± 3.4	27.9 ± 3.6	< 0.001
RV global longitudinal strain (%)	20.4 ± 2.4	26.8 ± 3.2	< 0.001

Data are presented as mean ± standard deviation or percentile. Bold values indicate statistical significance p < 0.05. GOLD: global initiative for chronic obstructive lung disease; RV: right ventricle; RA: right atrium; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TDI s': tissue Doppler imaging systolic excursion; MPI: myocardial performance index; LV: left ventricle.

Table 2 – Standard echocardiographic and ventricular strain data in patients before and after pulmonary rehabilitation

	Before pulmonary rehabilitation (n:46)	3 months after pulmonary rehabilitation (n:46)	p value
RV end-diastolic basal diameter (mm)	38.1 ± 4.1	37.7 ± 4.0	0.23
RV end-diastolic longitudinal diameter (mm)	74.2 ± 9.4	73.5 ± 9.3	0.69
RV anterior wall thickness (mm)	4.35 ± 0.21	4.22 ± 0.26	0.87
RA end-systolic area (mm^2)	17.2 ± 2.9	16.9 ± 2.4	0.18
sPAB (mmHg)	46.7 ± 15.4	43.2 ± 16.3	0.03
TAPSE (mm)	16.6 ± 2.6	17.2 ± 3.1	0.09
Tissue Doppler MPI	0.58 ± 0.08	0.55 ± 0.07	0.09
RV ejection fraction (%)	54.8 ± 4.9	55.2 ± 5.0	0.72
LV ejection fraction (%)	57.7 ± 5.5	57.4 ± 5.2	0.57
RV-TDI s'	12.9 ± 2.93	11.8 ± 3.06	0.47
RV free wall longitudinal strain (%)	18.1 ± 3.4	22.9 ± 3.7	< 0.001
RV global longitudinal strain (%)	20.4 ± 2.4	21.9 ± 2.9	< 0.001
Six-minute walk test (m)	326 ± 42.2	355 ± 57.1	< 0.001
mMRC score	1.8 ± 0.8	1.7 ± 0.7	0.14
BODE index	3.0 ± 2.1	2.8 ± 1.9	0.04

Data are presented as mean ± standard deviation. Bold values indicate statistical significance p < 0.05. RV: right ventricle; RA: right atrium; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; MPI: myocardial performance index; LV: left ventricle; TDI s': tissue Doppler imaging systolic excursion; mMRC; modified medical research council, BODE; Body mass index, degree of Obstruction (FEV_1), Dyspnea score (mMRC scale), Exercise capacity (six minute walk distance).

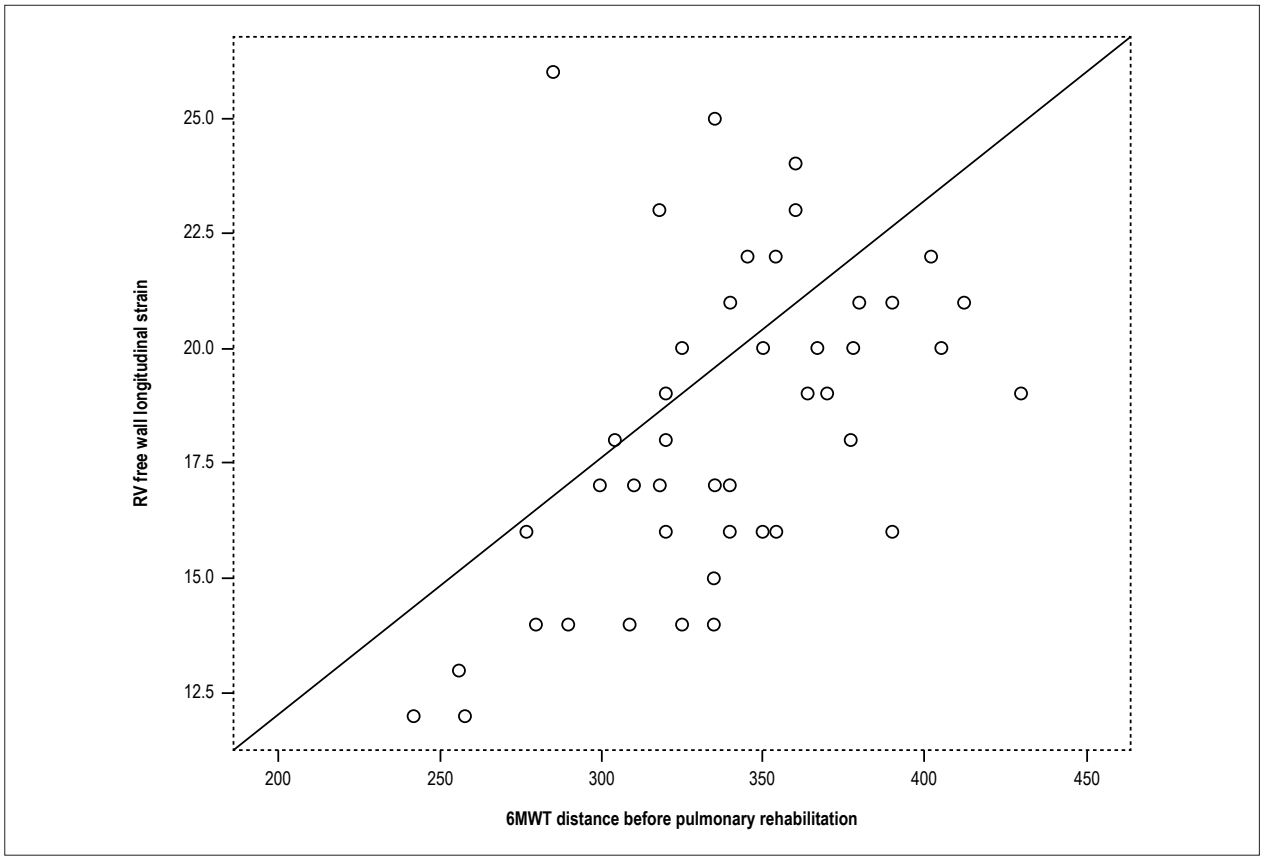

Figure 2 – *Correlation between right ventricular free wall longitudinal strain and six-minute walk test (6MWT) distance before pulmonary rehabilitation. (r = 0.58, p < 0.001). RV: right ventricular.*

contractility that are insufficient to affect global systolic function but have potential diagnostic and prognostic implications. The main result of the study by Focardi et al.[18] was that free wall and global RV LS had a stronger correlation with the RV ejection fraction (RVEF) calculated by CMR (cardiac magnetic resonance) than conventional echocardiographic indices. Between the two, the highest diagnostic accuracy and the strongest correlation with the RVEF measured by CMR were observed for RV free wall longitudinal strain.[18] In our study, RV free wall LS had higher improvement than RV global LS after PR program. Moreover, it had a statistically significant correlation with exercise tolerance indices of the patients, such as 6MWT distance and BODE index. One possible explanation for this is that the thin RV free wall contracts against low pulmonary resistance, thus leading to significantly higher strain improvement after the decline of pulmonary resistance by means of PR program. On the other hand, the septum consists of the same fibers as those forming the LV and must handle loading conditions in the RV, as well as higher LV afterload.16 Nevertheless, this hypothesis must be confirmed by further studies. In addition, we chose to analyze the septum as part of the RV. It cannot be considered simply a part of the LV because its shortening contributes to the ejection phase of the RV, and any impairment in its contractility reduces RV performance.[14,19]

Because of the paucity of data, no reference limits were established in the latest guidelines for RV global LS. Recent studies involving STE have focused on exploring RV function in patients with cardiopulmonary disease. Hardegree et al.[20] showed that RV free wall LS and 6MWT distance were increased after the initiation of medical therapy in patients with pulmonary arterial hypertension (PAH). Motoji et al.[21] showed that RV global LS < 19.4% indicates high risk of adverse cardiovascular events in patients with PAH. In addition, Guendouz et al.[22] reported that an absolute RV global LS value below 21% in patients with congestive heart failure identifies patients with high risk of adverse cardiac events. However, to the best of our knowledge, there are no published studies using STE to determine RV dysfunction and its improvement after PR program in patients with COPD.

The effect of PR on RV function in patients with COPD has been explored in 2DE-based studies. Caminiti et al.[8] showed that TAPSE ≤ 16 mm was an indicator of decreased 6MWT distance at baseline and 6MWT distance change in COPD patients undergoing PR. According to our study, STE was more sensitive in determining RV dysfunction than 2DE. Tanaka et al.,[23] in another 2DE-based study, showed an increase of MPI, and that there was a strong correlation between MPI and the MRC breathlessness

score in COPD patients.[23] Our data are in agreement with these 2DE studies of RV function in COPD patients undergoing PR program.

Study limitations

Several limitations of our study merit consideration. The main limitation was the small size of the study population. Moreover, RV strain was assessed only in the 4-chamber view of the six segments of the RV; however, the RV longitudinal function measured in the inlet chamber accounts for about 80% of RV function.[24] If we had followed up the study population, we could have investigated the impact of PR program on RV function, as well as mortality and morbidity. Finally, we did not compare our results with those of CMR. However, previous studies of LV speckle tracking–derived strain have already validated CMR use. Furthermore, although magnetic resonance imaging is considered the gold standard for determining RV volume and function, it is currently limited by cost and availability and is deemed unsuitable after the implantation of a cardiac pacemaker.[25]

Conclusion

Our study demonstrated that RV dysfunction improved after PR program in patients with COPD. STE might be as effective as the more established measurements of global RV function (i.e., TAPSE, RVEF, and MPI). RV global and regional strain assessment is a simple and effective tool in the routine clinical assessment of patients with COPD in order to explore the relationship between RV function and exercise tolerance.

Author contributions

Conception and design of the research, acquisition of data, obtaining financing, writing of the manuscript: Kanar BG, Ozmen I, Yildirim EO, Ozturk M, Sunbul M; Analysis and interpretation of the data and statistical analysis: Kanar BG, Sunbul M; Critical revision of the manuscript for intellectual content: Sunbul M.

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 Marmara University under the protocol number 70737436-050.06.04. 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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Right Ventricular Evaluation with Speckle Tracking Echocardiography in COPD after a Pulmonary Rehabilitation Program

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Short Editorial regarding the article: Right Ventricular Functional Improvement after Pulmonary Rehabilitation Program in Patients with COPD Determined by Speckle Tracking Echocardiography

Chronic obstructive pulmonary disease (COPD) is a serious public health problem, and is often related to smoking.[1] In advanced stages of COPD, the presence of PAH is a common development. PAH progression rate in COPD is usually slow (an increase of < 1 mmHg per year). However, the presence of even moderate PAH is a strong predictor of mortality.[2] During stable periods of the disease, the increase in mean pulmonary artery pressure is usually mild to moderate. However, severe PAH may occasionally occur in COPD patients COPD.[3]

Conventional two-dimensional (2D) echo parameters allow a reasonable assessment of RV Function. In the 1990s, the use of tissue Doppler (TD) to measure the intramyocardial velocity gradient allowed measuring the rate of myocardial strain and its percentage (strain rate and strain). About ten years ago, the speckle tracking technique, based on the tracking of the speckles which two-dimensional echo images, allowed assessing myocardial strain without limitation by the DT insonation angle.[4] 2D-STE strain can not only quantify the overall RV function, but it can also identify discrete, localized contractile losses, providing information regarding the pathophysiological mechanisms that lead to right ventricular failure.[5] In a heterogeneous group of patients, RV lateral wall longitudinal strain showed a strong correlation with RV ejection fraction calculated by cardiac magnetic resonance.[6]

Keywords

Chronic obstructive pulmonary disease (COPD); Two-dimensional Echo; Strain; Speckle Tracking; Pulmonary Rehabilitation.

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Peak longitudinal strain is a significant prognostic determinant in PAH patients, with greater value compared to other known clinical and echocardiographic predictors of mortality.[7]

Several studies have used 2D-STE in chronic PAH patients. Several authors advocate this method for serial evaluation of PAH patients since RV free-wall strain has proved an independent predictor of clinical deterioration and mortality after medical therapy is initiated.[8] Although 2D-STE is widely used in various clinical conditions, the guidelines on echocardiographic evaluation of RV function strongly recommends including other measures into echocardiographic examination and report.[9] In addition to the fact that there are no reference values, RV ST2D can be influenced by image quality, reverberation and other artifacts.[10]

The literature clearly shows the benefit of pulmonary rehabilitation (PR) programs. A prospective randomized study showed the effectiveness of respiratory training as an additional treatment of severe chronic PAH.[11] In this issue, Kanar et al. evaluated the RV function using 2D-STE with 46 COPD and 32 control patients.[12] The authors compared the 2D-STE values for the two groups and for patients before and after a pulmonary rehabilitation program. The conventional parameters for 2D-echo and 2D-STE showed a similar correlation between COPD and control patients, but RV longitudinal strain showed greater sensitivity in examining the relationship between RV function and exercise tolerance. The main limitations are pointed out in the article. There is no information on whether 2D-STE measurements were made in apnea or at the time of pre and post PR breathing. Since RV is sensitive to preload variations, the values could be influenced by respiratory variation. In any case, the usefulness of ST2D to evaluate RV in COPD was well demonstrated. Although there is controversy on the effectiveness of pulmonary rehabilitation programs in PAH,[13] the authors demonstrated in an original way, i.e., through ST2D, that RV improves after PR, thus creating new perspectives for the use of PR in COPD patients.

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Right Atrial Deformation Analysis in Cardiac Amyloidosis – Results from the Three-Dimensional Speckle-Tracking Echocardiographic MAGYAR-Path Study

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Abstract

Background: Light-chain (AL) cardiac amyloidosis (CA) is characterized by fibril deposits, which are composed of monoclonal immunoglobulin light chains. The right ventricle is mostly involved in AL-CA and impairment of its function is a predictor of worse prognosis.

Objectives: To characterize the volumetric and functional properties of the right atrium (RA) in AL-CA by three-dimensional speckle-tracking echocardiography (3DSTE).

Methods: A total of 16 patients (mean age: 64.5 ± 10.1 years, 11 males) with AL-CA were examined. Their results were compared to that of 15 age- and gender-matched healthy controls (mean age: 58.9 ± 6.9 years, 8 males). All cases have undergone complete two-dimensional Doppler and 3DSTE. A two-tailed p value of less than 0.05 was considered statistically significant.

Results: Significant differences could be demonstrated in RA volumes respecting cardiac cycle. Total (19.2 ± 9.3% vs. 27.9 ± 10.7%, p = 0.02) and active atrial emptying fractions (12.1 ± 8.1 vs. 18.6 ± 9.8%, p = 0.05) were significantly decreased in AL-CA patients. Peak global (16.7 ± 10.3% vs. 31.2 ± 19.4%, p = 0.01) and mean segmental (24.3 ± 11.1% vs. 38.6 ± 17.6%, p =0.01) RA area strains, together with some circumferential, longitudinal and segmental area strain parameters, proved to be reduced in patients with AL-CA. Global longitudinal (4.0 ± 5.2% vs. 8.2 ± 5.5%, p = 0.02) and area (7.8 ± 8.1% vs. 15.9 ± 10.3%, p = 0.03) strains at atrial contraction and some circumferential and area strain parameters at atrial contraction were reduced in AL-CA patients.

Conclusion: Significantly increased RA volumes and deteriorated RA functions could be demonstrated in AL-CA. (Arq Bras Cardiol. 2018; 111(3):384-391)

Keywords: Amyloidosis; Echocardiography, Three Dimensional / methods; Humans; Ventricular Dysfunction, Right; Speckle-Tracking.

Introduction

Systemic amyloidosis is a rare disease caused by the extracellular deposition of protein (amyloid) fibrils, which are composed of low molecular weight subunits (5 to 25 kD) of various serum proteins.[1] The amyloid fibrils progressively damage the structure and function of the affected tissue, with variable clinical symptoms.[2,3] For diagnosis of amyloidosis, biopsy from the affected tissue or from (abdominal) subcutaneous adipose tissue is necessary in most of cases.[4] The classification of amyloidosis depends on the type of the precursor protein, including acquired monoclonal immunoglobulin light-chain amyloidosis (AL), wild-type or hereditary transthyretin amyloidosis (TTR), acquired serum amyloid type (AA) and other rare types. The mortality is especially high in light-chain (AL) amyloidosis.[5,6]

There are some warning signs that can draw attention to amyloidosis, such as nephrotic syndrome, tissue infiltration such as macroglossia, respiratory disease, carpal tunnel syndrome, bleeding, cachexia, haematological disease such as multiple myeloma, and genetic predisposition. As for the clinical signs, syncope is a poor prognostic factor and occurs quite frequently in patients with cardiac involvement.[7] Cardiac involvement in amyloidosis varies according to the type of the disease.[1] The real incidence of cardiac amyloidosis (CA) is not known precisely and is often diagnosed only during autopsy.[8] Heart failure usually occurs in CA due to the combination of decreased myocardial compliance and compressed myocardial cells. These changes develop due to the infiltration by amyloid deposits and could lead to restrictive cardiomyopathy.[1] Arrhythmias, pleural and pericardial effusion can also be detected in some cases.[4,9,10] Although the right ventricle (RV) is mostly involved in CA, limited data is available about the involvement of the right atrium (RA).[11,12] Therefore, this study aimed to characterize the volumetric and functional properties of the RA in AL-CA by three-dimensional (3D) speckle-tracking echocardiography (3DSTE).

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Methods

Patient population

A total of 16 patients (mean age: 64.5 ± 10.1 years, 11 males) with biopsy-proven AL-CA were examined. Their results were compared to that of 15 age- and gender-matched healthy controls (mean age: 58.9 ± 6.9 years, 8 males). Baseline demographic characteristics of patients and controls are presented in Table 1. CA was defined in accordance with the current consensus criteria and practices.[6,13] None of the patients with AL-CA was on anticoagulant treatment, but 2 of them received acetylsalicylic acid. Five patients received β-blockers, 7 patients were on angiotensine-converting enzyme inhibitors, while 11 patients took diuretics. The source of the biopsy was the bone marrow in 3 patients, the subcutis in 3 patients, the kidney in 5 patients, the heart in 3 patients, the gastrointestinal tract in 4 patients and the salivary gland in 1 patient. In 3 cases, samples were collected from more than 1 organ. In 11 out of 16 AL-CA patients, the diagnosis of multiple myeloma was confirmed. In 1 case, no treatment information was available. In all other cases, different types of chemotherapy or immunomodulatory treatment were administered. None of the healthy subjects in the control group had cardiovascular risk factors or any known diseases or received any medications. For cardiac evaluation, complete two-dimensional (2D) Doppler, tissue Doppler echocardiography, 3DSTE and N-terminal pro-B natriuretic peptide (NT-proBNP) level assessment were performed in all patients and controls. The present study was designed as a part of the **M**otion **A**nalysis of the heart and **G**reat vessels b**Y** three-dimension**A**l speckle-t**R**acking echocardiography in **Path**ological cases (**MAGYAR-Path**) **Study**. It has been organized to examine alterations in 3DSTE-derived parameters in different disorders compared to matched healthy controls among others (*magyar* means "Hungarian" in Hungarian language). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (and updated versions) and was approved in advance by the local institutional ethical committee. Informed consent was obtained from each subject.

Two-dimensional Doppler echocardiography

2D grayscale harmonic images were performed in the lateral decubitus position with using a commercially available ultrasound system (Artida™, Toshiba Medical Systems, Tokyo, Japan) equipped with a broadband 1-5 MHz PST-30SBP phased-array transducer. During 2D Doppler echocardiography, chamber dimensions, volumes and ejection fraction were measured in accordance with the recommendations.[14,15] Degree of mitral and tricuspid regurgitations was visually quantified by colour Doppler echocardiography.

Three-dimensional speckle-tracking echocardiography

3D echocardiographic datasets were acquired with the same Toshiba Artida ultrasound system with a 1-4 MHz PST-25SX matrix phased-array transducer.[16] After gain setting optimalisation, wide-angled pictures were recorded, in which 6 wedge-shaped subvolumes were acquired over 6 consecutive cardiac cycles during a single breath-hold. We used raw data format for further analysis. 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan) was used for RA quantifications. Each 3D dataset was displayed in a 5-plane view: an apical 4-chamber (AP4CH) view, an apical 2-chamber (AP2CH) view and 3 short-axis views at different RA levels from the base to the apex. The examiner then set markers in the AP4CH and AP2CH views; in each plane, one marker was placed on the apex (superior region) and two other markers were placed at the edges of the tricuspid valve ring. As the next step, the software automatically detected the endocardium, and 3D wall motion-tracking analysis was performed through the entire cardiac cycle. During evaluations, RA appendage and the caval veins were excluded from the RA cavity (Figure 1).

From the acquired 3D echocardiographic datasets, time-global RA volume curves were created, allowing the measurement of maximum (V_{max}) and minimum (V_{min}) RA volumes and RA volume before atrial contraction (V_{preA}). V_{max} was measured just before tricuspid valve opening at end-systole, while V_{min} and V_{preA} were measured just before tricuspid valve closure at end-diastole and at the time of P wave on ECG in early diastole, respectively. The systolic reservoir and diastolic passive (conduit) and active emptying (booster pump) phases of RA function were measured from the RA volumetric datasets:[17]

Right atrial stroke volumes

- Total Atrial Stroke Volume (TASV): $V_{max} - V_{min}$ (reservoir function)
- Passive Atrial Stroke Volume (PASV): $V_{max} - V_{preA}$ (conduit function)
- Active Atrial Stroke Volume (AASV): $V_{preA} - V_{min}$ (booster pump/active contraction function)

Right atrial emptying fractions

- Total Atrial Emptying Fraction: $TASV/V_{max} \times 100$ (reservoir function)
- Passive Atrial Emptying Fraction: $PASV/V_{max} \times 100$ (conduit function)
- Active Atrial Emptying Fraction: $AASV/V_{preA} \times 100$ (booster pump/active contraction function)

Time-strain curves could also be created at the same time from the same 3D echocardiographic datasets. Unidirectional radial, longitudinal, circumferential and complex area and 3D strains could be also measured. Global strains were calculated by the software, which considered the whole RA, while mean segmental strains were obtained as the average of strains of 16 segments. A typical strain curve usually represents two peaks: the first peak indicates the reservoir phase, while the second peak shows characteristics of the booster pump phase of the RA function.[17]

Statistical analysis

All continuous variables were presented as mean ± standard deviation. Categorical data were presented as frequencies and percentages (%). Comparisons among groups were performed by unpaired Student *t* test and χ^2 test, when appropriate. Shapiro-Wilks test was used to test normal distribution in every dataset. Pearson correlation coefficient was calculated when needed. A 2-tailed *p* value < 0.05 was considered to indicate statistical significance. Reproducibility

Table 1 – Baseline demographic and two-dimensional echocardiographic data in patients with cardiac amyloidosis and matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
Risk factors			
Age (years)	64.5 ± 10.1	58.9 ± 6.9	0.08*
Male gender (%)	11 (69)	8 (53)	0.47**
Hypertension (%)	11 (69)	0 (0)	< 0.0001**
Diabetes mellitus (%)	1 (6)	0 (0)	0.46**
Hypercholesterolaemia (%)	6 (38)	0 (0)	0.02**
Two-dimensional echocardiography			
LA diameter (mm)	45.1 ± 6.7	36.6 ± 4.00	< 0.0001*
LV end-diastolic diameter (mm)	47.1 ± 5.7	47.3 ± 3.2	0.93*
LV end-diastolic volume (ml)	112.9 ± 31.9	104.9 ± 16.7	0.42*
LV end-systolic diameter (mm)	30.0 ± 5.3	30.4 ± 2.8	0.80*
LV end-systolic volume (ml)	41.7 ± 15.4	35.7 ± 6.9	0.11*
Interventricular septum (mm)	14.2 ± 1.9	10.4 ± 1.7	< 0.0001*
LV posterior wall (mm)	13.6 ± 1.7	10.4 ± 1.9	0.0003*
LV ejection fraction (%)	61.5 ± 11.9	65.7 ± 4.8	0.21*
E/A	1.71 ± 1.08	1.00 ± 0.45	0.14*

*CA: cardiac amyloidosis; LA: left atrial; LV: left ventricular. Data expressed as mean ± standard deviation or or absolute numbers (percentage). * Unpaired Student t test, ** χ^2 test.*

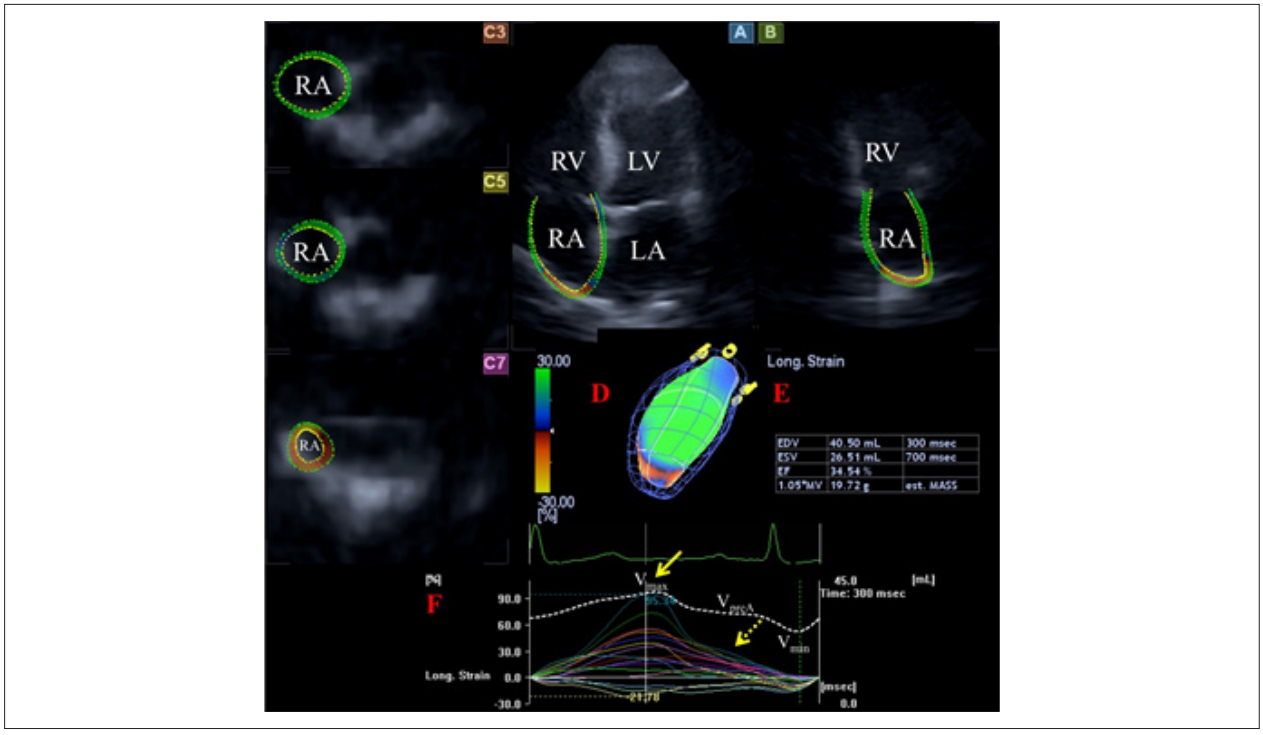

Figure 1 – *Images from three-dimensional (3D) full-volume dataset showing the right atrium (RA) are presented: apical four-chamber (A) and two-chamber views (B) and short-axis views at basal (C3), mid- (C5) and superior (C7) RA levels together with a virtual 3D model of the RA (red D) and with RA volumetric data (red E). Time – segmental (longitudinal) strain curves of all 16 RA segments (coloured lines) and a time - global RA volume change curve respecting cardiac cycle (white dashed line) are also presented (red F). Yellow arrow represents peak RA strain, while yellow dashed arrow represents RA strain at atrial contraction. V_{max}, V_{min} and V_{preA} represent maximum and minimum RA volumes and RA volume at atrial contraction, respectively. LV: left ventricle; LA: left atrium; RV: right ventricle; RA: right atrium.*

of 3DSTE-derived RA assessments has already been confirmed in a recent study.[17] All statistical analyses were carried out using MedCalc software (MedCalc, Inc., Mariakerke, Belgium).

Results

Two-dimensional Doppler echocardiographic and NT-proBNP data

Significantly increased left atrial diameter, interventricular septum (IVS) and left ventricular (LV) posterior wall could be demonstrated in AL-CA patients as compared to matched controls (Table 1). Significant differences could be detected between AL-CA patients and matched controls in tricuspid annular plane systolic excursion (16.7 ± 3.1 mm vs. 20.0 ± 1.8 mm, p = 0.05) and RV fractional area change (32.3 ± 5.3% vs. 39.2 ± 3.5%, p = 0.04). Significant (≥ grade 3) mitral regurgitation could not be detected in any of the patients or control subjects. Only 1 patient with AL-CA had grade 4 tricuspid regurgitation. NT-proBNP level proved to be 9983 ± 11101 U/l in AL-CA patients.

Three-dimensional speckle tracking echocardiographic data

Significant differences could be demonstrated in all RA volumes respecting the cardiac cycle. Total and active atrial emptying fractions were significantly decreased in AL-CA patients, while RA stroke volumes did not differ between the groups examined (Table 2). Peak global and mean segmental area strains proved to be reduced in AL-CA patients as compared to that of matched controls. Midatrial segmental circumferential, longitudinal and area strains, together with some basal strains, proved to be reduced in patients with AL-CA (Tables 3-4). Global longitudinal and area strains at atrial contraction were impaired in AL-CA patients, together with midatrial segmental circumferential and area strains (Tables 5-6). These results could suggest impaired longitudinal and circumferential RA function in the reservoir and active contraction phases of the RA function. Alterations in segmental RA strains could suggest non-uniformity of RA dysfunction in these cases.

Discussion

Among several types of amyloidosis, in AL amyloidosis is characterized by fibril deposits, which are composed of monoclonal immunoglobulin light chains and is mainly associated with B-cell type diseases, like clonal plasma cell or other B-cell dyscrasias.[18] The course of the disease can be progressive in case of cardiac involvement.[19] The main cause of death in patients with AL amyloidosis is cardiac involvement leading to heart failure or arrhythmias, and is considered to be an important prognostic factor. Without cardiac presentation, the survival is 4 years,[20] in some cases, it is only 8 months.[21]

In case of cardiac involvement, typically concentric ventricular thickening with RV involvement, biventricular function with normal or near normal ejection fraction and valvular thickening can be seen.[22,23] The speckled or granular myocardial appearance is characteristic of amyloid deposit, but the absence of this phenomenon is not rare.[2] Disproportionate septal deposition can mimic hypertrophic cardiomyopathy with dynamic LV outflow tract obstruction. Atrial thrombus is common, especially in AL-CA, and sometimes is associated to atrial fibrillation. Diastolic dysfunction is the earliest echocardiographic sign and can often be detected before any clinical symptom.[24,25] The end-diastolic thickness of the IVS is > 12 mm in the absence of any other cause of LV hypertrophy in heart involvement.[13] In CA, the thickness of the LV wall is not in correlation with the course and outcome of

Table 2 – Comparison of 3DSTE-derived volumetric and volume-based functional right atrial parameters in patients with cardiac amyloidosis and in matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
Calculated Volumes			
Vmax (ml)	85.0 ± 40.2	43.0 ± 13.2	< 0.0001*
Vmin (ml)	69.8 ± 37.3	30.8 ± 9.2	< 0.0001*
VpreA (ml)	79.2 ± 41.0	38.2 ± 12.8	< 0.0001*
Stroke Volumes			
TASV (ml)	15.2 ± 9.2	12.2 ± 7.3	0.40*
PASV (ml)	5.8 ± 5.1	4.8 ± 3.1	0.98*
AASV (ml)	9.4 ± 8.6	7.4 ± 5.9	0.47*
Emptying fractions			
TAEF (%)	19.2 ± 9.3	27.9 ± 10.7	0.02*
PAEF (%)	7.9 ± 8.0	11.5 ± 6.8	0.07*
AAEF (%)	12.1 ± 8.1	18.6 ± 9.8	0.05*

*3DSTE: three-dimensional speckle-tracking echocardiography; CA: cardiac amyloidosis; AAEF: active atrial emptying fraction; AASV: active atrial stroke volume; PAEF: passive atrial emptying fraction; PASV: passive atrial stroke volume; TAEF: total atrial emptying fraction; TASV: total atrial stroke volume; Vmax: maximum right atrial volume; Vmin: minimum right atrial volume; VpreA: right atrial volume before atrial contraction. Data expressed as mean ± standard deviation. * Unpaired Student t test.*

Table 3 – Comparison of 3DSTE-derived peak global and segmental peak right atrial strain parameters in patients with cardiac amyloidosis and in matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
Peak global strain			
RS (%)	-13.8 ± 8.8	-15.1 ± 7.2	0.52*
CS (%)	7.1 ± 5.7	10.7 ± 9.6	0.21*
LS (%)	14.4 ± 9.8	21.9 ± 9.3	0.18*
3DS (%)	-6.9 ± 6.2	-8.1 ± 4.8	0.55*
AS (%)	16.7 ± 10.3	31.2 ± 19.4	0.01*
Peak mean segmental strain			
RS (%)	-17.1 ± 8.8	-18.9 ± 6.6	0.54*
CS (%)	12.2 ± 6.3	16.0 ± 9.2	0.19*
LS (%)	16.1 ± 9.3	24.2 ± 9.6	0.10*
3DS (%)	-11.5 ± 6.1	-12.6 ± 4.7	0.60*
AS (%)	24.3 ± 11.1	38.6 ± 17.6	0.01*

*3DSTE: three-dimensional speckle-tracking echocardiography; CA: cardiac amyloidosis; 3DS: three-dimensional strain; AS: area strain; CS: circumferential strain; LS: longitudinal strain; RS: radial strain. Data expressed as mean ± standard deviation. * Unpaired Student t test.*

Table 4 – Comparison of 3DSTE-derived peak segmental right atrial strain parameters in patients with cardiac amyloidosis and in matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
RS basal (%)	-16.3 ± 10.2	-16.8 ± 5.7	0.87*
RS mid (%)	-14.9 ± 7.7	-18.5 ± 7.9	0.21*
RS superior (%)	-21.7 ± 16.5	-22.5 ± 11.9	0.87*
CS basal (%)	10.2 ± 4.9	15.1 ± 7.2	0.03*
CS mid (%)	7.9 ± 5.7	13.1 ± 6.9	0.02*
CS superior (%)	21.8 ± 16.7	20.8 ± 21.9	0.53*
LS basal (%)	17.6 ± 8.6	24.4 ± 13.4	0.19*
LS mid (%)	18.0 ± 13.3	30.7 ± 13.1	0.01*
LS superior (%)	10.9 ± 10.5	16.8 ± 9.9	0.07*
3DS basal (%)	-11.6 ± 7.2	-11.2 ± 5.3	0.86*
3DS mid (%)	-9.6 ± 5.6	-12.0 ± 5.9	0.24*
3DS superior (%)	-14.3 ± 10.8	-15.4 ± 9.3	0.77*
AS basal (%)	19.9 ± 9.1	30.1 ± 12.7	0.02*
AS mid (%)	21.9 ± 15.9	41.0 ± 15.4	0.002*
AS superior (%)	34.4 ± 30.9	47.9 ± 48.3	0.66*

*3DSTE: three-dimensional speckle-tracking echocardiography; CA: cardiac amyloidosis; 3DS: three-dimensional strain; AS: area strain; CS: circumferential strain; LS: longitudinal strain; RS: radial strain. Data expressed as mean ± standard deviation. * Unpaired Student t test.*

the disease.[6] Doppler myocardial imaging measures of the RV can identify early impairment of cardiac function or stratify risk of death in patients with AL-CA.[26] Impaired RV function was found to be a predictor of worse prognosis of early mortality in AL-CA.[27] However, detailed analysis of AL-CA-associated RA volumetric and functional alterations was not documented.

With 2D echocardiography, the assessment of RA is limited due to viewing dependency and geometric difficulties. Regularly, RA diameter and area are measured in AP4CH view.[14,15] 3D echocardiography is a new clinical modality that allows the accurate measurement of atrial phasic volume changes.[12,16,17] Moreover, several functional properties, including stroke volumes and emptying fractions and strains at different phases of the cardiac cycle, could be measured at the same time from the same 3D dataset, allowing detailed analysis of the RA during 3DSTE.[16,17] In the present study, over increased RA volumes in all phases, alterations in emptying fractions and strains characterizing systolic reservoir, and late-diastolic active booster pump RA functions could be demonstrated. These findings could be explained by infiltration of the atrial wall with amyloid fibrils, impaired left and/or right heart failure, effects of cardiovascular

Table 5 – Comparison of 3DSTE-derived global and segmental peak right atrial strain parameters at atrial contraction in patients with cardiac amyloidosis and in matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
Global strain at atrial contraction			
RS (%)	-6.4 ± 6.7	-6.2 ± 6.1	0.93*
CS (%)	10.6 ±11.9	7.8 ± 8.5	0.47*
LS (%)	4.0 ± 5.2	8.2 ± 5.5	0.02*
3DS (%)	-2.8 ± 4.9	-3.6 ± 4.4	0.62*
AS (%)	7.8 ± 8.1	15.9 ± 10.3	0.03*
Mean segmental strain at atrial contraction			
RS (%)	-8.5 ± 6.0	-8.5 ± 4.8	0.99*
CS (%)	5.3 ± 6.2	8.6 ± 7.3	0.10*
LS (%)	6.5 ± 4.0	9.0 ± 5.7	0.20*
3DS (%)	-5.3 ± 4.6	-6.2 ± 4.5	0.57*
AS (%)	11.2 ± 6.8	17.2 ± 12.3	0.11*

*3DSTE: three-dimensional speckle-tracking echocardiography; CA: cardiac amyloidosis; 3DS: three-dimensional strain; AS: area strain; CS: circumferential strain; LS: longitudinal strain; RS: radial strain. Data expressed as mean ± standard deviation. *Unpaired Student t test.*

Table 6 – Comparison of 3DSTE-derived segmental right atrial strain parameters at atrial contraction in patients with cardiac amyloidosis and in matched controls

	AL-CA patients (n = 16)	Controls (n = 15)	p-value
RS basal (%)	-9.6 ± 9.4	-8.5 ± 5.7	0.72*
RS mid (%)	-7.2 ± 5.5	-7.5 ± 4.5	0.89*
RS superior (%)	-9.0 ± 8.2	-10.2 ± 7.5	0.67*
CS basal (%)	4.6 ± 4.4	10.1 ± 10.5	0.07*
CS mid (%)	3.6 ± 4.4	8.4 ± 6.2	0.02*
CS superior (%)	10.6 ± 11.9	7.4 ± 9.8	0.42*
LS basal (%)	7.7 ± 4.0	8.9 ± 6.3	0.53*
LS mid (%)	6.8 ± 6.9	10.6 ± 7.3	0.12*
LS superior (%)	4.1 ± 5.7	7.0 ± 7.7	0.20*
3DS basal(%)	-5.4 ± 7.0	-6.0 ± 5.2	0.81*
3DS mid(%)	-4.2 ± 4.1	-6.0 ± 4.5	0.27*
3DS superior (%)	-6.8 ± 6.9	-7.1 ± 6.5	0.90*
AS basal (%)	9.9 ± 5.4	16.0 ± 10.6	0.06*
AS mid (%)	9.4 ± 9.1	18.2 ± 12.4	0.03*
AS superior (%)	15.9 ± 19.8	17.2 ± 22.3	0.87*

*3DSTE: three-dimensional speckle-tracking echocardiography; CA: cardiac amyloidosis; 3DS: three-dimensional strain; AS: area strain; CS: circumferential strain; LS: longitudinal strain; RS: radial strain. Data expressed as mean ± standard deviation. * Unpaired Student t test.*

risk factors, haemodynamic reasons, local fibrosis or oedema. In a recent study, severe LA dysfunction could be demonstrated in AL-CA, therefore the role of LA-RA interactions could also not be excluded.[28] Segmental RA strain analyses showed RA regional differences, suggesting their different contributions to RA (dys)function, as mentioned before (non-uniformity of RA dysfunction). Further studies are needed to confirm our findings in a larger population, comparing results to other diseases with LV hypertrophy as well. It should also be examined whether the demonstrated pattern of RA dysfunction is specific or not for AL-CA, and whether it has or not a diagnostic or prognostic value.

Limitations

The limited number of patients with AL-CA is one of the most important limitations of the study. However, biopsy-proven amyloidosis with cardiac involvement is a rare disease. Although the atrial septum is part of both atria, it was considered to be part of the RA in this study.

Conclusions

Significantly increased RA volumes and deterioration in RA functions could be demonstrated in AL-CA – theoretically due to infiltration of the atrial wall with amyloid fibrils – but other causes, including haemodynamic reasons, cannot be excluded.

Author contributions

Conception and design of the research: Nemes A, Földeák D, Domsik P, Kalapos A, Kormányos A, Borbényi Z, Forster T; Acquisition of data e Analysis and interpretation of the data: Nemes A, Domsik P, Kalapos A; Statistical analysis: Nemes A, Kormányos A; Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Nemes A, Földeák D.

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 University of Szeged under the protocol number 71/2011. 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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Three-dimensional Speckle Tracking Echocardiography in Amyloidosis: A New Assessment Method for a Rare Disease

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Short Editorial regarding the article: Right Atrial Deformation Analysis in Cardiac Amyloidosis – Results from the Three-Dimensional Speckle-Tracking Echocardiographic MAGYAR-Path Study

Immunoglobulin deposition in the myocardium characterizes involvement of cardiac amyloidosis (CA).[1] Fibrillary infiltration, which may happen in every heart cavity, leads to the restrictive cardiomyopathy phenotype, with complex pathophysiological mechanisms, which will result in the syndromic diagnosis of congestive heart failure.[2] Diastolic dysfunction is dominant in most cases, and it may or may not, follow diverse levels of systolic dysfunction in the most advanced phases of the disease. Atrial remodeling by amyloid infiltration may contribute to cardiac output decrease by means of insufficient or nonexistent telediastolic atrial contraction.[3] The onset of atrial electrical instability, ending in atrial fibrillation, highlights symptomatic worsening and these patients' reserved prognosis.[4]

Historically, the right cavities of the heart have been neglected in echocardiographic assessments. The complex morphology of the right ventricle (RV) has possibly contributed for the lack of reproducible data on echocardiographic cutting plans, diversely from the left ventricle (LV).[5] The development of three-dimensional echocardiography (3DE) has allowed for a more accurate calculation of right ventricle volume and function in the diverse pathologies involving that chamber.[6]

Regarding the importance of assessing the right atrium (RA), the relation between an increase in its area and adverse clinical outcomes has already been shown.[7-9] Nevertheless, its asymmetric shape, increased by the occurrence of remodeling, as observed in CA cases, limits a more precise assessment of its volume using two-dimensional echocardiography (2DE).[6] On the other hand, using three-dimensional echocardiography (3DE) overcomes these limitations, allowing not only for the accurate assessment of right atrium volume changes, but also for the detailed description of its size and function.[9]

Keywords

Immunoglobulin Light-Chain Amyloidosis; Cardiomyopathy, Restrictive/psysiopathology; Echocardiography, Three-Dimensional; Heart Failure.

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In this context, the study by Nemes et al.,[10] fills the gap regarding the use of 3DE to assess the RA for the diagnosis of CA. The authors noted significant increase in the left atrium diameter, in the interventricular septum thickness and in the LV posterior wall diameter, besides RV systolic dysfunction in patients with light-chain cardiac amyloidosis (LC-CA), when compared to healthy control group patients. These findings, compatible with restrictive cardiomyopathy, have been previously described for CA.[2] Assessing the RA by three-dimensional Speckle Tracking echocardiography (3DSTE), increased atrial volumes and smaller fractions of total and active atrial emptying in patients with LC-CA were found, when compared to control group patients. Furthermore, according to the authors, findings of reduced values on global strain peak and on segmental area, on circumferential strain in many levels, besides changes in the longitudinal and area strain in atrial contraction, suggest longitudinal e circumferential impairment in RA function in its reservoir and active contraction phases, as well as non-uniform atrial dysfunction. Although the authors have not managed to show differences on the stroke-volume values for RA when compared to healthy control-group patients, they describe the importance of measuring the RA emptying fractions and the strain-values for a proper LC-CA diagnosis.

Kado et al.,[11] studied longitudinal strain in heart cavities with the purpose of checking if change in a given cavity would have a higher prognostic value than traditional echocardiographic parameters regarding the occurrence of adverse cardiac events. Prognostic relevance was found on strain changes in the four cavities, also the RA longitudinal strain was capable of differentiating LC-CA from non-obstructive hypertrophic cardiomyopathy.

However, the drawing of the study by Nemes et al.[10] did not permit the conclusion whether the changes described by means of 3DSTE would be LC-CA-specific or if they could be found in another type of infiltrative/restrictive cardiomyopathy. On the other hand, it drives our attention to the need of a more detailed assessment on the right side of the heart, regardless of the underlying disease investigated.

At last, the appearance of innovations on echodopplercardiography, which always occur towards diagnosis improvement or accuracy, as well as to make early LC-CA therapy for the prevention of adverse clinical outcomes, one must not underestimate already established, traditional echocardiographic findings for disease assessment.

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Evaluation of the Bleeding Intensity of Patients Anticoagulated with Warfarin or Dabigatran Undergoing Dental Procedures

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Abstract

Background: **Thrombotic disorders remain one of the leading causes of death in the Western world. Dabigatran appeared as an alternative to warfarin for anticoagulation in the treatment of atrial fibrillation (AF). The risk associated with bleeding due to its use has been documented in several randomized clinical trials, but no large study has examined in detail the risk of bleeding during dental extraction and other dental procedures involving bleeding.**

Objective: **To compare the intensity of bleeding in individuals taking dabigatran or vitamin K antagonist (warfarin) and undergoing dental procedures.**

Methods: **Prospective, single-center, controlled study with one single observer. Patients diagnosed with nonvalvular AF, on warfarin or dabigatran, cared for at a cardiology referral center, and requiring single or multiple dental extractions, were evaluated up to seven days post-extraction. The following outcomes were assessed: bleeding time between the beginning and the end of suture and complete hemostasis; bleeding before the procedure, after 24 hours, 48 hours, 7 days, during and after suture removal (late); $p<0.05$ was defined as of statistical relevance.**

Results: **We evaluated 37 individuals, 25 in the warfarin group and 12 in the dabigatran group. Age, sex, weight, height, blood pressure, color, schooling, family income and comorbidities were similar between the two groups. Regarding bleeding after 24 hours of the procedure, no one in the dabigatran group had bleeding, whereas 32% in the warfarin group had documented bleeding ($p = 0.028$). The other variables analyzed did not differ between the groups.**

Conclusions: **This study suggests that, regarding dental extraction, there is no statistically significant difference in the intensity of bleeding of patients taking dabigatran as compared to those taking warfarin. Bleeding 24 hours after the procedure was less frequent among patients on dabigatran. (Arq Bras Cardiol. 2018; 111(3):394-399)**

Keywords: **Hemorrhage/complications; Anticoagulants; Oral Surgical Procedures; Bleeding Time; Warfarin; Dabigatran.**

Introduction

Thrombotic disorders remain one of the leading causes of death in the Western world. Several treatments with anticoagulants have been used, including unfractionated heparin, low-molecular-weight heparin, fondaparinux, vitamin K antagonists (warfarin), and novel oral anticoagulants (NOACs), such as apixaban, dabigatran and rivaroxaban.[1] Warfarin, the major anticoagulant, has been used for more than five decades in the United States and worldwide. Over two million people in the United States are estimated to use warfarin, with approximately 300,000 new prescriptions every year.[2]

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Despite their proven efficacy, the clinical use of vitamin K antagonists has some drawbacks, such as food and drug interaction, variable anticoagulation response, slow onset of therapeutic effects, need for therapeutic response monitoring by use of prothrombin time (PT) and International Normalized Ratio (INR), and narrow therapeutic range.[3] Based on the drawbacks of warfarin use and the low efficiency of anticoagulation rates in clinical practice, studies assessing NOACs have been planned and conducted in recent years.

The NOACs have been developed and properly assessed in phase 2 and 3 studies, which have clearly demonstrated their efficacy and safety. Some drugs are factor IIa inhibitors (thrombin inhibitor), such as dabigatran, while others are factor Xa inhibitors, such as apixaban, rivaroxaban and edoxaban. Patients with atrial fibrillation (AF) are at high risk for stroke. Although warfarin and other vitamin K antagonists are highly effective, reducing the risk of stroke in approximately two thirds of the cases, their use has the already described drawbacks. Recently, NOACs have shown to be as effective as warfarin, or even superior, in preventing stroke and systemic embolism.[4]

Dabigatran etexilate, an oral direct thrombin inhibitor, has a serum half-life of 12 to 17 hours and requires no INR monitoring. In the RE-LY trial,[5] which proved the non-inferiority and efficacy of that NOAC as compared to warfarin, 10% of the study participants needed to undergo dental procedures.[5] The RE-LY trial subgroups (dabigatran and warfarin) have shown similar periprocedural bleeding rates, with greater benefits for the dabigatran group regarding major bleedings because of the faster reversion of the drug's effect. Therefore, dabigatran has emerged as an alternative to warfarin for anticoagulation in the treatment of AF and venous thromboembolism.[6] Several guidelines have validated the use of warfarin or any NOAC (class of recommendation I, level of evidence A) for patients with nonvalvular AF and indication for antithrombotic therapy; however, NOACs are not indicated to patients with mechanical prosthetic valve or hemodynamically significant mitral stenosis, because such patients have been excluded from the major studies on NOACs in AF.[7]

Cardiologists are often sought for guidance regarding the suspension of anticoagulants before a dental procedure, because of the concern with bleeding. In addition, dentists should be aware of the NOACs prescribed, as well as of their peculiarities, to ensure that patients receive safe and proper dental treatment.[8] The risk for hemorrhagic events associated with the use of NOACs has been documented in several randomized clinical trials, but no large study has assessed specifically the risk for bleeding after a dental extraction or other dental procedure involving bleeding. Dental extraction is one of the most common surgical procedures and can cause significant bleeding. With the increasing use of direct thrombin inhibitors in clinical practice, the occurrence of bleeding and hemorrhagic complications in that context requires better assessment.[9]

The present study aimed at assessing the severity of bleeding associated with the use of dabigatran as compared to traditional oral anticoagulation (warfarin) in individuals undergoing dental procedures.

Methods and Sample Selection

This is a prospective single-center controlled study with one single observer. Patients diagnosed with nonvalvular AF and indication for anticoagulation, cared for at a cardiology referral center, and requiring single or multiple dental extractions were included. All patients provided written informed consent, and the study protocol was approved by the Ethics Committee in Research of the institution. The patients were followed up by a clinical cardiologist in two groups: group 1, warfarin (25); group 2, dabigatran (12).

Patients, independently of sex, aged 18 years or older, with nonvalvular AF and on an oral anticoagulant (warfarin) or NOAC (dabigatran) were selected. Those on oral dabigatran at the dose of 150mg every 12 hours received the drug from the Municipal Health Department. Dabigatran was specifically chosen because of a previously established care partnership between the Municipal Health Department and Boehringer Ingelheim's laboratories for anticoagulation of patients with nonvalvular AF. Individuals with the following characteristics were excluded: contraindication for anticoagulation; refusal to provide written informed consent; use of warfarin with an INR outside the therapeutic range (2.0 – 3.0) on the day of the dental procedure.

Before the procedure, the patients' vital data, such as systemic blood pressure and heart rate, as well as their weight and height were assessed. In addition, the patients were asked about their race (white, mixed or black), educational level and family income. Those of the warfarin group underwent blood collection to measure PT and INR before the procedure (same day) by use of hemostasis screening tests, while those of the dabigatran group took the predicted dose (150 mg every 12 hours). Patients received prophylaxis for infectious endocarditis, when indicated, in accordance with current guidelines. The dental extractions were performed according to the department's protocol for dental treatment of patients with heart diseases on anticoagulants. The local hemostatic measures comprised appropriate sutures, cellulose sponge and tranexamic acid (ground pill). All patients were prescribed dipyrone, 1 g up to every 6 hours for pain after the procedure, or, in case of allergy to dipyrone, paracetamol, 750mg up to every 6 hours.

Bleedings or hemorrhagic complications of the patients on oral anticoagulants were assessed by the surgical dentist (single observer) during and after the single or multiple dental extractions. Primary outcome was defined as bleeding time 1, between the beginning of suture and complete hemostasis. The following outcomes were also assessed: bleeding time 2 (between the end of suture and complete hemostasis), bleeding before dental extraction, bleeding during dental extraction, and bleeding 24 hours, 48 hours and 7 days after the procedure. The bleeding scale was used, and major bleedings were those from 2.1 on, as described by Iwabuchi et al. (Figure 1).[10]

Data analysis

Statistical analysis

The *Statistical Package for Social Sciences* (SPSS), version 15, was used for data analysis. Nonparametric tests were used for the analysis of continuous variables, because of the small sample size and the well-known low performance of the tests of adherence to normality in small samples. Continuous variables were described as median and interquartile range (IQR). Categorical variables were described as relative frequency and compared by use of Chi-square and Fisher exact tests. Continuous variables were compared by use of Wilcoxon test for dependent samples, while Mann-Whitney U test was used for independent samples. Statistical significance was defined as p value < 0.05.

Sample size calculation

The sample size was calculated to yield statistical power of 80% and an alpha of 5%, estimating, based on previous clinical experience, a total bleeding time around 180 ± 60 seconds for the warfarin group, and expecting a reduction of at least 60 seconds in the dabigatran group as compared to the warfarin group. Thus, the sample size calculated was 12 patients in each group. Because the inclusion of patients in the warfarin group was easy, its sample size was doubled.

Results

Clinical characteristics of the sample

From January to June 2017, 48 patients with nonvalvular AF were selected, and 11 patients who required no bloody dental procedure were excluded. This study included 37 patients, 19 (51.4%) of the female sex, ages ranging from 34 to 85 years (median, 69 years, IQR: 58-65 years). The patients had multiple comorbidities, such as hypertension (78.4%), diabetes (37.8%), and heart failure (27%). All patients were on regular medical follow-up and on regular use of the drugs prescribed by their attending physicians.

Of the patients included in the study, 25 were selected for the warfarin group and 12, for the dabigatran group (150 mg). When comparing both groups, before the intervention, no significant statistical difference was observed regarding age, sex, race, educational level, family income, systemic blood pressure, heart rate, weight, height and number of teeth to be extracted (Table 1).

Clinical outcomes

Regarding the primary outcome, bleeding time 1 showed no statistically significant difference between the groups (median of 300 seconds for both groups). Regarding the other outcomes, such as bleeding time 2, bleeding before dental extraction, bleeding during dental extraction, bleeding 48 hours after the procedure, and the bleeding scale, no significant difference was found. However, bleeding 24 hours after the procedure was not identified in any patient in the dabigatran group, but eight patients in the warfarin group (32%) had it, resulting in a statistically significant difference ($p=0.028$) between the groups. No significant difference was observed in delayed bleeding, during and after suture removal. Table 2 illustrates the clinical outcomes of bleeding in both groups before and after the intervention.

Continuous outcomes (expressed as median and 25th and 75th percentiles) were compared by use of Mann-Whitney U test. Categorical outcomes were compared by use of Fisher exact test (frequencies expected ≤ 5).

Discussion

This study's results show, in individuals submitted to dental extraction, no statistically significant difference in the bleeding intensity of individuals on dabigatran as compared to those on warfarin, but suggest a lower frequency of bleeding 24 hours after the procedure in those on dabigatran.

The InterFib registry has assessed 15,174 patients with AF in 47 countries, including Brazil and South America. When analyzing the data of our region, the rate of an oral anticoagulant use was 45%, of which 44% had INR within the 2-3 therapeutic range. Thus, of the patients with AF and indication for an oral anticoagulant, only 20% were properly anticoagulated.[11] There has been great controversy regarding the use of anticoagulants in planning dental treatments that involve bleeding. The major concerns about the use of NOACs in invasive dental procedures involving bleeding were the lack of a specific antidote for reversing the medicine effect and the risk of the thrombotic disease for which anticoagulation was indicated.[12] In April 2017, the Brazilian Sanitary Surveillance Agency (Anvisa) approved the use of idarucizumab in Brazil to reverse anticoagulation in patients on dabigatran. Idarucizumab is a fragment of monoclonal antibody, which, upon injection into the bloodstream, neutralizes dabigatran via direct binding, preventing its anticoagulant effect. It has been widely used in the emergency setting. The results of the RE-VERSE AD study have confirmed the efficacy and safety of that drug. More recent guidelines on the reversion of the effect of NOACs recommend its use.[13-15] Patients on oral anticoagulants for different reasons, such as AF, need to have their risk for bleeding and complications during a dental procedure assessed. The management of individuals on warfarin who need to undergo invasive dental procedures involving bleeding and/or oral and maxillofacial surgery has been well documented in the literature and follows the recommendations of the III Brazilian Guideline on Perioperative Assessment.[16] In contrast, there is no clinical trial in the literature providing specific recommendations for patients on NOACs who need to undergo dental procedures.[17]

A recent study on the use of dabigatran and perioperative management has recommended not to suspend that drug in patients submitted to minor procedures, such as dental cleaning, dental extraction, skin biopsy or cataract surgery, and to perform the procedure preferably 10 hours after the ingestion of the last dose to minimize the risk of bleeding.[18] Another study has recommended not to interrupt NOACs in simple procedures, such as up to three dental extractions, three implantations, radicular scraping and smoothing, and alveoloplasties.[19] Cohen et al.[20] have reported that, for more complex periodontal surgery or more than three extractions, the medication should be suspended 48 hours before and reinitiated 24 hours after the procedure in patients with normal renal function. Breik et al.[21] have suggested that dabigatran or any anticoagulant should only be interrupted before dental procedures after consultation with the patient's attending physician (clinician or

- 0. No bleeding
- 1. Hemostasis achieved before compression measures were taken
- 2. Significant bleeding on the following day
- 2.1. Significant bleeding present for 48 hours
- 3. Delayed bleeding

Figure 1 – *Bleeding scale.*

Table 1 – Clinical characteristics of the patients studied according to the intervention group

Variable	Warfarin (n = 25)	Dabigatran (n = 12)	p Value
Age (median, IQR) – years	67 (54.5-75.5)	71 (65.5-80)	0.360
Female sex - n (%)	12 (48)	7 (58.3)	0. 556
SBP (median, IQR) – mm Hg	120 (110-140)	130 (102.5-137.5)	0.810
DBP (median, IQR) – mm Hg	80 (70-85)	80 (62.5-80)	0.432
HR (median, IQR) – bpm	76 (62.5-88)	76.5 (67.5-90.3)	0.554
Weight (median, IQR) – kg	68 (56.5-78.5)	67.5 (60-75.3)	0.810
Height (median, IQR) – m	1.61 (1.49-1.69)	1.605 (1.52-1.70)	0.810
INR (median, IQR)	2.5 (2.2-2.97)	-	-
Teeth extracted (median, IQR)	1 (1-1.5)	1 (1-1.75)	0.962
Black color (%)	10 (40)	06 (50)	0.565
Family income (up to 1 minimum wage) – n (%)	20 (80)	10 (83.3)	0.594
Educational level (incomplete secondary level) – n (%)	16 (64)	7 (58.3)	0.507
Arterial hypertension – n (%)	18 (72)	11 (91.7)	0.177
Diabetes mellitus 2 - n (%)	10 (40)	04 (33.3)	0.493
Heart failure – n (%)	07 (28)	03 (25)	0.588
Traumatic dental extraction - n (%)	05 (20)	03 (33.3)	0.311

IQR: interquartile range; bpm: beats/minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; INR: International Normalized Ratio. Continuous variables (expressed as median and 25th and 75th percentiles) were compared by use of Mann-Whitney U test. The categorical variables "sex" and "black skin color" were compared by use of Chi-square test. The other variables were compared by use of Fisher exact test (expected frequencies ≤ 5).

Table 2 – Clinical outcomes of bleeding in the warfarin and dabigatran groups before and after dental extraction

Outcome	Warfarin	Dabigatran	p Value
Bleeding time 1 (median, IQR)	300 (240-390)	300 (240-360)	0.597
Bleeding time 2 (median, IQR)	0 (0-60)	0 (0-60)	0.666
Bleeding scale (median, IQR)	1 (1-2)	1 (1-1)	0.124
Bleeding before dental extraction – n (%)	24 (96)	12 (100)	0.676
Bleeding during dental extraction – n (%)	25 (100)	12 (100)	-
Bleeding after 24 hours – n (%)	8 (32)	0	0.028**
Bleeding after 48 hours – n (%)	5 (20)	0	0.122
Delayed bleeding – n (%)	5 (20)	0	0.122
Bleeding during suture removal – n (%)	8 (32)	2 (16.7)	0.285
Bleeding after suture removal – n (%)	0	0	-

(**): p value < 0.05
(-): statistical data not available because either all or no patient had the outcome in the two groups.

cardiologist), who will assess the risk of bleeding *versus* the risk of thrombosis for each patient. For those on dabigatran for AF without a previous stroke, suspending the medicine 24 hours before the procedure is considered relatively safe; however, for patients with a recent history of deep venous thrombosis, pulmonary thromboembolism or embolic stroke, suspending the medicine might be risky.[21]

The clinician should consider that the number of patients taking NOACs is rapidly increasing and that the conflicting findings of several studies have shown that no ideal management has been established for the use of those medicines in patients who need to undergo dental procedures with a high risk for significant bleeding.[22] More recent data have emphasized that there is no need to suspend dabigatran in dental extraction, and have suggested that, in cases involving the risk for major bleeding, the decision to temporarily interrupt the drug should be individualized and agreed with the attending physician.[23,24]

Implications

A recent survey has revealed that dentists are well informed about anticoagulation. They, however, tend to overestimate the risk of bleeding, being cautious about their treatment management, which differs in different parts of the world.[25] A Brazilian systematic review has highlighted the risk of bleeding in individuals taking anticoagulants, as well as the efficacy and safety of dental interventions in that population.[26] It is worth noting that the present study is pioneer in Brazil on approaching that practice in patients with nonvalvular AF, and its results should be used to foster the understanding of the magnitude of bleeding in that specific population when taking that class of drug.

Study limitations

The present study has some limitations: impossibility of being double-blind because of the lack of funding to pay for a double-dummy study, with specific placebo for the two drugs tested and their false INR for monitoring in the dabigatran group. In addition, choosing a continuous variable for primary outcome makes the analysis of subtle differences between the groups more objective, allowing a smaller sample size with statistical adequacy; however, that number is small to assess more robust and rare outcomes in this type of intervention.

Conclusions

This study suggests that, regarding dental extraction, there is no statistically significant difference in the intensity of bleeding of patients taking dabigatran as compared to those taking warfarin. Bleeding 24 hours after the procedure was less frequent among patients on dabigatran.

Author contributions

Conception and design of the research: Andrade MVS, Andrade LAP, Feitosa GS, Feitosa Filho GS; Acquisition of data: Andrade MVS, Andrade LAP, Bispo AF, Freitas LA; Analysis and interpretation of the data and Statistical analysis: Andrade MVS, Andrade MQS, Feitosa Filho GS; Obtaining financing and Writing of the manuscript: Andrade MVS; Critical revision of the manuscript for intellectual content: Andrade MVS, Feitosa GS, Feitosa Filho GS.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Santa Izabel da Santa Casa de Misericórdia da Bahia under the protocol number 1.857.480. CAAE: 61125916.10000.5520. 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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Fasting/Refeeding Cycles Prevent Myocardial Dysfunction and Morphology Damage in the Spontaneously Hypertensive Rats

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Abstract

Background: **Caloric restriction is known to impair the cardiac function and morphology in hypertrophied hearts of spontaneously hypertensive rats (SHR); however, the influence of fasting/refeeding (RF) is unknown.**

Objective: **To investigate the fasting/refeeding approach on myocardial remodeling and function. In addition, the current study was designed to bring information regarding the mechanisms underlying the participation of Ca^{2+} handling and β-adrenergic system.**

Methods: **Sixty-day-old male SHR rats were submitted to food *ad libitum* (C), 50% food restriction (R_{50}) or RF cycles for 90 days. Cardiac remodeling was assessed by ultrastructure analysis and isolated papillary muscle function. The level of significance considered was 5% ($\alpha = 0.05$).**

Results: **The RF rats presented lower cardiac atrophy than R_{50} in relation to C rats. The C rats increased weight gain, R_{50} maintained their initial body weight and RF rats increased and decreased weight during RF. The RF did not cause functional impairment because the isotonic and isometric parameters showed similar behavior to those of C. The isotonic and isometric cardiac parameters were significantly elevated in RF rats compared to R_{50} rats. In addition, the R_{50} rats had cardiac damage in relation to C for isotonic and isometric variables. While the R_{50} rats showed focal changes in many muscle fibers, the RF rats displayed mild alterations, such as loss or disorganization of myofibrils.**

Conclusion: **Fasting/refeeding promotes cardiac beneficial effects and attenuates myocardial injury caused by caloric restriction in SHR rats, contributing to reduce the cardiovascular risk profile and morphological injuries. Furthermore, RF promotes mild improvement in Ca^{2+} handling and β-adrenergic system. (Arq Bras Cardiol. 2018; 111(3):400-409)**

Keywords: **Rats; Hypertension; Myocardial/dysfunction; Chronic Disease; Fasting, Reffeding; Caloric Restriction.**

Introduction

The major causes of chronic non-communicable diseases (NCD)-attributable mortality are cardiovascular disease, cancers, chronic respiratory disease and diabetes.[1] These conditions share a small number of behavioral risk factors, which aggravate the NCD and include unhealthy diet, which is closely related to hypertension.

Caloric restriction (CR) has been recognized throughout history for promoting several beneficial effects.[2,3] Nevertheless, although CR may prevent cardiac damage in hypertrophied hearts of spontaneously hypertensive rats (SHR),[4] it is common to note body weight fluctuations typically referred to as the "*yo-yo syndrome*" while on a regimented diet, and these fluctuations have shown deleterious cardiovascular effects.[5,6] Researches from our laboratory and others have shown that, when dietary restriction is severe, it can promote morphological injuries and impairment of cardiac function in normal or SHR rats.[7-12]

Recently, intermittent fasting or fasting/refeeding has also shown to extend lifespan and have beneficial health effects as compared to *ad libitum* food consumption,[3,13,14] as it enhances cardiovascular function and improves several risk factors for cardiovascular diseases.[15,16] This dietary approach also implies a protective effect against oxidative stress, lower rates of kidney disease,[17] prolongation of reproductive function,[18] and leads to the normalization of resting energy expenditure and protein synthesis recuperation, but can cause many metabolic disturbances.[19,20]

In normotensive rats submitted to food restriction, chronic refeeding decreased the incidence of cardiac arrhythmia and reversed the depletion of heart proteins.[21,22] Food restriction caused cardiac function disturbances that were almost completely reversed back to normal after chronic refeeding in the isolated rat heart.[23] In our laboratory, we observed that fasting/refeeding cycles reversed the mechanical dysfunction

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and attenuated the structural injuries in papillary muscles caused by CR in normotensive rats.[24] Nevertheless, it is not yet clear whether fasting/refeeding cycles are able to promote similar effects and/or reverse the cardiac damage induced by food restriction in SHR rats.[7-12] Thus, the objective was to investigate the fasting/refeeding approach on myocardial remodeling and function. In addition, the current study was designed to bring information regarding the mechanisms underlying the participation of Ca^{2+} handling and β-adrenergic system. Our hypothesis is that fasting/refeeding condition would attenuate the myocardial injury caused by food restriction and would contribute to normal cardiac remodeling in SHR rats without alterations in the Ca^{2+} handling and β-adrenergic system.

Methods

Animal model and experimental protocol

Sixty-day-old male SHR were distributed into three groups: control (C, n = 7); food-restriction (R_{50}, n = 7); and fasting/refeeding cycles (RF, n = 7). The C group was fed *Labina rat chow* containing 7.0% fat, 20.55% protein, 62.95% carbohydrate, 5.0% fiber and 4.5% moisture (Agribands, Brazil), and water was provided *ad libitum*. Table 1 shows the ingredient composition of *Labina rat chow*. The R_{50} group received 50% of the amount of food consumed by the C group. The RF group was submitted to cycles of 50% food restriction and refeeding *ad libitum* weekly. All rats were maintained on this dietary regimen for 90 days and were then euthanized.

All animals were housed in individual cages in a room maintained at 23ºC with a 12-hour light/dark cycle and were weighed once a week. Initial and final body weights (IBW and FBW, respectively), the ratios between left and right ventricular weights to final body weight (LVW/FBW and RVW/FBW, respectively) and papillary muscle cross-sectional area (CSA) were also measured. All experiments and procedures were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the United States National Institutes of Health and were approved by the ethics committee of Botucatu School of Medicine, UNESP, São Paulo, Brazil.

Table 1 – Ingredient composition of the Labina rat experimental diet

Ingredient	(g/kg)
Starch	397.5
Dextrinized Corn Starch	132.0
Sucrose	100.0
Carbohydrates	629.5
Casein	200.0
L-Cysteine	3.0
Choline bitartrate	2.5
Protein	205.5
Soy oil	70.0
Fat	70.0
Fiber	50.0
Vitamin mix	10.0
Mineral mix	35.0
Total	1000

Systolic blood pressure

Systolic blood pressure evaluation was assessed by the non-invasive tail-cuff method with a Narco BioSystems Electro-Sphygmomanometer (International Biomedical, Austin, TX, USA) at the beginning and after the end of the experimental protocol. The average of two pressure readings was recorded for each animal.

Isolated muscle performance

Cardiac intrinsic contractile performance was evaluated by studying isolated left ventricular (LV) papillary muscle as described previously.[9,10,12] Isometric contraction parameters, including peak of developed tension (DT, g/mm^2, defined as peak isometric tension minus resting tension), resting tension (RT, g/mm^2), time to peak tension (TPT, ms), peak isometric tension development rate (+dT/dt, g/mm^2/s) and maximum tension decline rate (-dT/dt, g/mm^2/s), time from peak tension to 50% relaxation (RT_{50}, ms) were determined. The isotonic parameters were percentage of shortening (PS, %), time to peak shortening (TPS, ms), maximum shortening velocity (-dL/dt, ML/s) and maximum relaxation velocity (+dL/dt, ML/s).

The mechanical behavior of the papillary muscle was evaluated under baseline conditions at 1.25 mM [Ca^{2+}] and after the following inotropic maneuvers: increase in extracellular Ca^{2+} concentration from 0.625 to 1.25, 2.5 and 5.2 mM, and β-adrenergic stimulation with 0.01, 0.1 and 1.0 μM isoproterenol. The parameters used to characterize papillary muscle were as follows: length (mm), weight (mg) and CSA (mm^2). Muscle length (ML) at peak DT was defined as L_{max} in vitro and measured with a Gartner cathetometer (Chicago, IL, USA). To compare the mechanical function between different muscle lengths, isometric and isotonic parameters were normalized to CSA and L_{max}.

Morphological study

For the ultrastructural study (three animals per group), small pieces of the LV papillary muscle were fixed in Karnovsky's fixative in 0.12 M phosphate, pH 7.2, for 1-2 hours and were postfixed in 1% osmium tetroxide in 0.1 M phosphate buffer for 2 hours.[25] After dehydration in a graded ethanol series, the samples were embedded in epoxy resin. Ultrathin sections were cut from selected areas with a diamond knife, double-stained with uranyl acetate and lead citrate, and examined using a Philips EM 301 electron microscope. The LV myocyte CSA was measured using a compound microscope attached to a computerized imaging analysis system (Image-Pro Plus 3.0, Media Cybernetics, Silver Springs, MD, USA).

Statistical analysis

Statistical analyses were performed using SigmaStat 3.5 software (SYSTAT Software Inc., San Jose, CA, USA). Normally distributed variables from general characteristics and

myocardial function at baseline condition were reported as means ± standard deviation (SD). Comparisons between groups were performed using one-way analysis of variance (ANOVA) for independent samples. A repeated-measures two-way ANOVA was utilized to evaluate the body weight evolution and the positive and negative inotropic effects on myocardial function. When significant differences were found ($p < 0.05$), *post hoc* Tukey's or Bonferroni's test for multiple comparisons was carried out. The level of significance considered was 5%.

The sample size (n) was performed using the equation: $n = 1 + [2C * (s/d)^2]$, where C (z score $\alpha + z$ score $\beta)^2$ is dependent on the values chosen for statistical power of the test (90%; type II error) and level of significance (0.05; type I error); the standard deviation value (s) adopted was 0.25, and the minimal difference between groups (d) was 0.5. The sample size needed to detect a significant difference between groups is 6.25 rats per group; however, we decided to use 7 animals per group for most of the analyses.

Results

General and morphological characteristics of rats

Significantly higher values of FBW, LVW, RVW, LVW/FBW and RVW/FBW were found in C compared to R_{50} and RF rats (Table 2). After 12 weeks, fasting/refeeding cycles promoted a substantial elevation of FBW and food consumption that were significantly greater than those in the R_{50} group. In relation to cardiac parameters, the RF and R_{50} groups presented different behavior. Specifically, the LVW (RF: 12.12% and R_{50}: 48.5%; $p < 0.05$), RVW (RF: 19.04% and R_{50}: 47.62%; $p < 0.05$), LVW/FBW (RF: 6.64% and R_{50}: 19.2%; $p < 0.05$) and RVW/FBW (RF: 12.06% and R_{50}: 18.96%; $p < 0.05$) were reduced in percentage in the RF and R_{50} rats as compared to C rats. Nevertheless, the fasting/refeeding cycles presented lower cardiac atrophy than R_{50} rats in relation to C rats.

In addition, C rats experienced increasing weight gain, while R_{50} rats maintained their IBW after 12 weeks of experimental protocol (Figure 1). On the other hand, RF rats gained weight dependent on food intake, with body weight increasing and decreasing during refeeding and fasting, respectively (Figure 1).

Isolated muscle performance

Fasting/refeeding cycles did not cause functional impairment (Tables 3 and 4). Nevertheless, the isotonic [-dL/dt, TPS, and RT_{50})] and isometric parameters (TPT, +dT/dt, -dT/dt, RT_{50}) were significantly elevated in RF rats compared to those in the R_{50} group, indicating that fasting/refeeding cycles preserves the contraction and relaxation phase of cardiac function. Furthermore, the R_{50} rats presented cardiac damage in relation to the C group for isotonic and isometric variables. In addition, the papillary muscle CSA showed no difference among groups.

Calcium stimulation

After baseline condition, the increases in extracellular Ca^{2+} concentrations from 0.625 to 5.2 mM resulted in a positive inotropic effect in myocytes from all groups (Figures 2A-F). However, the results shown in Figures 2B, C and E indicate that extracellular Ca^{2+} (1.25 and 2.5 mM) induced a greater response in +dT/dt (RF: 99.1 ± 23.6; 132.1 ± 36.2 g/mm²/s *vs.* R_{50}: 63.2 ± 12.8; 91.5 ± 22.0 g/mm²/s; $p < 0.05$, respectively), -dT/dt (RF: 30.6 ± 5.9; 35.9 ± 5.8 g/mm²/s *vs.* R_{50}: 22.0 ± 4.4; 28.5 ± 6.1 g/mm²/s; $p < 0.05$, respectively) and -dL/dt (RF: 2.19 ± 0.45; 2.77 ± 0.51 ML/s *vs.* R_{50}: 1.47 ± 0.24; 1.99 ± 0.31 ML/s; $p < 0.05$, respectively) in the RF rats than in the R_{50} rats. In addition, -dT/dt and -dL/dt were significantly diminished in the R_{50} myocardium at Ca^{2+} concentration of 5.2 mM when compared to those in the RF group. When submitted to inotropic maneuvers, DT, PS and +dL/dt were similar between RF and R_{50}. In relation to the cardiac function of C rats after Ca^{2+}stimulation, the fasting/refeeding cycles presented similar behavior (Figures 2A-F). The only significant result between C and R_{50} was noted in the highest

Table 2 – General characteristics of rats

Parameters	Groups		
	C	R_{50}	RF
IBW (g)	247 ± 15	248 ± 12	249 ± 13
FBW (g)	366 ± 14	236 ± 17*	342 ± 21*†
FC (g/week)	159 ± 23	77 ± 4*	130 ± 55†
SBP initial (mmHg)	177 ± 8	177 ± 5	181 ± 7
SBP final (mmHg)	163 ± 13	157 ± 15	156 ± 5
LVW (g)	0.99 ± 0.04	0.51 ± 0.01*	0.87 ± 0.08*†
RVW (g)	0.21 ± 0.02	0.11 ± 0.01*	0.17 ± 0.02*†
LVW/FBW (mg/g)	2.71 ± 0.05	2.19 ± 0.16*	2.53 ± 0.08*†
RVW/FBW (mg/g)	0.58 ± 0.04	0.47 ± 0.05*	0.51 ± 0.05*

*C: control group; R_{50}: animals with food restriction of 50%; RF: animals with alternation between food restriction of 50% and refeeding; IBW: initial body weight; FBW: final body weight; FC: food consumption; SBP: systolic blood pressure; LVW: left ventricle weight; RVW: right ventricle weight. Values are means ± SD (n = 7). * significant at $p < 0.05$ vs. C; † $p < 0.05$ vs. R_{50}. One-way ANOVA and post hoc Tukey's test.*

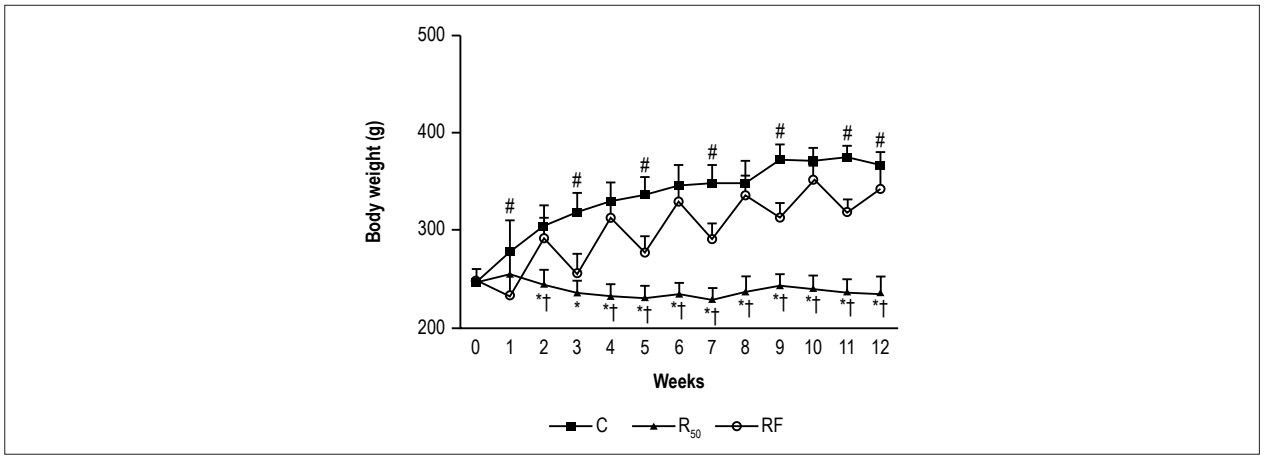

Figure 1 – *Changes in body weight after 90 days of treatment. Control (C; closed squares, n = 7), animals with food restriction of 50% (R_{50}; closed triangles, n = 7) and animals with alternation between food restriction of 50% and refeeding (RF; open circles, n = 7). Values are means ± SD; * significant at p < 0.05, R_{50}vs. C; † p < 0.05, RF vs. R_{50}; #p < 0.05, C vs. RF. Repeated measures two-way ANOVA; post hoc Bonferroni's test. Source: Research team.*

Table 3 – Isotonic contraction of groups at baseline condition

	Groups		
	C	R_{50}	RF
PS (%)	19 ± 3	18 ± 3	20 ± 2
-dL/dt (ML/s)	1.89 ± 0.40	1.60 ± 0.36	2.19 ± 0.45†
TPS (ms)	168 ± 26	205 ± 14*	161 ± 14†
+dL/dt (ML/s)	4.28 ± 1.26	4.13 ± 1.11	4.79 ± 0.86
RT_{50} (ms)	58 ± 10	76 ± 12*	53 ± 9†
CSA (mm^2)	0.95 ± 0.22	0.85 ± 0.17	0.91 ± 0.18

*C: control group; R_{50}: animals with food restriction of 50%; RF: animals with alternation between food restriction of 50% and refeeding; PS: percentage of shortening; -dL/dt: maximum shortening velocity; TPS: time to peak shortening; + dL/dt: maximum relaxation velocity; RT_{50}: time from peak tension to 50% relaxation; CSA - muscle cross-sectional area. Values are means ± SD (n = 7) at basal calcium concentration (1.25 mM); * significant at p < 0.05 vs. C; † p < 0.05 vs. R_{50}. One-way ANOVA and post hoc Tukey's test.*

Ca^{2+} concentration (5.2 mM); -dL/dt was significantly lower in R_{50} than in C group (C: 2.66 ± 0.35 *vs.* R_{50}: 2.18 ± 0.33 ML/s, p < 0.05) (Figure 2E).

Isoproterenol stimulation

The fasting/refeeding cycles increased +dT/dt, -dT/dt and -dL/dt at the highest isoproterenol concentration (1 μM) compared to those in the R_{50} group, indicating a positive inotropic effect in myocytes. In contrast, the RF group promoted a reduction in +dL/dt than the R_{50} group at the same isoproterenol concentration (Figure 3F). In addition, the similar effects were noted in +dT/dt and -dT/dt at 1μM isoproterenol of the C group when compared to the R_{50} (Figures 3B and C). Furthermore, RF rats presented higher +dL/dt at baseline and isoproterenol concentrations (0.01 μM) in comparison to C group (Figure 3F). There were no significant differences in mechanical data (DT and PS) under inotropic stimulation with isoproterenol among the groups (Figures 3A and D).

Myocardial morphology

The C group rats showed normal morphological characteristics, with myofibrils filling the entire sarcoplasm, well-defined sarcomeres, mitochondria with lamellar cristae, sarcoplasmic membranes with regular aspect, sarcoplasmic reticulum among myofibrils and nuclei with uncondensed chromatin (Figures 4A and B). The R_{50} group presented focal changes, including disorganization or absence of myofibrils, some polymorphic mitochondria with a decreased number of cristae and areas of sarcoplasmic reticulum dilation (Figures 4C, D and E). In RF rats, the only change observed was a loss of mitochondrial cristae in some organelles. Most of the fibers had normal morphology (Figures 4F and G).

Discussion

Interestingly, little information is available on the relationship between cardiac function and morphology during fasting/refeeding in SHR hypertrophied hearts. Within this context, this dietary regimen has become the subject of

Table 4 – Isometric contraction of groups at baseline condition

	Groups		
	C	R_{50}	RF
DT (g/mm²)	6.17 ± 1.24	6.37 ± 1.14	7.18 ± 1.20
RT (g/mm²)	1.06 ± 0.12	1.12 ± 0.31	1.07 ± 0.17
+dT/dt (g/mm²/s)	77 ± 17	63 ± 13	93 ± 18†
TPT (ms)	146 ± 27	184 ± 19*	128 ± 25†
-dT/dt (g/mm²/s)	29 ± 5	22 ± 4	33 ± 9†
RT_{50} (ms)	174 ± 40	224 ± 32*	171 ± 21†
CSA (mm²)	0.95 ± 0.22	0.85 ± 0.17	0.91 ± 0.18

*C: control group; R_{50}: animals with food restriction of 50%; RF: animals with alternation between food restriction of 50% and refeeding; DT: peak developed tension; RT: resting tension; TPT: time to peak tension; +dT/dt: maximum tension development rate; -dT/dt: maximum tension decline rate; RT_{50}: time from peak tension to 50% relaxation; CSA: muscle cross-sectional area. Values are means ± SD (n = 7) at basal calcium concentration (1.25 mM); * significant at p < 0.05 vs. C; † p < 0.05 vs. R_{50}. One-way ANOVA and post hoc Tukey's test.*

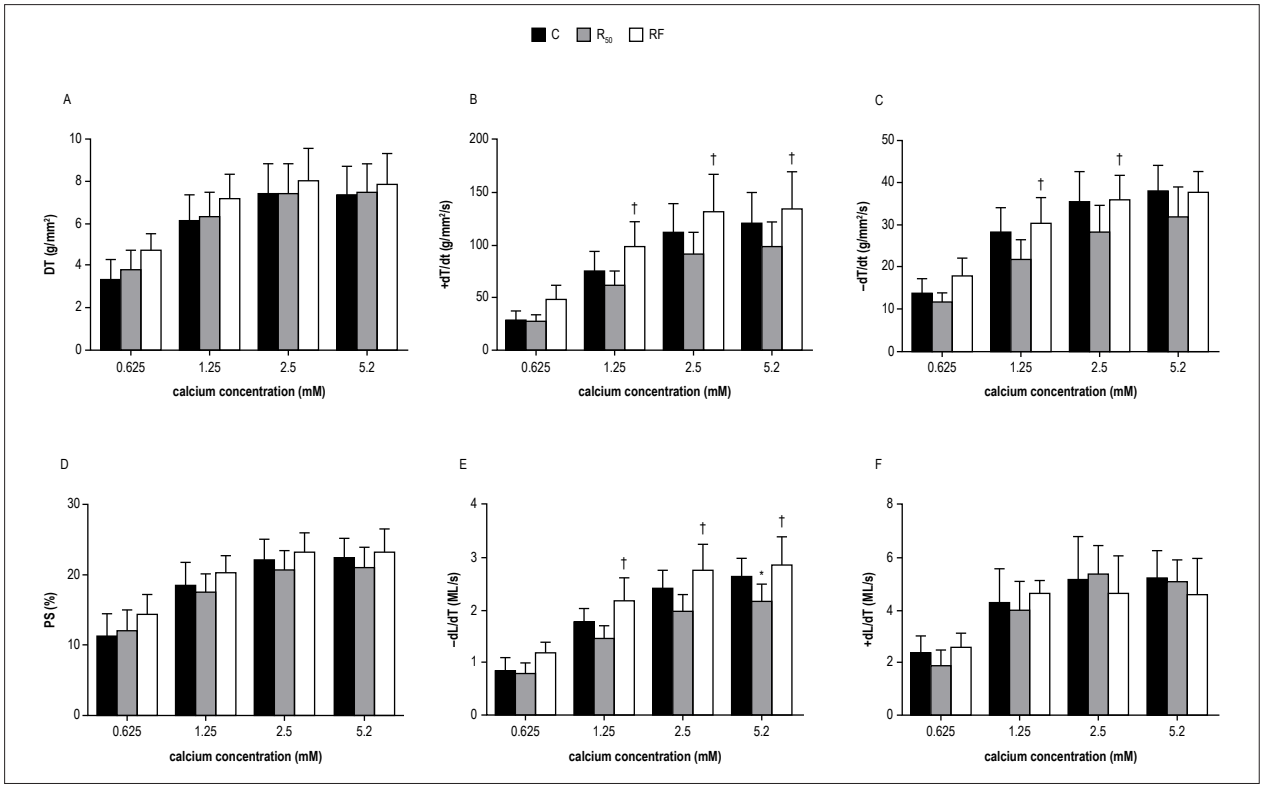

Figure 2 – *Effects of increased extracellular calcium on myocardial isotonic and isometric parameters in papillary muscles from control (C = black bars), animals with food restriction of 50% (R_{50} = gray bars) and animals with alternation between food restriction of 50% and refeeding (RF = white bars). Extracellular calcium experiment: 7 animals each group. Isometric parameters: A: DT (peak developed tension normalized per cross-sectional area); B: +dT/dt (peak isometric tension development rate normalized per cross-sectional area); C: -dT/dt, g/mm²/s (maximum tension decline rate normalized per cross-sectional area). Isotonic parameters: D: PS (percentage of shortening); E: -dL/dT (maximum shortening velocity); F: +dL/dT (maximum relaxation velocity). L_{max}: muscle length at peak DT. Values are means ± SD; * significant at p < 0.05 vs. C; † p < 0.05 vs. R_{50}. Repeated measures two-way ANOVA and post hoc Tukey's test. Source: Research team.*

considerable scientific interest for weight loss and improving cardiometabolic health. Thus, the main finding of this study was that fasting/refeeding attenuated the damage caused by CR. The results reveal that fasting/refeeding showed increased isotonic and isometric parameters at baseline, as well as improved the myocardial inotropic response to calcium and isoproterenol. In addition, fasting/refeeding prevented cardiac atrophy and morphological injuries.

Less body weight gain was observed in the RF group than in the C group (Table 1, Figure 1), but more body weight gain than in the R_{50} group. According to literature, body weight reduces approximately 13% when the animals are submitted

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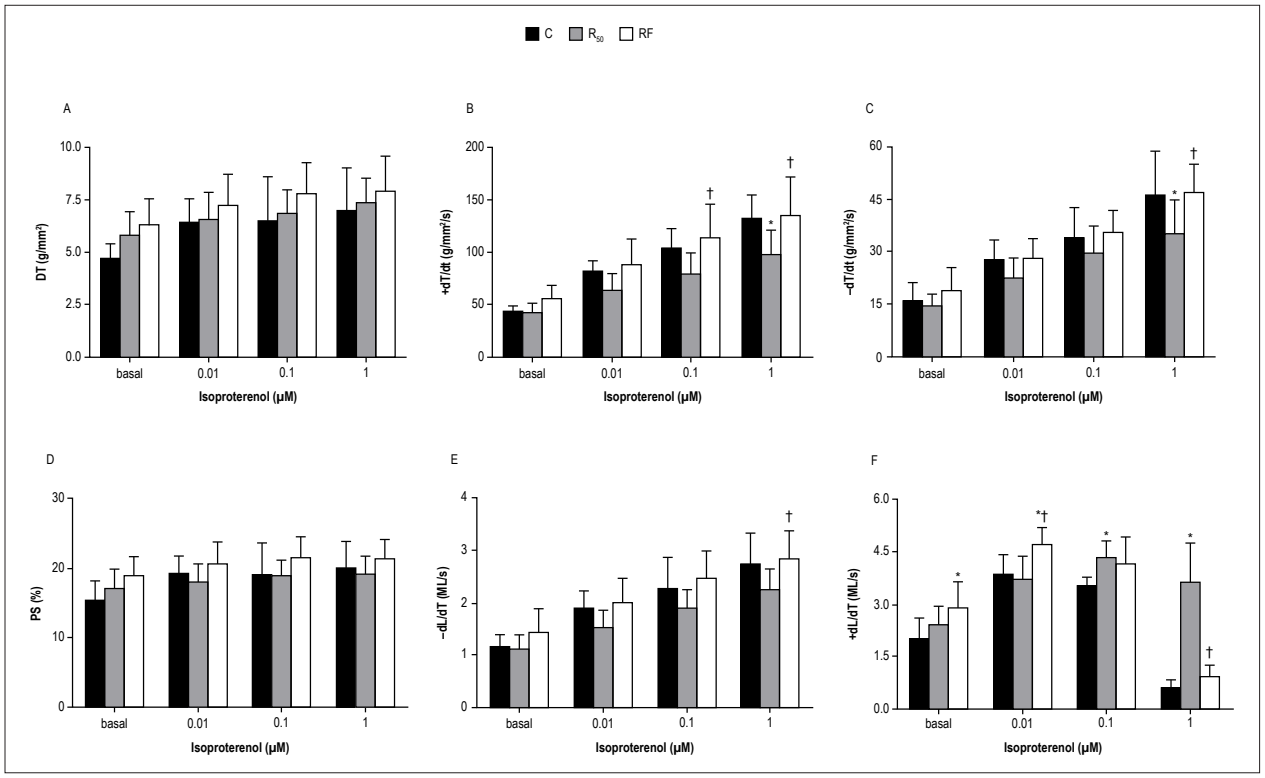

Figure 3 – *Effects of isoproterenol stimulation on myocardial function in papillary muscles from control (C = black bars), animals with food restriction of 50% (R_{50} = gray bars) and animals with alternation between food restriction of 50% and refeeding (RF = white bars). Isoproterenol stimulation experiment: 7 animals each group. Isometric parameters: A: DT (peak developed tension normalized per cross-sectional area); B: +dT/dt (peak isometric tension development rate normalized per cross-sectional area); C: -dT/dt, g/mm²/s (maximum tension decline rate normalized per cross-sectional area). Isotonic parameters: D: PS (percentage of shortening); E: -dL/dt (maximum shortening velocity at L_{max}); F: +dL/dt (maximum relaxation velocity at L_{max}). L_{max}: muscle length at peak DT. Values are means ± SD; * significant at p < 0.05 vs. C; † p < 0.05 vs. R_{50}.Repeated measures two-way ANOVA and post hoc Tukey's test. Source: Research team.*

to 48 hours of fasting.[25] This result appears to be mediated by hormones, such as leptin that acts regulating appetite and weight gain. A rapid inhibition of *ob gene* expression in the white adipose tissue occurs in fasting, and this effect can be reversed by refeeding.[25,26]

Cardiac hypertrophy, a major pathological process involved in cardiac remodeling, initially serves as a compensatory mechanism to preserve cardiac output.[27] Cardiac remodeling may be regarded as a first step in the sequence of adaptive responses of the heart to stress caused by a large number of physiological and pathological conditions, such as changes in volume and pressure loads and/or metabolic alterations.[28] Current study revealed that fasting/refeeding induced cardiac atrophy visualized by reduced total heart and left ventricle, as well as in the LVW/FBW. A decrease in left ventricle weight relative to body weight is very common in small animals submitted to food restriction[22] and fasting/refeeding.[29] Inhibition of myocardial protein synthesis and reduction in average protein half-lives are possible explanations for reduced cardiac mass under starvation.[30] Protein synthesis, an anabolic process, is required for cardiac hypertrophy. Two major pathways regulating protein synthesis are inhibited by AMPK, a primary regulator of metabolic pathways, which plays an essential role in a wide variety of cellular processes to protect against cardiac hypertrophy.[31] Therefore, cardiac atrophy could be regulated by the common signaling pathway of AMPK in the hypothalamus.

In the ultrastructural analysis, food restriction caused focal morphological damage in most papillary muscle fibers. The same alterations were less intense in the intermittent refeeding condition. Intermittent refeeding seems to aid in the attenuation of the mechanisms responsible for this damage and seems to act by enhancing protein anabolism and retarding protein degradation. Recent findings suggest that the beneficial effects of refeeding result from a reduction in oxidative injury and an increase in cellular stress resistance.[2,32] One possible mechanism for our result may be linked to the expression of atrogin-1, an E3 ubiquitin ligase also known as muscle atrophy F-box (MAFbx). E3-ligases are part of the ubiquitin proteasome pathway utilized for protein degradation during muscle atrophy. The literature has shown that atrogin-1/MAFbx expression results in muscle atrophy during catabolic condition.[33] In cardiac muscle, atrogin-1/MAFbx expression increases during heart failure and pressure overload.[33,34]

The isolated papillary muscle analysis showed that food restriction promotes cardiac dysfunction, but refeeding condition prevents the state. These stimuli provide evidence that the improvement of myocardial function assigned to fasting/refeeding cycles was related to changes in intracellular Ca^{2+} handling, mainly in the recapture and/or extrusion of

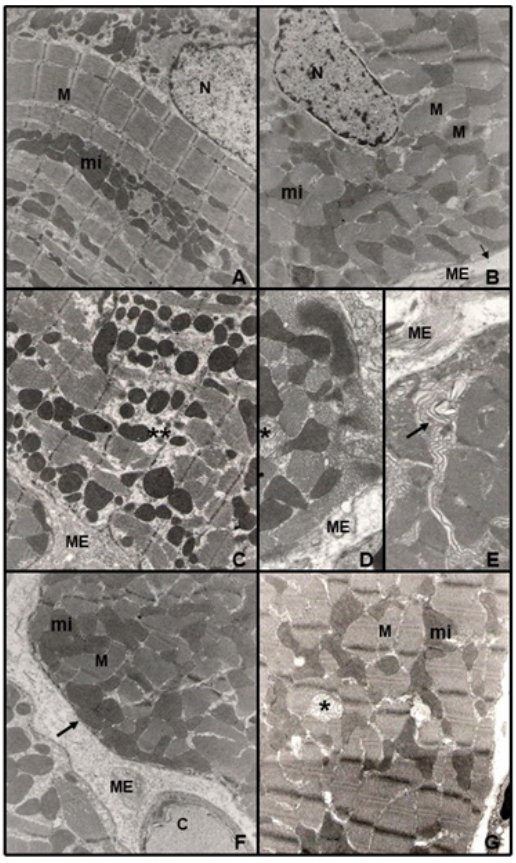

Figure 4 – *Ultrastructural study of LV papillary muscle (n = 3 per group). Photographs A and B correspond to the control group, photographs C, D and E to the food-restriction (R_{50}) group and photographs F and G to the refeeding group (RF) group. The control group showed preserved ultrastructure with normal myofibrils (M), sarcoplasmic reticulum (arrowhead), mitochondria (mi), nuclear membrane (N) and plasma membrane (arrow). Food restriction rats showed cellular changes, including polymorphic mitochondria (*), myofibril disorganization (**), and infolding of the plasma membrane (arrow). The papillary muscle during refeeding showed preserved myofibrils (M), mitochondria (mi), and plasma membranes (arrow), polymorphic mitochondria (*) and capillary (C). Source: Research team.*

cytosolic Ca^{2+}, and β-adrenergic system. Nevertheless, the lower response of food restricted rats to the increase of extracellular Ca^{2+} concentration can be related to changes in the general mechanisms involved in Ca^{2+} cycling such as sarcolemmal Na^{+}/Ca^{2+} exchanger, sarcolemmal L-type channel, sarcoplasmic reticulum (SR), ryanodine receptor, SR Ca^{2+} uptake pump, and the myofilament Ca^{2+} sensitivity.[35] In relation to RF, this process may be faster and more balanced, but no study was found to support this statement and show the activity and protein expression of Ca^{2+} handling regulatory proteins.

Another explanation could be related to the role of cytokine in intermittent fasting mediated cardioprotection. The influx of inflammatory cells and production of pro-inflammatory mediators contribute to myocardial injury.[36] Nevertheless, adiponectin can protect myocardial cells against ischemic injury by activating the cyclic AMP-dependent protein kinase - Akt pathway, being the latter mediated, in part, by caloric restriction.[37] Thus, the beneficial effects of fasting/refeeding may function through anti-inflammatory cytokine pathways.

Few studies have evaluated the β-adrenergic components in experimental models of fasting/refeeding.[25,35] Some studies have shown that cardiac function impairment is related to β-adrenergic system changes,[35] while other researchers have not reported reduced β-adrenergic response.[25] The literature shows that a decrease in cardiac β-receptor number has been reported in several hypertensive models known to be associated with an increase in sympathetic nerve activity, including SHR.[38] Thus, the association between increased sympathetic activity and cardiac β-receptor downregulation is sufficiently close to suggest that the finding of decreased β-receptor number after starvation and refeeding is indicative of persistently elevated cardiac sympathetic drive. However, in the current study, there is no damage of β-system in the RF rats, since the cardiac function was similar to that of the C group. The present data tend to support the hypothesis that isoproterenol stimulation reveals that the β-adrenergic system and cAMP phosphorylation of proteins related to Ca^{2+} handling were preserved in refeeding rats.

Thus, fasting/refeeding cycles have become the subject of considerable scientific interest as a potential dietary approach for weight-loss and improving cardiometabolic health.

The beneficial effects of the intermittent fasting result from at least two mechanisms: the oxidative stress and the stress resistance hypothesis.[39] According to literature, during the intermittent fasting, there are fewer free radicals produced in the mitochondria of cells and, therefore, less oxidative damage to the cells.[39] Another hypothesis is the resistance to stress that is associated with increased resistance of cells in many different tissues to injury induced by oxidative, genotoxic and metabolic insults. The conservation of stress resistance responses to intermittent fasting across a range of species provides strong evidence that this mechanism contributes to the lifespan-extending action of dietary restriction.[39]

It is worth noting that according to studies in rodents and humans, intermittent food restriction is capable of promoting weight loss and/or favorably influence an array of cardiometabolic health indices, with equal or greater efficacy than conventional continuous energy restriction approaches, such as food restriction.[29] Fasting/refeeding cycles increase cardiac tolerance to ischemic injury and can affect the development of cardiovascular disease, preventing postinfarct cardiac remodeling, and impending chronic heart failure.[29] Comparing the two dietary approaches, studies show that caloric restriction may exert its beneficial effects primarily by reducing oxidative stress, whereas RF may act primarily by a stress resistance mechanism,[40] which can have a cardioprotective effect.

Study limitations

The study did not investigate the activity and protein expression of Ca^{2+} handling regulatory proteins known to affect myocardial contraction and relaxation. In addition, the current study did not evaluate the involvement of anti-inflammatory cytokines, free-radical production and cellular stress response, which could help and consolidate the beneficial effects of intermittent fasting.

Conclusion

We demonstrated that fasting/refeeding promotes cardiac beneficial effects and attenuates myocardial injury caused by CR in SHR rats, contributing to the reduction of cardiovascular risk profile and morphological injuries. Furthermore, RF promotes mild improvement in the Ca^{2+} handling and β-adrenergic system.

Author contributions

Conception and design of the research: Pinotti MF, Cicogna AC, Leopoldo AS; Acquisition of data: Pinotti MF, Matias AM, Sugizaki MM, Nascimento AF, Pai MD, Leopoldo APL; Analysis and interpretation of the data: Pinotti MF, Sugizaki MM, Nascimento AF, Pai MD, Leopoldo APL; Statistical analysis: Sugizaki MM, Nascimento AF, Pai MD, Leopoldo APL; Obtaining financing: Cicogna AC; Writing of the manuscript: Pinotti MF, Matias AM, Cicogna AC, Leopoldo AS; Critical revision of the manuscript for intellectual content: Matias AM, Pai MD, Leopoldo APL, Cicogna AC, Leopoldo AS.

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 Faculdade de Medicina de Botucatu, UNESP under the protocol number 439/2004.

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Original Article

Anger and Coronary Artery Disease in Women Submitted to Coronary Angiography: A 48-Month Follow-Up

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Abstract

Background: Anger control was significantly lower in patients with coronary artery disease (CAD), regardless of traditionally known risk factors, occurrence of prior events or other anger aspects in a previous study of our research group.

Objective: To assess the association between anger and CAD, its clinical course and predictors of low anger control in women submitted to coronary angiography.

Methods: This is a cohort prospective study. Anger was assessed by use of Spielberger's State-Trait Anger Expression Inventory (STAXI). Women were consecutively scheduled to undergo coronary angiography, considering CAD definition as ≥ 50% stenosis of one epicardial coronary artery.

Results: During the study, 255 women were included, being divided into two groups according to their anger control average (26.99). Those with anger control below average were younger and had a family history of CAD. Patients were followed up for 48 months to verify the occurrence of major cardiovascular events.

Conclusion: Women with CAD undergoing coronary angiography had lower anger control, which was associated with age and CAD family history. On clinical follow-up, event-free survival did not significantly differ between patients with anger control above or below average. (Arq Bras Cardiol. 2018; 111(3):410-416)

Keywords: Anger; STAXI; Personality Inventory; Coronary Artery Disease/mortality.

Introduction

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality of women in several countries, such as USA and Brazil.[1] There are more deaths from CVD (41.3%) than from the next seven causes of death combined, and the risk of dying from CVD is six-fold greater than that from breast cancer, the major concern among women.[1] There are sex-specific differences regarding CVD presentation, pathophysiology and clinical outcomes; however, as observed by Shivpuri S. et al.[2], in a meta-analysis only 5 of 21 studies provided information specific to the female sex, and only a few reported sex-specific differences.[2-4]

Recent data have shown a significant increase in the incidence of cardiovascular disease and deaths among women aged 45 to 54 years, in contrast to the declining trend observed in Brazil and worldwide.[2,5] According to the American Heart Association, women show a worse risk factor profile and higher mortality among the youngsters as compared to the elderly, in addition to high in-hospital, early and late mortality rates as compared to men.[2,6-11] There is growing evidence that psychological factors and emotional stress, such as anger and hostility, can interfere with health behaviors and influence the onset and clinical course of ischemic heart disease.[2] At the biological level, the expression of anger can lead to a chronic increase in the levels of catecholamines, evoking an inflammatory response, increasing interleukin-6 levels,[12] leading to the progression of atherosclerosis, and, eventually, to the clinical manifestation of cardiovascular diseases.[13-15]

In a previous study, we have reported a significantly lower control of anger in patients with coronary artery disease (CAD), independently of the traditional risk factors, the occurrence of previous events or other aspects of anger.[16]

This study aimed at assessing the association between anger and CAD, its clinical course and predictors of low anger control in women undergoing cine coronary angiography.

Methods

Patients

This is a prospective cohort study. All women scheduled for elective coronary angiography because of suspected CAD during the study period were consecutively assessed. This study included women aged 18 years and older, who provided written informed consent to participate in the study. The exclusion criteria were: indication for catheterization for

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valvular heart disease; congenital heart disease; severe diseases with life expectancy <6 months; severe aortic stenosis; and ejection fraction <30%. The project was submitted to the Ethics Committee in Research of the institution and was in accordance with the Declaration of Helsinki and the Resolution 466/12 of the National Council of Health.

Coronary angiography

Coronary angiography was performed according to the Judkins technique, all analyses were performed in at least two views, and the severity of the coronary obstructions was assessed by use of a digital calibration system previously validated (Siemens AxiomArtis - Munich, German). Prior to the measurements, intracoronary nitroglycerin was administered routinely at the dose of 100-200 μg. Coronary artery disease was defined as ≥ 50% stenosis of at least one major epicardial artery.

Assessment of anger

Anger is an emotional state that consists of feelings that vary in intensity from mild irritation or annoyance to intense fury and rage, and changes over time spams depending on what is perceived as injustice or frustration.[17] Anger assessment was performed by use of Spielberger's State-Trait Anger Expression Inventory (STAXI),[17] a tool translated to several languages, validated in Brazil and recommended by the Federal Council of Psychology. It comprises 40 statements about the intensity of anger, how patients usually feel and how often they experience anger. Each item is rated on a four-point Likert-type scale, scored as follows: 1 for "rarely"; 2 for "sometimes"; 3 for "often"; and 4 for "almost always". The test is subdivided into subscales: state anger, trait anger (temperament and reaction) and anger expression (anger expression-in, anger expression-out, and anger control). Trait anger is defined as a predisposition to experiencing anger, indicating lasting personality trends. It is assessed by use of questions such as: "I get angry easily", "I get angry when my good work is not recognized". Anger expression provides an assessment of how anger is experienced: suppression, expression or control. (Examples: "I keep things to myself", "I do things such as slam the door", "I boil inside, but I do not show"). As state anger assesses the amount of anger that is experienced at a particular time, that subscale was not used in the sample of in-hospital patients.

Clinical characteristics at the beginning of the study

The clinical and socioeconomic characteristics, risk factors for CAD, previous medical history, clinical presentation of CAD and history of psychological diagnosis were assessed and included in a dedicated database. Hypertension was defined as previous diagnosis of the condition or use of anti-hypertensives. Dyslipidemia was considered present in those previously diagnosed with the condition or on lipid-lowering drugs. Diabetes mellitus was defined as the previous use of insulin or oral hypoglycemic drugs, or the presence of documented fasting blood sugar > 126 mg/dL on two occasions. Previous history of depression was defined as the occurrence of at least one major depressive episode that required treatment with antidepressants.

Outcomes

The outcome primary cardiovascular event was a combination of cardiovascular death, acute myocardial infarction (AMI), myocardial revascularization or hospitalization due to angina. Cardiovascular death was defined as any death due to immediate cardiac causes (AMI, cardiogenic shock, arrhythmia), or death of unknown cause. Acute myocardial infarction was considered in the presence of: 1) increase and/or gradual decrease in cardiac biomarkers (preferably troponin) with at least one measure over the 99th percentile and at least one of the following criteria: 1) chest pain > 10 minutes or new ST-T changes or new left bundle-branch block; or 2) development of pathological Q waves (duration ≥ 0.03 seconds; depth ≥1 mm) in at least two contiguous precordial leads or at least two leads of adjacent limbs; or 3) evidence of viable myocardial loss or new regional wall motion abnormality on any imaging test. Myocardial revascularization comprised primary percutaneous coronary intervention (PCIp) or coronary artery bypass grafting (CABG) occurring after entrance into the study. Hospitalization due to angina was defined as hospital length of stay longer than 24 hours to assess or treat cardiac chest pain, with neither AMI nor need for myocardial revascularization.

Follow-up

The participants were followed up for 48 months by use of visits and telephone contacts, to assess the occurrence of major cardiovascular events (MCVE), defined as cardiovascular death, AMI, myocardial revascularization (CABG or PCI) and hospitalization due to angina > 24 hours.

Statistical analysis and justification of the sample size

The sample size was calculated with power of 80, alpha of 0.05 and 95% confidence interval. At least 250 individuals were necessary to detect a relative risk of 1.60,[18] considering the 30% incidence of MCVE in the total group of women. Continuous variables were expressed as mean ± standard deviation, while categorical variables, as absolute number and percentage. The characteristics of the patients with CAD were compared to those of patients without CAD, using Student *t* test for independent samples for continuous variables and chi-square test for categorical variables. The women were divided into two groups according to their scores being above or below average range (26.99). Their demographic characteristics, risk factors, previous history and STAXI scores were compared by use of Student *t* test or chi-square test. Cronbach's alpha was used to assess the internal consistency of the STAXI subscales. Kolmogorov-Smirnov test was used to assess the normality of the distribution of the scores. Multiple logistic regression analysis was used to assess the variables associated with CAD on baseline angiography and control of anger. The Kaplan-Meier curves and the log-rank test were used to compare event-free survival between patients with anger control scores above and below the sample's average range. For all tests, a p value < 0.05 was considered statistically significant. All data were recorded in an Excel database for analysis with the SPSS program, version 24.0 for Windows.

Results

From November 29, 2009, to february 3, 2010, 255 participants were included. Table 1 shows the results according to the presence of CAD, clinical history and different STAXI subscales. The patients with CAD most frequently had previous cardiac procedures (CABG and PCIp) and a lower mean level of anger control than patients without CAD, who most often were married as compared to the former. Other risk factors, previous medical history and anger subscales showed no significant differences. The multiple logistic regression analysis (Table 2) identified a relationship between CAD and low anger control, previous CABG or PCI, and marital status.

The patients were followed up for 48 [39-49] months to assess the occurrence of MCVE. From the initial sample of 255 patients, 10 women (3.9%) could not be reached, leaving 245 to participate in this study, 89 with anger control below the average range, and 156, over the average range. Table 3 shows the baseline characteristics of the patients regarding anger control, with 36.3% of the women with anger control below the average range and 63.7%, over the average range. Those with anger control below the average range were younger (58.1 ± 8.9 vs 62.2 ± 10.9, $p < 0.001$) and had a higher prevalence of family history of CAD (53.9% vs 29.5%, $p < 0.001$) than those whose control of anger was above the average range. Other characteristics, such as weight, diabetes, previous coronary events (AMI, PCI, CABG) and other risk factors did not differ between the two groups. However, the patients with anger control below the average range had a tendency towards lower prevalence of hypertension ($p = 0.09$) and previous CABG ($p = 0.11$). On logistic regression (Table 4), only age and the family history of CAD were predictors of poor anger control. Figure 1 shows no significant difference in event-free survival in patients with anger control below and above 27 points ($p = 0.62$).

Table 1 – Clinical characteristics, medical history and STAXI scales according to the presence of coronary artery disease (CAD)

Characteristics	CAD n = 115 (45.1%)	No CAD n = 140 (54.9%)	Total: 255 p*
Age (years), mean ± SD	61.0 ± 10.5	60.5 ± 9.7	0.65
White, n (%)	97 (85.1)	111 (79.9)	0.27
Married, n (%)	50 (43.5)	81 (57.9)	0.02
Schooling, years	6.2 ± 5.4	5.9 ±4.4	0.65
Current job, n (%)	26 (22.6)	28 (20.0)	0.61
Living alone, n (%)	28 (24.3)	32 (22.9)	0.78
Risk factors			
Hypertension, n (%)	102 (88.7)	120 (85.7)	0.48
DM, n (%)	41 (35.7)	20 (27.9)	0.18
Dyslipidemia, n (%)	71 (61.7)	73 (52.1)	0.12
Smoking, n (%)	28 (24.3)	23 (16.4)	0.11
Family history of CAD, n (%)	44 (38.3)	52 (37.1)	0.85
Depression, n (%)	38 (33.0)	55 (39.3)	0.30
BMI (kg/m^2), mean ± SD	27.6 ± 5.3	28.4 ± 6.0	0.25
Previous medical history			
Previous AMI, n (%)	30 (26.1)	27 (19.3)	0.19
Previous PCI, n (%)	19 (16.5)	11 (7.9)	0.03
Previous CABG, n (%)	9 (7.8)	0 (0.0)	< 0.001
STAXI subscales			
Trait of anger (points), mean ± SD	20.0 ± 7.9	20.7 ± 8.5	0.54
Angry temperament (points), mean ± SD	8.6 ± 4.1	8.4 ± 4.0	0.69
Angry reaction (points), mean ± SD	8.0 ± 3.5	8.6 ± 4.2	0.20
Anger expression-In (points), mean ± SD	16.03 ± 4.26	16.6 ± 5.2	0.34
Anger expression-Out (points), mean ± SD	13.2 ± 4.6	12.9 ± 4.0	0.58
Control of anger (points), mean ± SD	26.2 ± 5.00	27.7 ± 3.7	< 0.001
Anger expression (points), mean ± SD	19.0 ± 10.3	17.8 ± 9.0	0.29

SD: standard deviation; p - p≤ 0.05, Student t test or chi-square test; DM: diabetes mellitus; BMI: body mass index; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.*

Table 2 – Relationship between coronary artery disease and baseline characteristics

Characteristics	Beta Coefficient	95% CI for Beta Coefficient	Total: 255 p *
Low control of anger	0.15	0.03 – 0.27	0.01
Married	- 0.12	- 0.24 – - 0.01	0.03
Previous PCI	0.14	0.04 – 0.40	0.02
Previous CABG	0.16	0.26 – 0.90	< 0.001

*p * - p ≤ 0.05, Wald test; CI: confidence interval; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.*

Table 3 – Patients' clinical characteristics, medical history and STAXI scales according to anger control in a 48-month follow-up

Characteristics	Control of anger below average n = 89	Control of anger above average n = 156	Total: 245 p *
Age (years), mean ± SD	58.1 ± 8.9	62.2 ± 10.9	0.001
White, n (%)	71 (79.8)	128 (83.1)	0.52
Married, n (%)	48 (53.9)	79 (50.6)	0.62
Schooling, years	6.1 ± 4.9	6.1 ± 4.9	0.97
Current job, n (%)	20 (22.5)	31 (19.9)	0.63
Living alone, n (%)	20.2 (18)	38 (24.4)	0.46
Risk factors			
Hypertension, n (%)	73 (82.0)	140 (89.7)	0.09
DM, n (%)	33 (37.1)	45 (28.8)	0.18
Dyslipidemia, n (%)	49 (55.1)	92 (59.0)	0.55
Smoking, n (%)	15 (16.9)	34 (21.8)	0.35
Family history of CAD, n (%)	48 (53.9)	46 (29.5)	< 0.001
Depression, n (%)	35 (39.3)	55 (35.3)	0.53
BMI (kg/m^2), mean ± SD	28.4 ± 5.4	27.9 ± 5.9	0.55
Previous medical history			
Previous AMI, n (%)	22 (24.7)	34 (21.8)	0.60
Previous PCI, n (%)	8 (9.0)	22 (14.1)	0.24
Previous CABG, n (%)	1 (1.1)	8 (5.1)	0.11
STAXI subscales			
Trait of anger (points), mean ± SD	23.67 ± 8.25	18.52 ± 7.53	< 0.001
Angry temperament (points), mean ± SD	10.20 ± 4.05	7.51 ± 3.74	< 0.001
Angry reaction (points), mean ± SD	9.19 ± 4.04	7.81 ± 3.70	0.007
Anger expression-In (points), mean ± SD	16.85 ± 5.08	16.06 ± 4.65	0.22
Anger expression-Out (points), mean ± SD	15.07 ± 4.97	11.81 ± 3.31	< 0.001
Control of anger (points), mean ± SD	22.19 ± 3.66	29.67 ± 1.72	< 0.001
Anger expression (points), mean ± SD	25.73 ± 9.79	14.21 ± 6.74	<0.001

p - p ≤ 0.05, Student t test or chi-square test; DM: diabetes mellitus; CAD: coronary artery disease; BMI: body mass index; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.*

Discussion

The present study identified that poor control of anger associated with CAD angiographically detected. This study found a higher percentage of married patients in the group without CAD, indicating the importance of social support in treatment adhesion and healthcare.[19] Women with poor control of anger had a positive family history for CAD and were younger. This study corroborates that by Haukalla et al.,[20] who reported that individuals with lower anger control were at higher risk for the first incidence of fatal and nonfatal cardiovascular disease than those who scored higher.

Table 4 – Association between control of anger and baseline characteristics

Characteristics	Beta Coefficient	95% CI for Beta Coefficient	p*
Age	0.15	0.002 - 0.013	0.01
Family history of CAD	0.22	0.100 - 0.340	< 0.001
Diabetes mellitus	0.007	- 0.039 - 0.170	0.21
Previous CABG	- 0.06	- 0.480 - 0.140	0.27

*p * - p ≤ 0.05, Wald test; CI: confidence interval; CAD: coronary artery disease; CABG: coronary artery bypass grafting.*

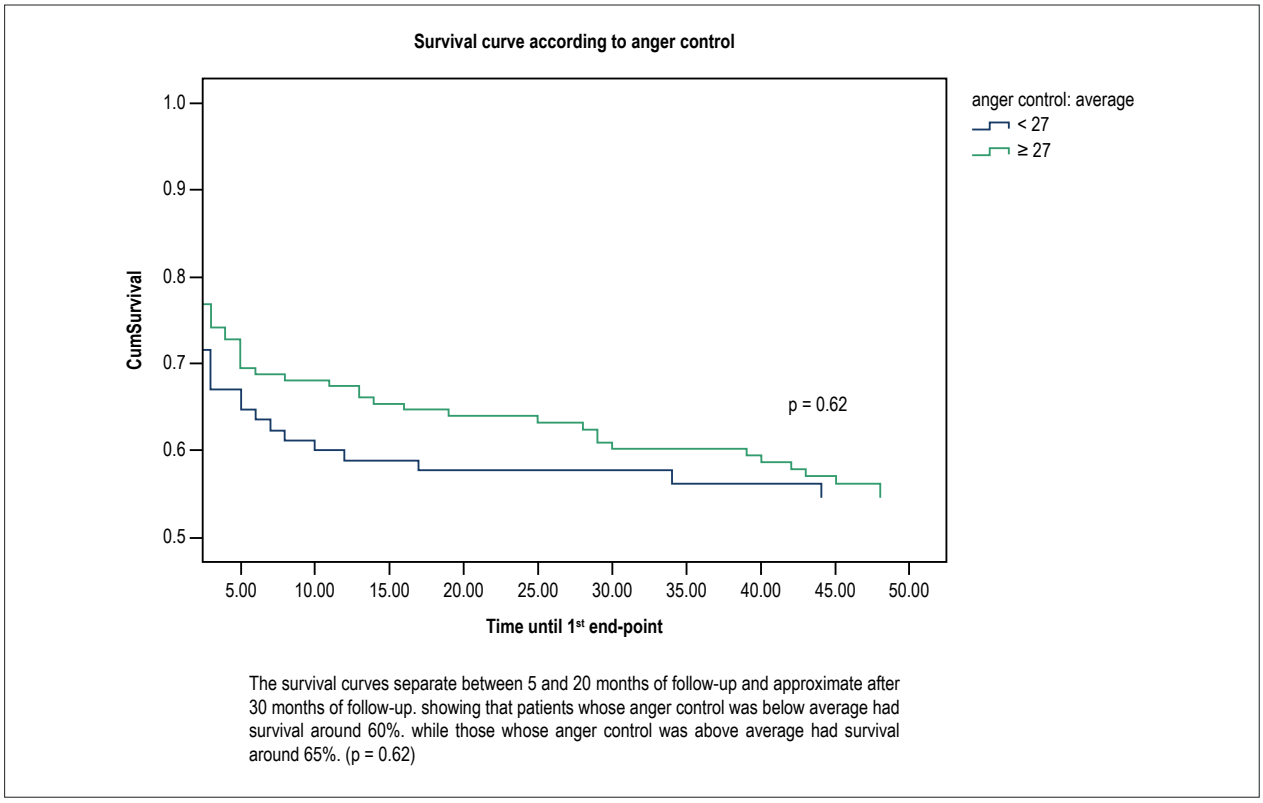

Figure 1 – *Survival curve for major cardiovascular events in up to 48 months of follow-up of women with anger control below and above average.*

In this sample, the women with low anger control were younger. That characteristic can be interpreted in the sense that, as age advances, social relations are modulated through emotional regulation, which means that, as time advances and with aging, more appropriate forms of social behavior are learned, with more control over emotions and reactions.[21] According to Cartensen's socioemotional selectivity theory, as age advances, people become increasingly selective, tending to place a high value on positive contents and to avoid negative emotional states, because of adaptation and life changes experienced in social contexts.[22,23]

According to Shirato et al.,[24] gender differences are evident in the success rates of the interventions to improve coronary circulation (myocardial revascularization). After a well-succeeded procedure, women submitted to coronary angioplasty had an excellent prognosis in the long run, similar to that observed in men. However, complications related to PCI and the mortality rates of women are three times higher as compared to those of men.[24] Haukalla et al.[20] have reported that low anger control in a 10- to 15-year clinical follow-up predicted ischemic myocardial disease in women, even after adjusting for sociodemographic variables, other cardiovascular risk factors and symptoms of depression. In the late clinical follow-up of this study, low control of anger was not associated with the occurrence of combined MCVE, myocardial revascularization included.

The literature available shows that anger is associated with several behavioral risk factors, such as tobacco use and inadequate dietary intake (hypercaloric and high sodium diets), and, in the long run, out of other cardiovascular risk factors, anger can cause LDL elevation, hypertension, diabetes mellitus, and obesity.[13,25] In a study, Pérez-García et al.[26] have reported

that emotional discomfort and symptoms were positively associated with higher inward expression of anger and lower control of anger. In addition, they have found that preventive practices were associated with lower supression and higher control of anger, with better channeling and regulation of anger feelings. The likelihood that patients with low anger control also have low control over other risk behaviors or use them as a comfort mechanism can be considered, because the effects of well-being through neuroendocrine mechanisms of hormone release, such as serotonin, producing well-being after energetic ingestion, have been described, which would be applicable to stress/anger situations.[27]

The compensation, cognitive and affective value attributed to food overlaps the homeostatic control and the physiological signs of hunger and satiety that control food ingestion and body weight.[27,28] However, if continuously evoked, that process would cause CAD as a factor associated not only with the feeling of anger, but with all the inappropriate coping mechanism that could accompany anger.

Study's forces and limitations

This study's force resides on its female sample, because women are usually under-represented in clinical trials. This is a segment of the real world, with few losses during a long follow-up. The risk factors were assessed based on interviews with the participants, and there might have been bias of information. Assessing anger and its control, even with a tool developed for that purpose, is a hard task, considering that personality traits can be combined. Research in this area is a challenge.

Conclusions

Women with CAD submitted to coronary angiography showed a trend towards lower control of anger, which was associated with age and the family history of CAD. The 48-month clinical follow-up showed no significant difference in the event-free time between patients with anger control scores above average range and those with anger control scores below it.

Author contributions

Conception and design of the research: Moura MR, Gottschall CAM, Schmidt MM; Acquisition of data: Schmidt KES, Schmidt MM; Analysis and interpretation of the data: Schmidt KES, Quadros AS, Moura MR, Gottschall CAM, Schmidt MM; Statistical analysis: Schmidt MM; Writing of the manuscript: Schmidt KES, Quadros AS, Schmidt MM; Critical revision of the manuscript for intellectual content: Quadros AS, Moura MR, Gottschall CAM.

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 de Cardiologia / Fundação Universitária de Cardiologia under the protocol number 466/12. 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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Anger and Cardiovascular Disease: An Old and Complicated Relationship

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Negative feelings have long been related to health problems. Buddhism, for example, refers to anger as one of the three "poisons of the mind" (greed, anger and madness).[1] In the first edition of *Circulation*, there was already an article suggesting the association between stress and cardiovascular disease.[2]

In the last decades, several studies have tried to correlate psychosocial factors, such as anger, anxiety, depression and stress, with coronary artery disease (CAD), demonstrating the increase in the incidence of CAD in patients with a higher incidence of these psychic conditions, for example, with a marked increase in events of acute myocardial infarction (AMI) between 2008 and 2009, in the United States, when there was a stock market crash.[3-5] This relationship tends to be significantly more important in women, since factors such as low socioeconomic status and double working hours (conciliation of employment with maternity), among other factors, are more common in the female population.[5] More recently, a longitudinal study of cohort was able to demonstrate the association between the activity of the cerebral amygdala (area involved with the emotions) and the increased risk of cardiovascular events.[6]

An important problem in studies that attempt to objectively demonstrate the relationship between anger and CAD is the difficulty of objectively measuring emotions, including anger. The study published in this edition of the Brazilian Articles of Cardiology by Schmidt et al.[7] measures the female patients' anger analyzed through the State-Trait Anger Expression Inventory of Spielberger (STAXI).[7] This score is validated in Brazil for the analysis of anger, being even recommended by the Federal Council of Psychology, and certainly underused in our settings.[8]

Dimsdale, in 2008, in his brilliant work on the state of the art of the relationship between psychological stress and cardiovascular disease explains that "anyone who starts reading the papers that analyze this association immediately notes that part of the problem is that the term stress is used in a variety of ways," so that any student who wants to deepen into this area has to be careful about the nuances that involve this subject.[9]

The study by Schmidt et al.[10] also shows that, as important as demonstrating the value of anger as a risk factor for the presence of CAD, it is evident that anger management may also play a role, as the study shows that women who have shown less control of anger had a tendency to the presence of CAD on the coronary angiography. However, this issue remains controversial. A systematic review of 36 studies, including 12,841 patients, of which 18 trials evaluated anger control, showed that there is no decrease in cardiovascular death, or need for new revascularizations, when psychotherapeutic strategies are implemented for patients with anger, anxiety or depression. There was a trend towards a decrease in nonfatal AMI in the intervention group, but the 2 largest trials involved in this review were null for this outcome.[11]

In summary, we still need more and better evidence to assess whether this millenarian relationship between anger and CAD is a modifiable risk factor or not, and whether we can intervene in these patients. Schmidt's study has great value because it is one of the few that have made gender differentiation, which is very important in the analysis of the risk factors for CAD. In addition, the fact that it involves only women makes it more valuable, since it is a population that is often "forgotten" in prospective studies. In addition, prospective analyzes in this regard are always welcome to improve the quality of the data we have so far on this very relevant topic.

Keywords

Anger/physiology; Stress,Psychological; Depression; Coronary Artery Disease; Anxiety Disorders.

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Silent Cerebral Infarctions with Reduced, Mid-Range and Preserved Ejection Fraction in Patients with Heart Failure

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Abstract

Heart failure predisposes to an increased risk of silent cerebral infarction, and data related to left ventricular ejection fraction are still limited. Our objective was to describe the clinical and echocardiographic characteristics and factors associated with silent cerebral infarction in patients with heart failure, according to the left ventricular ejection fraction groups. A prospective cohort was performed at a referral hospital in Cardiology between December 2015 and July 2017. The left ventricular ejection fraction groups were: reduced (≤ 40%), mid-range (41-49%) and preserved (≥ 50%). All patients underwent cranial tomography, transthoracic and transesophageal echocardiography. Seventy-five patients were studied. Silent cerebral infarction was observed in 14.7% of the study population (45.5% lacunar and 54.5% territorial) and was more frequent in patients in the reduced left ventricular ejection fraction group (29%) compared with the mid-range one (15.4%, p = 0.005). There were no cases of silent cerebral infarction in the group of preserved left ventricular ejection fraction. In the univariate analysis, an association was identified between silent cerebral infarction and reduced (OR = 8.59; 95%CI: 1.71 - 43.27; p = 0.009) and preserved (OR = 0.05; 95%CI: 0.003-0.817, p = 0.003) left ventricular ejection fraction and diabetes mellitus (OR = 4.28, 95%CI: 1.14-16.15, p = 0.031). In patients with heart failure and without a clinical diagnosis of stroke, reduced and mid-range left ventricular ejection fractions contributed to the occurrence of territorial and lacunar silent cerebral infarction, respectively. The lower the left ventricular ejection fraction, the higher the prevalence of silent cerebral infarction.

Introduction

Heart failure (HF) predisposes to an increased risk of cerebral abnormalities, including silent cerebral infarction, which is defined by the presence of infarctions (territorial or lacunar) in the brain parenchyma, verified through imaging methods, without a documented previous episode of stroke.[1,2]

The independent risk factors associated with silent stroke in HF are usually due to the impairment of left ventricular function, restrictive diastolic filling patterns in echocardiography, left atrial (LA) spontaneous echo contrast, and complex or calcified atherosclerotic aortic lesions.[3-5]

Ischemic stroke is a common complication of HF regardless of the Preserved (pLVEF) or reduced (rLVEF) Left Ventricular Ejection Fraction (LVEF).[5] LVEF predicts the risk of cerebral infarctions, especially with rLVEF. It is believed that reduced blood flow may favor the formation of spontaneous echo contrast, intracavitary thrombi and consequent cardioembolic events.[6] However, data explaining the stroke mechanism in HF in patients with LVEF are still limited,[7] and data related to stroke and mid-range LVEF are scarce.

The objective of this study was to describe the clinical and echocardiographic characteristics and factors associated with silent cerebral infarction in patients with HF according to the LVEF groups.

Keywords

Heart Failure; Cerebral Infarction; Stroke Volume; Stroke.

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Methods

This is a prospective cohort performed at a referral hospital for the care of patients with HF in the city of Salvador, state of Bahia, Brazil, between December 2015 and July 2017. The diagnosis of HF was made according to the recommendations of the European Society of Cardiology (ESC),[8] with patients who had signs and symptoms of HF, relevant structural heart disease (left ventricle (LV) body mass index ≥ 115 g in men and ≥ 95 g in women, or left atrial dilatation ≥ 40 mm) and or diastolic abnormality (E/A ratio < 0.75 or ≥ 1.5, or E-wave deceleration time < 140 ms). The LVEF groups were characterized as follows: rLVEF (≤ 40%), mid-range LVEF (mrLVEF; 41-49%) and pLVEF (≥ 50%).[9] The diagnosis of Atrial Fibrillation (AF) was based on information available in medical records and the electrocardiogram.

Assessment of cranial tomography

The cranial tomography was performed in all the patients to identify infarctions in the brain parenchyma (territorial or lacunar). The reports were analyzed by a neurologist, blinded to the patients' clinical data. These examinations were performed using a 1385 Toshiba Medical Systems Corporation device, (Shimo Ishigami, Otawara-Shi, Tochigi, Japan).

Evaluation of transthoracic and transesophageal echocardiography

The examinations were performed by two experienced echocardiographists, as recommended by the American Society of Echocardiography (ASE).[10] A commercially available device was used (Philips IE33, Philips Medical Systems, Andover, MA, USA), equipped with a 5 MHZ transducer with a multiplanar transesophageal probe. Subsequently, the images were recorded in a pen drive and reviewed by an echocardiographist.

The measures analyzed by the Transthoracic Echocardiogram (TTE) were: diastolic and systolic diameter of the LV, anteroposterior diameter of the LA, aortic root diameter, interventricular septum and posterior wall thickness. These analyses were obtained in the parasternal short axis and the parasternal long axis planes using the M-mode. The calculation of the LVEF was carried out using the LV modified biplane Simpson's method.

To perform the Transesophageal Echocardiography (TEE) images, the patient was placed in the left lateral decubitus position, and the left arm was extended over the head. The exams were performed under topical anesthesia with xylocaine spray at 10% and under intravenous sedation. The presence of spontaneous echo contrast and intracavitary thrombi were observed. The intracavitary thrombus was defined as an echodense intracardiac mass, and the spontaneous echo contrast was identified through its typical swirling movement, resembling smoke.[11]

Statistical analysis

The collected data were processed using the Statistical Program for Social Sciences (SPSS), version 21.0. For data analysis, descriptive statistics were used (proportions and measures of central tendency), mean and standard deviation. The Kolmogorov-Smirnov was used in the normality test. The means and proportions were evaluated by Student's *t* test, according to the variable distribution. Pearson's chi-square test or Fisher's exact test was applied for association measures. Values were considered statistically significant when $p \leq 0.05$ and the confidence interval $\geq 95\%$.

Results

Seventy-five patients were studied. Comparisons of clinical and echocardiographic parameters are described in Table 1. The mean LVEF was 46 ± 16.5%. Spontaneous echo contrast and intracavitary thrombi were observed in the rLVEF group (19.3%), followed by mrLVEF (15.3%) and pLVEF (9.6%). Silent cerebral infarction was observed in 14.7% of the study population (45.5% lacunar and 54.5% territorial) and was detected more frequently in patients in the rLVEF group (29%), when compared to mrLVEF (15.4%, p = 0.005). There were no cases of silent cerebral infarction in the pLVEF group. In the univariate analysis, an association was identified between silent cerebral infarction and rLVEF (Odds Ratio – OR = 8.59, 95% of Confidence Interval – 95%CI: 1.71-43.27, p = 0.009) and pLVEF (OR = 0.05, 95%CI: 0.003-0.817, p = 0.003). There was no association with mrLVEF (OR = 1.07, 95%CI: 0.20-5.65, p = 0.936). The association of silent cerebral infarction with diabetes mellitus (OR 4.28; 95%CI: 1.14-16.15; p = 0.031) was also identified.

Discussion

In our study, patients with rLVEF had silent cerebral infarction in the territory region, and those with mrLVEF had silent cerebral infarction of the lacunar type. There was no silent cerebral infarction in patients with pLVEF. It was demonstrated that the lower the LVEF, the higher the prevalence of silent cerebral infarction. A previous study showed that reduced LVEF values are associated with patients with silent stroke (p = 0.030).[12]

The prevalence of silent cerebral infarction in this study was considered small when compared to other studies of HF patients. In a study of 117 patients with HF evaluated for heart transplant, the prevalence of ischemic stroke was 34%.[13] In the study by Kozdag et al.,[12] with 72 patients with ischemic dilated cardiomyopathy, the prevalence of silent cerebral infarction was 39%. However, it is worth mentioning that the high prevalence of silent infarctions in these studies was probably the result of increased HF severity in the studied populations.

Another important finding was the association between diabetes mellitus and silent cerebral infarction. Chen et al.[14] found that abnormalities in early LV diastolic filling were commonly observed in diabetic patients, and the proposed mechanism includes, among other factors, microvascular disease, which may justify the data found in our study.

In the case of patients with mrLVEF, silent cerebral infarctions were reported to be of the lacunar type, usually associated with cerebral small vessel disease, but eventually of embolic etiology.[15] A recent study clearly demonstrated that the clinical characteristics of mrLVEF are intermediate between pLVEF and rLVEF, or close to pLVEF or rLVEF, and suggest that mrLVEF is a transitional stage from pLVEF to rLVEF, or from rLVEF to pLVEF, rather than a distinct HF class.[16] However, data are still limited regarding these patients.

Patients in the LVEFp group did not show silent cerebral infarction, differently from a study on LVEF groups, in which the rates of stroke or transient ischemic attack were slightly higher in patients with pLVEF vs. patients with rLVEF and mrLVEF. It is worth mentioning that AF was more common in these patients with pLVEF, although the AF was associated with an increased risk of stroke or transient ischemic attack, regardless of LVEF status.[17]

Conclusion

In patients with heart failure and without a clinical diagnosis of stroke, the reduced and mid-range left ventricular ejection fractions contributed to the occurrence of territorial and lacunar silent cerebral infarction, respectively. In cases of preserved left ventricular ejection fraction, there was no prevalence of silent cerebral infarction; reduced left ventricular ejection fraction and diabetes mellitus were associated with embolic cerebral infarction, and the lower the left ventricular ejection fraction, the higher the prevalence of silent cerebral infarction. Further studies are required to elucidate the mechanisms of silent cerebral infarction in the left ventricular ejection fraction groups.

Table 1 – Comparison of clinical and echocardiographic parameters between the groups of patients with heart failure with and without silent cerebral infarction

Parameters	Population n = 75	Silent cerebral infarctions		p value*
		Yes (n = 11)	No (n = 64)	
Age, years)	61.8 ± 10.6	62.5 ± 9.1	61.7 ± 10.9	0.817
Male gender	42 (56)	9 (81.8)	33 (51.6)	0.062
Arterial hypertension	60 (80)	8 (72.7)	52 (81.3)	0.514
Diabetes Mellitus	20 (26.7)	6 (54.5)	14 (21.9)	0.024
Ischemic heart disease	47 (62.7)	9 (81.8)	38 (59.4)	0.155
Permanent AF	13 (17.3)	3 (27.3)	10 (15.6)	0.346
NYHA class =				
I	20 (26.7)	2 (18.2)	18 (28.1)	0.491
II	41 (54.7)	7 (63.6)	34 (53.1)	0.518
III	14 (18.7)	2 (18.2)	12 (18.8)	0.964
HF etiology				
Idiopathic	33 (44)	3 (27.3)	30 (46.9)	0.226
Chagasic	27 (36)	5 (45.5)	22 (34.4)	0.479
Ischemic	10 (13.3)	2 (18.2)	8 (12.5)	0.609
Hypertensive	3 (4)	1 (9.1)	2 (3.1)	0.351
Valvar	1 (1.3)	-	1(6.9)	0.676
Rheumatic	1 (1.3)	-	1 (1.6)	0.676
LVEF subgroups				
Reduced (≤ 40%)	31 (41.3)	9 (81.8)	22 (34.4)	0.003
Mid-range (41-49%)	13 (17.3)	2 (18.2)	11 (17.2)	0.936
Preserved (≥ 50%)	31 (41.3)	0 (0)	31 (48.4)	
Echocardiographic data				
LA diameter, mm	43.9 ± 8.9	46.2 ± 10.6	42.9 ± 8.5	0.264
LV dilatation	31 (41.3)	8 (72.7)	23 (35.9)	0.022
Intracavitary thrombi/ spontaneous echo contrast				
Intracavitary thrombi / spontaneous echogenic contrast in LA	9 (12.1)	1 (9.1)	8 (12.5)	0.552
Intracavitary thrombi / spontaneous echo contrast in LAA	2 (2.6)	1 (9.1)	1 (1.6)	0.351
Medications				
Aspirin	41 (54.7)	6 (54.5)	35 (54.7)	0.993
Warfarin	13 (17.3)	1 (9.1)	12 (18.8)	0.434
NOAC	6 (8)	2 (18.2)	4 (6.3)	0.178

*Results expressed as mean ± standard deviation or n (%). *Student's t test for categorical variables and Pearson's chi-square for continuous variables. AF: arterial fibrillation; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; LA: left atrium; LV: left ventricle; LAA: left atrial appendage; NOAC: new oral anticoagulants.*

Limitations

The study was carried out in a single center, with a small sample and there were no analyses of intra- and interobserver variability between the echocardiographists.

Author contributions

Conception and design of the research: Oliveira MMC, Hatem MAB, Câmara EJN, Fernandes AMS, Oliveira-Filho J, Aras R; Acquisition of data: Oliveira MMC, Sampaio ES, Kawaoka JR, Hatem MAB, Câmara EJN; Analysis and interpretation of the data and Writing of the manuscript: Oliveira MMC, Sampaio ES, Kawaoka JR, Hatem MAB, Câmara EJN, Fernandes AMS, Oliveira-Filho J, Aras R; Statistical analysis: Oliveira MMC, Sampaio ES, Oliveira-Filho J; Critical revision of the manuscript for intellectual content: Oliveira MMC, Sampaio ES, Kawaoka JR, Hatem MAB, Câmara EJN, Fernandes AMS, Oliveira-Filho J, Aras R.

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For a Model of Self-Citation Governance in *Arquivos Brasileiros de Cardiologia*

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Arquivos Brasileiros de Cardiologia (ABC) has been the official scientific publication of Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia, SBC*) since 1948. Since its beginning, ABC has continuously published articles on a wide range of topics in cardiology, becoming the main organ of dissemination of scientific work in Brazil and Portuguese-speaking countries. Since 1950, the articles have been indexed in the main international databases (Institute of Scientific Information - ISI Web of Science; Cumulated Index Medicus - MEDLINE; Pubmed Central; EMBASE; SCOPUS; SCIELO and LILACS),[1] and are currently published in two languages (English and Portuguese). Thomson Reuters publishing company, owner of the Journal Citation Reports (JCR) statistical database, created the concept of impact factor in 1955, aiming to provide an instrument to evaluate the performance of scientific publications in a comparative and quantitative manner. Impact factor is calculated by dividing the number of citations of articles published in an academic or technical journal indexed in the ISI by the total number of articles published in that journal during the two preceding years. These estimates include approximately 3,300 journals, 200 subject areas and 100 countries.[2]

Impact factor is a metric for journal assessment, widely used by researchers to choose the best journal to submit their papers. However, its validity as an indicator of scientific impact has been questioned due to, among others, self-promoting journal self-citation in attempt to increase their impact factor.[3] Overuse of self-citation practices is punishable, and caused the exclusion of 5 Brazilian journals from the JCR for one year (2013).[4] For this reason, efficient control measures of this practice should be developed and implemented by scientific journals that seek to adhere to ethical precepts recommended by the scientific community.

In light of this, we developed an original model of regulation of self-citations of scientific publications, by analysis of ABC publications in terms of internal bibliographic referencing, known as self-citation, considered valid for the impact factor calculation, between 2000 and 2016.

Keywords

Periodical Index; Periodicals as Topic; Cardiology; Citation Databases; Journal Impact Factor.

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The search was performed on the ABC database available at (http://www.arquivosonline.com.br). Inclusion criteria were the period from 2000 to 2016, and the texts classified as "original articles". Aiming to avoid heterogeneity of data and eventual publication bias, manuscripts classified as "editorials", "letters to the editor", etc. were excluded from the search. Original articles were classified by month, year, total number of references, number of references of articles published in ABC, and number of "valid" references for impact factor calculation, i.e., articles published within two years prior to current publication.

Temporal trend analysis was performed for the number of "valid" publications and its relation to the number of citations in the same journal and the total number of references. Assumption of temporal stability was assessed by rolling window regression, including the following parameters – monthly periodicity, non-recursive sampling (i.e., a fixed window size), overlapping window of subsamples in a six-month range beyond sample size, fixed at 1,875, of "original articles" published between January 2000 and December 2016 in ABC. Rolling window regression was used for analysis of countable data (Poisson distribution), with the number of references considered "valid" for calculation of the impact factor, per month, used as dependent variable, and total number of references per month used as independent variable. Coefficients obtained from successive intervals of six months were exponentiated to represent the "effect size" of temporal series as incidence rate ratio (IRR). Values near 1 (margin of error of 5%) for a pre-established period indicated absence of the effect. Values lower than 1 indicated reduction and values greater than 1 suggested increment in incidence rate, with valid references.

To evaluate potential influence of journal volume proximity, previous trends, future predictions, preference for certain periods of the year and stationary processes, autoregressive integrated moving average (ARIMA) model was selected according to pre-estimation and post-estimation.

Pre-estimation was assessed by periodgrams, correlograms, partial and total autocorrelation plots with 95% confidence interval based on the Q test (or "portmanteau") and the Bartlett's test. Post-estimation was assessed using the Akaike information criterion (AIC) and smoothers for detection of the Gaussian white noise in time series graphs. These are characterized by a trend for asymmetry, lack of correlation with time, and presence of stationary processes. Result of ARIMA model was described according to time operators, such as "lag", "lead" and "difference". used in the analysis of the best performance.

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Stability of all parameters selected in ARIMA model was assessed by estimation of eigenvalues and their graphical display inside the unit circle of the inverse root of the ARIMA polynomials. Significance level was set at two-tailed $p < 0.05$. Statistical analysis was performed using Stata software (version 14.2). Results of the analyses are described in four stages, as follows:

Stage 1. A total of 1,875 articles were analyzed, corresponding to all "original articles" published between 2000 and 2016 in ABC. Table 1 describes the number of references per article, the number of references of articles previously published in ABC and the number of "valid" references for the impact factor calculation. Data were described per year, as mean and standard deviation.

Stage 2. Numerical and graphical analysis of autocorrelations did not reveal temporal, periodic or seasonal trends. Similarly, results of the Q-test were compatible with white noise in models in which lags were not included ($p = 0.49$) and in models with inclusion of up to 20 lags ($p = 0.27$), i.e., there was a random change of signal, with no temporal trends or autoregressive phenomena associated with such variation.

Stage 3. ARIMA regression models were tested. The model that met the adequacy criteria, yielding the lowest AIC values, used, as parameters, a "p" (lags) of 6, a first-order "d" (difference) of 1, and "m" (or cut offs after lags, in "leads") of 3. All coefficients had a p-value greater than 0.05, including the first-order difference and sigma, which test the hypothesis of variance in time series different from zero. The model stability was considered satisfactory in numeric terms, for showing eingenvalues lower than 1 in absolute number, as well as in graphical terms for showing the inverse root of polynomials inside the pre-established circle.

Stage 4. A sequential, six-month window was adopted as parameter in the rolling window regression. A Poisson regression model was used for analysis of countable data, with a robust estimate of both variance and covariance. Distribution of IRR of "valid" references is depicted in Figure 1. An IRR near 1 indicate absence of volatility, i.e., considering the total number of references, the rate of "valid" references did not significantly change throughout the analysis period. Therefore, the pattern of bibliographic referencing remained unchanged in the last 17 years. As shown in graph 1, IRR was extended by nearly 5%, ranging from approximately 0.98 to 1.04 from 2000 to 2016.

Analysis of time series during a 17-year period enabled a detailed description of parameters of bibliographic referencing distribution and self-citation pattern. These data may serve as a basis for future comparisons between different journals and within the same journal. Our main finding was the stationary pattern of self-citations in the bibliographic referencing of original articles, published in ABC between 2000 and 2016, considered "valid" for the impact factor calculation. This suggests that ABC resisted the temptation to encourage self-citation of their reports to increase its impact factor.

In Brazil, the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) a Brazilian government agency run

Table 1 – Total of references per year, number of references of articles published in Arquivos Brasileiros de Cardiologia (ABC) and number of valid references for estimation of the impact factor from 2000 to 2016

Year	References per article	SD	References or articles published in ABC	SD	References of impact	SD
2000	28.11	2.01	1.29	0.28	0.00	0.00
2001	28.06	1.85	1.21	0.21	0.06	0.02
2002	29.44	1.52	1.18	0.22	0.18	0.07
2003	29.29	1.52	1.18	0.22	0.18	0.07
2004	29.14	1.25	1.14	0.18	0.19	0.05
2005	31.32	1.52	1.36	0.20	0.06	0.02
2006	30.25	1.01	1.38	0.16	0.20	0.42
2007	27.88	0.70	1.54	0.17	0.30	0.04
2008	25.85	0.81	1.30	0.17	0.35	0.07
2009	27.27	0.72	1.92	0.20	0.39	0.07
2010	29.07	0.55	2.00	0.16	0.31	0.04
2011	29.24	0.89	1.47	0.18	0.46	0.07
2012	29.19	0.75	2.00	0.20	0.50	0.06
2013	28.41	0.75	1.92	0.19	0.30	0.05
2014	29.70	0.84	2.11	0.24	0.31	0.07
2015	29.23	0.84	1.59	0.20	0.38	0.08
2016	29.17	0.84	1.65	0.22	0.46	0.09
Mean	28.87	0.24	1.61	0.04	0.30	0.01

Data expressed as mean and standard deviation (SD)

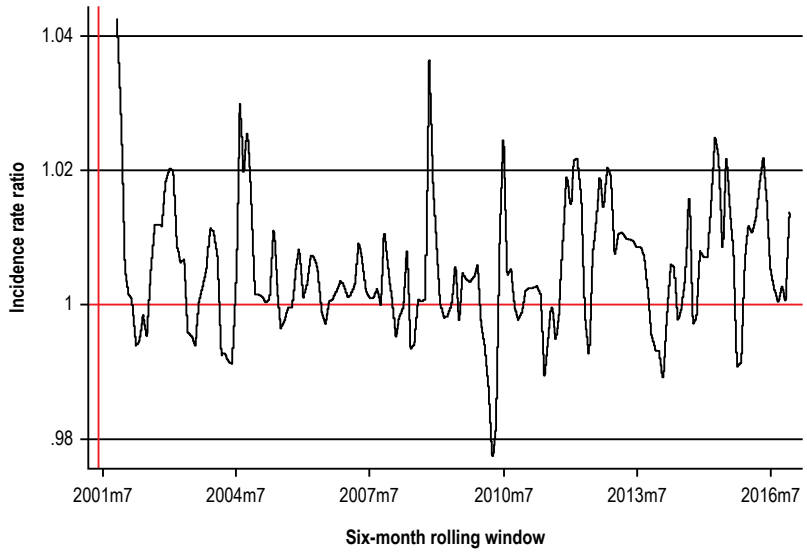

Figure 1 – *Incidence rate ratio (IRR) of self-citations during the period from 2000 to 2016. Note: results are presented from the year 2001 on, since the year 2000 was used as the starting point of the rolling window regression.*

by the Ministry of Education, adopts a set of procedures to classify the quality of intellectual production of (professional and academic) Master's degree and doctoral programs, named "Qualis classification". For the same journal, Qualis varies according to the subject area. Qualis classification criteria include the impact factor (or more precisely, the cutoff point) that defines each category,[5] which is available at Sucupira platform.[6]

ABC is indexed according to formal parameters of assessment of scientific journals, such as its format, the International Standard Serial Number (ISSN), periodicity and main scientific content, presence of a qualified editorial board, peer reviews, and conformity with the norms of the World Association of Medical Editors (WAME), formerly Vancouver group. The journal is also indexed in the National Library of Medicine, Pub Med/Medline, ISI, and SciELO, Lilacs databases, among others.[5,7]

The impact factor of ABC was calculated for the first time by the Journal of Citation Report (Thomson Reuters) in 2010, with a result of 1.315. Since then, values of this bibliometric index, documented by the Web of Science database (ISI) confirmed scientific relevance as well as the scope of the studies conducted in Brazil and of international studies published in ABC. These classifications place ABC at the same level of approximately 30% of international journals in cardiology indexed in the ISI database.[2] Strategies that may increase the impact factor include the improvement of publication and internationalization criteria of the journal. This has been performed in non-English-speaking countries, by publishing, for example, bilingual editions. Similar strategies have been used in the United States, Mexico and South Korea.[8]

Since its inception in scientific field, Thomson Reuters has developed citation indexes, and compilation of statistical reports, not only in terms of volume of publication but also of the frequency of citations. This used to be done by the Science Citation Index (SCI)[5] until 1975 and, since then, this process has been continued by Thomson Reuters by means of JCR, as part of the SCI and the Social Sciences Citation Index (SSCI).[10] JCR provides quantitative tools for classification, assessment, classification and comparison of journals.[9] The impact factor allows comparisons between different journals year by year.[10]

It's reasonable that the editors of scientific journals strive to improve the scientific quality of the articles to be published, which is achieved, among others, by increasing the number of articles received, by a rigorous selection process and training of reviewers. Not rarely, the prestige and even the survival of a journal depends on the maintenance or, even better, improvement of the impact factor.[11]

Nonetheless, the use of the impact factor has been a matter of controversy in scientific and academic communities. The instrument has been considered inadequate,[12] of low credibility,[6] a source of distraction,[13] a controversial stimulus,[14] a questionable metrics[15] to be extinguished[16] or, at least, a debatable subject.[13] Also, assessing the scientific quality of the articles in a two-year period may be considered arbitrary.[17]

Despite the criticisms, the impact factor has been used as a bibliometric indicator, i.e., as a discriminating parameter of the relevance of a publication for the scientific community.[12-18]

The use of an easy-to-understand bibliometric indicator represents a valuable contribution, especially considering the increase in the number of electronic journals and online journal access.[10-17]

However, governance instruments capable of auditing the temporal pattern of self-citation rate and identifying sudden or unexpected increments in the impact factor, possibly associated with inappropriate self-referencing should be developed.

The present model enabled an integrated, dynamic assessment of self-citation rates. During the period from January 2000 to December 2016, there was a stationary pattern of self-citation of original articles published in ABC, which is in accordance with ethical practices in scientific research. Based on our results, we believe that this governance instrument can be of great utility for monitoring the pattern of self-citation practices and increasing transparency of the impact factor as a metric parameter of the quality of scientific journals.

Author contributions

Conception and design of the research: Santos MAA, Barreto-Filho JÁ; Acquisition of data: Santos MAA, Santos DMS; Analysis and interpretation of the data and Statistical analysis: Santos MAA; Writing of the manuscript: Santos MAA, Santos DMS, Prado BS, Barreto-Filho JÁ; Critical revision of the manuscript for intellectual content: Santos MAA, Santos DMS, Prado BS, Barreto-Filho JÁ.

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Case 5/2018 - Severe Pulmonary Valve Stenosis (PVS), Relieved by a Double-balloon Catheter, in a 68-year-old Woman

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Clinical data

During a recent clinical evaluation for cholecystectomy surgery, a heart murmur was auscultated and complaint of fatigue at great efforts lasting for some months was reported by the patient. The diagnosis of severe PVS was attained, with a maximum gradient of 160 mmHg obtained at the echocardiography. The patient denied other symptoms and was unaware of the existence of this cardiopathy. She had no history of other morbidities and took vitamin D.

Physical examination: The patient was in good overall condition, eupneic, acyanotic, normal pulses in the 4 limbs. Weight: 70 kg, height: 160 cm, right upper limb blood pressure: 140/80 mmHg, heart rate: 80 bpm, oxygen saturation, 89%. Aorta not palpable in the suprasternal notch.

Precordium: Apex beat not palpable, discrete systolic impulses in the left sternal border (LSB). Muffled heart sounds, harsh systolic murmur, ++ / 4 in the pulmonary area, which irradiated to the entire LSB. The liver was not palpable, and the lungs were clear.

Complementary exams

Electrocardiogram: Sinus rhythm, 1st degree atrioventricular block and complete right bundle branch block. PR: 0.22, QRS: 0.12, with rsR' complexes in V1 and RS in V6. T wave was negative from V1 to V4 and the S wave was prominent in the left precordial leads. AP = +80°, AQRS = +200°, AT = -20° (Figure 1).

Chest radiography: Normal cardiac area (cardiothoracic index of 0.50) with enhanced ventricular arch and excavated, rounded and long middle arch, with a more prominent hilar pulmonary vascular network (Figure 1).

Echocardiogram: Heart cavities with normal diameter, except for dilated right atrium. The right ventricle was hypertrophic, with systolic function preservation, with TAPSE = 1.8. Diastolic dysfunction was present, with relaxation alteration at tissue Doppler with Tei index = 0.62. The pulmonary valve was thickened with a dome-shaped opening and a maximum pressure gradient of 160 and a mean of 86 mmHg. Pulmonary regurgitation was mild. The pulmonary trunk was dilated, and the pulmonary arteries were confluent. A small 10-mm atrial septal defect allowed right-to-left shunting. Aorta = 28 mm, LA = 30, RV = 29, LV = 39, PT = 37, AP's = 20, septum = 8, posterior wall = 10 mm, LVEF = 72%, TV diameters = 31, MV = 20, PV = 20, Ao = 21 mm.

Holter: Sinus rhythm, frequent ventricular and atrial extrasystoles and episodes of nonsustained ventricular and supraventricular tachycardia.

Clinical diagnosis: Severe PVS with natural disease evolution, without heart failure and good physical tolerance.

Clinical rationale: In an adult patient with few symptoms, the recently observed clinical elements of systolic murmur in the pulmonary area, complete right bundle branch block and pulmonary trunk dilation, led to the diagnosis of PVS. This supposition was confirmed by the echocardiogram, with an adequate demonstration of the dome-shaped valve opening and marked right ventricular hypertrophy.

Differential diagnosis: Aortic valve stenosis is the most important differential diagnosis in this case, due to the location of the murmur and the patient's older age. However, the fact that the heart murmur did not radiate to the lateral neck sides rules out this diagnosis, as well as the occurrence of middle arch dilation on the chest radiography, and the right bundle branch block on the ECG.

Conduct: The immediate relief of the right ventricle overload was indicated, as it was shown to be of the utmost importance. Surgical intervention was ruled out due to the patient's age and the enthusiastic use of percutaneous procedures, proven effective even in adult patients.

Cardiac catheterization performed in the right heart confirmed the diagnosis of PVS of great impact. The cavitary pressures found were: RA = 20, RV = 160 / 8-22, PT = 30/20-23 mmHg. Systemic pressure was 110/60 mmHg. Marked right ventricular hypertrophy was observed, and the dome-shaped pulmonary valve opening was limited with a little reduced pulmonary annulus size.

The pulmonary valvuloplasty was performed with two 20-and 18-mm balloons, which were inflated at the valve plane level, with the formation and disappearance of the hourglass image. Post-pulmonary valvuloplasty pressures were: RA = 12, RV = 80 /8-12, PT = 30 / 20-23 mmHg (Figure 2). Therefore, the procedure was considered very successful.

At the first reevaluation one week later, the patient showed clinical improvement, with more adequate breathing. The systolic murmur persisted in the pulmonary area, with lower intensity. The patient started receiving an adrenergic beta-blocker medication.

Keywords

Pulmonary Valve Stenosis; Cardiac Catheterization; Hypertrophy, Rigth Ventricular/physiopathology; Pulmonary Valve/surgery.

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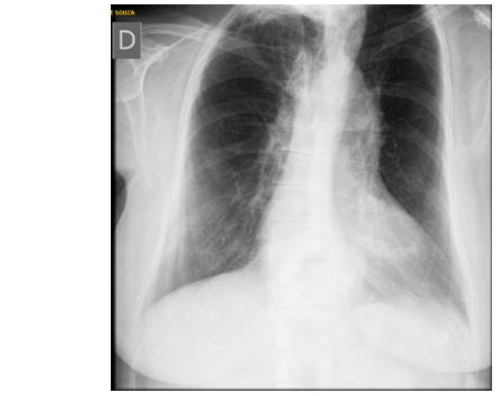

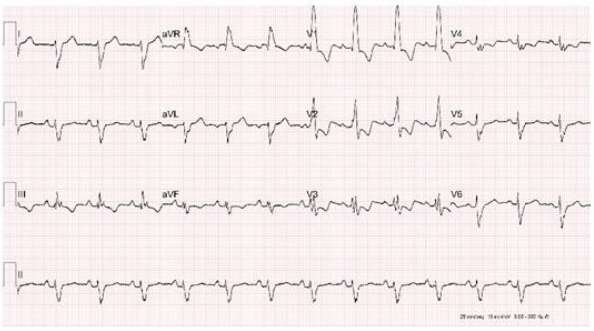

Figure 1 – *PA chest X-ray emphasizes normal cardiac area with prominent ventricular arch and slightly increased hilar pulmonary vascular network. Due to the marked increase of the pulmonary trunk, the middle arch draws attention due to the long concavity. The electrocardiogram highlights the signs of complete right bundle branch block.*

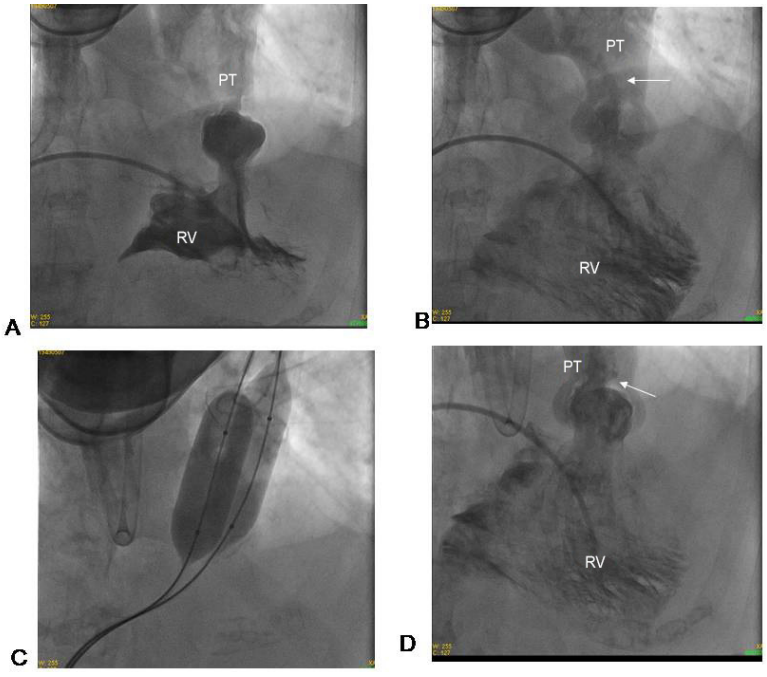

Figure 2 – *Cardiac angiography showing marked right ventricular hypertrophy in systole in* **A**, *and in diastole in* **B**, *with good ventricular contractility. Thinner contrast jet (arrow) passing through the stenotic pulmonary valve in* **B**, *before double-balloon valvuloplasty, in* **C**, *and after the procedure in* **D**, *with a thicker jet (arrow).*

Comments

Marked PVS has an unfavorable evolution, even at an early age in the neonatal period, as it can progress to sudden death due to right ventricular failure. After this age range, the disease evolution becomes more adequate, but right ventricular dysfunction, tricuspid valve regurgitation, arrhythmias and right heart failure appear in adulthood. These factors shorten patient survival to 30 to 40 years of age. Therefore, percutaneous pulmonary valvuloplasty has been indicated at early ages, aiming to prevent such unfavorable evolution. Thus, it can be affirmed that patient evolution in this clinical case is very peculiar, due to the marked degree of the congenital defect at a very old age. Also noteworthy is the rare occurrence of good ventricular function preservation and, as a result, the occurrence of few symptoms. A similar evolution has also been observed by other authors with percutaneous,[1,2] as well as surgical treatment[3] in adulthood. However, the literature shows that the effectiveness of percutaneous valvuloplasty becomes lower in adults (87%) in relation to younger ages (96%).[4]

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Partial Papillary Muscle Rupture after Myocardial Infarction and Early Severe Obstructive Bioprosthetic Valve Thrombosis: an Unusual Combination

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Introduction

Mechanical complications after myocardial infarction (MI) have become uncommon since the introduction of primary angioplasty.[1] They can lead to a rapid clinical deterioration and a fatal outcome, with patient's survival being dependent on their prompt recognition and intervention. We describe a case of two rare mechanical complications: a partial papillary muscle rupture after MI, followed by an early severe obstructive thrombosis of the implanted bioprosthetic valve.

Case report

We report a case of a 70 year-old male, with a history of dyslipidaemia and smoking habits, who suffered an inferior ST elevation myocardial infarction (STEMI). Given the impossibility to achieve a timely percutaneous coronary artery intervention, thrombolysis was performed within 4 hours of symptoms onset. Advanced atrioventricular block requiring a transcutaneous pacemaker occurred soon after, followed by cardiorespiratory arrest in ventricular fibrillation, which was reversed after one cycle of advanced life support. The patient was transported by airplane to a percutaneous coronary intervention (PCI)-capable centre. Coronary angiography showed a 50-60% stenosis in the proximal segment of the right coronary artery, which was treated with a bare metal stent. Echocardiography showed a moderate left ventricular systolic dysfunction (estimated ejection fraction of 35%), with inferior, inferolateral and inferoseptal akinesia and moderate mitral regurgitation. On the fifth day, the patient was transferred to our centre, after a 10-hour flight. On admission to intensive care unit, the patient was in cardiogenic shock with inotropes and non-invasive ventilation. A bedside transthoracic echocardiography revealed a severe mitral valve regurgitation of uncertain mechanism, along with moderate left ventricle systolic dysfunction and right ventricle systolic compromise. Additional characterisation by transoesophageal echocardiography revealed a 9 mm disruption of the posteromedial papillary muscle consistent with a contained, albeit morphologically imminent, rupture. The instability of the sub-valvular apparatus, leading to a broad posterior leaflet prolapse, caused severe mitral regurgitation with an eccentric jet with Coanda effect, reaching the left atria roof (Figure 1). The patient underwent urgent mitral valve replacement with a biological prosthetic valve (St. Jude #29), with preservation of anterior and posterior leaflets. The patient experienced a favourable post-operative recovery and was discharged 12 days after surgery with anticoagulant therapy for three months, in addition to dual antiplatelet therapy. On the fourth month after surgery, the patient initiated progressive heart failure symptoms (NYHA class III) without any further complaints. Additional transthoracic and transoesophageal evaluations were performed, revealing a significant restriction of the prosthetic mitral valve leaflets mobility due to thrombotic material deposition, leading to severe obstruction, with a mean gradient of 19 mmHg and an effective orifice area estimated by PISA method of 0.4 cm.^{2} Additionally, in continuity with the prosthesis, a large mural thrombus was present covering the left atrial posteroseptal wall (Figure 2). Urgent surgery, within twenty-four hours after diagnosis, was performed involving mitral bioprosthesis replacement with another biologic prosthesis with significant improvement in clinical status. After an extensive study, no evidence was found of atrial fibrillation or thrombotic disorders. Pathology examination of the excised prosthetic material confirmed prosthetic thrombosis, with no signs of endocarditis.

Discussion

In the current era of early mechanical reperfusion, the incidence of papillary muscle rupture (PMR) after MI has decreased, being less than 0.5%. Although rare, complete or partial PMR is a serious complication which can lead to rapid clinical deterioration and death.[1,2] A great deal of foresight is essential for an early recognition of this condition, especially in uncommon scenarios, like the case reported. Moreover, the patient was submitted to thrombolytic therapy and prolonged air travel in the acute phase of MI, which could have contributed to additional ischemia and injury.

Transthoracic echocardiography (TTE) is of critical importance in the evaluation of patients in cardiogenic shock after MI, and so it is the initial imaging modality used. It has a sensitivity of 65–85% for the diagnosis of PMR.[3] However, in some cases TTE is insufficient to accurately ascertain the mechanism causing mitral regurgitation, so an additional characterization with transoesophageal echocardiogram (TEE) becomes crucial to establish diagnosis. TEE can offer superior visibility and characterization of the posterior structures – such as mitral valve apparatus – with a diagnostic yield between 95% and

Keywords

Myocardial Infarction/complications; Thrombolytic Therapy; Atrioventricular Block/complications; Pacemaker Artificial; Heart Arrest; Heart Rupture.Post-Infarction; Bioprosthesis

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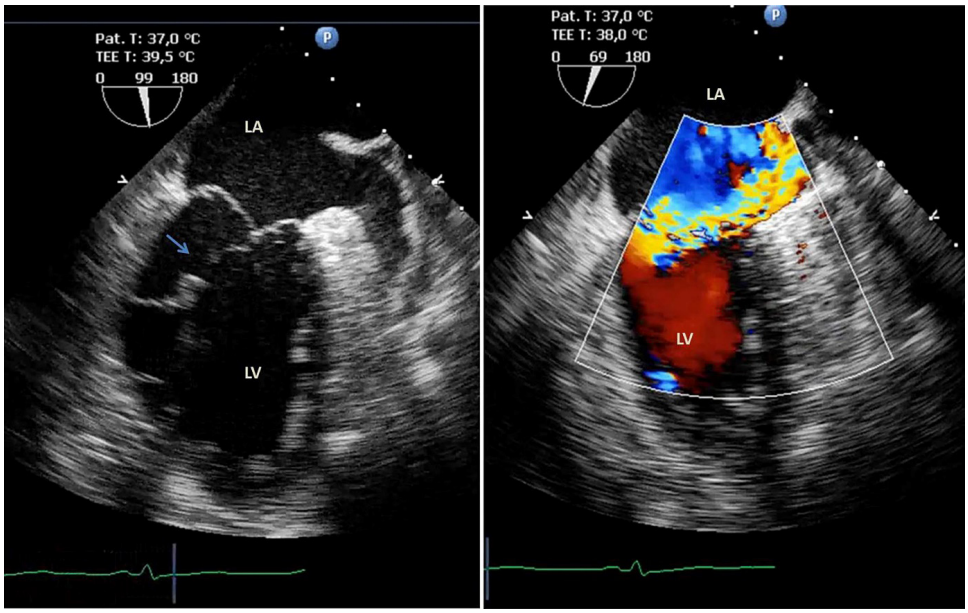

Figure 1 – *Transoesophageal echocardiogram two-chamber view showing a 9 mm disruption of the posteromedial papillary muscle (pointed with an arrow) consistent with a contained, but morphologically imminent rupture, leading to a broad posterior leaflet prolapse and a severe mitral regurgitation with an eccentric jet. LA: Left Atria; LV: Left Ventricle.*

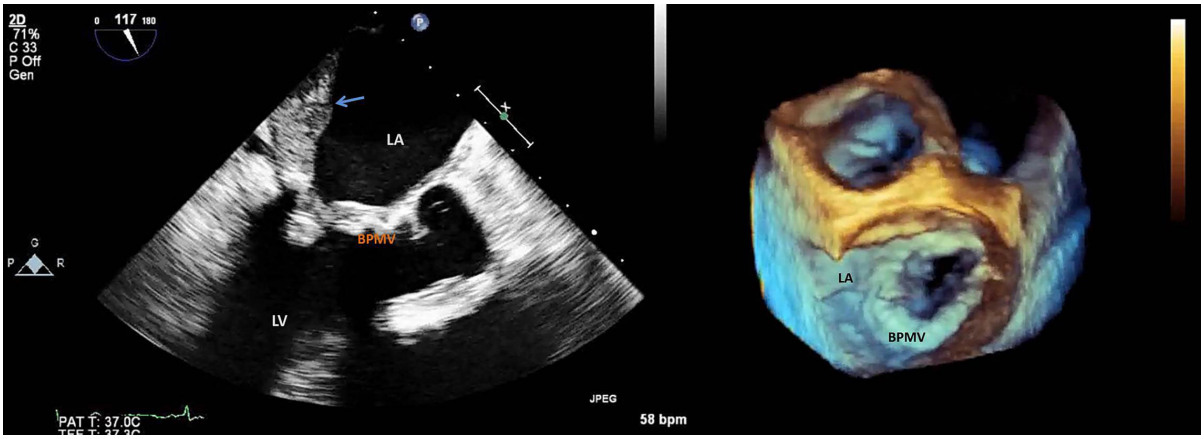

Figure 2 – *Transoesophageal echocardiogram long axis view and 3D zoom on face view of the mitral valve presenting a significant thickening of mitral bioprosthetic cusps due to thrombotic material deposition, leading to severe obstruction of the prosthetic valve and a large mural thrombus covering the left atrial posteroseptal wall (pointed with an arrow). BPMV: Bioprosthetic Mitral Valve; LA: Left Atria; LV: Left Ventricle.*

100%.[4,5] Although partial PMR may be more difficult to identify than complete rupture, it should always be closely investigated in the setting of a flail/prolapse mitral leaflet.[5] In our case, only TEE evaluation provided a full characterisation of mitral valve structure and an accurate identification of the mitral valve apparatus disarray. Due to the adverse hemodynamic complications associated with PMR, emergent identification and treatment are essential to improve patient outcomes. The natural history of post-MI PMR is extremely unfavourable under medical treatment alone.[6] Partial PMR is also considered a surgical emergency as most of the cases will progress to complete rupture.[7] In our case, the instability of the sub-valvular apparatus was notorious with potential imminent complete rupture, as can be seen in Figure 1.

Bioprosthetic valves are advantageous over mechanical ones due to their comparatively lower incidence of thromboembolic events and avoidance of long-term anticoagulation. Clinically significant bioprosthetic valve thrombosis (BPVT) is considered a rare phenomenon, however accumulated evidence suggests that it is an under-recognised

complication.[8] Its diagnosis remains challenging due to a general lack of awareness on this condition. A combination of clinical and echocardiographic features is helpful for diagnosis. Specific predisposing factors to BPVT include low cardiac output, left atrial dilatation, prior history of thromboembolic events, atrial fibrillation and hypercoagulability. New-onset acute heart failure symptoms, progressive dyspnoea, new thromboembolic event and regression of heart failure symptoms with anticoagulation therapy should be considered as flags for this condition. Some echocardiographic features support the diagnosis of BPVT, such as: direct visualisation of valve thrombosis, like the reported case; a 50% mean gradient increase compared with post-operative evaluation; increased cusp thickness (>2 mm), especially on the downstream aspect of the BPV; abnormal leaflet mobility; regression of BPV abnormalities with anticoagulation, usually within 1–3 months of its initiation or reduced leaflet motion in a cardiac CT scan.[8,9] The optimal treatment of BPVT remains a matter of debate. The strategy depends on clinical presentation, patient's hemodynamic status, presence of BPV obstruction and valve location. Conventional treatment options include surgery, fibrinolysis and anticoagulation, but anticoagulation coupled with surgery remains the mainstay of treatment.[10] Although independence from long term anticoagulation is an advantage of bioprosthetic valve replacement, cases like the one we described highlight the importance of considering this condition even in patients without significant risk factors, who display heart failure symptoms early after valve replacement. Post-operatively, patients must be categorised according to risk, and perhaps long-term anticoagulation should be considered for high risk patients, as well as periodic echocardiographic evaluation of biological prosthetic valves. In both complications described in this case, echocardiographic characterization with 2D/3D images was essential for the establishment of a correct diagnosis and for guiding treatment.

This case illustrates two uncommon cardiac mechanical complications, being peculiar their association in the same patient. Despite their distinct pathophysiology, both conditions represent cardiac emergencies requiring a high index of suspicion and an accurate diagnosis. Cardiovascular imaging stands as an extremely valuable supporting technique in a critical-care setting. The precise recognition of the partial papillary muscle rupture (occasionally a missed diagnosis) and the early obstructive bioprosthetic valve thrombosis allowed a prompt and successfully surgical correction of these conditions, with significant impact on patient's health and recovery.

Author contributions

Conception and design of the research: Silveira I, Oliveira M; Writing of the manuscript: Silveira I, Oliveira M, Gomes C; Critical revision of the manuscript for intellectual content: Gomes C, Cabral S, Luz A, Torres S.

Potential Conflict of Interest

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

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Study Association

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

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Case Report

Right Ventricular Wound And Complete Mammary Artery Transection

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Many patients die immediately after suffering a heart wound; on the other hand, many others die before the surgery, during surgery or later, due to complications.[1]

We admitted a 33-year-old man after a suicide attempt occurring one hour before, with eleven knife-wounds localized in the left-anterior chest wall (Figure:1-A). Physical exam showed hypotension, dyspnea, high central venous pressure and mild external bleeding. Hemodynamic monitoring, tracheal intubation, vasopressor perfusion, fluid therapy and urgent echocardiogram and tomography were undertaken. ACT showed severe pericardial effusion and moderate left pleural effusion (Figure:1-B, white arrows). Emergency cardiac surgery was performed through median sternotomy. Multiple pericardial tears were visualized. The pericardial clot was removed (Figure:1-C) and the right ventricular wound was closed using a monofilament suture (Figure:1-D, black arrow). In the inner chest wall, a complete left mammary artery transection was observed with severe bleeding into the left pleural cavity (Figure:1-E, white arrow). The mammary artery was repaired, and the bleeding was controlled. The postoperative course was uneventful.

Keywords

Stab Wounds/heart; Suicide, Attempted; Heart Injuries/cirurgia.

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Heart wounds are serious health problems. The dramatic statistics have shown that many problems connected with traumatic cardiac lesions are not ultimately resolved. Knife stabs to the right ventricle are perhaps the most common penetrating injury to the heart, but the additional complete transection of the mammary artery is very uncommon. The most important factor for survival is the urgency treatment and the immediate surgical repair.

Author contributions

Conception and design of the research: Laguna G, Blanco M, García-Rico C, Carrascal Y; Acquisition of data and Analysis and interpretation of the data: Laguna G, García-Rico C, Carrascal Y; Writing of the manuscript: Laguna G, Blanco M; Critical revision of the manuscript for intellectual content: Laguna G, Blanco M, Carrascal Y.

Potential Conflict of Interest

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Image

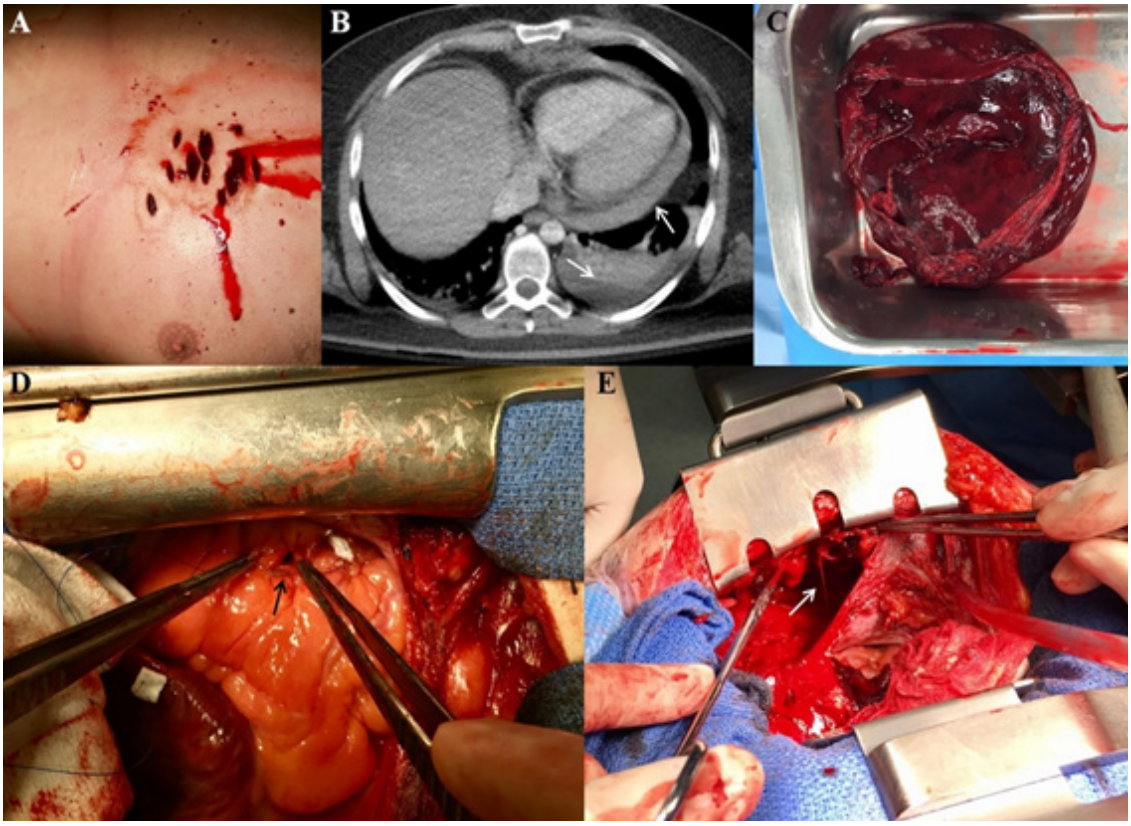

Figure 1 – *Panel A: Eleven knife-wounds localized in the left-anterior chest wall. Panel B: Axial computed tomography showed severe pericardial and left pleural effusion (white arrows). Panel C: The clot drained from the pericardial cavity. Panel D: Right ventricular perforation repaired using a monofilament suture (black arrow). Panel E: Complete mammary artery transection bleeding into left pleural cavity (white arrow).*

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