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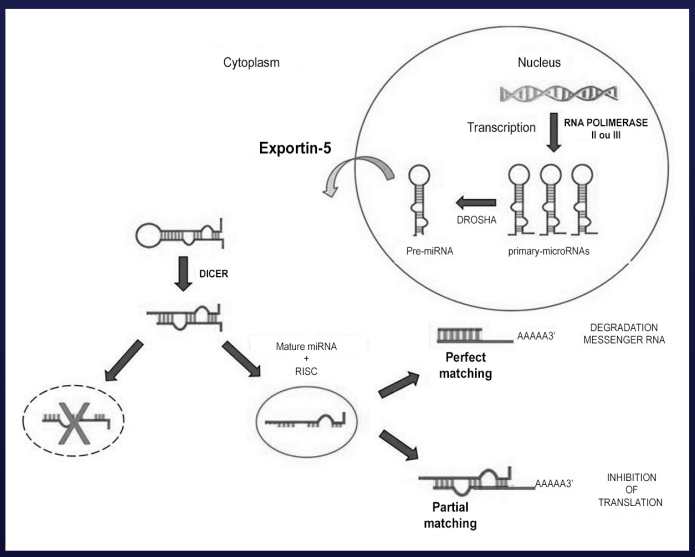

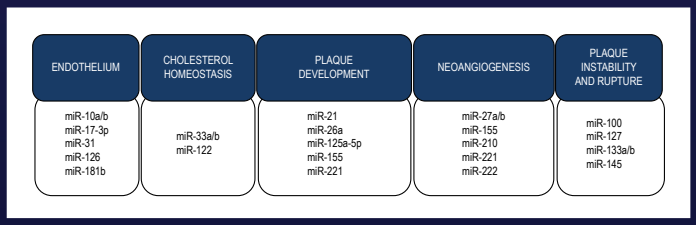

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REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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SUPPORT

Structural Heart Interventional Imagers – The New Face of Cardiac Imaging

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With the aging of the world's population, there has been a parallel growth of valvular heart disease. The development and establishment of less-invasive transcatheter aortic valve replacement (TAVR) has provided a different framework to approach these patients through a multi-disciplinary heart team for planning and treatment. This multi-disciplinary heart team allows the sharing of different expertise and knowledge in order to improve patient care. Although TAVR is one example, many other transcatheter structural heart interventions for the mitral valve, left atrial appendage, paravalvular leak closure, and tricuspid valve, will continue to expand the armamentarium of less-invasive therapies for these typically high-risk patients.

Within this context of continued expansion of devices and procedures, there has been increased demand for physicians with specific procedural-based skills and advanced cardiac imaging training in both echocardiography and cardiac computed tomography (CCT). However, the relative novelty of this subspecialty, brings many challenges. In the presence of poorly defined training requisites and skill-sets and lack of appropriate procedural reimbursement and recognition of the advanced level of peri-procedural imaging and medical care provided, there are many barriers to sustainability and expansion of this unique subspecialty.

Training in structural heart disease imaging

Although training in multi-modality imaging has been well outlined,[1] there are no specific training guidelines and/or requirements for SHD imagers as demonstrated by the results of a recent European survey.[2] Some of the challenges currently faced by cardiology fellows who look for SHD imaging training include finding training centers with enough high-risk clinical volume and exposure to a variety of high-risk procedures so they can train beyond traditional TAVR procedures. This brings an inevitable question of whether adequate SHD imaging training should therefore be reserved to a small number of centers with sufficient knowledge and experience in these procedures. What should constitute the minimal portfolio of procedures, their degree of complexity, the number of cases performed for procedural planning and for intraprocedural guidance to achieve adequate proficiency are some of the questions whose answers remain unclear.

The majority of high-volume programs can provide comprehensive exposure for adequate training, particularly in TAVR, Atrial Septal Defect (ASD) and Left Atrial Appendage (LAA) closure procedures. Transcatheter mitral valve repair with MitraClip system (Abbott Vascular, Menlo Park, CA) is also becoming increasingly more commonly performed and should become a standard part of the SHD imager training. On the other hand, transcatheter procedures such as paravalvular leak closure, transcatheter mitral valve replacement and percutaneous tricuspid interventions are more complex and less frequently performed, and therefore should involve different expectations for what is considered the minimal requirement to achieve proficiency.

Important job attributes

We have recently provided a brief outline including some of the main characteristics and attributes necessary for the success of Structural Heart Disease (SHD) imagers.[3] One of the key components is to have exquisite understanding of and training in these imaging modalities so the imager can integrate and succinctly present information to the heart team, as well as provide value for further recommendations in diagnostic testing and interpretation of data, particularly when there are conflicting reports.

In pre-procedural planning, review and synthesis of serial imaging studies is required to evaluate for progressive changes in cardiac function, chamber size, and severity of valvular pathology. This is particularly important when multi-valvular disease is present, which can pose a challenge in both diagnostic and therapeutic decisions. More often than not, using multi-modality imaging and hemodynamic evaluation can be necessary to clarify the clinical question(s).

During intraprocedural guidance, SHD imagers learn to be agile, focused, mindful and able to protect themselves from radiation exposure. The ability to apply multi-modality critical thinking to integrate and combine clinical information and imaging findings (fluoroscopy and TEE) implies a physician trained skill-set that imagers can develop overtime. Interventional imaging physician driving critical-thinking imaging becomes invaluable to procedural success, much more than any form of imaging overlay or fusion. In-depth knowledge of particular devices and procedural steps, as well as clear, succinct and timely communication with the interventional cardiologist and other team members are critical attributes of a successful SHD Imager, thus implying solid knowledge of the timing and importance of his/her role.

Post-procedurally, SHD imagers must be able to correlate imaging findings with intraprocedural results and potential

Keywords

Cardiology/education; Cardiology/trends; Diffusion of Innovation; Education, Medical, Graduate/trends; Multimodal Imaging/trends; Transcatheter Aortic Valve Replacement/economic.

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device complications. Exposure to a variety of SHD interventions is required in order to generate sufficient imaging experience, to allow the mitigation of complications and to promote safety during high-risk transcatheter procedures. A SHD imager who has developed these unique skill sets will be an indispensable asset to a SHD heart team and a key component to achieve excellent procedure safety and outcomes.

Given the dynamic nature of this field, continued changes are expected on the standard training curriculum, reflecting important updates in the medical literature, device iterations and procedural changes. This can be done by attending annual meetings and industry-sponsored seminars, participating in online CME opportunities and structural imaging workshops, all of which can help refresh and enhance imaging skills.

Radiation exposure is a potential job hazard for the shd imager

Although the issue of radiation exposure was not adequately studied until relatively recently,[4,5] it certainly represents one of the most important job hazards for the SHD imager. Both publications[4,5] confirm that the SHD imager can be subject to very high levels of radiation exposure in structural cases.

Therefore, given the increased complexity of these procedures, which demand more fluoroscopic and imaging guidance, one can only hope that it remains an important area for future research and technological development. At present time, a number of simple measures, such as the use of protective lead apron, portable ceiling-suspended lead shield and distancing from the X-ray source, can provide important strategies to minimize exposure and the potential risk associated with it.[5,6]

Work environments and hospital management teams need to be supportive of and accomodating to providing the necessary resources that can minimize the potential consequences of excessive radiation exposure outlined by the authors.

Reimbursement and sustainability of work enviroment

At the majority of programs in the United States, the SHD Interventional Imager is considered part of the non-invasive general cardiologist group. This occurs at private-practice groups, hospital-employed group-practices or at major academic centers. This creates a significant mismatch between the amount of time that is required to plan and guide complex SHD procedures, and the reimbursement currently allocated to the SHD imager. In the current model, the amount of work relative value units (wRVU) dictates the metrics for purposes of reimbursement and final wages. Simply put, the more procedures a physician does, the more studies he/she reads, the more he/she can charge.

The current model does not reflect the time spent on procedural planning, the required skill-set to successfully guide complex SHD interventions, nor does it account for the potential adverse health-effects on the SHD imager, such as radiation exposure. Let's take, for example, an uncomplicated MitraClip procedure. This Mitraclip procedure is dependent on intraprocedural transesophageal (TEE) guidance, and requires 90+ mins of uninterrupted real-time TEE 3D imaging procedural guidance. This is billed as one umbrella SHD intraprocedural TEE code (93355), with an associated wRVU measure of 4.66, therefore amounting to a $230 charge. Within the same time frame, another "non-invasive" cardiologist could have read 10-15 transthoracic echocardiograms (valued at 1.3 wRVU per study) or 3-4 TEEs (valued at 2.3 wRVU per study), which demonstrates, by traditional productivity metrics, more value to an institution than the Interventional Imaging physician functioning as a second operator in the Mitraclip procedure who is additionally getting radiation exposure. [source: http://asecho.org/2018-medicare-physician-fee-schedule-final-rule].

SHD imagers must continue to advocate recognition for the unique requirements to thrive in this emerging subspecialty. Sustainability within a SHD imaging career track is directly dependent upon fair productivity metrics. Many graduating fellows show a clear interest in pursuing further SHD Interventional Imaging training. However, current reimbursement practice models will deter potential trainees from embracing this new subspecialty field of medicine. A salary-based model is more likely to facilitate a successful SHD imaging career, as opposed to the traditional wRVU productivity model. Until societal guidelines are established for this emerging field, differential procedural codes will continue to fall short on allocating and compensating SHD imaging time properly.

Future directions

The presence of a skilled SHD imager is critical to the growth and success of any high-volume SHD program. The recent, strongly positive results of the COAPT trial[7] emphasize the opportunity for a multi-societal level discussion. In order to allow sustainable growth and continue to provide the imaging support necessary for patient safety and the success of these high-risk transcatheter procedures, it is necessary to revise the current structural and payment model which provides insignificant acknowledgement to the SHD imager; a Co-operator who is absolutely necessary to successfully execute this procedure.

Together, these findings emphasize the critical need for and the opportunity to recognize SHD interventional imaging as a subspecialty within Cardiology and Cardiac Imaging and importantly, to legitimize the SHD imager as the second procedure operator, equally dedicated to exceptional patient care.

References

1. Chandrashekhar Y, Dilsizian V, Kramer CM, Marwick T, Min JK, Shaw L, et al. Implementing multimodality imaging in the future. *JACC Cardiovasc Imaging*. 2016;9(2):91-8.
2. Grapsa J, Kunadian V, Capodanno D, Vidal-Perez R, Radu M, Christia P, et al. Joint EACVI HIT/EAPCI young survey/ESC CoT survey: training and education for 'multimodality imaging in structural interventions': the rise of a new sub-specialty? *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1432-3.
3. Wang DD, Geske J, Choi AD, Khalique O, Lee J, Atianzar K, et al. Navigating a career in structural heart disease interventional imaging. *JACC Cardiovasc Imaging*. 2018 Sep 6:pii:S1936-878X(18)30651-X [Epub ahead of print]
4. Salaun E, Carles S, Bigand E, Pankert M, Aldebert P, Jaussaud N, et al. High Radiation Exposure of the imaging specialist during structural heart interventions with echocardiographic guidance. *JACC Cardiovasc Interv*. 2017;10(6):626-7.
5. Crowhurst JA, Scalia GM, Whitby M, Murdoch D, Robinson BJ, Turner A,et al. Radiation exposure of operators performing transesophageal echocardiography during percutaneous structural cardiac interventions. *J Am Coll Cardiol*. 2018;71(11):1246-54.
6. Hirshfeld JW Jr, Ferrari VA, Bengel FM, Bergersen L, Chambers CE, Einstein AJ, et al. 2018 ACC/HRS/NASCI/SCAI/SCCT Expert Consensus Document on Optimal Use of Ionizing Radiation in Cardiovascular Imaging: Best Practices for Safety and Effectiveness: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;71(24):2829-55.
7. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Weissman NJ, et al.and Investigators C. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018 Sep 23 [Epub ahead of print]

Prognostic Differences between Men and Women with Acute Coronary Syndrome. Data from a Brazilian Registry

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Abstract

Background: **Gender-related differences have been reported in patients with acute coronary syndrome. The description of this comparative finding in a Brazilian registry has not yet been documented.**

Objective: **To compare male vs. female patients regarding the baseline characteristics, coronary findings, treatment and in-hospital and long-term prognosis.**

Methods: **This is a retrospective, multicenter and observational study that included 3,745 patients (2,437 males and 1,308 females) between May 2010 and May 2015. The primary in-hospital outcome was all-cause mortality. The secondary outcome consisted of combined events (cardiogenic shock, reinfarction, death, stroke and bleeding). The comparison between groups was performed using the chi-square and the t test, considering $p < 0.05$ as significant. In the long term, mortality and combined events were assessed using the Kaplan-Meier method, with a mean follow-up of 8.79 months.**

Results: **The mean age was 60.3 years for males and 64.6 for females ($p < 0.0001$). The most prevalent risk factor was systemic arterial hypertension in 72.9% of the women and 67.8% of the men ($p = 0.001$). Percutaneous coronary intervention was carried out in 44.9% of the males and 35.4% of the females ($p < 0.0001$), and coronary artery bypass grafting (CABG) was performed in 17% of the males and 11.8% of females ($p < 0.0001$), with a higher prevalence of three-vessel coronary artery disease in males (27.3% vs. 16.2%, $p < 0.0001$). Approximately 79.9% of the female patients received a diagnosis of acute coronary syndrome without ST-segment elevation, while in the male patients, this diagnosis was attained in 71.5% ($p < 0.0001$). No significant differences were observed between the groups in the short and long term, regarding both mortality and the combined events.**

Conclusion: **Several gender-related differences were observed in patients with acute coronary syndrome regarding the demographic characteristics, coronary artery disease pattern and implemented treatment. However, the prognostic evolution was similar between the groups. (Arq Bras Cardiol. 2018; 111(5):648-653)**

Keywords: **Acute Coronary Syndrome/epidemiology; Prognosis; Gender Indentify; Multicenter Study; Mortality; Hypertension; Percutaneous Coronary Intervention.**

Introduction

Coronary heart disease and, particularly Acute Coronary Syndrome (ACS), is the leading cause of mortality and morbidity in the Western world, both in women and men. The benefits of early reperfusion therapy for ACS patients are well established. However, recent studies have shown that, according to gender, there may be variations in diagnosis, coronary stratification, and chosen reperfusion method. It has also been shown that women with acute myocardial infarction (AMI) are less likely to undergo reperfusion strategies and clinical treatment than men, and there is a lack of risk awareness among women. Differences in survival between men and women, reported in some studies, may reflect not only the gender bias but also differences in coronary anatomy, age, and comorbidities.[1,2]

The description of these comparative data between men and women in a Brazilian registry has yet to be documented. This study was developed aiming at comparing ACS male vs. female patients regarding the baseline characteristics, coronary findings, treatment, in-hospital and medium-term prognosis.

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Methods

Study population

This is a retrospective, multicenter and observational study. A total of 3,745 patients with ACS admitted at an Emergency Sector between May 2010 and May 2015 were

included. The patients were divided into two groups: male (n = 2,437) and female gender (n = 1,308). There was no exclusion criterion. All patients were submitted to a coronary angiography within 48 hours of admission.

All patients who met the criteria established by the last Brazilian Society of Cardiology (SBC) and American Heart Association (AHA) guidelines were considered to be SCA patients.[3,4] Non-ST elevation ACS (NSTE-ACS) was defined as the presence of chest pain associated with electrocardiographic changes, or rise/fall of troponin at hospitalization, or, in the absence of these, as clinical picture and risk factors compatible with unstable angina (chest pain at rest or at minimal effort, severe or occurring with a crescendo pattern). Major bleeding was defined by types 3 and 5 Bleeding Academic Research Consortium (BARC)[4] score, and minor bleeding by types 1 and 2. Reinfarction was considered when there was chest pain recurrence associated with a new elevation in troponin levels. Ischemic cerebrovascular accident (iCVA) was considered when the patient had a new focal motor neurological deficit confirmed by cranial computed tomography. The heart failure outcome was considered when hospitalization was associated with the disease or symptoms with functional class ≥ 2, according to the New York Heart Association classification.

The following data were obtained: age, gender, body mass index, presence of diabetes mellitus, systemic arterial hypertension, smoking, dyslipidemia, family history of early coronary disease, heart failure, previous coronary artery disease (AMI, angioplasty or previous CABG), hemoglobin, creatinine, troponin peak, Killip classification, left ventricular ejection fraction, systolic blood pressure, medications used in the first 24 hours of hospitalization and chosen coronary treatment.

All patients were referred to the post-discharge consultation between 14 and 30 days, and to a new consultation in 6 months, undergoing ischemia or catheterization tests, requested according to the medical evaluation of the team in charge. Coronary reintervention was necessary in 7.2% of the male patients and 6.4% of the female patients at the follow-up (p = 0.48). The follow-up was carried out through telephone contact and medical record review. The study was submitted to and approved by the Research Ethics Committee. The Free and Informed Consent form was filled out by all the patients included in the study.

Statistical analysis

The primary in-hospital outcome was all-cause mortality. The secondary outcome consisted of combined events (cardiogenic shock, reinfarction, death, iCVA and bleeding). A descriptive analysis was performed using means and standard deviations, when using parametric tests, and median and interquartile intervals in non-parametric tests. The comparison between groups was performed using the chi-square test for categorical variables. The unpaired t-test was used for continuous variables, when the Komolgorov-Smirnov normality test showed a normal distribution, considering $p < 0.05$ as significant. The Mann-Whitney U test was used when the distribution was non-normal. The multivariate analysis was performed by logistic regression only when there was a significant difference between groups in some assessed outcome, considering $p < 0.05$ as significant. All baseline characteristics shown in Table 1 that showed a significant difference between the groups were considered as variables in the analysis.

The medium-term analysis was performed by Log-rank using Kaplan-Meier curves to assess the difference between the groups, with a mean follow-up of 8.79 months. A total of 274 patients were lost to follow-up. The evaluated outcomes were combined events (reinfarction, death and heart failure). A p value < 0.05 was considered significant. The multivariate adjustment was performed only when there was a significant difference between groups in some evaluated outcome.

All calculations were performed using the Statistical Package for Social Science (SPSS), version 10.0.

Results

The mean age was 60.3 years for males and 64.6 for females ($p < 0.0001$). The most prevalent risk factor was systemic arterial hypertension, observed in 72.9% of the women and 67.8% of the men (p = 0.001). The baseline characteristics of the study population are shown in table 1.

Regarding the treatment, percutaneous coronary intervention was performed in 44.9% of the males and 35.4% of female patients ($p < 0.0001$). Coronary artery bypass grafting was performed in 17.0% of the men vs. 11.8% of the women ($p < 0.0001$). Regarding the coronary artery disease pattern and the clinical presentation, significant differences were observed between the male and female groups, with 27.3% vs. 16.2% with a three-vessel pattern ($p < 0.0001$), 18.9% vs. 19.9% with a two-vessel pattern (p = 0.381), 28.5% vs. 20.1% of STE-ACS (p = 0.01) and 71.5% vs. 79.9% of non-ST elevation ACS (NSTE-ACS), respectively ($p < 0.0001$).

Regarding the comparison of in-hospital outcomes, there were no significant differences between the groups regarding mortality (3.1% vs. 3.7%, p = 0.293) and the combined events (12.2% vs. 12, 0%, p = 0.885), respectively, between males and females (Table 2).

The medium-term follow-up did not show a significant difference regarding combined events in the male and female groups (31.3% vs. 27.7%, p = 0.769), or in relation to mortality, respectively (Figure 1 and Table 3).

Discussion

The study showed important data found in the Brazilian population, which are consistent with the results of recent publications in the literature. Significant differences were observed regarding the presence of a greater number of risk factors and older age in the female group. Higher rates of reperfusion (percutaneous or surgical) and ST-elevation ACS in men in comparison to women have also been reported as being significant. Regarding mortality and combined events, there were no significant differences between male and female patients in the short and medium-term.

It is estimated that 43 million women have coronary artery disease, which is the leading cause of death in women, with approximately 400,000 deaths per year in the United States.[5] Nearly 43% of ACS patients are women, with approximately

Table 1 – Baseline clinical characteristics of male vs. female patients

Characteristic	Male (n = 2,437)	Female (n = 1,308)	p-value
Age	60.3 ± 11.6	64.7 ± 10.4	< 0.0001*
BMI	26.1 ± 6.5	24.3 ± 6.1	< 0.0001†
Diabetes Mellitus	1,041 (42.7)	627 (47.9)	0.011‡
SAH	1,652 (67,8)	968 (72.9)	0.001‡
Smoking	819 (33.6)	332 (25.4)	< 0.0001‡
FH positive for CAD	361 (14.8)	171 (12.9)	0.113‡
Dyslipidemia	1,136 (46.6)	666 (50.9)	0.011‡
Heart failure	214 (8.8)	133 (10)	0.778‡
Previous iCVA	124 (5.1)	67 (5.1)	0.925‡
Previous AMI	819 (33.6)	378 (28.9)	0.004‡
Previous CABG	356 (14.6)	140 (10.7)	0.001‡
Previous CA	522 (21.4)	234 (17.9)	0.011‡
Hemoglobin, mg/dL	14.6 ± 1.9	13.2 ± 1.7	< 0.001*
Peak troponin, ng/dL	11.8 ± 5.9	8.0 ± 7.2	< 0.001*
Creatinine, mg/dL	1.3 ± 0.5	1.5 ± 0.4	< 0.0001*
SBP, mmHg	134.2 ± 29.4	133.0 ± 27.2	0.104†
LVEF,%	52.3 ± 19.9	51.8 ± 18.7	0.09†
Killip ≥ 2	212 (8.7)	99 (7.6)	0.259‡
ASA	2,383 (97.8)	1,267 (96.9)	0.081‡
Beta-blocker	2,149 (88.2)	1,105 (84.5)	0.002‡
GPI IIb/IIIa	202 (8.3)	114 (8.7)	0.292‡
Enoxaparin	1,859 (76.3)	981 (75)	0.405‡
Fondaparinux	258 (10.6)	128 (9.8)	0.46‡
Clopidogrel	1,772 (72.7)	920 (70.3)	0.132‡
Statins	1,228 (50.4)	647 (49.5)	0.768‡
ACE inhibitor	1.694 (69.5)	870 (66.5)	0.065‡

*Results are expressed as mean ± standard deviation, median ± standard deviation or n (%). *Unpaired t test; † Mann-Whitney U test; ‡ chi-square test. BMI: body mass index; SAH: systemic arterial hypertension; FH: family history; CAD: coronary artery disease; iCVA: ischemic cerebrovascular accident; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; CA: coronary angioplasty; SBP: systolic blood pressure; LVEF: left ventricular ejection fraction; ASA: acetylsalicylic acid; GPI: glycoprotein inhibitor; ACE inhibitor: angiotensin-converting enzyme inhibitor.*

360,000 women submitted to Percutaneous Coronary Intervention (PCI) only in 2007.[5] The number of women with ACS (34.9%) found in this study is proportionally lower than the data published in most international studies. One of the hypotheses for this fact is that there is still a reasonable index of diagnostic error regarding ACS in women, perhaps more pronounced in Brazil, due to the difficulty of access to health care services. Some studies make it clear that the clinical manifestations of coronary disease in women are sometimes non-specific and/or underrated, and a large number of female patients are discharged without a correct diagnosis.[2]

Another interesting finding of this study was the fact that the group of women, in addition to being older, also had a higher number of comorbidities, such as diabetes mellitus, hypertension and dyslipidemia. Women, in most instances, are older when they exhibit their first manifestation of ACS, at a mean age of 71.8 years, compared to 65 years for men.[2,5-10] The older age of onset in women, when compared to men, is probably due to the protective role of estrogen circulation in the vascular endothelium. This hypothesis derives mainly from the observation that the incidence of AMI increases substantially in postmenopausal women. The effects of estrogen on the vascular system include increased nitric oxide release, which leads to vasodilation, prostaglandin production regulation, and smooth muscle proliferation inhibition.[2] Corroborating these data, a retrospective study in patients with STE-ACS showed that women were significantly older (70.9 years vs. 63 years, $p < 0.001$) and more often had diabetes mellitus (36.2% vs. 21.0%, $p < 0.001$) and hypertension (82.3% vs. 73.7%, $p = 0.006$).[6]

As for the ACS presentation, due perhaps to the greater number of comorbidities and the older age at presentation, women classically had a higher proportion of NSTE-ACS when compared to men.[2,5,7-9,11,12] In a retrospective

Table 2 – Univariate analysis comparing different in-hospital outcomes between male vs. female patients

Outcomes	Male (n = 2,437) n (%)	Female (n = 1,308) n (%)	p-value
Reinfarction	24 (1.0)	14 (1.1)	0.519
Cardiogenic shock	107 (4.4)	41 (3.1)	0.066
Bleeding	73 (3.0)	47 (3.6)	0.655
iCVA	17 (0.7)	7 (0.5)	0.678
Mortality	76 (3.1)	48 (3.7)	0.293
Combined events	297 (12.2)	157 (12.0)	0.885

iCVA: ischemic cerebrovascular accident.

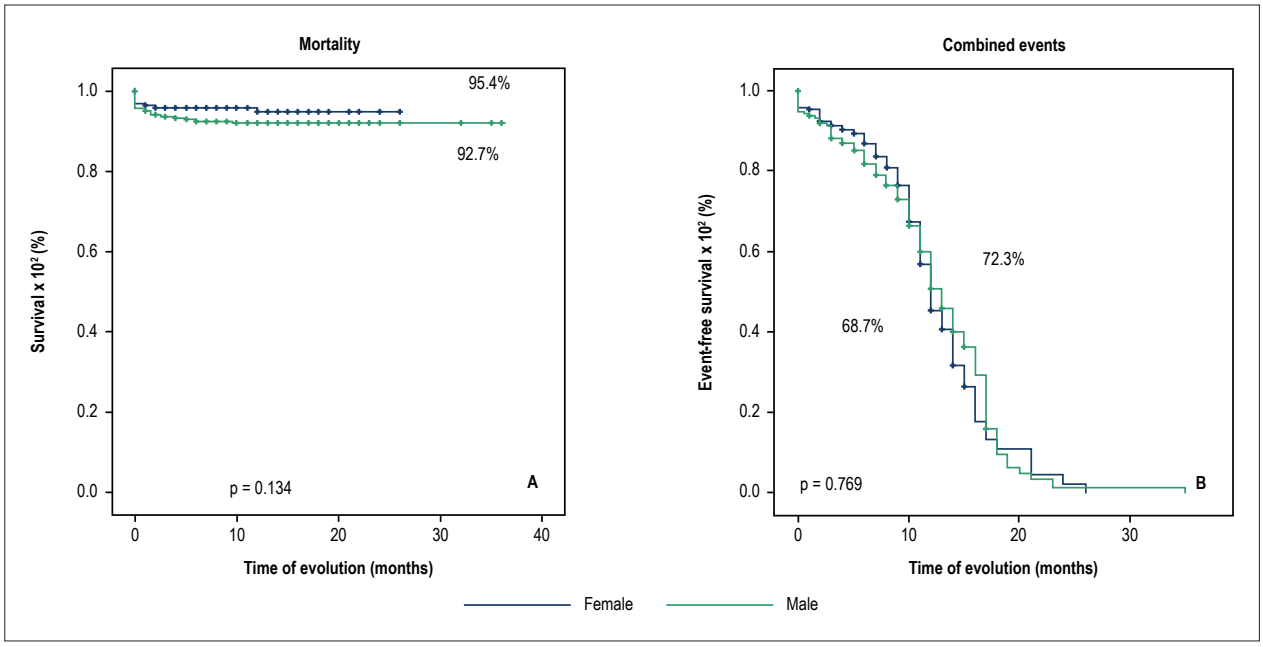

Figure 1 – *Event-free survival and percentage of combined events in the medium-term comparison between males and females.*

Table 3 – Comparison of different medium-term outcomes between the groups of male vs. female patients

Outcomes	Male (n = 2,256) n (%)	Female (n = 1,215) n (%)	p-value
Reinfarction	183 (8.1)	77 (6.3)	0.980
Heart Failure	359 (15.9)	204 (16.8)	0.783
Mortality	165 (7.3)	56 (4.6)	0.134
Combined events	706 (31.3)	337 (27.7)	0.769

cohort published in 2015, Worrall-Carter et al.,[8] assessed 28,985 patients with ACS, showing that the diagnosis of NSTE-ACS was more prevalent among women than men (86% vs. 80%; $p < 0.001$).[8] In another study, with 7,304 patients, the higher prevalence of NSTE-ACS in women was repeated, accounting for 70.7% of the presentations in the female gender ($p < 0.01$).[9] As observed in our study, the findings in the Brazilian population follow the same global trends regarding the clinical/ electrocardiographic presentation of ACS between the genders.

The coronary anatomy in female patients tends to be less complex, with a lower prevalence of three-vessel disease described in female patients, similarly to our results. The description of the three-vessel coronary artery pattern varies from 15.4% to 36.8% in females, and from 20.5% to 40.8% in males, always with a significant difference in the different analyses.[9,13,14] However, despite the theoretic simpler anatomy regarding the percutaneous coronary reperfusion approach, women are less frequently referred for appropriate treatment in comparison to men.

Regardless the treatment strategy, either with thrombolytic therapy or PCI, women generally have worse outcomes than men. These data become controversial, as women have a more favorable outcome with PCI compared to thrombolytic therapy in the STE-ACS scenario and clearly benefit from an early invasive strategy in any situation.[1,8,12,14] As an example, a registry published in 2007 on patients with ACS showed that women underwent PCI less frequently than men (Odds Ratio – OR = 0.65; 95% Confidence Interval – 95%CI: 0,61-0,69), and their in-hospital mortality showed a worse index (10.7% vs. 6.3%, p < 0.001).[1] This description in the literature is once again reinforced by the data from our study, showing higher rates of surgical and percutaneous revascularization in men. The most plausible explanation for this scenario is that women are more likely to have unusual pathophysiological mechanisms of coronary disease, such as spontaneous coronary artery dissection or coronary artery spasm. Furthermore, the fact that they have more comorbidities, such as diabetes and dyslipidemia, favors the occurrence of lesions in thinner vessels and more extensive lesions.[2]

Finally, in the present study, we did not find any prognostic differences, either in-hospital or in the medium term, between the genders in our population. Some studies follow the same line and also have not shown any significant differences between the genders regarding mortality in ACS.[6,8,9,11,13] Reinforcing our finding, a study published in 2012 with 1,640 patients with ACS showed no differences in cardiovascular mortality according to gender (1.3% vs. 2.7%, p = 0.18) at the end of one year after PCI for men and women, respectively.[13] Finding similar mortality rates between men and women in a context of less invasive treatment in the female group may seem odd. However, drug treatment adequacy, early diagnosis and distinct pathophysiology between the genders may help to explain this finding.[14]

Nevertheless, in most studies, regardless of age, within 1 year after the first AMI, more women died when compared to men (26% vs. 19%), with similar results after 5 years (47% vs. 36%).[2,5,7,15] In one of the largest registries ever published on the subject, more than 2 million patients submitted to CABG were analyzed, comparing the prognosis between the genders. Unadjusted in-hospital mortality was higher in women (3.2% vs. 1.8%, p < 0.001). The female gender remained an independent predictor of mortality after the multivariate adjustment (OR = 1.40, 95%CI: 1.36-1.43, p < 0.001) in all age groups. However, an interesting result was the observation that in-hospital mortality declined at a faster rate in women (3.8% to 2.7%) than in men (2.2% to 1.6%) between 2003 and 2012.[15]

Limitations

Despite the large sample, this study is retrospective and has a much higher number of male patients in relation to the female group. Such differences are based on the actual incidence of ACS in the population and also on the failure to recognize the disease in women. Also, we do not have a description of the type of vascular access used, something that may influence the rate of bleeding associated with the percutaneous coronary intervention. Unusual manifestations of coronary disease, such as spasm or spontaneous dissection, were not described separately. The loss to follow-up of 7.3% of the patients may have influenced the results. Finally, patients with systemic diseases or neoplasias were not excluded, which could have influenced survival.

Conclusion

Multiple gender-related differences were observed in patients with acute coronary syndrome, regarding demographic characteristics, coronary artery disease pattern and implemented treatment. However, the in-hospital and medium-term prognostic evolution was similar between the groups.

Author contributions

Conception and design of the research: Soeiro AM, Silva PGMB, Roque EAC; Acquisition of data: Soeiro AM, Silva PGMB, Roque EAC, Biselli B, Leal TCAT, Soeiro MCFA; Analysis and interpretation of the data: Soeiro AM, Bossa AS, Biselli B, Leal TCAT, Soeiro MCFA; Statistical analysis: Soeiro AM; Writing of the manuscript: Soeiro AM, Pitta FG; Critical revision of the manuscript for intellectual content: Soeiro AM, Serrano Jr. CV, Oliveira Jr. MT.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number 38511114.7.0000.0068. 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.

References

1. Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz JM. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. Heart. 2007;93(11):1369-75.
2. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016;133(9):916-47.
3. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJDG, Franci A, et al. Sociedade Brasileira de Cardiologia. Diretrizes da Sociedade Brasileira de Cardiologia sobre angina instável e infarto agudo do miocárdio sem supradesnível do segmento ST. Arq Bras Cardiol 2014; 102(3supl.1):1-61.
4. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report ofthe American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;126(7):875-910.
5. Pendyala LK, Torguson R, Loh JP, Kitabata H, Minha S, Badr S, et al. Comparison of adverse outcomes after contemporary percutaneous coronary intervention in women versus men with acute coronary syndrome. Am J Cardiol. 2013;111(8):1092-8.
6. D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. Am J Cardiol. 2011;107(5):651-4.
7. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. Circulation. 2008;117(14):1787-801.
8. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Gender differences in presentation, coronary intervention, and outcomes of 28,985 acute coronary syndrome patients in Victoria, Australia. Womens Health Issues. 2016;26(1):14-20.
9. Pain TE, Jones DA, Rathod KS, Gallagher SM, Knight CJ, Mathur A, et al. Influence of female sex on long-term mortality after acute coronary syndromes treated by percutaneous coronary intervention: a cohort study of 7304 patients. Coron Artery Dis. 2013;24(3):183-90.
10. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Impact of comorbidities and gender on the use of coronary interventions in patients with high-risk non-ST-segment elevation acute coronary syndrome. Catheter Cardiovasc Interv. 2016;87(4):E128-E36.
11. Zimmermann S, Ruthrof S, Nowak K, Alff A, Klinghammer L, Schneider R, et al. Short-term prognosis of contemporary interventional therapy of ST-elevation myocardial infarction: does gender matter? Clin Res Cardiol. 2009;98(11):709-15.
12. Roe YL, Zeitz CJ, Mittinty MN, McDermott RA, Chew DP. Impact of age, gender and indigenous status on access to diagnostic coronary angiography for patients presenting with non-ST segment elevation acute coronary syndromes in Australia. Intern Med J. 2013;43(3):317-22.
13. Fath-Ordoubadi F, Barac Y, Abergel E, Danzi GB, Kerner A, Nikolsky E, et al. Gender impact on prognosis of acute coronary syndrome patients treated with drug-eluting stents. Am J Cardiol. 2012;110(5):636-42.
14. Tavris D, Shoaibi A, Chen AY, Uchida T, Roe MT, Chen J. Gender differences in the treatment of non-ST-segment elevation myocardial infarction. Clin Cardiol. 2010;33(2):99-103.
15. Swaminathan RV, Feldman DN, Pashun RA, Patil RK, Shah T, Geleris JD. Gender Differences in In-Hospital Outcomes After Coronary Artery Bypass Grafting. Am J Cardiol. 2016;118(3):362-8.

Gender Disparities and Outcomes Of Acute Coronary Syndromes In Brazil

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Shor Editorial related to the article: Prognostic Differences between Men and Women with Acute Coronary Syndrome. Data from a Brazilian Registry

Coronary artery disease (CAD) was considered, for years, a "male disease", a concept that influenced diagnostic and clinical decision-making processes.[1,2] However, currently there is consistent evidence showing that CAD is a leading cause of death in women. On the basis of pooled data from studies of the National Heart, Lung and Blood Institute (1995–2012), it is estimated that within one year after a first myocardial infarction, 18% of males and 23% of females will die, and the median survival time is, at ≥ 45 years of age, 8.2 years for males and 5.5 for females.[3] The underestimation of cardiovascular risk among women frequently resulted in a more conservative treatment and contributed to poorer outcomes.[4] In the last decade, several studies have assessed the issue of gender disparities in the diagnosis, treatment, and outcomes of acute coronary syndromes (ACS).[2,4] In this context, the study by Soeiro et al.[5] contributes to the understanding of this issue by presenting data from a Brazilian registry of ACS.

In this multicenter registry, the primary endpoint was in-hospital, all-cause mortality, and the secondary endpoint was the combination of cardiogenic shock, death, reinfarction, ischemic stroke and bleeding during a mean follow-up of 8 months. Just like any registry, it has limitations, such as the absence of data on other diseases like cancer, as well as on the differences in post-discharge management, adherence to treatment, among others, all which might influence survival in any group. Nonetheless, it has a large number of patients (2,437 men and 1,308 women) and may offer an interesting view of the Brazilian scenario of gender differences in ACS.

Keywords

Acute Coronary Syndrome; Prognosis; Gender Identity; Myocardial Infarction; Risk Factors; Percutaneous Coronary Intervention; Aged, Women

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Of note, at presentation, women less often had ST-elevation and multivessel CAD than men, but were older and more frequently diabetic, dyslipidemic and hypertensive. These data are in line with other studies.[6] Unfortunately, data on symptoms at presentation are not available. It is known that, in ACS, women are less likely to present with classical angina symptoms, which may lead to under and/or misdiagnoses in women, and in turn may explain the worse outcomes, particularly in younger women.[6,7] Accordingly, in the present study, it was noteworthy that percutaneous coronary interventions and coronary artery bypass grafting were more frequently performed in men than in women.

Regarding outcomes, there were no significant differences between men and women. This contrasts to other studies in which women had worse outcome after ACS, what has been attributed, among other factors, to older age or the presence of more comorbidities in women.[4,8] On the other hand, similar short-term outcomes in men and women have also been reported,[9] especially after adjustment for clinical differences and the severity of angiographic disease.[10] Gaui et al,[11] in an analysis of Brazilian death certificates from 2004 to 2011, reported higher proportional mortality due to acute ischemic heart disease in women from the Northeastern region, aged 40-49 years, than in men, despite overall lower proportional mortality. Globally, this demonstrates that the outcomes of ACS in women are at least equivalent to those of men, if not worse.

The longstanding "knowledge gap" on CAD in women, both on the part of physicians and of patients, has created inequalities in healthcare access and processes. However, fortunately, our understanding of gender-specific differences in the initial presentation, pathophysiology, treatment effectiveness, and clinical outcomes have changed. The currently presented data are important to underscore the need to increase knowledge about the importance of CAD in women, so that possible gender biases may be effectively avoided, and better results obtained for the cardiovascular health of women.

References

1. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med. 1993;329(4):247-56.
2. Wenger NK. Women and coronary heart disease: A century after Herrick: Understudied, underdiagnosed, and undertreated. Circulation. 2012;126((5):604-11.
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association.Circulation. 2018;137(12):e67-e492.
4. Poon S, Goodman SG, Yan RT, Bugiardin R, Bierman AS, Eagle KA, et al. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. Am Heart J. 2012;163(1):66-73.
5. Soeiro AM, Barros e Silva PGM, Roque EAC, Bossa AS, Bruno Biselli,Leal TCAT et al. Prognostic Differences between Men and Women with Acute Coronary Syndrome. Data from a Brazilian Registry. Arq Bras Cardiol. 2018; 111(5):648-653)
6. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009;157(1):141-8.
7. Redberg RF, Cannon RO 3rd, Bairey Merz N, Lerman A, Reis SE, Sheps DS, et al. Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop October 2-4,2002:Section 2:stable ischemia pathophysiology and gender differences. Circulation. 2004;109(6):e47-e49.
8. Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? Circulation. 1995;91(6):1861-71.
9. Ghadri JR, Sarcon A, Jaguszewski M, Diekmann J, Bataiosu RD, Hellermann J, et al. Gender disparities in acute coronary syndrome: a closing gap in the short-term outcome. J Cardiovasc Med. 2015;16(5):355-62.
10. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, et al. Sex differences in mortality following acute coronary syndromes. JAMA. 2009;302(8):874-8.
11. Gaui EG, Klein CH, Oliveira GMM. Proportional mortality due to heart failure and ischemic heart diseases in the brazilian regions from 2004 to 2011. Arq Bras Cardiol. 2016; 107(3):230-8.

Assessment of Subclinical Cardiac Alterations and Atrial Electromechanical Delay by Tissue Doppler Echocardiography in Patients with Nonfunctioning Adrenal Incidentaloma

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Abstract

Background: **Majority of the incidentally discovered adrenal masses, called adrenal incidentaloma (AI), are nonfunctioning adrenal adenomas. The appropriate management of AI is still a matter debate, so it is necessary to investigate their associated morbidity. However, data regarding morphological and functional cardiac alterations are limited in this group.**

Objective: **In this study, we aimed to assess cardiac structural and functional characteristics and atrial conduction properties in patients with nonfunctioning AI.**

Methods: **Thirty patients with nonfunctioning AI and 46 properly matched control subjects were included in the study. After hormonal and biochemical analysis, all participants underwent transthoracic echocardiography to obtain systolic and diastolic parameters of both ventricles, in addition to atrial conduction times by tissue Doppler echocardiography. Data were analyzed with Statistical Package for the Social Sciences (SPSS, Chicago, IL, United States) statistics, version 17.0 for Windows. $P < 0.05$ was considered statistically significant.**

Results: **Left ventricular (LV) mass index and LV myocardial performance index were significantly increased in AI group. Among atrial conduction times, both intra- and interatrial electromechanical delays were significantly prolonged in patients with nonfunctioning AI. Other laboratory and echocardiographic findings were similar between groups.**

Conclusion: **Our study revealed that intra- and inter-atrial conduction times were prolonged, and LV mass index was increased in patients with nonfunctioning AI. These findings may be markers of subclinical cardiac involvement and tendency to cardiovascular complications. Close follow-up is necessary for individuals with nonfunctioning AI for their increased cardiovascular risk. (Arq Bras Cardiol. 2018; 111(5):656-663)**

Keywords: **Incidental Findings; Diastole/function; Adrenocortical Adenoma; Diagnostic ,Imaging; Metabolic Syndrome; Cardiac Conduction System Disease**

Introduction

Adrenal incidentaloma (AI) is defined as an adrenal mass, generally discovered in radiological interventions for indications other than adrenal disease. The classic definition excludes patients with clinically overt adrenal hormone secretion, and those with concurrent malignancy, known as metastasis to the adrenals . The prevalence of adrenal masses in general population has been reported to be as high as 6% at autopsy, and 2.5–4.2% on evaluation of abdomen and thorax by computerized tomography (CT).[1] Majority of the incidentally discovered adrenal masses are nonfunctioning adrenal adenomas.[2] The appropriate management of these patients is still a matter of debate, and it is necessary to investigate their associated morbidity. The presence of AI has been proposed as a new cause of metabolic syndrome and reported to increase cardiovascular disease risk. The burden of disturbances showed diversity from impaired glucose tolerance to increased epicardial fat thickness and intima-media thickness of common carotid arteries.[2-6] However, data regarding morphological and functional cardiac alterations are still limited in this particular group.

Atrial fibrillation (AF) is one of the most common arrhythmias observed in clinical practice. Several electrocardiographic and echocardiographic markers reflecting electrophysiological and electromechanical abnormalities of atria prone to develop AF have been studied with the aim of early identification of patients susceptible to develop AF. Atrial electromechanical delay (EMD) has been defined as the temporal delay between

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the onset of electrical activity and the mechanical activation of atrial myocardium. Tissue Doppler echocardiography (TDE) is a simple, noninvasive and reliable method to measure atrial EMD.[7] Several studies report that atrial EMD measured by TDE is a valuable parameter to predict new onset AF or recurrence of AF.[8-11]

There are few studies evaluating cardiac functions in patients having nonfunctioning AI, but to our knowledge data concerning atrial electromechanical properties are lacking.[5,12] The aim of this study was to assess intra- and inter-atrial conduction times along with cardiac structural and functional characteristics in patients with nonfunctioning AI.

Methods

Study population

All subjects who were referred to the Department of Endocrinology and Metabolism of Kahramanmaras Sutcu Imam University, in Kahramanmaras, Turkey, with incidentally discovered adrenal tumors between March 2014 and November 2015 were recorded (n = 82). The study was approved by local Research Ethics Committee of the institution in compliance with the Declaration of Helsinki. All of the participants gave written consent.

At the first visit, all subjects underwent a CT or *magnetic resonance imaging* (MRI) scan to confirm the diagnosis. Adrenal adenoma was diagnosed if the following criteria were met:

- tumor size less than 4.0 cm;
- regular shape with well-defined margins;
- homogenous and attenuation value of 10 or less Hounsfield units on unenhanced CT scan, and 30 or less Hounsfield units on enhanced CT scan.[13]

After confirming the presence of adrenal adenoma, detailed physical examination and basal hormonal and dynamic tests were performed. Among participants, 30 patients having nonfunctional adrenal adenomas were included in the study. Totally 52 patients with uncompleted tests or hormone-secreting tumors – high levels of dehydroepiandrosterone sulphate (DHEAS), hyperaldosteronism, Cushing syndrome (CS), pheochromocytoma – and patients having large adrenal tumors (>4 cm) with irregular borders and invasion to adjacent structures raising the suspicion of malignancy were excluded. Additionally, patients with known malignancies, coronary artery disease, valvular heart diseases, cardiomyopathies, thyroid dysfunction, chronic renal failure, liver failure, previous surrenal or hypophysial intervention or patients taking steroids were not included in the study. In an attempt to determine the hormonal activity of adrenal tumors, blood samples were collected at 8.30 am to analyze sodium (Na), potassium (K), adrenocorticotropic hormone (ACTH), DHEAS and plasma cortisol levels. For exclusion of CS, 1 mg dexamethasone suppression test (DST), the most common screening test for CS, was performed to the patients. The suppression in overnight DST was adequate when morning cortisol level fell below 1.8 μ/dl. Blood samples for plasma renin and aldosterone measurements were collected after at least 4–6 hours of nocturnal resting, following two hours of standing or wandering, and after 15 minutes of resting, respectively. Plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio was used as the screening test to exclude primary aldosteronism. PAC/PRA ≤ 20 values were accepted as normal.[14] Moreover, patients were given a diet free of food containing phenolic acid for five days. Then, 24-hour urine specimens were collected for metanephrine and normetanephrine analyses. Pheochromocytoma was defined as elevated levels of urinary normetanephrine (normal range: 88–444 μg/day) and/or urinary metanephrine (normal range: 52–341 μg/day).[13] Age and sex matched 46 subjects without clinical suspicion of hypercortisolism, with normal DHEAS level (female 35–430 μg/dl, male 80–560 μg/dl), suppressed 1 mg DST (≤ 1.8 μg/dl) and without adrenal mass on abdominal ultrasonography were taken as the control group. Blood pressure measurements of all subjects were taken from right arm in the sitting position after 5 minutes of resting. Height (meter) and weights (kg) of all participants were recorded, and body mass index (BMI, kg/m^2) was calculated.

Conventional echocardiographic examination

All participants were performed transthoracic echocardiography (Vivid 7 Pro, GE, Horten, Norway, 2–4 MHz phased array transducer), including two-dimensional, M-mode, pulsed, and color flow Doppler examinations by the same experienced cardiologist blinded to the clinical status of the subjects. Recordings were made on left lateral decubitus position by using standard parasternal, apical, and subcostal views. Left atrial dimension, left ventricular (LV) end-diastolic and end-systolic diameters, diastolic thickness of ventricular septum and posterior wall were measured from M-mode in parasternal long axis view according to the criteria of the American Society of Echocardiography guidelines. The early (E-wave) and late diastolic (A-wave) velocities of mitral inflow were measured from apical four chamber view with pulsed Doppler echocardiography by placing the sample volume at the tips of mitral leaflets, and E/A ratio was calculated. Ejection fraction was estimated by Simpson's rule. LV mass was calculated by Devereux formula and indexed to the body surface area.[15-17]

Right ventricular (RV) morphological and functional parameters including right atrial dimension, RV diameter, and tricuspid annular plane systolic excursion (TAPSE) were measured according to the American Society of Echocardiography guidelines.[15] Systolic pulmonary artery pressure (sPAP) was obtained from the maximum velocity of the regurgitant tricuspid jet, and pulmonary acceleration time (PAT) was measured as the time between the onset and peak of pulmonary velocity obtained by pulsed Doppler recording.[18]

Tissue doppler echocardiography and atrial electromechanical delay

TDE was performed with transducer frequencies of 3.5–4.0 MHz using a 5 mm pulsed Doppler sample volume. Spectral Doppler signal filters were set to obtain a Nyquist limit of 15 to 20 cm/s with minimal optimal gain settings. The sweep speed was set at 50 to 100 mm/s. A single lead electrocardiogram (ECG) was recorded simultaneously during measurements. In the apical four chamber view, the sample

volume was subsequently placed at the level of LV lateral mitral annulus, septal mitral annulus and RV tricuspid annulus. The sampling window was positioned as parallel as possible to the myocardial segment of interest to obtain the optimal angle of imaging. Time intervals from the onset of P wave on the surface ECG to the beginning of the A wave (PA) representing atrial EMD were obtained from lateral mitral annulus, septal mitral annulus, and tricuspid annulus and named PA lateral, PA septum and PA tricuspid, respectively. The difference between PA lateral and PA tricuspid was defined as inter-atrial EMD (PA lateral-PA tricuspid), the difference between PA lateral and PA septum was defined as intra-atrial EMD (PA lateral-PA septum). Peak systolic (Sm), early diastolic (Em), late diastolic (Am) velocities, and isovolumic contraction time (ICTm; time interval between the end of Am and the beginning of Sm), isovolumic relaxation time (IRTm; time interval between the end of Sm and the beginning of Em), and ejection time (ETm; time interval between the beginning and the end of Sm) were obtained from mitral and tricuspid annulus. Em/Am ratio for both ventricle and E/Em for LV were calculated. The myocardial performance index (MPI), a noninvasive Doppler measurement of global ventricular function incorporating both systolic and diastolic function, was calculated by the formula of (ICTm+IRTm)/ETm for both ventricles.

Reproducibility

Intraobserver variability was assessed in 20 subjects randomly chosen from the participants, and the echocardiographic measurements were repeated under the same basal conditions. Simple random sampling method was used in the selection of 20 subjects. *1,96*(S_w/√2n(m-1)) = confidence in the estimate* formula was used to estimate the sample size for reproducibility. Reproducibility was evaluated by coefficient of variation. Intraobserver coefficients of variation were found to be nonsignificant (< 5%).

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS, Chicago, IL, United States) statistics, version 17.0 for Windows. Shapiro-Wilk test was used to test the normality of distribution for continuous variables. Continuous variables were expressed as means ± standard deviation. Non-normal distributed variables were expressed as Median and quartiles (1.Quartile-3.Quartile). Categorical data were presented as numbers and percentages. Difference between groups was detected using χ^2 test for categorical variables. Mean values of continuous variables were compared between groups using Independent samples t-test or Mann-Whitney U-test, according to whether normally distributed or not. Correlation between continuous variables was evaluated by Pearson correlation tests. A linear regression analysis and generalized linear models were used to identify predictors of atrial EMD. $P < 0.05$ was considered statistically significant.

Results

Clinical and laboratory data of the study groups are given in Table 1. Age, gender, BMI, systolic and diastolic pressures, heart rate, and ratio of diabetic and hypertensive subjects were similar between groups ($p > 0.05$). ACTH and DHEAS

Table 1 – Baseline characteristics of the study population

Characteristics	Non-functioning AI (n = 30)	Control (n = 46)	p value
Age[a] (years)	51.77 ± 8.23	50.80 ± 6.62	0.46
Female sex[c], n (%)	25 (83.3)	41 (89.1)	0.84
BMI[a] (kg/m^2)	34.30 ± 4.63	32.43 ± 3,93	0.07
Diabetes mellitus[c], n (%)	3 (10)	6 (13)	0.76
Hypertension[c], n (%)	5 (16.7)	8 (17.4)	0.94
DM and Hypertension[c], n (%)	5 (16.7)	7 (15.2)	0.89
Systolic blood pressure[a] (mmHg)	131.33 ± 16.49	125.85 ± 12.36	0.07
Diastolic blood pressure[a] (mmHg)	81.57 ± 10.36	78.46 ± 10.62	0.21
Heart rate[a] (bpm)	82.93 ± 13.00	77.72 ± 9.19	0.09
Cortisol[a] (µg/dl)	12.88 ± 2.94	11.71 ± 3.80	0.15
Post DST cortisol[a] (µg/dl)	1.11 ± 0.38	0.70 ± 0.26	< 0.001*
ACTH[b] (pg/ml) Median (Q1-Q3)	14,70(12,50–20,30)	22,40(13,70–35,70)	0.009*
DHEAS[b] (µg/dl) Median (Q1-Q3)	55,15(27,90–86,30)	113(73,80–157,00)	< 0.001*
Fasting plasma glucose[b] (mg/dl) Median (Q1-Q3)	98(87,00–111,00)	97(84,00–113,00)	0.61
LDL cholesterol[b] (mg/dl) Median (Q1-Q3)	101,45(91,00–123,70)	109(91,90–135,00)	0.56
HDL cholesterol[a] (mg/dl)	45.50 ± 9.10	45.57 ± 9.49	0.97
Triglycerides[b] (mg/dl) *Median (Q1-Q3)*	116,50(84,00–153,00)	142(105,00–235,00)	0.1

*[a]Independent samples t test; [b]Mann-Whitney U test ; Median (Q1-Q3): Median (1.Quartile-3.Quartile); [c]χ^2 test; *difference is statistically significant; AI: adrenal incidentaloma; BMI: body mass index; DM: diabetes mellitus; DST: dexamethasone supression test; ACTH: adrenocorticotrophic hormone; DHEAS: dedhydroepiandrostenedione sulphate; LDL: low-density lipoprotein; HDL: high-density lipoprotein.*

levels were significantly lower in nonfunctioning AI group ($p = 0.009$ and $p < 0.001$, respectively). Cortisol levels were similar, but suppression with 1 mg DST was pronounced significantly in the control group ($p < 0.001$). Other laboratory data including fasting plasma glucose, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride and insulin levels did not differ between groups.

Conventional echocardiographic parameters were shown in Table 2. There were no significant differences between groups considering LV end-diastolic and end-systolic diameters, LV ejection fraction, diameter of left and right atrium, RV diameter, TAPSE and systolic PAP. Diastolic thickness of interventricular septum (IVS), posterior wall (PW) and LV mass index was significantly higher ($p = 0.03$, $p = 0.03$, and $p = 0.004$ respectively), and PAT was significantly lower ($p = 0.004$) in nonfunctioning AI group. Although mitral E/A ratio was lower in nonfunctioning AI compared to the control group, the difference was not statistically significant ($p = 0.07$).

Comparison of tissue Doppler parameters and atrial conduction times were demonstrated in Table 3. LV lateral, LV septal, global LV Em/Am and RV Em/Am were decreased significantly in nonfunctioning AI group ($p = 0.02$, $p = 0.03$, $p = 0.01$, and $p = 0.004$, respectively). LV septal MPI and LV MPI were significantly higher in nonfunctioning AI group ($p = 0.004$ and $p = 0.03$, respectively), whereas LV lateral and RV MPI did not differ significantly between groups. There was no significant difference between groups with regard to Sm and E/Em. PA lateral, PA septum and PA tricuspid were not different between groups. Inter-atrial EMD and intra-atrial EMD were significantly higher in nonfunctioning AI group compared to the controls ($p = 0.008$ and $p = 0.016$, respectively).

Bivariate correlation analysis revealed that inter-atrial EMD was negatively correlated with ACTH level ($r = -0.29$, $p = 0.027$), mitral E/A ratio ($r = -0.33$, $p = 0.004$), and RV Em/Am ratio ($r = -0.29$, $p = 0.011$), and positively correlated with LV mass index ($r = 0.38$, $p = 0.001$), left atrial diameter ($r = 0.23$, $p = 0.04$), age ($r = 0.32$, $p = 0.004$) and systolic blood pressure ($r = 0.23$, $p = 0.04$). Intra-atrial EMD was positively correlated with post DST cortisol level ($r = 0.23$, $p = 0.04$), LV mass index ($r = 0.33$, $p = 0.004$), age ($r = 0.34$, $p = 0.003$) and systolic blood pressure ($r = 0.32$, $p = 0.004$), and negatively correlated with mitral E/A ratio ($r = -0.36$, $p = 0.002$). Multivariate relationships of inter- and intra-atrial EMD with clinical parameters revealed that changes in post DST cortisol levels affected intra-atrial EMD significantly (Wald $\chi^2 = 3.810$, $p = 0.049$) (Table 4). We also found that increase of post DST cortisol level by 1 μg/dl lengthened intra-atrial EMD by 4.752 msec.

Discussion

This is the first tissue Doppler echocardiographic study evaluating abnormalities of atrial conduction together with cardiac structure and function in nonfunctional adrenal incidentalomas. We obtained two important findings:

- LV mass increased significantly;
- Intra- and inter-atrial conduction times were delayed significantly in these patients.

It is well known that overt cortisol excess, as in Cushing syndrome, may lead to systemic complications responsible for increased cardiovascular risk (hypertension, obesity, impaired glucose metabolism, dyslipidemia) and cardiovascular complications such as coronary heart disease and congestive heart failure.[6,19] It has also been shown previously that Cushing syndrome causes cardiac structural changes associated with LV dysfunction.[20,21] However, it is still a matter of debate whether nonfunctional AI increases the risk of cardiovascular disease and whether this type of adrenal tumor has some

Table 2 – Comparison of conventional echocardiographic parameters between groups

Variable	Non-functioning AI (n = 30)	Control (n = 46)	p value
LV end-diastolic diameter[a] (mm)	48.83 ± 3.70	46.93 ± 3.64	0.07
LV end-systolic diameter[b] (mm) Median (Q1-Q3)	27(26,00–28,00)	27(25,00–30,00)	0.96
LV ejection fraction[a] (%)	71.93 ± 7.54	72.26 ± 5.84	0.68
IVS diastolic thickness[b] (mm) Median (Q1-Q3)	10(9,00–11,00)	9(8,00–11,00)	0.03*
PW diastolic thickness[b] (mm) Median(Q1-Q3)	11(9,00–12,00)	10(9,00–11,00)	0.03*
LV mass index[a] (gr/m^2)	112.01 ± 26.93	95.33 ± 21.69	0.004*
Left atrial diameter[a] (mm)	36.27 ± 2.79	35.59 ± 2.84	0.31
Mitral E/A ratio[a]	0.87 ± 0.25	1.01 ± 0.30	0.07
RV basal diameter[a] (mm)	32.14 ± 3.54	32.74 ± 3.91	0.51
RA diameter[a] (mm)	32.20 ± 4.71	32.61 ± 3.98	0.69
TAPSE[b] (mm) Median (Q1-Q3)	24(20,00–26,00)	22,50(21,00–27,00)	0.42
sPAP[a] (mmHg)	25.67 ± 3.45	26.11 ± 3.92	0.65
PAT[a] (ms)	96.38 ± 22.08	113.48 ± 26.36	0.004*

*[a]Independent samples t test; [b]Mann-Whitney U test; Median (Q1-Q3): Median (1.Quartile-3.Quartile); *difference is statistically significant; AI: adrenal incidentaloma; LV: left ventricular; IVS: interventricular septum; PW: posterior wall; RV: right ventricular; RA: right atrial; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; PAT: pulmonary acceleration time.*

Table 3 – Comparison of tissue Doppler parameters and atrial conduction times between groups

Variable	Non-functioning AI (n = 30)	Control (n = 46)	p value
LV lateral annulus			
Sm[b] (cm/s) Median (Q1-Q3)	9(8,00–11,00)	10(8,00–11,00)	0.39
Em/Am[b] Median (Q1-Q3)	0,72(0,62–1,00)	0,93(0,79–1,20)	0.02*
E/Em[b] Median (Q1-Q3)	6,77(5,29–8,33)	6,82(5,50–7,46)	0.52
MPI[b] Median (Q1-Q3)	0,44(0,39–0,53)	0,46(0,42–,52)	0.81
LV septal annulus			
Sm[a] (cm/s)	8.80 ± 2.11	8.37 ± 1.43	0.43
Em/Am[b] Median (Q1-Q3)	0,64(0,55–0,83)	0,73(0,63–1,00)	0.03*
E/Em[a]	10.16 ± 3.36	10.18 ± 2.22	0.77
MPI[a]	0.52 ± 0.07	0.47 ± 0.11	0.004*
RV tricuspid annulus			
Sm[a] (cm/s)	15.57 ± 3.57	14.35 ± 2.77	0.11
Em/Am[b] Median (Q1-Q3)	0,58(0,46–0,67)	0,67(0,60–0,81)	0.004*
MPI[a]	0.46 ± 0.06	0.43 ± 0.10	0.11
LV Sm[b] (cm/s) Median (Q1-Q3)	9,00(7,50–10,00)	9,00(8,00–10,50)	0.96
LV Em/Am[a]	0.76 ± 0.24	0.88 ± 0.22	0.01*
LV E/Em[b] Median (Q1-Q3)	7,85(6,25–10,00)	8,15(6,79–9,29)	0.90
LV MPI[a]	0.50 ± 0.05	0.47 ± 0.12	0.03*
Atrial conduction times			
Lateral PA[a] (ms)	45.97 ± 10.95	42.35 ± 8.16	0.09
Septum PA[a] (ms)	30.87 ± 9.86	31.11 ± 7.21	0.78
Tricuspid PA[b] (ms) Median (Q1-Q3)	21,00(18,00–26,00)	22,00(18,00–26,00)	0.34
Intra-atrial EMD[a] (ms)	15.10 ± 7.97	11.24 ± 4.08	0.016*
Inter-atrial EMD[a] (ms)	23.53 ± 7.99	18.85 ± 5.79	0.008*

*[a]Independent samples t test; [b]Mann-Whitney U test; Median (Q1-Q3): Median (1.Quartile-3Quartile); *difference is statistically significant; AI: adrenal incidentaloma; LV: left ventricular; MPI: myocardial performance index; RV: right ventricular; PA: time interval from the onset of P wave on electrocardiogram (ECG) to the beginning of the A wave; EMD: electromechanical delay.*

Table 4 – Assessment of subtle cortisol secretion related effects on intra-atrial electromechanical delay (EMD)

			Hypothesis Test	
Parameter	**B**	**Standard Error**	**Wald Chi-square**	**p**
Intercept	13.121	4,0795	10.345	0.001
Post DST cortisol	4.752	2.4347	3.810	0.049*
Cortisol	-0.265	0.2642	1.004	0.316
ACTH	-0.090	0.0725	1.551	0.213
DHEAS	0.008	0.0167	0.258	0.611

*Generalized Linear Models; α: 0,05; *effect is statistically significant; DST: dexamathasone supression test; ACTH: adrenocorticotrophic hormone; DHEAS: dedhydroepiandrostenedione sulphate.*

degree of autonomous adrenal function. In this study, we obtained some indirect evidence of subtle cortisol autonomy and cardiovascular risk in patients with nonfunctioning AI. There are few studies analyzing cardiac morphology and function in nonfunctional AI. Ermetici et al.[12] reported the presence of LV hypertrophy and LV diastolic dysfunction in patients with nonfunctional AI.[12] Iacobellis et al.[5] showed increased epicardial fat thickness and LV mass by transthoracic echocardiography in these subjects.[5] Similarly, we found that LV mass index was increased significantly in patients with nonfunctional AI compared to the control group. The impact of LV hypertrophy on cardiac mortality and morbidity has been understood increasingly.[16] It has been suggested that cortisol production by AI may have a broad spectrum, ranging

from normal to various degrees of excess daily production rate, and this may not be detectable by standard endocrine work-up.[12] In our study, basal cortisol levels of the groups were similar, but post DST cortisol levels were significantly elevated (not exceeding the cut-off, 1.8 μg/dl), and DHEAS levels were significantly reduced (not below the cut-off, 40 μg/dl) in nonfunctioning AI group. Additionally, post DST cortisol level was correlated with LV mass index. According to these findings, we speculated that subtle cortisol autonomy of adrenal adenoma might play a role in cardiac hypertrophy.

Myocardial performance index is a parameter calculated from tissue Doppler echocardiographic measurements, and predicts both systolic and diastolic ventricular function. In our study, LV MPI was found to be increased in patients with AI indicating impaired global LV function. This impairment may be attributed largely to the impairment of LV diastolic function, because the predictors of LV systolic function such as LV EF and LV Sm were similar in both groups.

Considering structural and functional parameters of RV, decreased RV Em/Am ratio might indicate the tendency to impairment of RV diastolic function. PAT was also shortened, indicating increased pulmonary vascular resistance in patients with AI.

Atrial fibrillation is the most common arrhythmia encountered in clinical practice, and associated with significant mortality and morbidity due to hemodynamic impairment and thromboembolic events. Impaired atrial conduction is an important step in the pathophysiology of AF. Atrial conduction times can be evaluated by both invasive (electrophysiological study) and noninvasive (P wave dispersion on ECG and EMD on echocardiography) methods.[22] It has been shown that impaired atrial conduction is an independent and strong predictor for development and recurrence of AF, and TDE is a useful and reliable technique to evaluate atrial electromechanical properties.[7-9] Numerous studies demonstrated that atrial conduction time was prolonged in various diseases including obesity, thyroid diseases, chronic obstructive lung diseases, non-alcoholic fatty liver disease, acromegaly and diabetes mellitus (DM).[23-28] Cushing disease is associated with many cardiovascular risk factors, including glucose intolerance, hypertension, LV hypertrophy, central obesity and metabolic syndrome, and may lead to cardiovascular events such as coronary heart disease, heart failure and arrhythmias.[21] So, we hypothesized that AI might be associated with cardiac structural and functional changes, and increased risk of AF. Earlier studies showed increased epicardial fat, increased LV mass and LV diastolic dysfunction in AI similar to our results.[5,12] However, they did not study atrial conduction properties in this patient group.

Therefore, this study showed for the first time that both intra- and inter-atrial EMD were impaired in patients with nonfunctioning AI. Moreover, atrial EMD was correlated significantly with post DST cortisol level, ACTH level, LV mass index, LV diastolic dysfunction, age and systolic blood pressure. Post DST cortisol level was an important predictor of intra-atrial EMD, such that 1 μg/dl increase in post DST cortisol level caused the prolongation of intra-atrial EMD by 4.752 msec. We may explain these findings by a few mechanisms. First, subtle cortisol excretion can affect cardiac structure and function as mentioned previously, which in turn is supposed to have detrimental effects on atrial conduction. Secondly, AI and AF share common metabolic risk factors such as increased blood pressure, insulin resistance, endothelial dysfunction and obesity. Lastly, low-level but long-standing subtle cortisol excretion may have direct toxic effect on myocardium by glucocorticoid receptors leading to myocardial fibrosis.[4-6,13,29] Detection of prolonged atrial EMD in these patients may be an earlier sign of atrial dysfunction preceding AF.

Study limitations

The major limitation of the study was the relatively small number of the subjects in adenoma group, besides the inability to define the length of the disease owing to the lack of overt clinical features. Finally, our study lacks long-term follow-up data, since it is a cross-sectional study. The patients could not be followed for future arrhythmic episodes to see whether the ones with prolonged atrial EMD develop AF.

Conclusion

Our study revealed that intra- and inter-atrial conduction times were prolonged and LV mass index was increased in patients with nonfunctioning AI. These findings may be markers of subclinical cardiac involvement and tendency to cardiovascular complications. Thus, individuals diagnosed to have nonfunctioning AI should be followed up closely for their increased cardiovascular risk.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Sokmen G, Gul K; Acquisition of data: Sahin M, Tuzun D, Sokmen A, Bolat H, Oguz A, Nacar H; Analysis and interpretation of the data: Sokmen G, Sahin M, Tuzun D, Sokmen A; Statistical analysis: Doganer A; Writing of the manuscript: Sokmen G, Sahin 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 Kahramanmaras Sutcu Imam University under the protocol number 2013/16-02. 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.

References

1. Davenport C, Liew A, Doherty B, Win HH, Misran H, Hanna S, et al. The prevalence of adrenal incidentaloma in routine clinical practice. Endocrine. 2011;40(1):80-3.
2. Yener S, Comlekci A, Yuksel F, Sevinc A, Ertilav S, Yesil S. Traditional and novel cardiovascular risk factors in nonfunctioning adrenal adenomas. Eur J Intern Med. 2012;23(1):83-7.
3. Erbil Y, Ozbey N, Barbaros U, Unalp HR, Salmaslioglu A, Ozarmagan S. Cardiovascular risk in patients with nonfunctional adrenal incidentaloma: myth or reality? World J Surg. 2009; 33(10):2099-105.
4. Yener S, Genc S, Akinci B, Secil M, Demir T, Comlekci A, et al. Carotid intima media thickness is increased and associated with morning cortisol in subjects with nonfunctioning adrenal incidentaloma. Endocrine. 2009;35(3):365-70.
5. Iacobellis G, Petramala L, Barbaro G, Kargi AY, Serra V, Zinnamosca L, et al. Epicardial fat thickness and left ventricular mass in subjects with adrenal incidentaloma. Endocrine. 2013;44(2):532-6.
6. Di Dalmazi G, Vicennati V, Rinaldi E, Morselli-Labate AM, Giampalma E, Mosconi C, et al. Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study. Eur J Endocrinol. 2012;166(4):669-77.
7. Deniz A, Sahiner L, Aytemir K, Kaya B, Kabakci G, Tokgozoglu L, et al. Tissue Doppler echocardiography can be a useful technique to evaluate atrial conduction time. Cardiol J. 2012;19(5):487-93.
8. Calik AN, Ozcan KS, Cagdas M, Güngör B, Karaca G, Gürkan U, et al. Electromechanical delay detected by tissue Doppler echocardiography is associated with the frequency of attacks in patients with lone atrial fibrillation. Cardiol J. 2014;21(2):138-43.
9. Den Uijl DW, Gawrysiak M, Tops LF, Trines SA, Zeppenfeld K, Schalij MJ, et al. Prognostic value of total atrial conduction time estimated with tissue Doppler imaging to predict the recurrence of atrial fibrillation after radiofrequency catheter ablation. Europace. 2011;13(11):1533-40.
10. Evranos B, Aytemir K, Oto A, Okutucu S, Karakulak U, Şahiner L, et al. Predictors of atrial fibrillation recurrence after atrial fibrillation ablation with cryoballoon. Cardiol J. 2013;20(3):294-303.
11. De Vos CB, Weijs B, Crijins HJ, Cheriex EC, Palmans A, Habets J, et al. Atrial tissue Doppler imaging for prediction of new onset atrial fibrillation. Heart. 2009;95(10):835-40.
12. Ermetici F, Dall'Asta C, Malavazos AE, Coman C, Morricone L, Montericcio V, et al. Echocardiographic alterations in patients with nonfunctioning adrenal incidentaloma. J Endocrinol Invest 2008;31(6):573-7.
13. Comlekci A, Yener S, Ertilav S, Secil M, Akinci B, Demir T, et al. Adrenal incidentaloma, clinical, metabolic, follow-up aspects: single centre experience. Endocrine. 2010;37(1):40-6.
14. Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol. 2007;66(5):607-18.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.
16. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):227-314.
17. Devereux RB, Reiche N. Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. Circulation 1977;55(4):613-8.
18. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in aduts. A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23(7):685-713.
19. De Leo M, Pivonello R, Auriemma RS, Cozzolino A, Vitale P, Simeoli C, et al. Cardiovascular disease in Cushing's syndrome: heart vs vasculature. Neuroendocrinology. 2010;92(Suppl 1):50-4.
20. Muiesan ML, Lupia M, Salvetti M, Grigoletto C, Sonino N, Boscaro M, et al. Left ventricular structural and functional characteristics in Cushing's syndrome. J Am Coll Cardiol. 2003;41(12):2275-9.
21. Kamenicky P, Redheuil A, Roux C, Salenave S, Kachenoura N, Raissouni Z, et al. Cardiac structure and function in Cushing's syndrome: A cardiac magnetic resonance imaging study. J Clin Endocrinol Metab. 2014;99(11):E2144-E55.
22. Daubert JC, Pavin D, Jauvert G, Mabo P. Intra- and inter-atrial conduction delay: Implications for cardiac pacing. Pacing Clin Electrophysiol. 2004;27(4):507-25.
23. Erdem FH, Ozturk S, Baltacı D, Donmez I, Alçelik A, Ayhan S, et al. Detection of atrial electromechanical dysfunction in obesity. Acta Cardiol. 2015;70(6):678-84.
24. Sokmen A, Acar G, Sokmen G, Akcay A, Akkoyun M, Koroglu S, et al. Evaluation of atrial electromechanical delay and diastolic functions in patients with hyperthyroidism. Echocardiography 2013;30(10):1194-201.
25. Acar G, Kahraman H, Akkoyun M, Kilinc M, Zencir C, Yusufoglu E, et al. Evaluation of atrial electromechanical delay and its relationship to inflammation and oxidative stress in patients with chronic obstructive pulmonary disease. Echocardiography. 2014;31(5):579-85.
26. Ozveren O, Izgi C, Eroglu E, Simsek MA, Turer A, Kucukdurmaz Z, et al. Doppler tissue evaluation of atrial conduction properties in patients with non-alcoholic fatty liver disease. Ultrason Imaging. 2016;38(3):225-35.
27. Yayla C, Canpolat U, Sahinarslan A, Özkan Ç, Eroğlu Altinova A, Gayretli Yayla K, et al. The assessment of atrial electromechanical delay in patients with acromegaly. Can J Cardiol. 2015;31(8):1012-8.
28. Demir K, Avcı A, Kaya Z, Marakoglu K, Ceylan E, Yilmaz A, et al. Assessment of atrial electromechanical delay and P-wave dispersion in patients with type 2 diabetes mellitus. J Cardiol. 2016;67:378-83.
29. Oakley RH, Cidlowski JA. Glucocorticoid signaling in the heart: A cardiomyocyte perspective. J Steroid Biochem Mol Biol. 2015 Sep;153:27-34.

Nonfunctioning Adrenal Incidentalomas: The Search for Subclinical Cardiac Alterations

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Short editorial related to the article: Assessment of Subclinical Cardiac Alterations and Atrial Electromechanical Delay by Tissue Doppler Echocardiography in Patients with Nonfunctioning Adrenal Incidentaloma

By definition, an adrenal incidentaloma (AI) is an asymptomatic adrenal mass detected incidentally on imaging examination not performed for suspected adrenal diseases.[1] The prevalence of AI has been estimated to be as high as 4.2% upon evaluation of abdomen or thorax by computed tomography (CT) scans. In most cases (85%), AIs are nonfunctioning.

In this issue of *Arquivos Brasileiros de Cardiologia*, Sokmen et al.[2] selected patients (Pts) following the European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. After confirming the presence of an adrenal adenoma through imaging tests, computed tomography, or magnetic resonance imaging, they excluded Cushing Syndrome through 1-mg dexamethasone suppression test (DST), pheochromocytoma by urinary fractionated metanephrine test, and primary aldosteronism.[3]

Patients with nonfunctioning AIs may have mild hypercortisolism, reduced insulin sensitivity, and increased blood pressure levels when compared to controls.[4] Previous studies have demonstrated that insulin resistance, hypertension, dyslipidemia, fatty liver disease, and metabolic syndrome were identified in Pts with nonfunctioning AIs.[4,5] Current understanding is that nonfunctioning AIs may secrete small or undetectable amounts of cortisol that may cause mild systemic changes.[4] Adequate management and follow up of these Pts has yet to be established. Morphological and functional cardiac alterations have been insufficiently reported for this particular group.[4-6]

Keywords

Incidental Findings; Diagnostic Imaging; Metabolic Syndrome; Hidrocortisone; Echocardiography Doppler; Cohort Studies

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Echocardiography seems to be to most versatile noninvasive imaging technique to assess volumes, ejection fraction, myocardial mass index, diastolic function, right ventricular (RV) function, hemodynamics, and valvular regurgitation.[7] This study by Sokmen et al. is important as it measures atrial electromechanical delay (EMD) by utilizing tissue Doppler echocardiography (TDE). EMD has proven to be valuable in predicting new onset or recurrence of atrial fibrillation.[7] Atrial fibrillation is one of the most common arrhythmias in clinical practice, associated with significant mortality, morbidity, and thromboembolic events. Several publications confirm the value of tissue Doppler when measuring EMD parameters to identify Pts susceptible to this condition.[8] In this particular AI group, atrial conduction times were measured.

Both inter-atrial EMD and intra-atrial EMD were higher in the nonfunctioning AI group compared to controls. According to the authors, this is the first time these abnormal measurements have been demonstrated in the literature. The authors found some indirect evidence of autonomous adrenal secretion and identified that post-DST cortisol level was an important predictor of intra-atrial EMD. They deduced that the increase of post-DST cortisol level by 1 μg/dL lengthened intra-atrial EMD by 4.752 ms.

The anatomical and morphological findings demonstrated that diastolic thickness of the interventricular septum, posterior wall, and left ventricular (LV) mass index were significantly higher and pulmonary acceleration time significantly lower in the nonfunctioning AI group compared to the control group. Tissue Doppler Em/Am measurements in LV lateral, septal, global, and RV were significantly decreased in the nonfunctioning AI group, confirming tissue Doppler as a tool of both global and regional functions.[9]

The results would have been more robust if these Pts had been followed up for a longer period. The deformation indices (strain/strain rate) of both ventricles and atria could add important data to the study, as they are superior to tissue Doppler in detecting subclinical abnormalities. Notwithstanding, the authors demonstrated that indeed subclinical cardiac involvement exists in nonfunctioning AI Pts. Therefore, as they show increased cardiovascular risk, they should be followed up more frequently.

References

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the nonfunctioStudy of Adrenal Tumors. Eur J Endocrinol. 2016; 175 (2): G1-G34.
2. Sokmen G, Sahin M,Tuzun D, Sokmen A,Bolat H, Oguz A, et al. Assessment of subclinical cardiac alterations and atrial electromechanical delay by] Tissue Doppler echocardiography in patients with nonfunctioning adrenal incidentaloma. Arq Bras Cardiol. 2018; 111(5):656-663
3. Iacobellis G, Petramala L, Barbaro G, Kargi AY, Serra V, Zinnamosca L, et al. Epicardial fat thickness and left ventricular mass in subjects with adrenal incidentaloma. Endocrine. 2013;44(2):532-6.
4. Tabarin A. Do the diagnostic criteria for subclinical hypercortisolism exist? Ann Endocrinol. (Paris) 2018;79(3):146-8.
5. Imga NN, Elalmıs OU, Tuna MM, Dogan BA, Sahın D, Gursoy T et al. Comparison of echocardiographic findings in patients with nonfunctioning adrenal incidentalomas. Kaohsiung J Med Sci. 2017;33(6):295-301.
6. Ermetici F, Dall'Asta C, Malavazos AE, Coman C, Morricone L, Montericcio V,et al. Echocardiographic alterations in patients with nonfunctioning adrenal incidentaloma. J Endocrinol Invest. 2008;31(6):573-7.
7. Marwick TH. The role of echocardiography in heart failure. J Nucl Med. 2015; 56(Suppl 4):31S-38S.
8. De Vos CB, Weijs B, Crijins HJ, Cheriex EC, Palmans A, Habets J, et al. Atrial tissue Doppler imaging for prediction of new onset atrial fibrillation. Heart. 2009;95(10):835-40.
9. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. J Am Coll Cardiol. 2007;49(19):1903-14.

Mortality for Critical Congenital Heart Diseases and Associated Risk Factors in Newborns. A Cohort Study

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Abstract

Background: **Congenital heart diseases are the most common type of congenital defects, and account for more deaths in the first year of life than any other condition, when infectious etiologies are ruled out.**

Objectives: **To evaluate survival, and to identify risk factors in deaths in newborns with critical and/or complex congenital heart disease in the neonatal period.**

Methods: **A cohort study, nested to a randomized case-control, was performed, considering the Confidence Interval of 95% (95% CI) and significance level of 5%, paired by gender of the newborn and maternal age. Case-finding, interviews, medical record analysis, clinical evaluation of pulse oximetry (heart test) and Doppler echocardiogram were performed, as well as survival analysis, and identification of death-related risk factors.**

Results: **The risk factors found were newborns younger than 37 weeks (Relative Risk - RR: 2.89; 95% CI [1.49-5.56]; p = 0.0015), weight of less than 2,500 grams (RR: 2.33 [; 95% CI 1.26-4.29]; p = 0.0068), occurrence of twinning (RR: 11.96 [95% CI 1.43-99.85]; p = 0.022) and presence of comorbidity (RR: 2.27 [95% CI 1.58-3.26]; p < 0.0001). The incidence rate of mortality from congenital heart disease was 81 cases per 100,000 live births. The lethality attributed to critical congenital heart diseases was 64.7%, with proportional mortality of 12.0%. The survival rate at 28 days of life decreased by almost 70% in newborns with congenital heart disease. The main cause of death was cardiogenic shock.**

Conclusion: **Preterm infants with low birth weight and comorbidities presented a higher risk of mortality related to congenital heart diseases. This cohort was extinguished very quickly, signaling the need for greater investment in assistance technology in populations with this profile. (Arq Bras Cardiol. 2018; 111(5):666-673)**

Keywords: **Heart Defects Congenital/mortality; Infant Newborn/mortality; Risk Factors; Survival Analysis.**

Introduction

Before the age of cardiac surgery, less than 50 years ago, just over 30% of children with severe Congenital Heart Diseases (CHD) survived into adulthood. This change was due to the evolution not only in the technique of cardiac surgery, and adaptation of cardiac catheterization to newborns, but also in the anesthetic technique, as well as the improvements in neonatal and pediatric intensive care units. Thus, the countries that have organized their care network, following this evolution pattern, have been able to considerably increase survival with quality of life for children with severe CHD. In these countries, mortality from heart disease has dropped dramatically, with up to 85% of these newborns surviving adulthood.[1-3]

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In spite of all this progress, CHDs are related to increased fetal losses,[4] being present in up to 85% of the deaths in necropsy findings in stillbirths, newborns, and infants,[5] being the main cause of cardiac arrest up to 24 years of age, ranging from 84% in the first two years to 21% in the second decade of life.[6]

In addition, CHD mortality has a great variability worldwide. Low-industrialized or developing countries, where access to health is precarious, have substantially higher mortality rates than developed countries, which are consistent with national studies.[7-9]

In the statistics with more methodological strictness, it is expected that, for serious heart diseases, such as conotruncal defects, tetralogy of Fallot, transposition of large arteries, and truncus arteriosus, survival in the first year of life fluctuates from 62.8% to 79, 6%, with a worse result for truncus arteriosus.[10] For hypoplastic left heart syndrome, data are more discouraging even in the main centers, with neonatal mortality of 68%, and mortality up to 3 months of 81%, depending on the moment that this newborn is seen. The later the care in a reference center, the greater the mortality.[6,11]

The literature indicates that premature newborn infants with a low Apgar score, and who require invasive ventilatory support, are those who present higher risk of mortality when more complex procedures are required.[12,13]

The objective of this article was to describe the mortality, fatality, and survival rates of CHD newborns in a Brazilian large urban center, as well as to characterize the associated risk and morbidity factors.

Methods

A nested case-control study cohort was performed, paired with newborns selected by lot, born in the city of Salvador (state of Bahia) and in its respective metropolitan region, from December 2014 to January 2016. The original sample was a case-control study paired by maternal age and newborn age, in which 52 cases of critical and complex CHD were selected in the neonatal period.

Data were prospectively collected in the four largest public maternity hospitals in the city of Salvador. All newborns were placed in the process of regulation to a specialized center, but they did not undergo any interventional procedure until transfer, since none of the maternities had a cardiac surgery service. The follow-up and the recording of newborns monitoring were performed up to the moment of discharge from the maternity ward (due to clinical improvement, transference or death).

The independent variables were: gestational age, low birth weight (weight less than < 2,500 grams), pulse oximetry test (POT), cardiac auscultation (presence or absence of murmur or irregular heart rhythm), Apgar, twinning, and presence of comorbidities (neonatal sepsis, and respiratory insufficiency, with demand for invasive ventilatory support).

The dependent variable was the occurrence of critical and/or complex CHD, and the secondary outcome was death.

The CHD cases included were the critical CHD newborns, which were channel-type or shunt-dependent, or considered complex (those with three or more defects), born in the services included in the study, in the reported period. For the comparison group, the neonates without CHD were included, selected by lot, of the same gender of the case, with more than 24 hours of life who, on physical examination, did not present murmurs or arrhythmias, with pre- and post-ductal oximetry, and differential not exceeding 3% and above 95% saturation.

Considering a possible fallibility of POT, and aiming at minimizing possible losses, these newborns were followed by telephone or at the childcare outpatient clinic up to 3 months after discharge from the maternity ward. In addition, in order to minimize possible losses, and to identify allocation errors, in the first year after completion of data collection, all newborns and infants entries were monitored in the only public high-complexity pediatric cardiac surgery service of the state of Bahia.

Newborns whose only identified heart disease was the presence of Patent Arterial Duct (PAD), or other simple heart diseases; with pulmonary hypertension without structural heart disease; cases that were not characterized as CHD; newborns whose parents or guardians did not sign the Free and Informed Consent Form (FICF) were excluded from the study.

This study was approved by the Research Ethics Committee (CEP) of Hospital Ana Nery and by the local Ethics Committees of each hospital involved (CAAE: 17970413200000045). The FICF was used to make the child's legal guardian aware of the process.

For the proportional mortality calculations, mortality data were used in the neonatal period, for the same sampled population and period studied.

Sample size estimation was performed primarily for the case-control study, considering the proportion of exposed cases within of 20%; proportion of exposed, among controls/comparison group of 11.11%,%; Odds Ratio (OR) 2; and significance level of 5% (test power: 80%).

Statistical analysis

For the direct estimation of gross relative risks, we chose to perform simple Poisson regression modeling, associated to the robust estimation of standard errors, aiming to control some possible average violation of the assumption of equality between mean and variance of the distribution of Poisson, and consequent more adequate estimation of the model p values, and level of significance of 5%.[14] For the calculation of the Confidence Intervals of 95% (95% CI), the use of the Delta 2 method was added. The model goodness of fit was evaluated by analyzing the residual *deviance* and the *Akaike* Information Criterion (AIC).[15]

In the Kaplan-Meier survival curves analysis, Cox regression modeling with right censorship was used to obtain survival probability and hazard ratio (HR), assuming proportionality risk. For the comparison of the survival curves, Log rank test was used. The database was created in Epidata,[16] version 3.1, and the statistical analyzes were performed in the statistical package R, version 3.2.3.[17]

Results

Fifty-two cases of CHD newborns with critical and complex congenital heart disease and their respective comparison groups, in the maternity hospitals studied, were identified and monitored. The most frequent heart diseases were formation of aortic arch defects, which depended on the ductus arteriosus (62 cases/100,000 live births), followed by pulmonary atresia with or without hypoplasia of the right ventricle (53 cases/100,000 births), and transposition of the great arteries (38 cases/100,000 live births).

As a consequence of gender pairing, the distribution was equal between the groups (OR: 0.92; 95% CI: 0.67-1.27]). In the initial data, there was one case of ambiguous genitalia; however, during follow-up it was confirmed that it was a female newborn.

The risk of death among newborn infants with CHD was twice as high among premature infants (RR: 2.14; 95% CI [1.22-3.75]; p = 0.003), with low birth weight (RR: 2.14; 95% CI [1.22-3.75]; p < 0.0001) and Apgar < 7 in the first minute of life (RR: 2.08; 95% CI [1.13-3.82]; p = 0.017). The presence of some comorbidity, besides CHD, was associated with the outcome, and increased the risk by almost three times (p < 0.0001). There was a higher proportion of

twins among the cases (9.9%) (RR: 13.1; 95% IC [1.59-109.1]; p = 0.018) than newborns without heart disease (2.2%), and for this condition, the risk of death was 12 times higher among twin newborns with CHD (Table 1).

Clinical data on changed cardiac auscultation were found in 72% of cases and in only 1% of infants without CHD. The difference of this finding was related to the higher risk for CHD (p < 0.0001). Pulse oximetry was recorded even for cases of CHD with intrauterine diagnosis or in those in which another finding was the clinical suspicion and where the diagnosis had been made before 24 hours of life. Figure 1 illustrates the differential distribution density of pulse oximetry measurements among newborns with and without CHD. Some records below the cut-off level are noted for newborns without CHD, for whom the echocardiogram was required, and the possibility of CHD was ruled out.

The incidence of death in CHD cases was 81/100 thousand live births. The case fatality rate attributed to CHD was 64.7%, with proportional mortality of 12.0% (17/142). The main cause of death was cardiogenic shock in 41.1% of the cases, followed by sepsis (17.6%) in three newborns with Double Right Ventricular Outflow Tract (DRVOT), and impossibility of therapy for cardiopathy (17.6%) - CHD anatomy was not consistent with any surgical procedure available, progressing to refractory hypoxemia followed by death - in neonates with hypoplastic left heart syndrome and untreatable ill-defined cardiac defects (Table 2).

The median hospital stay was 75 days, with an increased risk of death of 0.4 to 0.8 (HR: 0,4->0.8). Still in the neonatal period, 25% of CHD newborns had already died (Figure 2).

There was no statistical difference for survival rates when the death event was compared between those who died from CHD and due to other causes (p = 0.076). Although survival in these newborns has declined by more than 50% in the first 10 days of life and within the neonatal period, this survival declined by more than 60% (Figure 3) before newborns achieved 28 days of life.

Discussion

CHD newborns presented higher morbidity attributed to prematurity, low birth weight, some degree of intrauterine fetal distress, both due to physical examination and changed pulse oximetry. The literature has drawn attention to the greater morbidity, especially of premature newborn infants, who already present a range of other pathologies due to their constitution, which can substantially aggravate these patients progress.[12]

For both post-ductal (RR: 46; 95% CI [11.54-184.0]) and pre-ductal (RR: 39; 95% CI [9.72-157.5]) variable oximetry, the differences between groups were well established. This data not only reinforced the validation of the controls, but also confirmed the importance of making this screening test universal. On the other hand, the physical examination had low specificity (40%) and regular sensitivity, a little higher than the POT (89%), but, alone, it was insufficient to rule out the possibility of CHD. The literature states that when the physical examination is performed by a well-trained and experienced pediatrician, there is an increase in the sensitivity of the POT by up to 20%,[18] optimizing the detection capacity when they are appropriately associated.[19,20]

The finding of a low Apgar score in the first minute denoted the importance of knowing that some cardiopathies may be active in the uterus, impairing the blood flow that would allow adequate supply of nutrients and oxygen to the fetus, which may affect the morbidity and mortality of this newborn; this

Table 1 – Association between congenital heart disease and factors related to the newborn

Variable	Factor	RR *	CI 95%	p value	AIC
Gender	Female	1		-	
	Male	0.92	0.66-1.27	0.6	301.2
Weight	Above > 2,500 g	1		-	
	Low Weight (< 2,500 g)	2.33	1.26-4.29	0.0068	170.5
Gestational Age	> 37 weeks	1		-	
	< 37 weeks	2.89	1.49-5.56	0.0015	157.9
Apgar 1st minute	≥ 7	1		-	
	Less than < 7	2.35	1.25-4.45	0.0084	163.1
Apgar 5th minute	≥ 7	1		-	
	<7	9.49	1.09-82.85	0.042	43.9
Twinning	No	1		-	
	Yes	11.96	1.43-99.85	0.022	48.8
Heart auscultation alteration	Normal	1		-	
	Changed	84	11.83-596.21	< 0.0001	112.6
Comorbidities	No	1		-	
	Yes	2.27	1.58-3.26	< 0.0001	215.5

(*) Gross RR by Poisson regression; p value - Z statistic. RR: relative risks; 95% CI: 95% confidence interval; AIC: Akaike Information Criterion.

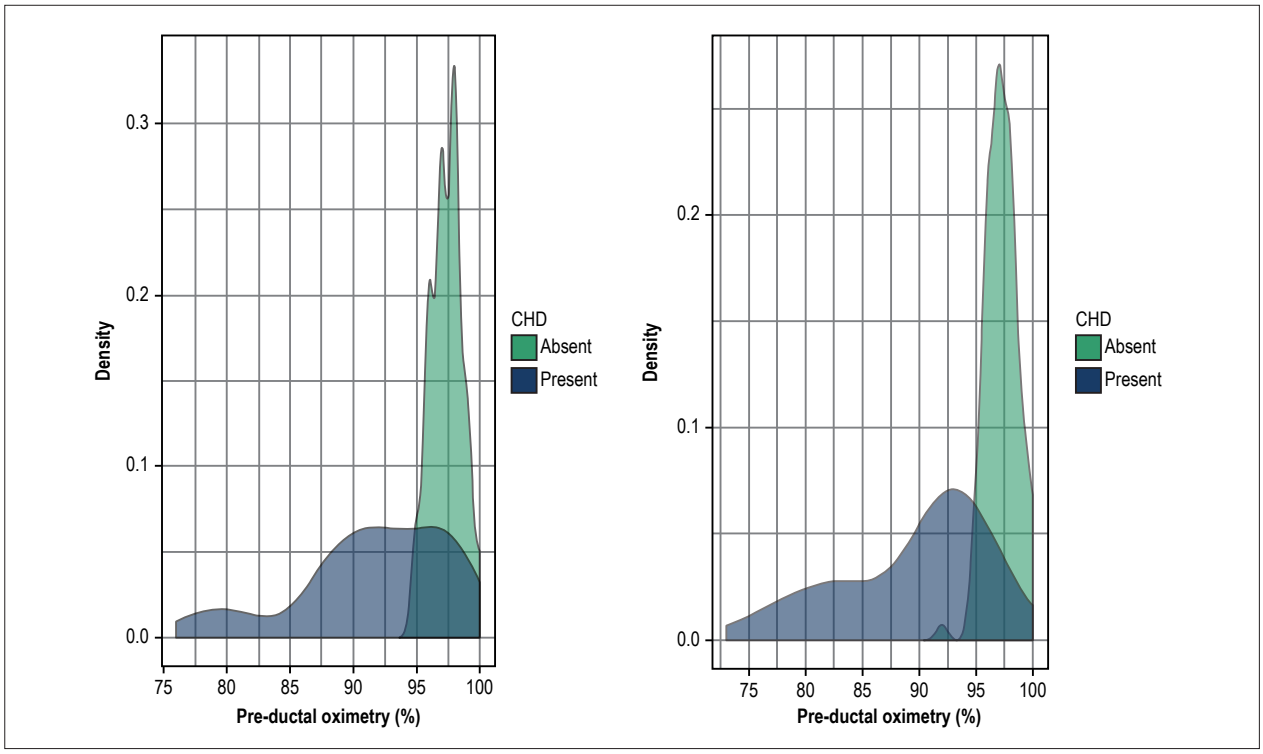

Figure 1 – *Distribution of recording density of pre- and post-ductal pulse oximetry levels, according to the presence or absence of congenital heart diseases (CHD).*

Table 2 – Causes of death, according to the type of cardiopathy

Type of cardiopathy	Cause of death	n (%)
PVA, IVCa, PVAD, HLV, GAT, AVI, and TrA	Cardiogenic shock	7 (41,1)
Ebstein's anomaly	Supraventricular tachycardia	1 (5,9)
RVDO	Sepsis	3 (17,6)
LHHS, pentalogy of Cantrell	Through CHD (basic cause/palliative care)	3 (17,6)
PVAD, GAT	Ill-defined causes	3 (17,6)

PVA: post-varicella angiopathy; IVC: interventricular communication; PVAD: Pulmonary vein anomalous drainage; HLV: hypoplasic left ventricle; GAT: great arteries transposition; AVI: aortic valve insufficiency; TrA: Truncus arteriosus; RVDO: right ventricle double outlet; CHD: congenital heart disease.

reinforces the importance of adequate prenatal diagnosis and follow-up. Studies in Brazil have already indicated that low access to prenatal and/or at birth diagnosis makes the treatment of CHD considerably difficult, which leads to a worse clinical condition at birth.[9]

The frequency of twin pregnancies among the cases was proportionally higher within the comparison group. This data was reported with controversy in other studies, due to the difficulty of concomitantly evaluating the association of other risk factors, but for the outcome death, this finding was determinant.[21]

The early and high mortality rate found here was one of the most discordant data in the world literature. In developed countries, it is expected that the CHD fatality in the neonatal period will only exceed 60% for the late diagnoses of the hypoplastic left heart syndrome (HLHS); for the other types of CHD, the expected fatality rate does not exceed 40%, when the diagnosis of CHD is made before hospital discharge.[22] Countries with socioeconomic classification similar to that of Brazil, although also coping with glaring regional differences in relation to neonatal care, have an overall incidence rate of CHD deaths of 20 to 30/100,000 births.[2] Fixler et al.[3] measured the mortality rate according to the time of referral, considering first day, up to 5 days, 4 to 27 days, and no referral after 27 days, and found mortality near 38% when the newborn was not referred before 27 days of life. In addition, mortality increased considerably at 3 months, getting close to 80% for HLHS.[3]

The literature has shown a significant improvement in the quality of care, which has led to a decrease in morbidity and mortality in developed countries,[3,4] but this is not a reality for developing countries, as can be seen in the high mortality and lethality rate despite the same incidence of CHD described herein.

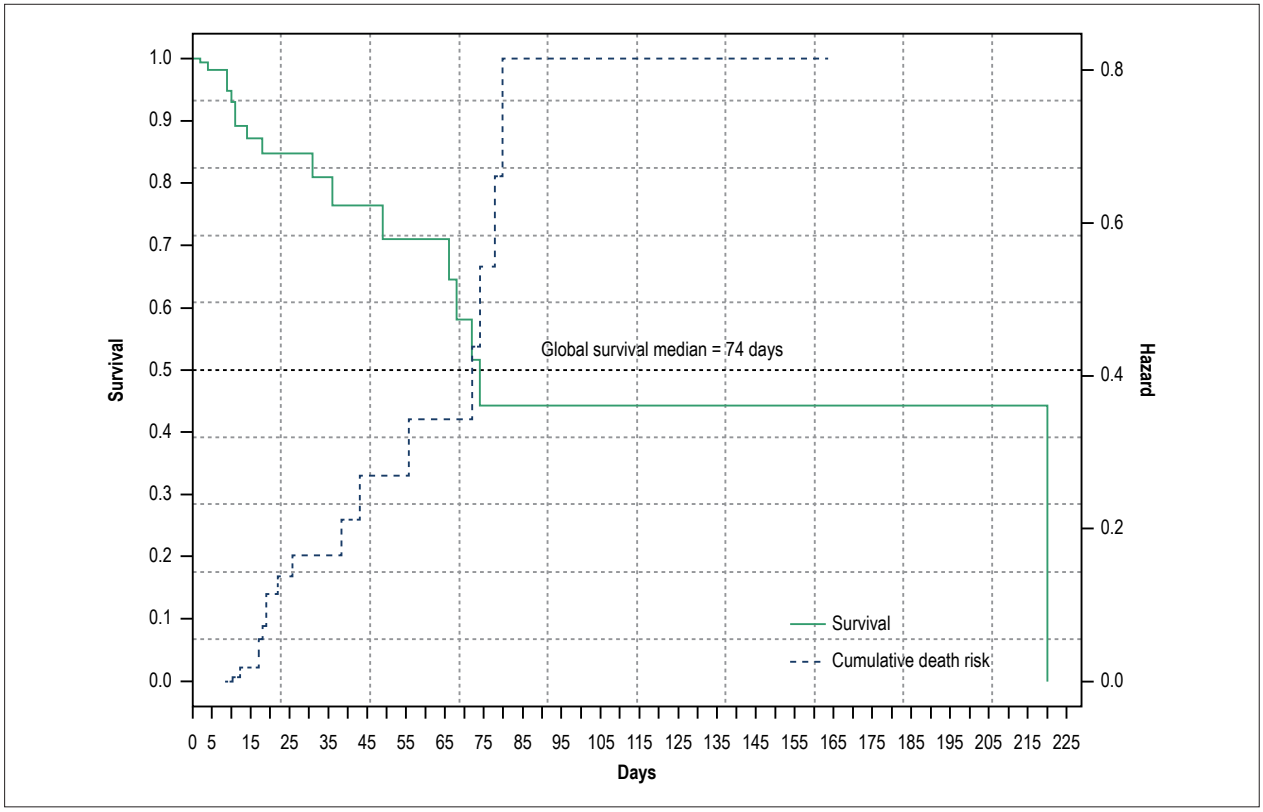

Figure 2 – *Kaplan-Meier Curves and Cumulative Risk Function for Global Mortality for Congenital Heart Diseases.*

Neonatal deaths due to congenital defects are classified by some authors,[23] and by the Brazilian Ministry of Health as avoidable, because they may be reduced for some conditions, if adequate and prompt assistance is offered to the pregnant woman and the newborn, aiming at the diagnosis and treatment, associated with adequate support by other spheres of the government – other than health services.[24] In addition, pathologies with this classification have the possibility of reducing mortality by such actions, depending on the condition considered. [25,26]

The Ministry of Health recently launched a project to extend care to CHD children,[27] to reduce the mortality from these defects, which is in agreement with the findings in this study. This mobilization was necessary because it was estimated, within the national context, that up to 80% of newborns with CHD require a surgical procedure at some point in their development. Not infrequently, there is some demand for a surgical approach until late adolescence and early adulthood.[28] These data, while they may be underestimated,[29] should be monitored by independent and prospectively validated scientific investigations as the policy in question is being implemented.

Limitations of the study

Although the minimum sample size was calculated, considering the local prevalence of CHD in a pilot study, some variables could not be included in the regression model due to the numerical insufficiency, a consequence of the multivariate approach. The absence of statistical difference for survival rates, when the death event was compared within those who died from CHD and other causes ($p = 0.076$), is possibly related to the numerical insufficiency of this subgroup. In addition, in the period from September 2015 to January 2016, there was a substantial reduction in the number of occurrences of CHD from not yet well specified causes (data from the Department of Information Technology of the National Unified Health System – DATASUS, and direct observation in the collection of data), which resulted in longer collection time.

Conclusion

The high lethality rate of the disease in question demands critical attention for structuring a specialized care network, which can adequately serve the volume of neonates with congenital heart disease, as well as provide real investments in training and care technology, even within the neonatal age group. As an example, we can cite the policies that are directed to actions, aiming to deepen the scientific knowledge about the cardiopathies and their clinical interpellations.

The neonatal mortality rate from critical congenital heart diseases was higher in this study than in countries with the same economic classification. In addition, this cohort was very quickly extinguished, which is very concerning, considering that death was the main outcome in very young patients, who did not have the opportunity to receive the specialized treatment. These findings point to the need for greater investment in care technology in populations with this profile.

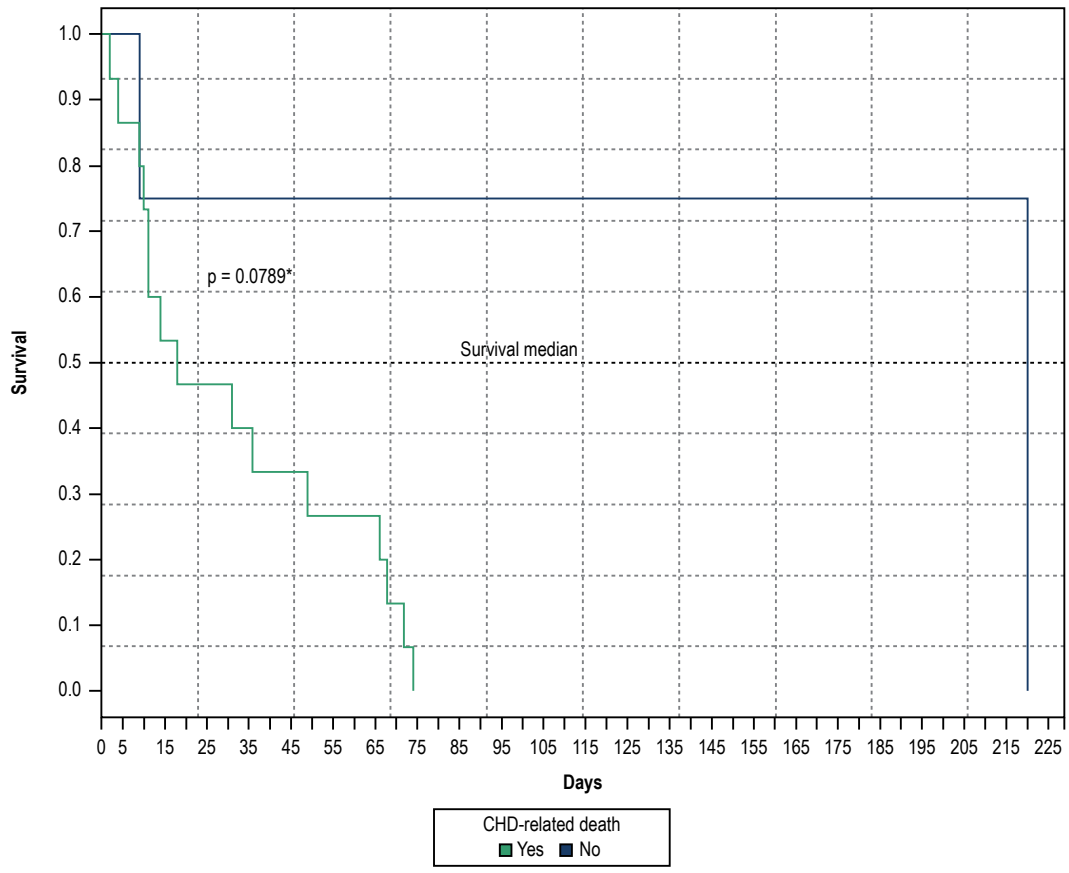

Figure 3 – *Kaplan-Meier curves, according to deaths related or not to heart disease. CHD: congenital heart defects.*

Author contributions

Conception and design of the research: Lopes SAVA; Acquisition of data: Lopes SAVA, Costa SFO; Analysis and interpretation of the data and Statistical analysis: Lopes SAVA, Mendes CMC; Obtaining financing: Lopes SAVA, Guimarães ICB; Writing of the manuscript: Lopes SAVA; Critical revision of the manuscript for intellectual content: Lopes SAVA, Mendes CMC, Acosta AX, Sandes KA, Costa SFO.

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 Ana Nery under the protocol number CAAE: 17970413200000045. 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.

References

1. Jenkins K. Mortality with congenital heart defects in England and Wales, 1959–2009. Much progress, but more to do. Arch Dis Child. 2012;97(10):859-60.
2. Knowles RL, Bull C, Wren C, Dezateux C. Mortality with congenital heart defects in England and Wales, 1959–2009: exploring technological change through period and birth cohort analysis. Arch Dis Child. 2012;97(10):861-5.
3. Fixler DE, Xu P, Nembhard WN, Ethen MK, Canfield MA. Age at referral and mortality from critical congenital heart disease. Pediatrics. 2014;134(1):e98-105.
4. MacColl CE, Manlhiot C, Page C, McCrindle BW, Miner SE, Jaeggi ET, et al. Factors associated with in utero demise of fetuses that have underlying cardiac pathologies. Pediatr Cardiol. 2014;35(8):1403-14.
5. Leite Dde L, Miziara H, Veloso M. Congenital cardiac malformations in pediatric necropsies: characteristics, associations and prevalence. Arq Bras Cardiol. 2010;94(3):275-80, 294-9.
6. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics 2016 update: a report from the American Heart Association. Circulation. 2016;133(4):e38-360.
7. Hoffman JIe. The global burden of congenital heart disease : review article. Cardiovasc J Afr. 2013;24(4):141-5.
8. Torres-Cosme JL, Rolón-Porras C, Aguinaga-Ríos M, Acosta-Granado PM, Reyes-Muñoz E, Murguía-Peniche T. Mortality from congenital heart disease in Mexico: a problem on the rise. Plos One. 2016;11(3):e0150422.
9. Salim TR, Soares GP, Klein CH, Oliveira GM. Mortality from circulatory system diseases and malformations in children in the State of Rio de Janeiro. Arq Bras Cardiol. 2016;106(6):464-73.
10. Stavsky M, Robinson R, Sade MY, Krymko H, Zalstein E, Ioffe V, et al. Elevated birth prevalence of conotruncal heart defects in a population with high consanguinity rate. Cardiol Young. 2017;27(1):109-16.
11. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics. 2013;131(5):e1502-8.
12. Cheng HH, Almodovar MC, Laussen PC, Wypij D, Polito A, Brown DW, et al. Outcomes and risk factors for mortality in premature neonates with critical congenital heart disease. Pediatr Cardiol. 2011;32(8):1139-46.
13. Polito A, Piga S, Cogo PE, Corchia C, Carnielli V, Da Frè M, et al. Increased morbidity and mortality in very preterm/VLBW infants with congenital heart disease. Intensive Care Med. 2013;39(6):1104-12.
14. Zou G. A Modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.
15. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol. 2003;157(10):940-3.
16. Christiansen TB, Lauritsen JM (eds.). Comprehensive Data Management and Basic Statistical Analysis System. Odense Denmark: EpiData Association; 2010. [Internet]. [Cited in 2017 Mar 18]. Available from: http://www.epidata.dk.
17. R Development Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2016. [Cited in 2017 Mar 18]. Available from: http://www.R-project.org
18. Zuppa AA, Riccardi R, Catenazzi P, D'Andrea V, Cavani M, D'Antuono A, et al. Clinical examination and pulse oximetry as screening for congenital heart disease in low-risk newborn. J Matern Fetal Neonatal Med. 2015;28(1):7-11.
19. Albuquerque FC, Maia ET, Figueiredo VL, Mourato FA, Mattos SS. Clinical examination and pulse oximetry to detect congenital heart defects. Int J Cardiovasc Sci. 2015;28(2):48-151.
20. Ewer AK. Review of pulse oximetry screening for critical congenital heart defects in newborn infants: Curr Opin Cardiol. 2013;28(2):92-6.
21. Dawson AL, Tinker SC, Jamieson DJ, Hobbs CA, Berry RJ, Rasmussen SA, et al; National Birth Defects Prevention Study. Twinning and major birth defects, National Birth Defects Prevention Study, 1997–2007. J Epidemiol Community Health. 2016;70(11):1114-21.
22. Eckersley L, Sadler L, Parry E, Finucane K, Gentles TL. Timing of diagnosis affects mortality in critical congenital heart disease. Arch Dis Child. 2016;101(6):516-20.
23. Malta DC, Duarte EC, Almeida MF, Dias MA, Morais Neto OL, Moura L, et al. Lista de causas de mortes evitáveis por intervenções do Sistema Único de Saúde do Brasil. 2007. Epidemiol Serv Saúde Brasília; 16(4):233-44.
24. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Manual de vigilância do óbito infantil e fetal e do Comitê de Prevenção do Óbito Infantil e Fetal. 2ª. ed. Brasília; 2009. 96 p. (Série A: Normas e Manuais Técnicos).
25. Malta DC, Duarte EC, Escalante JJ, Almeida MF, Sardinha LMV, Macário EM, et al. [Avoidable causes of infant mortality in Brazil, 197-2006: contributions to performance evaluation of the Unified National Health System]. Cad Saude Publica. 2010;26(3):481-91.
26. Boing AF, Boing AC. [Infant mortality from preventable causes in Brazil: an ecological study in 2000-2002. Cad Saude Publica. 2008;24(2):447-55.
27. Brasil, Ministério da Saúde. Portaria nº 1.727, de 11 de julho de 2017. Aprova o plano nacional de assistência à criança com cardiopatia congênita. Diário Oficial da União. DOU. n. 132, 12 de jul. 2017. Seção I, p. 47.
28. Caneo LF, Jatene MB, Riso AA, Tanamati C, Penha J, Moreira LF, et al . Evaluation of surgical treatment of congenital heart disease in patients aged above 16 years. Arq Bras Cardiol. 2012;98(5):390-7.
29. Pinto Júnior VC, Branco KM, Cavalcante RC, Carvalho Junior W, Lima JR, Freitas SM, et al. Epidemiology of congenital heart disease in Brazil. Rev Bras Cir Cardiovasc. 2015;30(2):219-24.

Original Article

Mortality for Critical Congenital Heart Diseases and Associated Risk Factors in Newborns. A Cohort Study

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Short Editorial related to the article: Mortality for Critical Congenital Heart Diseases and Associated Risk Factors in Newborns. A Cohort Study

Congenital heart disease (CHD) is any change in the anatomy of the heart and its blood vessels that occurs within the first 8 weeks of gestation. The manifestation of CHD is very variable and may occur soon after birth or appear later in childhood or adolescence.

The incidence of CHD is 8 to 10 per 1000 live births, or one in one hundred births. In Brazil, 28,900 children are born with CHD per year (1% of the total birth), of which about 80% (23,800) need cardiac surgery, and half of them need to be operated in the first year of life.[1]

Congenital malformations represent the second main cause of mortality in children under one year of age. CHD is the most frequent and with high mortality in the first year of life in Brazil, and the third cause of death up to 30 days of life.[2]

About five decades ago, nearly 70 percent of children with CHD had an unfavorable outcome and were unable to reach adulthood, as surgery and interventional procedures were not yet available. This panorama has changed much, especially in the developed countries, which have been organized in relation to care in all its stages, from the fetal life to the adult with CHD. In these countries, the life expectancy of newborns (NB) with CHD reaches 85%.[3,4]

The current national panorama requires urgent measures to improve survival, especially in the neonatal age group. The article "Mortality for Critical Congenital Heart Diseases and Associated Risk Factors in Newborns. A Cohort Study" depicts clearly in a sample of 52 cases of critical CHD, the overall situation of our country, even considering the regional differences. It is known that comprehensive care for the child with CHD in Brazil is still one of the major challenges of Health Unic System (SUS). The continental dimensions of country and the unequal geographical distribution of reference centers of cardiology and pediatric surgery are determining factors in this process.

In this study,[5] the authors identified that the risk of death in NB infants with CHD was twice as high among premature infants with low birth weight and Apgar < 7 in the first minute of life. The presence of some comorbidity, besides CHD, was associated with the outcome and increased the risk by almost three times. All NB with CHD were placed in the regulation process and did not perform any interventional procedures until the transfer, since none of the maternity hospitals had cardiac surgery services. This reality is frequent in our country, since there are only 69 centers in pediatric cardiac surgery. The average time of hospital stay in this study was 75 days and 25% of the NB with CHD had already died in the neonatal period. The incidence of death in cases of CHD was alarming in a total of 81/100 thousand live births, with cardiogenic shock being the main cause in 41.1% of the cases. Countries in socioeconomic conditions similar to those in Brazil have a global incidence rate of deaths due to CHD of 20 to 30/100 thousand births.[6]

The time of referencing of the NB with critical CHD is proportionally related to mortality, the longer the delay, the higher the mortality, as demonstrated in the study by Fixler et al.,[3] reaching the next 80% for hypoplastic left heart syndrome.

In 2017, the Brazilian Ministry of Health launched a federal project to expand childcare with CHD,[2] with the goal of increasing the care of children with CHD per year by 30%, which corresponds to more than 3,400 procedures per year, totalizing about 12,600 procedures / year, which would impact in great reduction of neonatal mortality. The study in question corroborates that CHD care in our country needs intervention, remodeling and restructuring in several phases of its process,[7] in order to achieve effective goals of reducing the morbidity and mortality of NB and children.

Establishing sustainable cardiac surgery and hemodynamic programs requires more than a financial investment; it involves specific political, social, and cultural issues in each region. Organizations wishing to assist in the development of congenital and pediatric cardiac centers need to focus on two-way communication and education and to maintain a long-term commitment to each location.[8,9] The commitment of the nation in several spheres is fundamental to change this panorama in the public health and is a matter of social security in our country.

Keywords

Heart Defects, Congenital/physiopathology; Heart Defects, Congenital/surgery; Infant,Newborn; Mortality; Hypoplastic Left Heart Syndrome; Health Programs and Plans; Maternal and Child Health

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References

1. Malta DC, Duarte EC, Escalante JJC, Almeida MF de, Sardinha LMV, Macário EM, et al. Mortes evitáveis em menores de um ano, Brasil, 1997 a 2006: contribuições para a avaliação de desempenho do Sistema Único de Saúde. Cad Saúde Pública. 2010;26(3):481–91.
2. Brasil. Ministério da Saúde. PORTARIA Nº 1.727, DE 11 DE JULHO DE 2017. Aprova o Plano Nacional de Assistência à Criança com Cardiopatia Congênita. Diário Oficial [da República Federativa do Brasil], Brasília, DF, n. 132, 12 de jul. 2017. Seção I, p.47. [citado em 2018 mar 21]. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prt1727_12_07_2017.html
3. Fixler DE, Xu P, Nembhard WN, Ethen MK, Canfield MA. Age at referral and mortality from critical congenital heart disease. Pediatrics. 2014;134(1):e98–105.
4. Baldacci S, Pierini A, Santoro M, Spadoni I, Bianchi F. Prevalence, mortality and lethality of congenital heart defects from the Tuscan Registry (Tuscany Region, Central Italy), 1992-2009]. Epidemiol Prev. 2015; 39(1):36-44.
5. Lopes SA, Guimarães ICB, Costa SF, Acosta AX, Sandes KA, Mendes CM. Mortalidade para cardiopatias congênitas e fatores de risco associados em recém nascidos. Um estudo de coorte. Arq Bras Cardiol. 2018; 111(5):666-673
6. Knowles RL, Bull C, Wren C, Dezateux C. Mortality with congenital heart defects in England and Wales, 1959–2009: exploring technological change through period and birth cohort analysis. Arch Dis Child. 2012;97(10):861–5.
7. Dilli D, Köse MR, Gündüz RC, Özbaş S, Tezel B, Okumuş N. Recent Declines in infant and neonatal mortality in Turkey from 2007 to 2012: impact of improvements in health policies. Cent Eur J Public Health. 2016;24(1):52-7.
8. Fenton K, Cardarelli M, Molloy F, Novick W. Establishing sustainable cardiothoracic surgery programs in underserved countries. Thorac Cardiovasc Surg. 2018 Aug 24. [Epub ahead of print].
9. L Preston, J Turner, A Booth et al. Is there a relationship between surgical case volume and mortality in congenital heart disease services? A rapid evidence review. BMJ Open. 2015 Dec 18;5(12):e009252. doi: 10.1136/bmjopen-2015-009252.

Gender-Based Differences in Anxiety and Depression Following Acute Myocardial Infarction

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Abstract

Background: **Among patients with heart disease, depression and anxiety disorders are highly prevalent and persistent. Both depression and anxiety play a significant role in cardiovascular disease progression and are acknowledged to be independent risk factors. However, there is very little gender-related analysis concerning cardiovascular diseases and emotional disorders.**

Objective: **We aimed to evaluate depression and anxiety levels in patients suffering from myocardial infarction [MI] within the first month after the MI and to assess the association between cardiovascular disease risk factors, demographic indicators and emotional disorders, as well as to determine whether there are gender-based differences or similarities.**

Methods: **This survey included demographic questions, clinical characteristics, questions about cardiovascular disease risk factors and the use of the Hospital Anxiety and Depression Scale [HADS]. All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.**

Results: **It was determined that 71.4% of female and 60.4% of male patients had concomitant anxiety and/or depression symptomatology (p = 0.006). Using men as the reference point, women had an elevated risk of having some type of psychiatric disorder (odds ratio, 2.86, p = 0.007). The HADS-D score was notably higher in women (8.66 ± 3.717) than men (6.87 ± 4.531, p = 0.004). It was determined that male patients who developed depression were on average younger than those without depression (p = 0.005).**

Conclusions: **Women demonstrated an elevated risk of having anxiety and/or depression disorder compared to men. Furthermore, depression severity increased with age in men, while anxiety severity decreased. In contrast, depression and anxiety severity was similar for women of all ages after the MI. A higher depression score was associated with diabetes and physical inactivity, whereas a higher anxiety score was associated with smoking in men. Hypercholesterolemia was associated with both higher anxiety and depression scores, and a higher depression score was associated with physical inactivity in women. (Arq Bras Cardiol. 2018; 111(5):676-683)**

Keywords: **Cardiovascular Diseases; Myocardial Infarction; Anxiety, Depression; Risk Factors; Gender Identify.**

Introduction

By 2020, depression is predicted to be the second highest cause of disability and mortality worldwide, surpassed only by ischemic heart disease (WHO). Myocardial infarction [MI] is a severe life-threatening event that is accompanied by an increased risk of depression and anxiety.[1,2] A recent meta-analysis that explored the effect of the interactions of risk factors on all-cause mortality in patients with MI concluded that women have worse coronary artery disease [CAD] outcomes compared to men, with more women (17%) than men (12%) dying within 3 years of having their first MI.[3] In addition, hospital mortality rates after acute MI have also been shown to be higher in women (16%) than in men (11%).[4] Gender differences are correspondingly evident regarding mental stress-induced MI when assessing laboratory-based proxies, with a higher prevalence being observed in women than in men,[5] even more so in women aged 50 years or younger.[6] A large-scale case-control study indicated that post-MI depressive symptoms were associated with an increased risk of mortality, whereas anxiety symptoms were not an independent prognostic risk factor for new cardiovascular events or death.[7] In contrast, another study of 5,750 patients with MI demonstrated that patients with anxiety are at a higher risk of both adverse cardiac events and all-cause mortality.[8] The suicide risk is at its highest during the first month following discharge for MI for both patients with no history of psychiatric illness (adjusted rate ratio – 3.25) and for those with a history of psychiatric disorders (adjusted rate ratio – 64.05), with the rate ratios being comparable with those with no history of MI or psychiatric illness.[7] The suicide risk remained higher for at least five years after the MI.[7] Although post-MI depression is a common and burdensome condition, it remains underrecognized and undertreated.[9,10] There are also very few gender-related analyses concerning cardiovascular

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diseases and emotional disorders.[11] We, therefore, aimed to evaluate depression and anxiety levels in patients suffering from MI and to assess the association between cardiovascular disease risk factors, demographic indicators and emotional disorders, as well as to determine whether there are gender-based differences or similarities.

Methods

Participants and Recruitment

Patients with a documented MI who were admitted to a tertiary health care institution from 1 November 2012 to 31 May 2013 were included.

Patients were included in the study according to the following inclusion criteria:

1. Possessing a full understanding of the survey instructions;
2. Age > 18 years;
3. Either gender;
4. A diagnosis of acute MI verified based on two of the three standard criteria: typical chest pain, ECG presentation, elevated cardiac biomarkers;
5. Time after MI < 31 days;
6. Knowledge of Lithuanian language;
7. Completion of the survey.

Exclusion criteria were:

1. Cognitive impairment or physical inability to complete the survey;
2. Diagnosed depression or anxiety disorder prior to MI;
3. Antidepressant or benzodiazepine use prior to MI;
4. Patient refusal;
5. Participation in another research study.

Of the 180 patients recruited, a total of 160 patients met the inclusion criteria and were assessed. This survey included demographic questions (gender, age), clinical characteristics and questions about cardiovascular disease risk factors: diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking, hypodynamia, and obesity. Furthermore, the Hospital Anxiety and Depression Scale [HADS] was used to determine anxiety and depression symptomatology. The scale contains 14 items: seven to assess anxiety and seven to assess depression. The score can be interpreted according to the following range: 0–7 – no depression or anxiety disorder; 8–10 – mild depression or anxiety disorder; 11–14 – moderate disorder; and 15–21 – severe disorder. The anxiety subscale (HADS-A) specificity is 0.78 and the sensitivity is 0.9, while the depression subscale (HADS-D) specificity is 0.79 and the sensitivity is 0.83.[12]

Statistical analysis

The analysis was conducted using SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows. Version 20.0. Armonk, NY: IBM Corp) software. The Shapiro-Wilk's test of normality was performed to verify the assumption of normality. Categorical variables were compared using the χ^2 test. Binary logistic regression analysis and the χ^2 test were used for categorical variables to assess the odds ratio [OR] for depression and anxiety presence associated with gender. The independent sample *t*-test, when the distribution of variables was normal, and the Mann–Whitney–Wilcoxon test, when variables showed an abnormal distribution, were used to assess continuous variables. Normally-distributed continuous variables are expressed as mean (mean ± standard deviation), whereas those with an abnormal distribution are expressed as median and interquartile range (IQR, Q1 – Q3). Correlation was assessed using Spearman's rank correlation coefficient (p). All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

Results

Of the 180 patients recruited, a total of 160 met the inclusion criteria (88.8%) and were assessed. A total of 101 patients (63.1%) were males and 59 (36.9%) were females. The mean age of female patients was 69.9 years, whilst the mean age of male patients was significantly lower, at 62.3 years (p < 0.001). The youngest female patient was 33 and the oldest was 92 years of age. Similarly, the youngest male patient was 26 and the oldest was 85 years of age. The overall age range of 59 years was identical for both genders. Based on the accumulated data, it was determined that 71.4% of female and 60.4% of male respondents (68.1% of all respondents) had concomitant anxiety and/or depression symptomatology (Table 1). Logistic regressions were used to assess the differences regarding the risk of each psychiatric disorder according to gender. Using men as the reference point, women had an increased risk of having some type of psychiatric disorder (odds ratio, 2.86, p = 0.007) (Table 1).

The all-patient mean HADS-D subscale score was 7.54 ± 4.322. It is particularly important to note that the HADS-D score was notably higher in women (8.66 ± 3.717) than in men (6.87 ± 4.531, p = 0.004). About 54.2% of female and 47.5% of male patients exhibited a depression disorder, being mild in 30.5%, moderate in 16.9% and severe in 6.8% of females, while the respective percentages for males were mild in 24.8%, moderate in 16.8% and severe in 5.9% (Table 2). It should be noted that the distribution of the aforementioned depression symptomatology severity degrees did not statistically differ between genders (p = 0.841).

The HADS-A subscale score analysis revealed that all-patient mean HADS-A subscale score was 7.59 ± 4.335 and women had a higher mean score of 8.2 ± 3.938, while the mean score in men was 7.18 ± 4.532 (p = 0.142). 64.4% of female and 39.6% of male respondents had anxiety symptoms (mild in 35.6%, moderate in 23.7% and severe in 5.1% of females, while the respective percentages for males were mild in 17.8%, moderate in 15.8% and severe in 5.9%) (Table 2). According to the anxiety severity degree data, the prevalence of anxiety was considerably higher in women (p = 0.014), with this difference being more significant in the mild anxiety group (p = 0.012). Logistic regression analysis demonstrated that women had an elevated risk of having an anxiety disorder, with an OR of 2.76 (Table 2).

Table 1 – Emotional disorder presentation in both genders

Emotional disorder	Men		Women		χ^2 or β	p value
Any emotional disorder						
Prevalence	n = 61	60.4%	n = 48	81.4%	χ^2 = 7.54	0.006*
Odds ratio	1		2.861 (1.33 – 6.16)		β = 1.05	0.007*
Anxiety disorder						
Prevalence	n = 40	39.6%	n = 38	64.4%	χ^2 = 9.17	0.002*
Odds ratio	1		2.760 (1.42 – 5.37)		β = 1.02	0.003*
Depression disorder						
Prevalence	n = 48	47.5%	n = 32	54.2%	χ^2 = 0.67	0.413
Odds ratio	1		0.764 (0.4 – 1.46)		β = 0.269	0.413
Both depression and anxiety disorders						
Prevalence	n = 27	26.7%	n = 22	37.3%	χ^2 = 1.95	0.162
Odds ratio	1		1.630 (0.82 – 3.24)		β = 0.49	0.164

**Significant p values. Odds ratio reported as odds ratio (95% confidence interval).*

Table 2 – Prevalence of anxiety and depression based on gender and severity

Severity of anxiety/ depression	Hospital Anxiety and Depression Scale (HADS)													
	Anxiety subscale							Depression subscale						
	Total		Men		Women		p value	Total		Men		Women		p value
	n	%	n	%	n	%		n	%	n	%	n	%	
No disorder	82	51.3	61	60.4	21	35.6	0.002*	80	50	53	52.5	27	45.8	0.413
Mild disorder	39	24.4	18	17.8	21	35.6	0.012*	43	26.9	25	24.8	18	30.5	0.428
Moderate disorder	30	18.8	16	15.8	14	23.7	0.217	27	16.9	17	16.8	10	16.9	0.985
Severe disorder	9	5.6	6	5.9	3	5.1	0.821	10	6.3	6	5.9	4	6.8	0.832
Total	82	51.3	61	60.4	21	35.6	0.002*	80	50	53	52.5	27	45.8	0.413

**Significant p values (between men and women, χ^2).*

There was no significant association between patient age and anxiety severity. However, a weak positive significant correlation was found between patient age and depression severity (p = 0.233, p = 0.003). In addition, it was determined that male patients who developed depression were on average younger than those without the disease, with a mean age of 58 years and 66 years, respectively (p = 0.005). The age with the highest risk of developing depression was determined to be between 55 and 62 years of age for males, whilst 95% of female patients who developed depression were between 66 and 75 years of age. A subsequent gender-based analysis showed that there was a significant weak positive correlation between male patient age and depression severity (p = 0.212, p = 0.033) and a weak negative correlation between male patient age and anxiety severity (p = - 0,278, p = 0.005). In contrast, the data analysis in women did not demonstrate any statistical association, thus meaning that depression and anxiety severity is similar for women of all age after MI. (Table 3)

Cardiovascular risk factor analysis showed an association between diabetes mellitus and HADS-D score in males who had a significantly higher median depression score compared to those who were not diabetic (10, IQR 5 – 11 vs. 5, IQR 3 – 9.75, p = 0.043). In contrast, female patients did not show any significant association between diabetes mellitus and emotional disorders. Hypercholesterolemia was associated with both higher median anxiety (8, IQR 6 – 12 vs. 6.5, IQR – 4 – 8, p = 0.02) and depression (9, IQR 7 – 12 vs. 7, IQR 4 – 8.75, p = 0.015) scores in women, while men did not show any association between the aforementioned factors (Table 4). Moreover, it was determined that arterial hypertension and body mass index were not, in any way, associated with anxiety or depression. The evaluation of patient smoking habits revealed that 15.6% of respondents were daily smokers (Table 3). Smoking was more prevalent amongst men than women (20.8% vs. 6.8%, p = 0.019). Furthermore, a higher HADS-A score was identified in male patients who did smoke (10, IQR 7.5 – 14) vs. 6.5, IQR 3 – 9, p = 0.002), whilst the HADS-A score did not differ between women who smoked or did not smoke (p = 0.311). Likewise, there was no statistically significant difference in the HADS-D subscale scores between smoking and non-smoking patients. Exercise habit analysis showed that the group of patients who did not exercise had a higher median HADS-D score than the group that exercised (9, IQR 6 – 12 vs. 5, IQR 3 – 9, p < 0.001). Gender-based

Table 3 – Cardiovascular risk factor characteristics distributed by gender

Risk factors	Men		Women		p value
	n = 101	%	n = 59	%	
Current smoker	21	20.8	4	6.8	0.019*
Physical inactivity	49	48.5	27	45.8	0.737
Diabetes mellitus	21	20.8	21	35.6	0.040*
Hypertension	87	86.1	57	96.6	0.033*
Hypercholesterolemia	52	51.5	39	66.1	0.072

**Significant p values (between men and women, χ^2).*

Table 4 – Cardiovascular risk factors and Hospital Anxiety and Depression Scale score

Risk factors		HADS-A		HADS-D	
		Median (interquartile range)		Median (interquartile range)	
		Men	Women	Men	Women
Current smoker	Yes	10 (7.5 – 14)	9 (7.25 – 13)	5 (2 – 11.5)	6 (4 – 11.75)
	No	6.5 (3 – 9)	8 (5 – 10)	6 (4 – 10)	8 (7 – 11)
	p value	0.002*	0.311	0.473	0.439
Physical inactivity	Yes	7.5 (4 – 11)	7 (5 – 10.75)	7.5 (5 – 12)	9 (7.25 – 11.75)
	No	7 (3 – 10)	8 (6 – 10)	4 (3 – 8)	8 (4 – 10)
	p value	0.286	0.364	0.002*	0.027*
Diabetes mellitus	Yes	7 (4 – 9)	8 (6 – 11)	10 (5 – 11)	9 (7 – 13)
	No	7 (3 – 11)	8 (5 – 10)	5 (3 – 9.75)	8 (5.75 – 10.25)
	p value	0.943	0.537	0.043*	0.283
Hypertension	Yes	7 (4 – 10)	8 (5.5 – 10.5)	6 (3 – 10)	8 (6.5 – 11)
	No	6 (2.75 – 10.75)	N/A	8 (4.75 – 10.25)	N/A
	p value	0.756	N/A	0.287	N/A
Hypercholesterolemia	Yes	7 (4 – 9)	8 (6 – 12)	6.5 (4 – 10)	9 (7 – 12)
	No	8 (3.5 – 12.5)	6.5 (4 – 8)	6 (3 – 10.5)	7 (4 – 8.75)
	p value	0.2	0.02*	0.859	0.015*

**Significant p values. HADS: Hospital Anxiety and Depression Scale; HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression.*

analysis similarly revealed significantly higher median HADS-D scores in male (7.5, IQR 5 – 12 vs. 4, IQR 3 – 8, p = 0.002) and female patients (9, IQR 7.25 – 11.75 vs. 8, IQR 4 – 10, p = 0.027) who were hypodynamic. In contrast, the median HADS-A score did not significantly differ between females and males who exercised and did not exercise (p = 0.676) (Table 4).

Discussion

This study assessed gender differences regarding the associations between emotional disorders and MI that had occurred less than one month before the initial assessment. Our investigation showed that 71.4% of female and 60.4% of male patients had some type of emotional mental health problem after having been diagnosed with MI. Subsequently, we observed an elevated risk of concomitant emotional disorders in women, in comparison to men (p = 0.006). Likewise, a gender-associated difference was displayed by Carvalho et al. who used the same HAD scale and found depression symptoms in 17.5% of adult inpatients with cardiovascular disease and anxiety symptoms in 32.5% and, amongst these, the highest prevalence of mental disorders were also associated with female gender (anxiety: p = 0.002; depression: p = 0.022).[13] Although the incidence of depression in women in society is nearly double than that in men,[14] it is of utmost importance to stress that this gender-based discrepancy in society is quite probably irrelevant to our study, as the mean age of women in our study was 70 years and the incidence of depression in women after menopause (when reproductive hormones stabilize) is similar to that in men.[15] The high prevalence of emotional disorders that we observed may be partially explained by the fact that we only assessed those with a more severe condition, i.e., MI. A similar study that also used the HAD scale, but assessed dermatological patients in the same region (Vilnius

city, Lithuania), found the prevalence of mental disorders to be higher than in other comparable studies, although lower than that observed in our study.[16] Another noteworthy explanation for the high prevalence might be the fact that mental health problems in Lithuania are particularly widespread, as demonstrated by the suicide rates that are amongst the highest worldwide.[17]

It is particularly important to note that the HADS-D score was especially higher in women. Although we did not assess the impact of depression on patient outcomes, it is nonetheless necessary to stress the predictive influence of depressive symptoms in acute coronary syndrome [ACS]. A meta-analysis including 22 studies, carried out by Van Melle et al.,[18] concluded that depression is associated with a two-fold increase in mortality following MI. Furthermore, depression is associated with worse long-term outcomes after MI. For example, it was determined that moderate or high stress at the time of the MI is associated with an increased two-year mortality and an increased risk of angina in the first year.[19] Bush et al.[20] prospectively studied patients with MI who survived to discharge and determined that the highest mortality rates were observed in patients with the most severe depressive symptoms. Moreover, the ENRICHD study[21] also concluded that depression increases the risk of all-cause mortality for 30 months, even after adjusting for confounders. After the extensive review of 53 studies and four meta-analyses, the American Heart Association [AHA] stated that depression is an individual risk factor for adverse medical outcomes in patients with acute coronary syndrome.[21] Depression is an important risk factor that should be taken into consideration, not only after ACS but prior to CAD as well. Results of an 11-cohort study meta-analysis by Rugulies et al.[11] support this statement, since they concluded that clinical depression was a strong predictor of the development of coronary heart disease in an initially healthy population. Furthermore, another study demonstrated that depression was a stronger CHD predictor, especially for women ($p = 0.002$).[22]

Our study revealed that women had a markedly elevated risk of having anxiety disorder. It should be highlighted that the prognostic significance of anxiety raises discussions, since some studies suggest that post-MI anxiety symptoms were not an independent prognostic risk factor for new cardiovascular events or death.[23] Moreover, according to Hosseini et al.,[24] post-MI anxiety does not predict long-term quality of life in MI survivors. Nonetheless, we believe that post-MI anxiety should be taken into consideration in clinical practice, since it has been shown that not only depression but also pre-myocardial anxiety in the preceding 2 hours increase 10-year mortality rates in those aged > 65 years.[25] Moreover, Paine et al.[26] recently published an article stating that women with anxiety and no CAD history had higher rates of ischemia than women without anxiety. Since women are more prone to anxiety, it is important to mention that many CAD symptoms (for example, fatigue, chest pain and shortness of breath) overlap with anxiety symptoms and might mask CAD. This is more evident in women than men and contributes to the referral to other specialists and, thus, diagnostic delays.[27]

Although a recent publication by Feng et al.[1] determined that especially those women between 45 and 64 years of age had the greatest risk for anxiety when it comes to cardiovascular disease, our findings did not support this conclusion. First, our study showed that women had the highest probability to develop anxiety from 68 to 75 years of age. Second, the analysis showed that age did not have any influence on either anxiety or depression prevalence in women. On the other hand, there was a significant association between age in men and depressive symptomatology prevalence and it was shown that a relatively younger population, aged 55 to 62 years, had the highest risk of developing depression. Furthermore, male patients showed a significant weak positive correlation between age and depression severity and a weak negative correlation between age and anxiety severity.

The cardiovascular risk factor analysis showed that a higher anxiety score was identified in male patients who smoked, whereas the HADS-A score did not differ between women who smoked and did not smoke. Similarly, a significantly higher HADS-D score was found in those patients who were hypodynamic. Also, an association between diabetes mellitus and the HADS-D score was evident and men who had diabetes mellitus also had a significantly higher depression score, whereas female patients did not show any significant association between diabetes mellitus and emotional disorders. Although our analysis did not demonstrate any association between hypertension and mental disorders, another study listed depression as being associated with several known prognostic factors, such as a history of treatment of hypertension, diabetes, advanced Killip Class and left ventricular ejection fraction of 35% or less.[28] We would also like to address the association found between elevated anxiety and depression levels and hypercholesterolemia in females. A quite recent experimental study by Engel et al.[29] aimed to investigate this pathophysiological association and concluded that depressive-like behavior in hypercholesterolemic mice is accompanied by alterations in the monoaminergic metabolism, providing new evidence about the association between hypercholesterolemia and depression.

It is of paramount importance to mention the need for routine screening for depression since it is also associated with decreased adherence to medications[30] and a three-fold increase in the risk of noncompliance with medical treatment regimens.[31] Moreover, it leads to significantly reduced quality of life[32,33] and higher healthcare costs.[34] All patients should be screened within one month of MI. The AHA recommends using Patient Health Questionnaire-2, which consists of one question seeking to identify a depressive mood in the preceding two weeks and another for anhedonia in the preceding two weeks.[35] If the answer is positive to either question, then the patient should be referred for a more thorough clinical evaluation by a professional qualified in the diagnosis and management of depression or screened with the Patient Health Questionnaire-9, which has shown to be diagnostically superior in patients with CHD.[36] In contrast, there are no specific guidelines from the AHA for anxiety disorder screening in CHD. This can be partially due to the high prevalence of anxiety symptoms in angina and MI. Furthermore, it has been shown that anxiety rating scales have relatively high false positive scores that result in reduced cost-effectiveness of routine screening.[37]

Both depression and anxiety treatment options include cardiac rehabilitation and exercise therapy, disease management programs, cognitive behavior therapy and pharmacotherapy.[38] Data from the Secondary Prevention in Uppsala Primary Health Care study further support the heart-helping benefits of cognitive-behavioral therapy since at follow-up, the psychotherapy intervention group had 45% fewer recurrent heart attacks and a 41% lower rate of both non-fatal and fatal first recurrent cardiovascular events than the group receiving traditional care.[39] On the other hand, there are still ongoing discussions concerning the optimal treatment algorithm, as a few studies have had disappointing results concerning behavior therapy. For example, the ENRICHD study found that a six-month intervention focused on treating patients' depression made patients feel better, but had no positive impact when it came to preventing repeat heart attacks or death.[40]

Possible limitations of our study include unequal sample sizes between genders, with the male group being larger. However, this gender inequality reflects the real rates of patients with MI admitted to hospitals in Lithuania. Second, the absence of a control group can be considered a limitation, though we have attempted to mitigate this by discussing and comparing our data with results of previous similar studies. Third, the study design did not include mental health evaluation by a psychiatrist. Finally, our study was not a longitudinal one and patients were not reassessed several times to determine a more long-term association between MI and mental disease.

Conclusions

MI is especially closely associated with anxiety and depression. More than two-thirds of patients with MI had a depression and/or anxiety comorbidity within the first month of MI. Women showed an elevated risk of having anxiety and/or depression disorder compared to men. Furthermore, both anxiety and depression severity had a tendency to be higher in women. In addition, depression severity increased with age in men, while anxiety severity decreased. In contrast, depression and anxiety severity are similar for women of all ages after MI. A higher depression score was associated with diabetes and physical inactivity, whereas a higher anxiety score was associated with smoking in men. Hypercholesterolemia was associated with both higher anxiety and depression scores, whereas a higher depression score was associated with physical inactivity in women.

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PS conceived the study, wrote the protocol, designed and adopted the database system, and oversaw data collection. PN, LL, AN performed the statistical data analysis, wrote the manuscript and contributed to the design of the study. RA, RS, AD contributed to study design, provided other technical support and edited the manuscript. SG, ZP, RS oversaw data collection and edited the manuscript. All authors approved this version for publication.

Author contributions

Conception and design of the research: Serpytis P, Navickas A, Deksnyte A; Acquisition of data: Serpytis P, Serpytis R, Petrulioniene Z, Samalavicius R; Analysis and interpretation of the data: Navickas P, Lukaviciute L, Glaveckaite S, Samalavicius R; Statistical analysis: Aranauskas R, Serpytis R, Deksnyte A; Writing of the manuscript: Navickas P, Lukaviciute L; Critical revision of the manuscript for intellectual content: Serpytis P, Navickas A, Petrulioniene Z.

Potential Conflict of Interest

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

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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 Regional Biomedical Research Ethics Committee in Vilnius based at the Medical Faculty of Vilnius University under the protocol number 158200-04-301-78, 2011-04-06. 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.

References

1. Feng HP, Chien WC, Cheng WT, Chung CH, Cheng SM, Tzeng WC. Risk of anxiety and depressive disorders in patients with myocardial infarction: A nationwide population-based cohort study. Medicine (Baltimore). 2016;95(34):e4464.
2. Figueiredo JHC, Silva N, Pereira BB, Oliveira GMM. Major depression and acute coronary syndrome-related factors. Arq Bras Cardiol. 2017;108(3):217-27.
3. van Loo HM, van den Heuvel ER, Schoevers RA, Anselmino M, Carney RM, Denollet J, et al. Sex dependent risk factors for mortality after myocardial infarction: individual patient data meta-analysis. BMC Med. 2014 Dec 14;12:242.
4. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, et al. Association of age and sex with myocardial infarction symptom presentation and in hospital mortality. JAMA. 2012;307(8):813-22.
5. Jiang W, Samad Z, Boyle S, Becker RC, Williams R, Kuhn C, et al. Prevalence and clinical characteristics of mental stress-induced myocardial ischemia in patients with coronary heart disease. J Am Coll Cardiol. 2013;61(7):714-22.
6. Vaccarino V, Shah AJ, Rooks C, Ibeanu I, Nye JA, Pimple P, et al. Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction. Psychosom Med. 2014;76(3):171-80.

7. Larsen KK, Agerbo E, Christensen B, Sondergaard J, Vestergaard M. Myocardial infarction and risk of suicide: a population-based case-control study. Circulation. 2010;122(23):2388-93.

8. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. Psychosom Med. 2010;72(6):563-9.

9. Larsen KK. Depression following myocardial infarction--an overseen complication with prognostic importance. Dan Med J. 2013;60(8):B4689.

10. Feinstein RE, Blumenfield M, Orlowski B, Frishman WH, Ovanessian S. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. Cardiol Rev. 2006;14(4):164-9.

11. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002;23(1):51-61.

12. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.

13. Carvalho IG, Bertolli ED, Paiva L, Rossi LA, Dantas RA, Pompeo DA. Anxiety, depression, resilience and self-esteem in individuals with cardiovascular diseases. Rev Lat Am Enf. 2016;24:e2836.

14. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU. Sex differences in rates of depression: cross-national perspectives. J Affect Disord. 1993;29(2-3):77-84.

15. Bebbington P, Dunn G, Jenkins R, Lewis G, Brugha T, Farrell M, et al. The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. Int Rev Psychiatry. 2003;15(1-2):74-83.

16. Lukaviciute L, Navickas P, Navickas A, Grigaitiene J, Ganceviciene R, Zouboulis CC. Quality of life, anxiety prevalence, depression symptomatology and suicidal ideation among acne patients in Lithuania. J Eur Acad Dermatol Venereol. 2017;31(11):1900-6.

17. WHO. World Health Statistics. Monitoring Health for the Sustainable Development Goals. Geneva: WHO Press; 2016.p.62-3.

18. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med. 2004;66(6):814-22.

19. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. Perceived stress in myocardial infarction: long-term mortality and health status outcomes. J Am Coll Cardiol. 2012;60(18):1756-63.

20. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol. 2001;88(4):337-41.

21. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014;129(12):1350-69.

22. Mendes de Leon CF, Krumholz HM, Seeman TS, Vaccarino V, Williams CS, Kasl SV, et al. Depression and risk of coronary heart disease in elderly men and women: New Haven EPESE, 1982-1991. Established Populations for the Epidemiologic Studies of the Elderly. Arch Intern Med. 1998;158(21):2341-8.

23. Larsen KK, Christensen B, Nielsen TJ, Vestergaard M. Post-myocardial infarction anxiety or depressive symptoms and risk of new cardiovascular events or death: a population-based longitudinal study. Psychosom Med. 2014;76(9):739-46.

24. Hosseini SH, Ghaemian A, Mehdizadeh E, Ashraf H. Contribution of depression and anxiety to impaired quality of life in survivors of myocardial infarction. Int J Psychiatry Clin Pract. 2014;18(3):175-81.

25. Smeijers L, Mostofsky E, Tofler GH, Muller JE, Kop WJ, Mittleman MA. Anxiety and anger immediately prior to myocardial infarction and long-term mortality: Characteristics of high-risk patients. J Psychosom Res. 2017;93:19-27.

26. Paine NJ, Bacon SL, Pelletier R, Arsenault A, Diodati JG, Lavoie KL. Do Women with anxiety or depression have higher rates of myocardial ischemia during exercise testing than men? Circ Cardiovasc Qual Outcomes. 2016;9(2 Suppl 1):S53-61.

27. Halvorsen S, Eritsland J, Abdelnoor M, Holst Hansen C, Risoe C, Midtbo K, et al. Gender differences in management and outcome of acute myocardial infarctions treated in 2006-2007. Cardiology. 2009;114(2):83-8.

28. Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation. 2002;105(9):1049-53.

29. Engel DF, de Oliveira J, Lopes JB, Santos DB, Moreira ELG, Farina M, et al. Is there an association between hypercholesterolemia and depression? Behavioral evidence from the LDLr(-/-) mouse experimental model. Behav Brain Res. 2016 Sep 15;311:31-8.

30. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med. 2005;165(21):2508-13.

31. Di Matteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101-7.

32. Swenson JR. Quality of life in patients with coronary artery disease and the impact of depression. Curr Psychiatry Rep. 2004;6(6):438-45.

33. Rodrigues GH, Gebara OC, Gerbi CC, Pierri H, Wajngarten M. Depression as a clinical determinant of dependence and low quality of life in elderly patients with cardiovascular disease. Arq Bras Cardiol. 2015;104(6):443-9.

34. Frasure-Smith N, Lesperance F, Gravel G, Masson A, Juneau M, Talajic M, et al. Depression and health-care costs during the first year following myocardial infarction. J Psychosom Res. 2000;48(4-5):471-8.

35. Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008;118(17):1768-75.

36. Haddad M, Walters P, Phillips R, Tsakok J, Williams P, Mann A, et al. Detecting depression in patients with coronary heart disease: a diagnostic evaluation of the PHQ-9 and HADS-D in primary care, findings from the UPBEAT-UK study. PLoS One. 2013;8(10):e78493.

37. Bunevicius A, Staniute M, Brozaitiene J, Pop VJ, Neverauskas J, Bunevicius R. Screening for anxiety disorders in patients with coronary artery disease. Health Qual Life Outcomes. 2013;11:37.

38. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014;35(21):1365-72.

39. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med. 2011;171(2):134-40.

40. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, et al. Depression as a risk factor for mortality after acute myocardial infarction. Am J Cardiol. 2003;92(11):1277-81.

Anxiety and Depression after Myocardial Infarction: Can Inflammatory Factors be Involved?

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Short Editorial related to the article: Gender-Based Differences in Anxiety and Depression Following Acute Myocardial Infarction

This interesting article published by Serpytis et al.,[1] evaluated the presence of depression and anxiety disorders after acute myocardial infarction, and the different forms of presentation and prevalence according to patient gender and age.

The authors observed that over a period of up to 31 days after an acute myocardial infarction, more than two-thirds of the patients had depression and /or anxiety disorders. Women had a higher prevalence of these comorbidities when compared to men and also tended to have more severe presentations of both depression and anxiety disorders. Additionally, in men, depression was more severe and anxiety disorder was less severe as they were older; whereas in women these comorbidities showed a linear presentation regarding severity, regardless of the age factor.[1]

Other interesting points were that diabetic and / or sedentary men showed a higher score of depression, whereas men who smoked had a higher anxiety score. Regarding hypercholesterolemia, it was observed that women showed higher scores for depression and anxiety disorder, which did not occur with men.

Also, regarding risk factors for coronary artery disease, a sedentary lifestyle was associated with higher scores of depression and anxiety disorder in women.

Finally, it is noteworthy the fact that systemic arterial hypertension and body mass index were not associated at all to the presence of depression and/or anxiety disorder. Considering the data presented herein, despite the limitations already described by the authors, one can say there is a high prevalence of depression and anxiety disorder in the 31 days following acute myocardial infarction.[1]

Literature data show us that the association of some risk factors for coronary artery disease, such as diabetes mellitus, hypercholesterolemia, smoking and a sedentary lifestyle, has been studied in the last two decades and the studies agree regarding their association with depression and anxiety disorder in these patients.[2-6]

As for the mechanism that could trigger depression and anxiety disorder after acute myocardial infarction, it might be explained as a type of post-traumatic stress, in which individuals affected by a disease that puts them at risk of impending death makes them think about how their life will be altered after this clinical event, such as changes in habits, possible sequelae, and limitations to the activities of daily living. The disease experience can precipitate stressful feelings and reactions, which include pictures of depression and anxiety disorder.[7,8]

Moreover, in recent years, when searching for new concepts to understand the development of depression, and so come up with better treatments, research has demonstrated the immune system participation, particularly the inflammatory response, as a potentially important contributor to the pathophysiology of depression.[9] It is noteworthy the fact that these inflammatory factors, such as C-reactive protein, TNF-α and Interleukin-6 are also elevated in the acute phase of myocardial infarction.[10]

Finally, it is very interesting that two diseases with a strong association with inflammatory factors appear concomitantly and with their prevalence presented herein.

We hope future studies will be designed with the specific aim of elucidating this interesting association.

Keywords

Myocardial Infarction; Anxiety; Depression; Risk Factors, Inflammation; Gender Identity; C-Reactive Protein.

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References

1. Serpytis P, Navickas P, Lukaviciute L, Navickas A, Aranauskas R, Serpytis R, et al. Gender-based differences in anxiety and depression following acute myocardial infarction. Arq Bras Cardiol. 2018; 111(5):676-683
2. Moreira RO, Papelbaum M, Appolinario JC, Matos AG, Coutinho WF, Meirelles RMR, et al. Diabetes mellitus and depression: a systematic review. Arq Bras Endocrinol Metab. 2003;47(1):19-29.
3. Fráguas R, Soares SMSR, Bronstei MD. Depression and diabetes mellitus. Rev Psiq Clín. 2009;36(suppl 3):93-9.
4. Vural M, Acer M, Akbaş B. The scores of Hamilton depression, anxiety, and panic agoraphobia rating scales in patients with acute coronary syndrome. Anatol J Cardiol. 2008;8(1):43-7.
5. Farinha H, Almeida J, Aleixo AR, Oliveira H, Xavier F, Santos AL. Relationship between smoking and anxiety and depression in primary care. Acta Med Port. 2013;26(5):523-30.
6. Zhai L, Zhang Y, Zhang D. Sedentary behaviour and the risk of depression: a meta-analysis. Br J Sports Med. 2015;49(11):705-9.
7. Yehuda R. Post-traumatic stress disorder. N Engl J Med. 2002; 346(2):108-14.
8. Sardinha A, Nardi AE, Zin WA. Ataques de pânico são realmente inofensivos? O impacto cardiovascular do transtorno de pânico. Rev Bras Psiquiatr. 2009;31(1):57-62.
9. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171-86.
10. Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012;379(9822):1214–24.

Usefulness of Preoperative Venography in Patients with Cardiac Implantable Electronic Devices Submitted to Lead Replacement or Device Upgrade Procedures

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Abstract

Background: Venous obstructions are common in patients with transvenous cardiac implantable electronic devices, but they rarely cause immediate clinical problems. The main consequence of these lesions is the difficulty in obtaining venous access for additional leads implantation.

Objectives: We aimed to assess the prevalence and predictor factors of venous lesions in patients referred to lead reoperations, and to define the role of preoperative venography in the planning of these procedures.

Methods: From April 2013 to July 2016, contrast venography was performed in 100 patients referred to device upgrade, revision and lead extraction. Venous lesions were classified as non-significant (< 50%), moderate stenosis (51-70%), severe stenosis (71-99%) or occlusion (100%). Collateral circulation was classified as absent, discrete, moderate or accentuated. The surgical strategy was defined according to the result of the preoperative venography. Univariate analysis was used to investigate predictor factors related to the occurrence of these lesions, with 5% of significance level.

Results: Moderate venous stenosis was observed in 23%, severe in 13% and occlusions in 11%. There were no significant differences in relation to the device side or the venous segment. The usefulness of the preoperative venography to define the operative tactic was proven, and in 99% of the cases, the established surgical strategy could be performed according to plan.

Conclusions: The prevalence of venous obstruction is high in CIED recipients referred to reoperations. Venography is highly indicated as a preoperative examination for allowing the adequate surgical planning of procedures involving previous transvenous leads. (Arq Bras Cardiol. 2018; 111(5):686-696)

Keywords: Pacemaker, implantable defibrillators, phlebography, venous stenosis, extraction of leads, risk factors.

Introduction

Venous obstructions frequently occur in patients with transvenous cardiac implantable electronic devices (CIED), with an estimated 14 to 64% prevalence.[1-11] Those lesions are mostly asymptomatic, although visible collateral circulation in the thoracic region is usually found. Although deep venous thrombosis, pulmonary thromboembolism, or superior vena cava syndrome were found in 1.6 to 12% of the cases, the difficulty in gaining access to implant new additional leads or other types of transvenous devices has been the main consequence of those lesions.[12-16]

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Recent studies have shown an increase in the number of reoperations in which it is necessary to handle the intravascular territory with leads previously implanted.[17-23] The increase in this type of procedure is due to three main factors: (1) patients' increasing longevity, which is directly related to the longer period of time leads remain in the territory and, consequently, to a greater chance of dysfunction of the stimulation system's components; (2) an increase in comorbidities leading to an increase in the occurrence of infectious complications, whose treatment necessarily requires the complete CIED removal[17-23] and (3) an increasing prevalence heart failure and, consequently, of the need to upgrade from the conventional pacemaker to more advanced modes, such as implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT), which require the implantation of additional leads.[24-27]

Digital subtraction venography provides excellent characterization of the venous anatomy and has been deemed the gold standard for studying venous lesions in CIED patients.[11,28-30] Although other imaging techniques are used for the same purpose, such as Doppler ultrasonography or contrast

recirculation in thoracic computed tomography images, these methods are not as accurate as digital venography to quantify and define where obstructions are located and any collateral circulation developed.[31-34]

This study is part of a prospective registry, with data derived from medical practice, and its goals are: (1) to identify the prevalence, degree and location of venous lesions in CIED patients with an indication of reoperation; (2) to identify predisposing factors of these venographic changes; and (3) to define the role of digital subtraction venography when intravascular reinterventions are planned in individuals with leads previously implanted.

Methods

Study Design and Population

This is a cross-section analysis derived from a cohort where thromboembolic complications are studied in patients submitted to lead revision or upgraded procedures. This study was conducted in a high-complexity cardiology hospital and it was approved by that hospital's Committee of Ethics in Research. All subjects signed a free and informed consent form.

From April 2013 to July 2016, patients who met the following criteria were consecutively included: (1) having CIED implanted at the territory of the superior vena cava for more than six months; (2) being between 18 and 90 years of age; (3) having an indication for lead revision or upgrade procedures. The following candidates were not included: (1) individuals with creatinine > 1.5 mg/dL due to the risk of renal damage from iodinated contrast; (2) candidates that had known allergy to iodinated contrast media; and (3) those who declined to participate in the study.

Considering the high rates of venous lesions in these patients, a convenience sample of 100 patients was defined to detect the outcomes studied.

Study Outcomes

The outcomes of the study included: (1) venographic findings of significant venous obstructions and collateral circulation, and (2) usefulness of the preoperative venographic findings when planning and performing the surgical procedure.

Study Workflow

Patients with an indication of reoperation for implantation of additional leads, replacement or removal of previously-implanted transvenous leads, and who met the eligibility to the study were submitted to preoperative evaluation comprising patient background assessment, clinical evaluation and evaluation of imaging exams.

Thorax radiography was conducted to help determining the position of the leads in use or abandoned.

The venous system was evaluated using digital subtraction venography through images acquired with an Allura DSA unit or Allura Xper FD20 (Philips, The Netherlands) to bilaterally assess the axillary, cephalic, subclavian, innominate (or brachiocephalic trunk) veins, and superior vena cava. Continuous infusion of low-osmolality nonionic iodinated contrast media (Visipaque-Iodixanol, 320 [652 mg/mL Iodixanol], GE, Healthcare, Europe) was performed using a MEDRAD injection pump with controlled volume (100 mL to 120 mL) and infusion speed (10 mL/s at 600 psi pressure). All exams were simultaneously evaluated by two specialists: a Vascular Interventional Radiologist and a Cardiac Pacing Specialist.

The images obtained were classified according to the presence or absence of venous lesions and of collateral circulation. Venous lesions were classified according to their stenosis level: without significant alteration (< 50%), moderate stenosis (51-70%), severe stenosis (71-99%), and occlusion (100%).

Surgical Procedures

Surgical procedures were performed according to the hospital's usual routines, always under the supervision of an anesthesiologist. Operations were grouped in three main types: (1) Implanting new leads without further removal (due to dysfunction of a previously implanted lead, or upgrade procedures); (2) Replacing leads with the removal of previously implanted leads; or (3) Isolated lead extraction.

Operations were planned according to the radiological function of the venous territory obtained through venography: (1) In cases where the venous pattern was deemed without significant lesions or with moderate lesions, no special care was taken to implant new leads and, similarly, the decision of removing a deactivated lead was made at the surgical team's discretion. (2) In cases with stenosis deemed severe or occlusions, surgical planning considered: a) careful evaluation of the venography to check the possibility of using the ipsilateral internal jugular vein; b) preparing the patient for transvenous lead extraction to provide access for the new lead when using the ipsilateral internal jugular was not possible; c) reserving material for attempts to go beyond a lesion and perform venous dilation.

The decision whether to remove or abandon in situ the previously abandoned leads or the ones that would be deactivated in the current surgical procedure was made considering the following criteria: (1) patient's age and life expectancy; (2) number of leads remaining in the superior vena cava at the end of the surgical procedure performed in this study; (3) risk of worsening the lesions observed in the venography.

Although the criteria for defining an access to deactivated leads and whether to remove or abandon them were previously discussed with the surgical team involved in the study, the final decision on both topics was to be made by the team itself during the procedure due to the intraoperative findings and technical resources available.

Agreement between Planned and Actually Performed Procedure

To assess the agreement between the procedure planned according with the venography findings and the procedure actually performed, three conditions were considered: (1) possibility of access to the heart by the subclavian vein without any special strategies; (2) possibility of access to the heart by the ipsilateral internal jugular vein when there was a severe

lesion or subclavian vein occlusion; (3) whether lead extraction or other unconventional technique was required to gain access in cases of critical lesion affecting the subclavian vein, internal jugular vein and venous brachiocephalic trunk.

Care Provided for Study Subjects

The risks associated with the present study were related to the use of iodinated contrast media. Special care was taken to reduce the risk of renal damage following digital subtraction venography, although adverse reactions related to the use of non-ionic iodinated contrast agents are rare. Diabetic patients receiving oral hypoglycemic metformin hydrochloride were instructed to discontinue the use of that drug for 48 hours before the test and resume use 48 hours after the test. The cases of allergic reactions to iodinated contrast during or after the exams were treated according to the institution's protocol for allergic reactions to contrast.

Electronic Data Collection and Management

The demographic, clinical and surgical data obtained were stored at the database developed in the REDCap system (*Research Electronic Data Capture*)[35] hosted at the hospital's server.

Variables Studied and Statistical Analysis

The following data were analyzed as independent variables for the risk of occurrence of the outcomes studied: demographic data, preoperative clinical data at baseline, type of CIED, and type of procedure performed.

The data recorded in the database (REDCap) were exported in the format of Excel worksheets (*Microsoft Excel*) and analyzed using SAS software (*Statistical Analysis System*).

Initially all variables were analyzed descriptively. The quantitative variables were analyzed by considering the minimal and maximum values, means, standard deviation and median. The qualitative variables were analyzed by calculating the absolute and relative frequencies. We compared means using Student t-test, and tested homogeneity among the variable proportions using chi-square test. The significance level chosen for statistical tests was 5%.

The outcomes of the study were described according to absolute and relative frequencies. The calculation of *Odds Ratio* (OR) and its confidence intervals at 95% were used as an effect measure between exposure variables and outcome development.

Results

Of 289 patients with an indication of reoperation involving the handling of leads, 100 were included in this study. (Figure 1)

The population was balanced with regard to gender, had a predominance of Caucasian individuals (82%) and a mean age of 58.5 ± 15.1 years, with median 60. Most individuals studied were oligosymptomatic for heart failure (77%), with a left ventricular ejection fraction of 53.4 ± 15.5, 39% of which had no structural cardiac disease identified. Only 20% of cases did not have any comorbidity. One third of this population was using antiplatelet agents, while anticoagulants were used by 12% of the patients (Table 1).

There was a balance in the number of cases with devices implanted on the right side (48%) and those on the left side (52%). Marking differences were observed, however, concerning time since implantation, with an average 14.3 ± 6.1 years for the right side, and 8.0 ± 7.9 years for the left side; as to the type of device, there were more conventional pacemakers on the right, while the four device types were more evenly distributed for the left side. (Table 2)

Results of Digital Subtraction Venography

Analyses of the venographies showed that 47 patients had significant venous lesions and that in 36 out of those there was venous collateral circulation. Moderate venous obstructions were observed in 23 exams, severe in 13, and occlusions in 11. Of the 53 patients without significant obstructions (< 50% of

Table 1 – Demographic and clinical characteristics of the study subjects

Demographic and Clinical characteristics at baseline	
Male, n (%)	48%
Age (years), means ± DP	58.5 ± 15.1
Caucasian, n (%)	82%
Body mass index, means ± DP	25.7 ± 3.2
Functional class (NYHA), n (%)	
I	40%
II	37%
III	23%
Structural heart disease, n (%)	
None	39%
Chagas disease	23%
Ischemic heart disease	8%
Non-ischemic heart disease	24%
Other	6%
Associated comorbities	
None	20%
Systemic arterial hypertension	62%
Diabetes	17%
Dyslipidemia	33%
Coronary arterial disease	9%
Valvopathy	7%
Smoker (current)	1%
Smoker (previously)	9%
Medicines being used, n (%)	
Antiplatelet agents	33%
Oral anticoagulants	12%
Statins	39%
Left ventricular ejection (%) means ± DP	53.4 ± 15.5

SD: Standard deviation; NYHA: New York Heart Association.

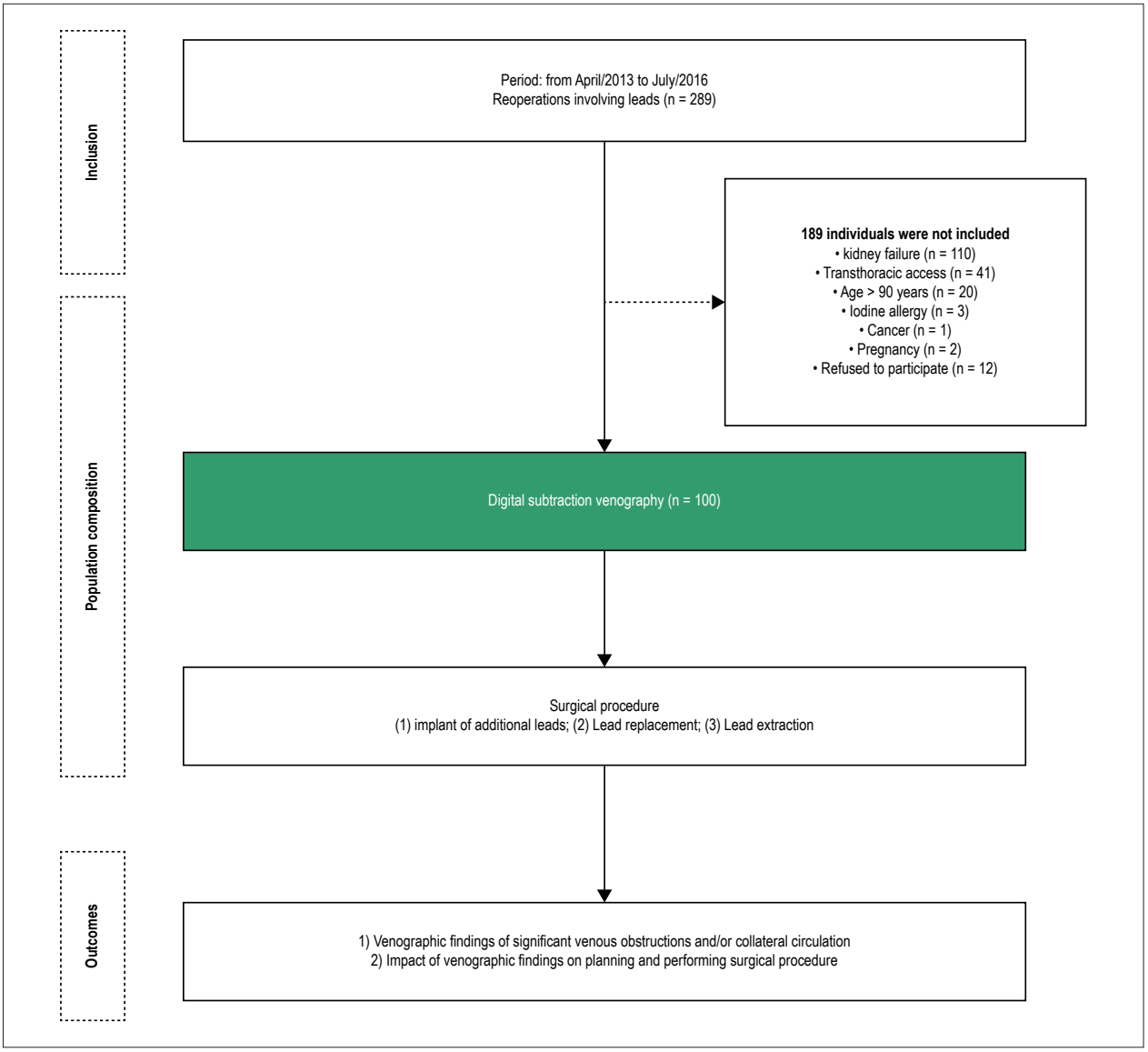

Figure 1 – *Composition of the population studied and Study phases.*

blood vessel lumen), only 4 had collateral circulation. On the other hand, out of the 24 individuals with venous lesion deemed severe or with venous occlusion, just 2 did not present collateral circulation in their venography. Therefore, finding collateral circulation in venography was observed to be a strong marker of the presence of venous lesion, increasing 4.9 times the prevalence rate (CI 95% 3.05 – 8.10; $p < 0.0001$) of those lesions (Figures 2 and 3).

Despite the differences of time since implantation and types of devices implanted, there was balance between the findings of venous lesions ($p = 0.865$) and of collateral circulation ($p = 0.715$) in patients with devices implanted on the right and left sides. Regardless of the side the CIED had been implanted, subclavian veins and the transition from subclavian veins to the brachiocephalic trunk were the regions that presented the highest number of significant lesions (Table 3). No significant lesions were identified in the superior vena cava.

Indication of surgical procedure

The main reason to perform a surgical procedure was lead dysfunction, in 71 patients. Upgrade procedures was the cause of reoperation in 25 cases. Only for 4 patients the operation was caused solely by a need of lead removal (Table 4).

Leads were removed from 52 patients. Transvenous extraction with mechanical or laser sheaths was performed in 36 patients, while leads were removed through simple traction in just 16 cases. At the end of the operation, only 4 patients remained without any transvenous lead implanted, and in most cases (90%), two or three leads remained in the venous territory.

Table 2 – Characteristics of the cardiac device being used at the time of inclusion in the study according to the side of the implant

Characteristics of the previous CIED	Right side (n = 48)	Left side (n = 52)	p
Type of CIED, n (%)			
Conventional pacemaker	45	31	
Conventional ICD	1	18	< 0.001 (1)
CRT	1	1	
CRT-D	1	2	
Total number of transvenous leads, n (%)			
One	10	12	
Two	33	37	0.306 (1)
Three	4	3	
Four	1	-	
Dwelling time of transvenous leads, years			
Means ± SD	14.3 ± 6.1	8.0 ± 7.9	0.075 (2)
Variation	5 - 37	1 - 32	

CIED: cardiac implantable electronic device; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy associated with implantable cardioverter-defibrillator. (1) Chi-square test; (2) Student t-test

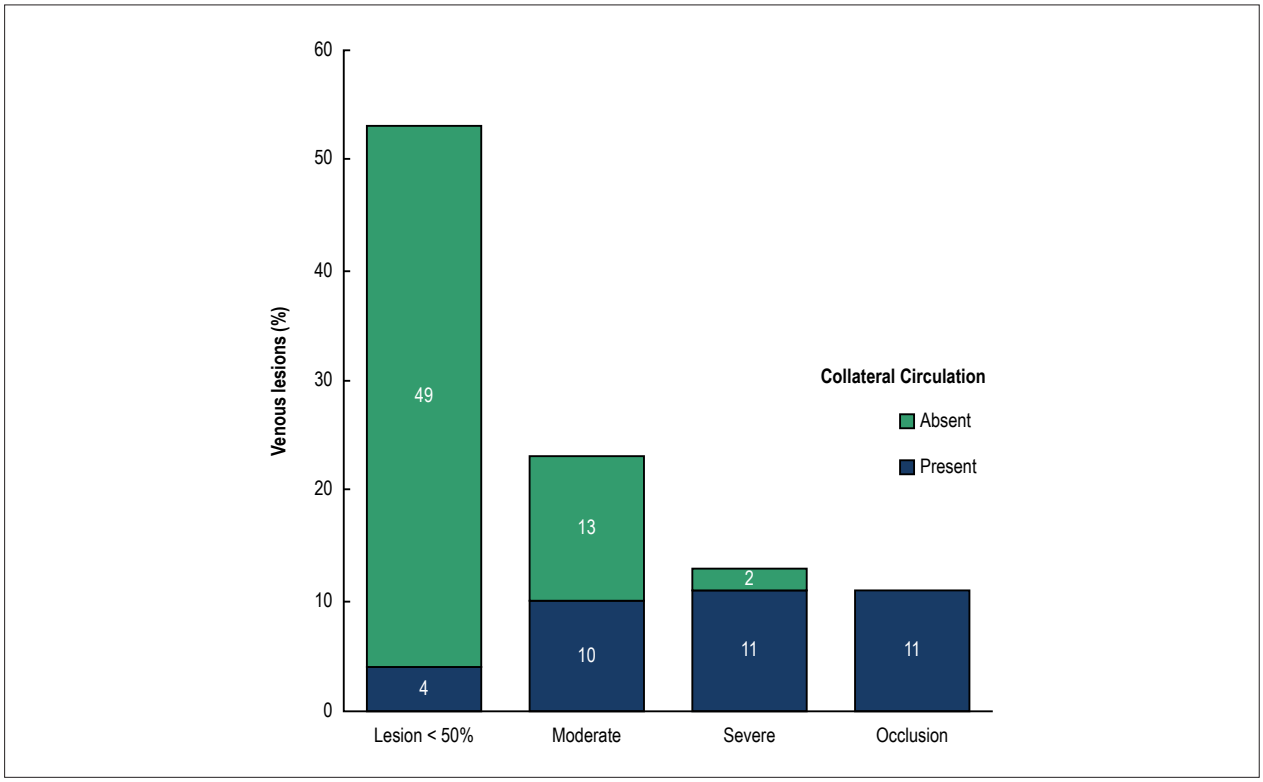

Figure 2 – *Distribution of the four types of venous lesions and their associations with the presence of collateral circulation.*

Usefulness of Venography to Define Surgical Planning

Agreement between the surgical strategy based on the analysis of digital subtraction venography and the surgical procedure actually performed occurred in 99 out of the 100 patients operated. Lack of agreement, which occurred with a single patient, arose from a mistake in classifying the degree of a lesion in the right subclavian vein, which was deemed moderate in the preoperative period, but during the operation was found to be a sub-occlusive lesion (Table 5).

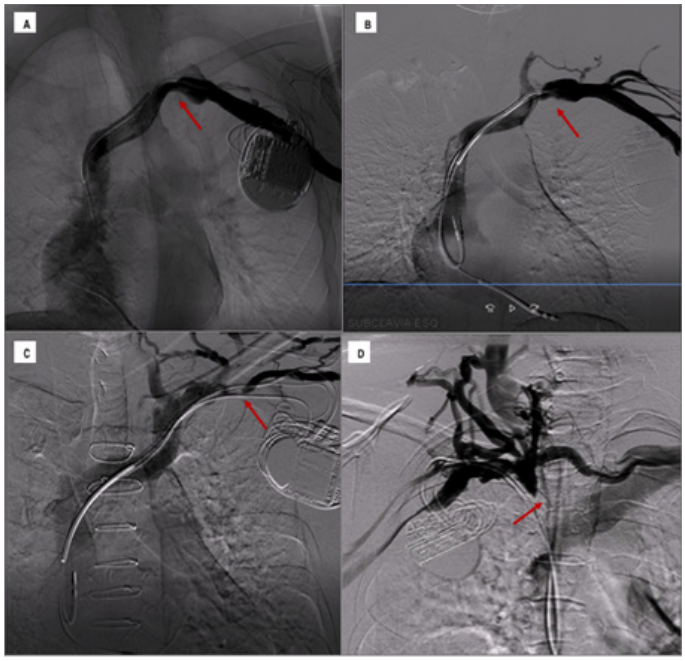

Figure 3 – *Classification of venous lesions and collateral circulation. Examples of the four types of lesion according to the classification adopted in the study. Figure 3A: non-significant lesions characterized with obstruction of less than 50% of the blood vessel lumen and absence of collateral circulation; Figure 3B: moderate lesion in 51% to 70% of the vessel, with discrete collateral circulation; Figure 3C: severe lesion compromising 71% to 99% of the vessel with moderate collateral circulation; Figure 3D: venous occlusion with accentuated collateral circulation.*

In all the cases studied, surgical planning was based on the findings of preoperative venography. Of the 53 patients without significant lesions, there were 28 cases in which we decided to implant new leads without removing the old ones, while in 22 cases the implantation of new leads was combined with removal of old ones in order to avoid overpopulation. There was complete removal of the system in other 3 cases.

On the other hand, of the 23 cases where moderate stenosis had been diagnosed, there were 14 in which there was the implantation of new leads combined with the removal of old ones; only in 9 cases our decision was to implant new leads and maintain the old ones.

In the 24 cases where new leads did not require any removal and severe stenosis or venous occlusion had been diagnosed, the findings in the venography showed that in 13 cases the internal jugular vein and the ipsilateral brachiocephalic trunk of the implant were free from any obstructions. Of those, only in 2, because the patients were young, a transvenous extraction procedure was planned to avoid overpopulation of leads. Of the 11 cases where no extraction was performed, there were 5 in which the internal jugular vein was used as access. In the other 5 cases, it was possible to go beyond the lesion in the subclavian vein with the aid of 0,14" hydrophilic wire guides. Of the 8 cases where the internal jugular veins could not be used as access because there was obstruction in the ipsilateral venous brachiocephalic trunk, in only one case the medical team chose to conduct a new contralateral implantation. In the remainder (7), transvenous extraction was the chosen access.

Leads were removed without implanting new ones in only 4 cases: in 3, to treat an infection related to the device, and in 1 to remove a dysfunctional lead which was causing noise in an ICD. In this last case the venography showed venous occlusion.

Prognostic Factors of Venographic Alterations

Despite the high rate of venographic outcomes in the patients studied, it was not possible to identify prognostic factors for the occurrence of venographic alterations. The following variables were tested as probable prognostic factors: gender, age at the time of the venographic study, cardiopathy at baseline, functional class for heart failure, use of oral anticoagulants and antiplatelet agents, having an ICD lead, CIED implantation side, time since CIED implantation, number of leads implanted, left ventricular ejection, and previous procedures of reoperation (Figure 4).

Discussion

Venous obstructions seldom cause immediate clinical problems. However, when new leads have to be implanted, the presence of those lesions can make the procedure impossible with conventional techniques. Thus, digital subtraction venography has been mostly used because it allows identifying precisely how serious venous lesions are, as well as their location, thus allowing the planning of proper surgical strategy.[11,28-30]

Table 3 – Distribution of venographic findings according to the CIED side and the anatomical location of the lesion

Venographic findings	Right side (n = 48)	Left side (n = 52)
Normal exam / discrete lesions (< 50% of vessel lumen)		
Subclavian vein	37	43
Transition from subclavian vein to innominate vein	46	44
Innominate vein	42	46
Joint of innominate vein and superior vena cava	33	46
Moderate stenosis		
Subclavian vein	4	5
Transition from subclavian vein to innominate vein	-	4
Innominate vein	1	2
Joint of innominate vein and superior vena cava	8	2
Severe stenosis		
Subclavian vein	3	2
Transition from subclavian vein to innominate vein	2	3
Innominate vein	1	1
Joint of innominate vein and superior vena cava	3	3
Venous occlusion		
Subclavian vein	4	2
Transition from subclavian vein to innominate vein	-	1
Innominate vein	4	3
Joint of innominate vein and superior vena cava	4	1
Collateral circulation		
Absent	19	29
Discrete	13	7
Moderate	5	8
Strong	11	8

CIED: cardiac implantable electronic device.

Table 4 – Characteristics of surgical procedures performed in the study

Characteristics of Surgical Procedures	n = 100
Procedure performed, (%)	
Implant of additional lead without removing previously implanted lead	48
Implant of additional lead with removal of previously implanted lead	48
Only lead removal	4
Total number of transvenous leads at the end of the procedure, (%)	
None	4
One	6
Two	41
Three	42
Four	7
CIED side at the end of the procedure, n (%)	
Right	45
Left	54
Subxiphoid	1

CIED: cardiac implantable electronic device.

Table 5 – Agreement between the surgical strategy defined using preoperative venography and the surgical procedure performed

Surgical planning	Cases planned	Cases performed
• Venous stenosis < 50% to moderate stenosis Direct access through the cephalic subclavian/cephalic vein	76	75
• Severe stenosis or occlusion, with jugular vein and/or brachiocephalic trunk without obstructive lesions Access through internal jugular vein	11	11
• Severe stenosis or occlusion, with jugular vein and/or brachiocephalic trunk with obstructive lesions Lead extraction	13	14

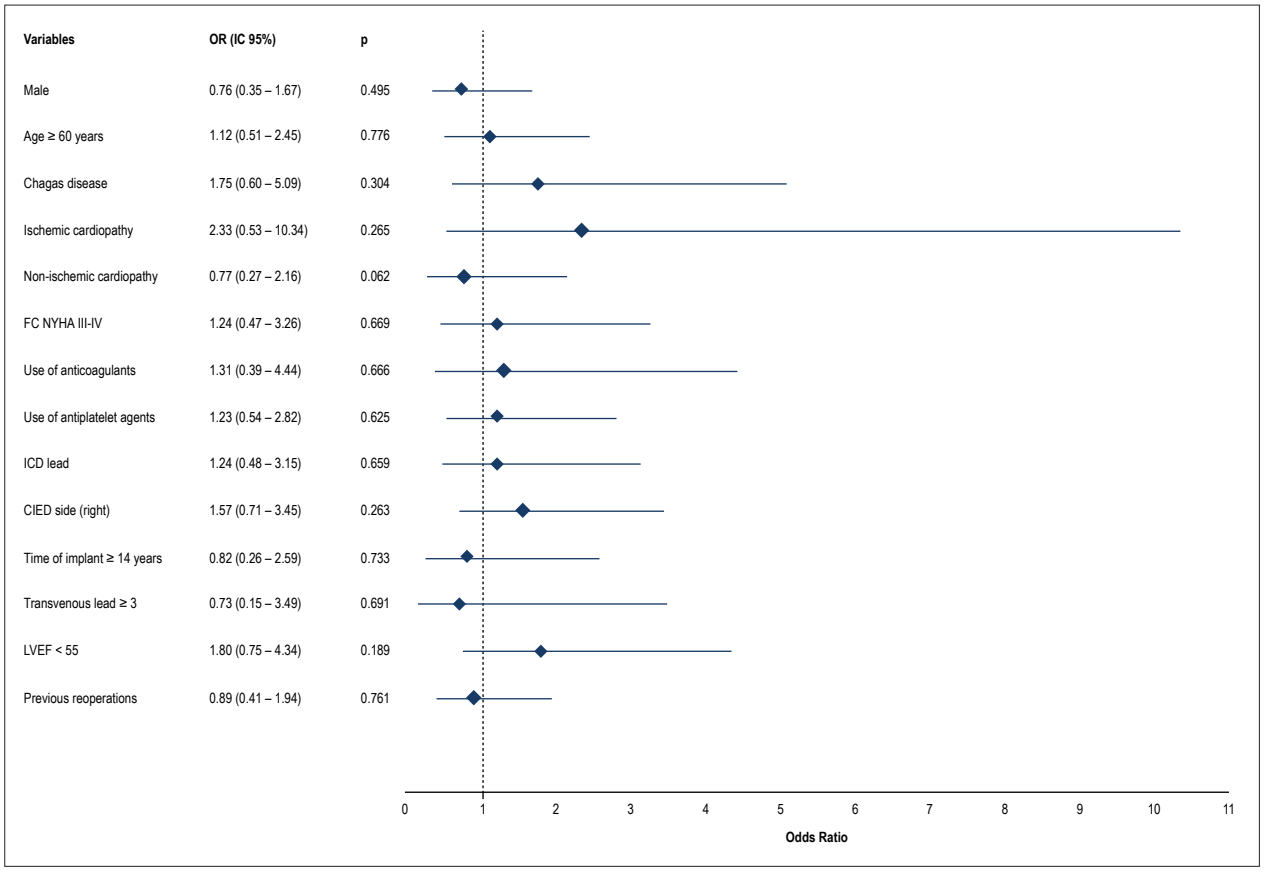

Figure 4 – *Risk factors for the occurrence of significant venous lesions (> 50% of obstruction of blood vessel lumen) and/or presence of collateral circulation.*

The high prevalence of individuals with lesions deemed significant in this study was compatible with other experiences reported in the literature.[1-11] Regardless of lesion seriousness, their distribution was balanced among the subclavian veins, the venous brachiocephalic trunk or the transitional areas of those veins.

Despite the particularities existing among the anatomy of the veins draining the left side and the right side of the thorax, the venographic study did not identify significant differences in the frequency of those findings, in how serious the stenosis was, or in the location of the lesions between the two sides. However, there were differences in the average time leads had remained implanted, i.e., longer for patients who had the device implanted on the right side, which may have increased the rate of occurrences of lesions in the right territory. On the other hand, despite the balance between the numbers of leads implanted, the number of defibrillator leads, which is deemed a risk factor for venous lesions, was significantly higher in the cases where the CIED had been implanted on the left side.[1-4-8]

The strong association between the presence of collateral circulation and severe or occlusive venous lesions, which was observed in this study, is quite useful to interpret venographies. Therefore, we can say that whenever there is collateral circulation, lesions difficult to be defined have to be carefully

looked for. In this respect, we suggest maintaining dynamic venography images, which allow following the iodinated contrast path. Often enough, when the contrast passes exclusively through the collateral circulation, it fully fills up the blood vessel lumen soon after the critical lesion, which prevents it from being detected in still images.

The high rate of patients with severe or occlusive lesions observed in this study, which agrees with the data in the literature, evidenced the importance of venography for surgical planning. In cases where significant venous lesions could not be identified, the surgical team were able to plan a procedure in which deactivated leads should (or should not) be extracted by considering solely factors such as patient age or the number of leads that would remain in the venous territory. On the other hand, in patients where moderate lesions were observed, the medical team could plan which leads should be extracted in order to avoid an overpopulation of leads that could worsen obstructions. And, finally, in the cases where severe or occlusive venous lesions were observed, the knowledge of the venous anatomy was of essence to plan the surgery, since it raises the possibility of using the ipsilateral jugular vein or the need of extracting leads to gain proper access.

Since causes are multifactorial, the literature is controversial as to defining predictive factors of thromboembolic complications in CIED patients.[2-11-36-37] In this respect, the absence of risk factors for venous lesions found in this study sample confirms the importance of preoperative venography in patients requiring lead reoperations, since it was not possible to identify any subgroup of individuals less subject to venous obstructions.

Study Limitations

Although this study is part of a prospective registry derived from medical practice, due to the non-inclusion criteria used, our conclusions cannot be extended to children, to individuals over 90 years of age and to those with renal dysfunction with serum creatinine over 1,5 mg/dL.

As to the rate of venous alterations found and their predisposing factors, this analysis has the same limitations as other cross-sectional studies, as they were assessed at a particular time.

Conclusions

The high prevalence of severe obstructions or venous occlusions in CIED patients makes a transvenous implant of new leads difficult in a considerable number of patients. Sometimes, using non-conventional techniques, such as the extraction of leads to achieve access, can be mandatory. The lack of predisposing factors and the absence of clinical signs of venous obstruction, which occurs in most patients with severe or occlusive lesions, can hinder the planning of a surgery. Thus, digital subtraction venography is quite useful to define a surgical strategy in operations for lead revision or upgrade procedures. The finding of collateral veins in this exam has a high predictive value for diagnosing severe and occlusive lesions.

Author contributions

Conception and design of the research and Writing of the manuscript: Albertini CMM, Silva KR, Costa R; Acquisition of data: Albertini CMM, Leal Filho JMM, Crevelari ES; Analysis and interpretation of the data: Albertini CMM, Silva KR, Leal Filho JMM, Costa R; Statistical analysis: Silva KR; Critical revision of the manuscript for intellectual content: Albertini CMM, Silva KR, Martinelli Filho M, Carnevale FC, Costa R.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Análise de Projetos de Pesquisa (CAPPesq) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number 0730/11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Mond HG, Crozier I. The Australian and New Zealand cardiac pacemaker and implantable cardioverter-defibrillator survey: calendar year 2013. *Heart Lung Circ*. 2015;24(3):291-7.
2. Oginosawa Y, Abe H, Nakashima Y. The incidence and risk factors for venous obstruction after implantation of transvenous pacing leads. *Pacing Clin Electrophysiol*. 2002;25(11):1605-11.
3. Costa SS, Scalabrini Neto A, Costa R, Caldas JG, Martinelli Filho M Incidence and risk factors of upper extremity deep vein lesions after permanent transvenous pacemaker implant: a 6-month follow-up prospective study. *Pacing Clin Electrophysiol*. 2002;25(1):1301-6.
4. Lickfett L, Bitzen A, Arepally A, Nasir K, Wolpert C, Jeong KM et al. Incidence of venous obstruction following insertion of an implantable cardioverter defibrillator. A study of systematic contrast venography in patient presenting for their first elective ICD generator replacement. *Europace*. 2004;6(1):25-31.
5. Van Rooden CJ, Molhoek SG, Rosendaal FR, Schalij MJ, Meinders AE, Huisman MV. Incidence and risk factors of early venous thrombosis associated with permanent pacemaker leads. *J Cardiovasc Electrophysiol*. 2004;15(11):1258-62.
6. Rozmus G, Daubert JP, Huang DT, Rosero S, Hall B, Francis C. Venous thrombosis and stenosis after implantation of pacemakers and defibrillators. *J Interv Card Electrophysiol*. 2005;13(1):9-19.

7. Korkeila P, Nyman K, Ylitalo A, Koistinen J, Karjalainen P, Lund J, et al. Venous obstruction after pacemaker implantation. *Pacing Clin Electrophysiol*. 2007;30(2):199-206.

8. Haghjoo M, Nikoo MH, Fazelifar AF, Alizadeh A, Emkanjoo Z, Sadr-Ameli MA. Predictors of venous obstruction following pacemaker or implantable cardioverter-defibrillator implantation: a contrast venographic study on 100 patients admitted for generator change, lead revision, or device upgrade. *Europace*. 2007;9(5):328-32.

9. Costa R, Silva KR, Rached RA, Martinelli Filho M, Carnevale FC, Moreira LFP, Stolf NAG. Prevention of venous thrombosis by warfarin after permanent transvenous leads implantation in high-risk patients. *Pacing Clin Electrophysiol*. 2009;32(Suppl 1):S247-51.

10. Pieper CC, Weis V, Fimmers R, Rajab I, Linhart M, Schild HH, et al. Venous obstruction in asymptomatic patients undergoing first implantation or revision of a cardiac pacemaker or implantable cardioverter-defibrillator: A Retrospective Single Center Analysis. *RoFo*. 2015;187(11):1029-35.

11. Boczar K, Zabek A, Haberka K, Hardzina M, Debski M, Rydlewska A, et al. Venous stenosis and occlusion in the presence of endocardial leads. *Adv Clin Exp Med*. 2016;25(1):83-91.

12. Lin CT, Kuo CT, Lin KH, Hsu TS. Superior vena cava syndrome as a complication of transvenous permanent pacemaker implantation. *Jpn Heart J*. 1999;40(4):477-80.

13. Sbragia P, Nait-Saïdi L, Trigano JA, Saadjian A, Barnay P, Lévy S. Intra-atrial thrombosis and pulmonary embolism complicating pacemaker leads for cardiac resynchronization therapy. *J Interv Card Electrophysiol* .2003;9(1):25-7.

14. Aryana A, Sobota KD, Esterbrooks DJ, Gelbman AI. Superior vena cava syndrome induced by endocardial defibrillator and pacemaker leads. *Am J Cardiol* .2007;99(12):1765-7.

15. Noheria A, Ponamgi SP, Desimone C V, Vaidya VR, Aakre CA, Ebrille E, et al. Pulmonary embolism in patients with transvenous cardiac implantable electronic device leads. *Europace*. 2015;18(2):246-52.

16. Korkeila P, Mustonen P, Koistinen J, Nyman K, Ylitalo A, Karjalainen P, et al. Clinical and laboratory risk factors of thrombotic complications after pacemaker implantation: a prospective study. *Europace*. 2010;12(6):817-24.

17. Brasil. Ministério da Saúde. DATASUS - Secretaria Executiva. [Citado em 2017 dez 12]. Disponível em: http://w3.datasus.gov.br/datasus/datasus.php

18. Li X, Ze F, Wang L, Li D, Duan J, Guo F, et al. Prevalence of venous occlusion in patients referred for lead extraction: implications for tool selection. *Europace*. 2014;16(12):1795-9.

19. Harrison JL, Prendergast BD, Sandoe JA. Guidelines for the diagnosis, management and prevention of implantable cardiac electronic device infection. Heart. 2015;101(4):250-2.

20. Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM,et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med*. 2007;167(7):669-75.

21. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, et al. PEOPLE Study Group. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* .2007;116(12):1349-55.

22. de Oliveira JC, Martinelli M, Nishioka SA, Varejão T, Uipe D, Pedrosa AA, et al. Efi cacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol*. 2009;(1):29-34.

23. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter- defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol*. 2011;58(10):1001-6.

24. Martinelli M, Lorga A, Fagundes AA, Barros ARC, De Paola AAV, Pedrosa A, et al; Sociedade Brasileira de Cardiologia. Diretrizes Brasileiras de Dispositivos Cardíacos Eletrônicos Implantáveis (DCEI). *Arq Bras Cardiol*. 2007;89(6):e210-37.

25. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2013;127(3):e283-352.

26. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace*. 2013;15(8):1070-118.

27. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-327.

28. Marx E, Schulte HD, Balau J, Buyusch KH. Phlebographic and clinical early and late findings in transvenously implanted pacemaker electrodes. *Z Kreislaufforsch* .1972;61(2):115-23.

29. Stoney WS, Addlestone RB, Alford WC Jr, Burrus GR, Frist RA, Thomas CS Jr. The incidence of venous thrombosis following long term transvenous pacing. *Ann Thorac Surg*. 1976;22(2):166-70.

30. Fritz T, Richeson JF, Fitzpatrick P, Wilson G. Venous obstruction: a potential complication of transvenous pacemaker electrodes. *Chest*. 1983;83(3):534-9.

31. Mustafa BO, Rathbun SW, Whitsett TL, Raskob GE. Sensitivity and specificity of ultrasonography in the diagnosis of upper extremity deep vein thrombosis: a systematic review. *Arch Intern Med*. 2002; 25:162(4):401-4.

32. Baarslag HJ, van Beek EJ, Koopman MM, Reekers JA. Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. *Ann Intern Med* .2002;136(12):865-72.

33. Bettmann MA. Noninvasive and venographic diagnosis of deep vein thrombosis. *Cardiovasc Intervent Radiol*. 1988;11(Suppl)S15-20.

34. Baldt MM, Zontsich T, Kainberger F, Fleischmann G, Mostbeck G. Spiral CT evaluation of deep venous thrombosis.

35. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCAP) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81.

36. Hosoda J, Toshiyuki I, Matsumoto K, Sugano T, Ishigami T, Kimura K , et al. Clinical significance of collateral superficial vein across clavicle in patients with cardiovascular implantable electronic device. *Circ J*. 2014;78(8)**:**1846-50.

37. Abu-El-Haija B, Bhave P, Campbell D, Mazur A, Hodgson-Zingman D, Cotarlan V, et al. Venous stenosis after transvenous lead placement: A Study of Outcomes and Risk Factors in 212 Consecutive Patients. *J Am Heart Assoc*. 2015;4(8):e001878

Reintervention in Artificial Cardiac Pacing Systems

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Short Editorial related to the acrticle: Usefulness of Preoperative Venography in Patients with Cardiac Implantable Electronic Devices Submitted to Lead Replacement or Device Upgrade Procedures

Reintervention in artificial cardiac pacing systems that involves lead approach, either for the implantation of a new lead and/or the removal of an old one, is most frequently a difficult procedure, with a high probability of complications. Since the transvenous endocardial route started being used by artificial cardiac pacing systems, lead cables have shown to be more vulnerable to complications;[1] however, when it comes to reintervention, the complications are much more frequent.

The significant prevalence of venous obstruction[2] and the consequent difficulty in obtaining a new venous access, the complexity of percutaneous extraction of old lead cables,[3] in addition to the higher prevalence of surgical infections,[4] constitute some of the complications that determine the greater complexity of reinterventions.

The study "Usefulness of preoperative venography in patients with cardiac implantable electronic devices submitted to lead replacement or device upgrade procedures",[5] calls attention to this ever-growing problem,[6] as the implantable electronic cardiac devices use more lead cables and increase the patients' life expectancy, in addition to emphasizing the importance of a previous venography to program the approach strategy. In the present study, approximately 1/4 of the patients submitted to reintervention had severe venous obstructions or occlusions. In such cases, when a new lead cable is required, the extraction of old ones may be absolutely necessary to attain access.

The venous system exploration through the venography can be performed intraoperatively; however, prior knowledge of possible obstructions allows better programming of the surgical procedure, with a previous request of special materials, such as mechanical or laser-energized sheath systems for lead cable extraction, which should always be available in these cases.

Moreover, considering the cost of these special materials, it is very important in the real world and in our country to have prior authorization from the health care providers to use them, determining cost predictability and minimizing problems when charging for the procedure. The agreement between the programmed and the actual surgical procedure, which occurred in the study in 99% of the cases, strongly reinforced the importance of performing a prior venography when scheduling reintervention procedures.

The lack of knowledge of venous obstructions at the reinterventions leads to the unavailability of lead extraction systems during the procedure, and in those cases requiring the implantation of new lead(s) and in which access cannot be attained, implantation of a contralateral artificial cardiac pacing system while abandoning the old lead cables may be the only option. However, the increase in surgical time, which can result in a higher risk of infection, as well as the increased number of implanted leads, are considerable drawbacks of this approach.

Advances in technology with the development of leadless pacemaker systems will, in the future, address problems with transvenous leads. Nevertheless, the current state of this technology[7,8] with the use of single-chamber devices, is still not able in most cases, to dispense with traditional dual-chamber artificial heart pacing systems with leads, suggesting we will be facing such situations for a long time yet.

As they constitute one of the most difficult and delicate surgical procedures in the area of artificial heart stimulation, re-interventions in lead cables must be very well programmed, in addition to requiring a level of high expertise by the surgeon/rhythmologist. In this sense, performing a venography prior to the procedure is very important, as it was well demonstrated by this article.

Keywords

Electrodes, Implanted; Intraoperative Complications; Catheter Ablation; Pacemaker, Artificial/trends; Arrhythmias, Cardiac.

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References

1. de Voog WG. Pacemaker leads: performance and progress. Am J Cardiol. 1999;83(5B):187D-191D.
2. Santini M, Di Fusco SA, Santini A, Magris B, Pignalberi C, Aquilanis S, et al. Prevalence and predictor fator of severe venous obstruction after cardiovascular electronic device implantation. Europace 2016;18(8):1220-6.
3. Barakat AF, Wazni OM, Tarakji K, Saliba WI, Nimri N, Rickard J, et al. Transvenous lead extraction at the time of cardiac implantable electronic device upgrade: complexity, safety and outcomes. Heart Rhythm 2017;14(12):1807-11.
4. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular electronic device infection in the United States: temporal trends and causative insights. Pacing Clin Electrophysiol 2010;33(4):414-9.
5. Albertini CMM, Silva KR, Motta Leal Filho JMM, Crevelari ES, Martinelli Filho M, Carnevale FC, et al. Utilidade da Venografia Pré-Operatória em Procedimentos de Troca de Cabos-Eletrodos ou Mudança do Modo de Estimulação. Arq Bras Cardiol. 2018; 111(5):686-696.
6. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. J Am Coll Cardiol. 2012;60(16):1540-5.
7. Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, et al. Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker. N Engl J Med. 2015;373(12):1225-35.
8. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, et al. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med. 2016;374(6):533-41.

Vasodilation and Reduction of Systolic Blood Pressure after One Session of High-Intensity Interval Training in Patients With Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is a multifactorial syndrome characterized by a limited exercising capacity. High-intensity interval training (HIIT) is an emerging strategy for exercise rehabilitation in different settings. In patients with HFpEF, HIIT subacute effects on endothelial function and blood pressure are still unknown.

Objective: To evaluate the subacute effect of one HIIT session on endothelial function and blood pressure in patients with HFpEF.

Methods: Sixteen patients with HFpEF underwent a 36-minute session of HIIT on a treadmill, alternating four minutes of high-intensity intervals with three minutes of active recovery. Brachial artery diameter, flow-mediated dilation, and blood pressure were assessed immediately before and 30 minutes after the HIIT session. In all analyses, $p < 0.05$ was considered statistically significant.

Results: There was an increase in brachial artery diameter (pre-exercise: 3.96 ± 0.57 mm; post-exercise: 4.33 ± 0.69 mm; $p < 0.01$) and a decrease in systolic blood pressure (pre-exercise: 138 ± 21 mmHg; post-exercise: 125 ± 20 mmHg; $p < 0.01$). Flow-mediated dilation (pre-exercise: 5.91 ± 5.20%; post-exercise: 3.55 ± 6.59%; $p = 0.162$) and diastolic blood pressure (pre-exercise: 81 ± 11 mmHg; post-exercise: 77 ± 8 mmHg; $p = 1.000$) did not change significantly. There were no adverse events throughout the experiment.

Conclusions: One single HIIT session promoted an increase in brachial artery diameter and reduction in systolic blood pressure, but it did not change flow-mediated dilation and diastolic blood pressure. (Arq Bras Cardiol. 2018; 111(5):699-707)

Keywords: Heart Failure; Arterial Pressure; Exercise; Vasodilatation; Brachial Artery; Endothelium/function.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex and prevalent clinical syndrome characterized by a significant limitation to exercising capacity, and pharmacological treatment has not evidenced any improvement in mortality rates in this scenario yet.[1,2] Therapeutic approaches are limited and they are mainly based on symptom management and control of cardiovascular risk factors, such as high blood pressure (BP).[3-5]

Hypertension is associated with increased oxidative stress and vascular inflammation, closely related to endothelial dysfunction.[6,7] On the other hand, attenuated endothelial function in individuals with HFpEF contributes to intolerance to exercising[8-10] and it is an independent predictor of adverse cardiovascular events.[11,12] As a non-pharmacological intervention, exercise training appears as a potential strategy to be included in HFpEF's therapeutic arsenal.[13,14]

High-intensity interval training (HIIT) has emerged as an exercise modality with a positive impact on some cardiovascular outcomes, and it is at least as effective as moderate-intensity continuous training in patients with heart failure with reduced ejection fraction.[15-17] Recent meta-analyses have demonstrated that HIIT, in a long-term basis, is more effective in promoting endothelial function improvement and BP reduction in individuals with cardiovascular risk factors.[18,19] In previous studies, after one single HIIT session, patients with coronary artery disease and hypertension showed increased brachial artery diameter,[20,21] improved endothelial function,[20] and reduced BP.[21-23]

It is well known that HFpEF patients have attenuated vasodilator reserve while exercising and their ventricular-arterial coupling responses are impaired.[9,10,24] However, the effect of one HIIT session on endothelial function and BP in these patients is still unknown. Considering this gap in the literature, the aim of this study was to evaluate brachial artery diameter, endothelial function, and BP 30 minutes after one HIIT session in patients with HFpEF.

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Methods

Study design and patients

This before-and-after (quasi-experimental) study was conducted between June 2014 and November 2015. Nineteen patients with HFpEF, according to the European Society of Cardiology criteria,[25] were sequentially recruited in an outpatient cardiology clinic of a tertiary hospital in southern Brazil. Eligibility criteria were presence of signs and symptoms of heart failure, preserved ejection fraction (> 50%), diastolic dysfunction (left ventricular end-diastolic volume index < 97 mL/m^2) with increased filling pressure (E/e' > 8), and in the case of E/e' < 15, at least one diagnostic criterion for HFpEF, according to the abovementioned document. Age between 40–75 years, New York Heart Association (NYHA) functional class I to III, and clinical stability under optimal drug therapy in previous 3 months, was also considered criteria for eligibility. Patients with severe lung disease, moderate-to-severe valvular disease and peripheral arterial disease were excluded. Similarly, autonomic neuropathy, unstable angina, a history of complex arrhythmias induced by stress, patients with implantable cardiac electronic devices and those with cognitive and/or limiting musculoskeletal conditions, were excluded.

Firstly, patients underwent a Doppler echocardiography with color flow mapping to confirm the diagnosis criteria for HFpEF. Then, a maximal cardiopulmonary exercise testing was performed to assess ventilatory thresholds and peak oxygen consumption, as well as heart rate response to exercise. Up to 14 days after the cardiopulmonary exercise testing, brachial artery diameter, flow-mediated dilation (FMD) and endothelium-independent dilation were assessed immediately before and 30 minutes after a HIIT session. In the same experimental session, BP and heart rate were measured at two different moments before and after exercise as described below.

Measurements and instruments

Patients' characteristics at baseline

Demographic and clinical data were collected on the first day through a questionnaire and verified in the medical records of each patient. Anthropometric data were collected at the time the questionnaire was completed.

Transthoracic echocardiogram

All echocardiographic examinations were performed using equipment Envisor C HD or HD 11 (Philips, USA) with a standard multifrequency sectorial transducer by a trained cardiologist. Images were acquired following a standardized protocol, following recommendations present in the current guidelines.[25,26] Cine loops and static images of 3 consecutive beats were recorded on standard 2D, M-mode, Doppler and tissue Doppler echocardiographic views. Left ventricular ejection fraction was calculated using the Teichholz formula from the parasternal long-axis view. For patients with regional wall motion abnormalities, the Simpson rule was used to calculate the ejection fraction. Left atrium volume was measured at ventricular systole, just before mitral valve opening, and calculated from apical 4-and 2-chamber views using the biplane method of disks. Left ventricular diastolic function was evaluated with transmitral pulsed Doppler (peak E velocity, peak A velocity, E/A ratio and deceleration time) and mitral annulus tissue Doppler velocity (early diastolic velocity – e', late diastolic velocity – a').

Cardiopulmonary exercise test

The test was performed on a treadmill (General Electric T-2100, GE Healthcare, Waukesha, USA), and breath-by-breath expired gas analysis was carried out using a Cortex Metalyzer 3B system (Cortex Medical, Leipzig, Germany). Heart rate was monitored with a 12-lead electrocardiograph (Nihon Kohden Corporation, Tokyo, Japan), with electrode placement as described by Mason and Likar.[27] BP was measured with a sphygmomanometer (PA 2001, P.A. MED, São Paulo, Brazil) every 3 minutes during the test and also at the physician's discretion. All tests were performed in the morning, with room temperature between 18 and 22°C and relative humidity around 60%, and they were conducted always by the same researcher (ADS), a cardiologist with expertise in cardiopulmonary exercise testing, certified by the Department of Exercise Testing and Cardiovascular Rehabilitation of the Brazilian Society of Cardiology. An individualized ramp protocol was used as described elsewhere in this study.[28] Tests were considered maximal when the respiratory quotient (R) was equal to or higher than 1.10.

Blood pressure

BP was measured with a digital device (G-Tech MA100, Shenzen, China) at four different points in time: 1) pre-assessment of endothelial function (after 15 minutes seating at rest); 2) immediately before HIIT session; 3) 5 minutes after HIIT session; 4) 30 minutes after HIIT session.

Endothelial function

Patients were instructed not to do any type of exercise, not to smoke, and not to dear or drink any caffeine or alcohol for 24 hours before the evaluation. The evaluation started after 15 minutes of seated rest in a room with temperature between 18 and 22ºC. Patients stood in the supine position with their left arm positioned comfortably. Noninvasive measurements of endothelial function were performed using a two-dimensional Philips EnVisor Ultrasound system (Philips, USA) with an electrocardiogram module and a high-frequency (7-12 MHz) vascular transducer.

An image of the brachial artery was obtained 2-5 cm from the antecubital fossa on a longitudinal plane. Artery diameter was manually measured from the anterior and posterior intimal layer. Visual inspection of single frames was performed and calipers were placed at discrete points along the long axis of the B-mode image, when means were calculated.

After measurements of brachial artery diameter were taken at baseline, a sphygmomanometer was inflated on patient's left forearm with 50 mmHg above the systolic BP, remaining there for 5 minutes. Sixty seconds after deflation of the sphygmomanometer cuff, a new image was recorded synchronized with the R wave of the electrocardiogram to identify the artery diameter, enabling FMD measurements.

After 15 minutes (for normalization), the artery diameter was measured again. Then, a dose (0.4 mg) of nitroglycerin spray was administered sublingually. After 5 minutes, another image was recorded to measure endothelium-independent dilation. These data were obtained before exercise and 30 minutes after the HIIT session.

FMD was expressed as the relative change in brachial artery diameter during the hyperemic phase, as follows: [(post-hyperemic diameter – baseline diameter) / baseline diameter] × 100.

High-intensity interval training protocol

The HIIT session was performed on a treadmill according to the protocol recommended by the European Society of Cardiology (ESC).[15] The session started with an 8-minute warm-up at moderate intensity followed by four blocks of 4 minutes each at 85-95% maximal heart rate, 15 to 17 on Borg rating of perceived exertion scale,[29] alternated with 3 minutes at 60-70% maximal heart rate, 11 to 13 on Borg scale. It ended with 3 minutes of cool-down at moderate intensity, totaling 36 minutes. The heart rate target zone stipulated for each block was based on the maximal heart rate reached at cardiopulmonary exercise testing and was continuously measured during training through 12-lead electrocardiographic monitoring (Nihon Kohden Corporation, Tokyo, Japan).

Statistical analysis

Data were analyzed using SPSS, version 20.0. Categorical variables are described as absolute frequencies and percentages. Continuous variables with normal distribution are described as means and standard deviations. The only variable without normal distribution (VE/VCO_2 slope) was described as median and interquartile range. After meeting the assumptions of normality, the Student t-test for paired samples was used to compare means of the endothelial function variables (brachial artery diameter, FMD, and endothelium-independent dilation) pre- and post-exercise. Generalized estimating equations (GEE) were used to compare mean BP and heart rate between four different moments during the experiment. In all analyses, $p < 0.05$ was considered statistically significant.

Results

Initially nineteen patients were included in the study. After the first evaluation, two patients who did not complete the cardiopulmonary exercise testing and one who had a limiting medical condition were excluded, as shown in Figure 1.

Table 1 shows the demographic, anthropometric, and clinical characteristics of the sample.

All patients presented normal ejection fraction, reduced left ventricular end-diastolic volume index and increased filling pressure, as shown in table 2. However, eight patients presented $15 > E/e' > 8$. Among these individuals at least one diagnostic criterion for HFpEF was confirmed. Reduced functional capacity and increased ventilatory inefficiency were identified by cardiopulmonary exercise testing. The mean peak respiratory exchange ratio > 1.1 was reach as maximality criterion as shown in table 3.

All patients tolerated exercise and completed the experimental session. Exercise protocol variables are described in table 4.

One single HIIT session promoted subacute increase of 0.37 ± 0.44 mm in brachial artery diameter, as shown in Figure 2. This increase was also observed in brachial artery diameter post-hyperemia. However, when these data were used to calculate pre- and post-HIIT variation in the artery diameter, there was no difference in absolute FMD and relative FMD. Also, there was no difference in the brachial artery diameter pre-NTG (Nitrogen) and post-NTG. Similarly, there was no difference in absolute endothelium-independent dilation and relative endothelium-independent dilation after one HIIT session, as presented in table 5.

Baseline systolic and diastolic BP were 138 ± 21 mmHg and 81 ± 11 mmHg, respectively. Figure 3 shows variation in BP at four different points in time of the experiment. A significant reduction in systolic BP was observed 5 and 30 minutes after the HIIT session compared to the first measurement. There was no difference in diastolic BP and mean BP before and after the HIIT session.

Discussion

To our knowledge, this is the first study to show that one single session of HIIT is effective in promoting a significant subacute increase in brachial artery diameter, which was accompanied by a significant reduction in systolic BP in patients with HFpEF. Borlaug et al.[9] demonstrated that these individuals have global dysfunction in cardiovascular reserve, showing an impaired reduction in systemic vascular resistance and a blunted increase in blood flow while exercising. According to the authors, these phenomena are potential contributors to limited functional capacity in this situation.

Patients with HFpEF in our sample showed vasodilation after one single HIIT session suggesting that this type of exercise is a stimulus capable of promoting subacute systemic vasomotor changes, even in patients with impaired ventricular-arterial coupling[9-11] and chronic vascular dysfunction.[6,8,30] It is important to mention that some acute and subacute physiological responses to exercise may be clinically relevant. These responses can be superimposed after consecutive exercise sessions are carried out as a temporal summation and they may contribute to chronic adaptations of exercise training.[31] Thus, successive sessions of exercise that increase blood flow, shear stress and, consequently, bioavailability of nitric oxide, may be a key mechanism for chronic adaptations in peripheral hemodynamics.[32] Fu et al. found that after 12 weeks of HIIT, patients with HFpEF increased the VO_2peak and improved peripheral hemodynamics, through increased blood distribution and oxygen extraction by the musculature while exercising.[33]

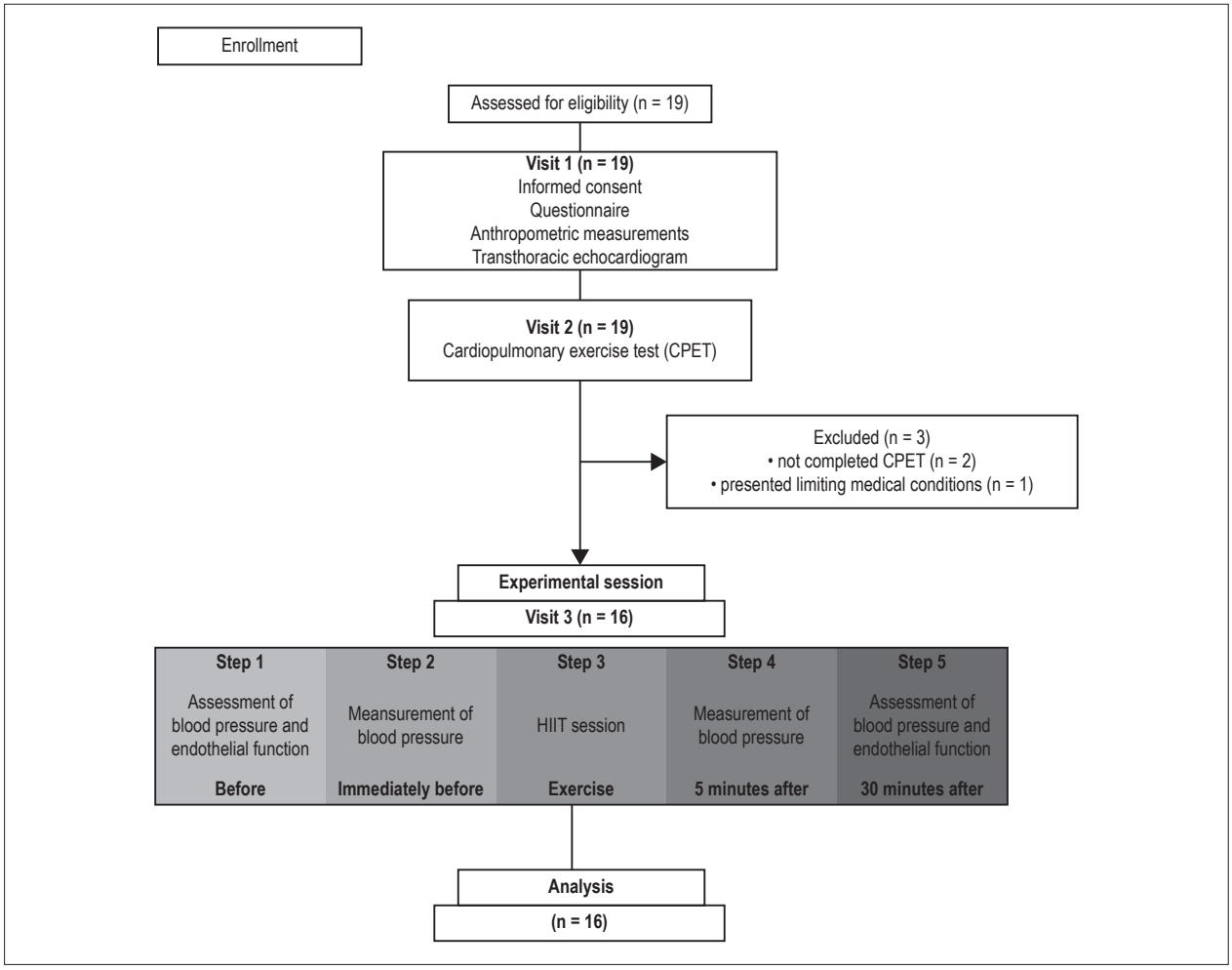

Figure 1 – *Study flow diagram.*

Exercise-mediated increases in shear stress have a strong and dose-dependent effect on conduit artery dilation.[33] Birk et al.[34] observed that vasodilation occurred in a greater extent immediately after highly intensive exercising compared to lowly intensive exercise sessions.[34] However, it seems that the greater the vasodilation promoted by exercise, the lower the vasodilating response observed by occlusion immediately after the exercise session in healthy individuals.

Although there is no previous publication concerning subacute effect of an exercise session on endothelial function in patients with HFpEF, previous studies have evaluated patients with heart failure with reduced ejection fraction in a similar context.[35,36] Those participants responded to a single cycling exercise session with improved forearm endothelium-dependent vasodilation (reactive hyperemia) evaluated by plethysmography up to 30 minutes after exercise.[35] Currie et al.[20] evaluated coronary artery disease patients after one single HIIT session and found an increase in the endothelial function after 60 minutes.[20] In other experiment, the same group showed that only individuals with coronary artery disease with endothelial dysfunction presented augmentation in FMD after 15 minutes of a HIIT session.[21] Interestingly, as in our experiment, in both studies the brachial artery diameter was increased.

Some evidence points out that exercising performed at submaximal intensities closer to the peak of exercise promotes a greater and longer reduction in BP after exercising than when exercising less intensively.[37,38] The hypotensive effect of HIIT is already well established in the literature, but prior to this study, BP had not been evaluated in patients with HFpEF after a session of any type of exercise. In our experiment, we observed an absolute reduction of 12.7 ± 3.8 mmHg in systolic BP 30 minutes after an exercise session. On a chronic basis, this reduction may have clinical relevance, especially in the case of a syndrome whose strict control of BP pressure is crucial. Interestingly, a recent meta-analysis has demonstrated that HIIT performed at least 3 times a week for 12 weeks resulted in a significant reduction in systolic BP in overweigh/obese individuals.[19]

It is noteworthy that in this subgroup of individuals with HFpEF and reduced functional capacity, high-intensity exercising was well tolerated, once appropriate overload (speed and slope) was individually prescribed, always considering the target zones established based on maximal cardiopulmonary exercise test results of each individual.

Table 1 – Participants' characteristics at baseline

Characteristic	n = 16
Female	9 (56%)
Age (years)	59 ± 7
Weight (kg)	87 ± 28
Height (cm)	159 ± 10
Body mass index (kg/m^2)	34 ± 7
Waist circumference (cm)	110 ± 27
Smoking	
Active smoker	2 (12%)
Former smoker	7 (44%)
NYHA functional classification	
II	12 (75%)
III	4 (25%)
Comorbidities	
Hypertension	16 (100%)
Diabetes	7(44%)
Rheumatic disease (gout)	2 (12%)
Atrial fibrillation	1 (6%)
CRF	4 (25%)
AMI	2 (12%)
Stroke	3 (19%)
Medications	
ACEI/ARA	16 (100%)
Beta-blockers	13 (81%)
Diuretics	13 (81%)
Calcium channel blockers	11 (69%)
Statins	10 (62%)
Antiplatelets	9 (56%)
Vasodilators	7 (44%)
Hypoglycemic drugs	7 (44%)

Values are described as mean ± standard deviation or absolute frequency (percentage). Former smoker: more than 1 year without smoking; NYHA: New York Heart Association; CRF: chronic renal failure; AMI: acute myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; ARA: angiotensin receptor antagonists.

Table 2 – Echocardiographic variables

Variables	n = 16
LVEF (%)	68 ± 5
E/e'	13 ± 4
LAD (cm)	4.22 ± 0.41
LVESV (ml)	37.9 ± 9.10
LVEDV (ml)	124.41 ± 23.24
LVEDVI (ml/m^2)	67.09 ± 6.35
IVST (cm)	1.15 ± 0.17
PWT (cm)	1.10 ± 0.19
LVM (g)	244.35 ± 58
LVMI (g/m^2)	146.2 ± 35.84
LAVI (ml/m^2)	20.81 ± 3.40

Values are described as mean ± standard deviation.LVEF: left ventricular ejection fraction; E/e': early diastolic peak velocity and diastolic peak velocities of the mitral annulus ratio; LAD: left atrium diameter; LVESV: left ventricular end-systolic volume; LVEDV: left ventricular end-diastolic volume; LVEDVI: left ventricular end-diastolic volume indexed to body surface; IVST: interventricular septum thickness; PWT: posterior wall thickness; LVM: left ventricular mass; LVMI: left ventricular mass indexed by body surface; LAVI: left atrial volume indexed to body surface.

Table 3 – Cardiopulmonary exercise testing variables

Variables	n = 16
VO_2 peak (mL.kg^{-1}min^{-1})	18.40 ± 3.16
HR max. (bpm)	125 ± 23
VE/VCO_2 slope	33 ± 6
PET CO_2 rest (mmHg)	33 ± 3
Pulse O_2	11.36 ± 4.45
R peak	1.16 ± 0.13

Values are described as mean ± standard deviation or median±interquartile range. VO_2 peak: peak oxygen consumption; HR max.: maximum heart rate; VE/VCO_2 slope: incline of the ventilatory equivalent of carbon dioxide; PET CO_2 rest: expired pressure of carbon dioxide; O_2 pulse: oxygen pulse; R peak: respiratory quotient.

Finally, in a condition characterized by exercise limitation, aerobic exercise training has a significant role and is indicated for all patients capable of performing it. In an acute and subacute setting, HIIT reduced BP and increased brachial artery diameter, suggesting that this training modality could be a beneficial alternative for individuals with HFpEF.

Limitations and future perspectives

This was a small, single-center; before-and-after study with HEpEF patients where the presence of diabetes, atherosclerosis, gout, and use of tobacco may have influenced the study outcomes. However, these characteristics represent the reality of this complex syndrome which have multiple comorbidities. We acknowledge that further studies are necessary to evaluate the effect of a HIIT session, especially after one hour, as well as the long-term efficacy of this exercise strategy as part of a cardiovascular rehabilitation program for these patients. Finally, the presence of a control group of matched individuals without HFpEF could help establishing which responses can be attributed to the syndrome under study. Likewise, comparing a HIIT session with a continuous moderate-intensity training session could help establishing the differences in hemodynamic response among these different exercise protocols.

Table 4 – Exercise protocol variables

Variables	Moderate intensity	High Intensity
HR (bpm)	98 ± 19	113 ± 24
BORG	13 ± 2	16 ± 2
Speed (km/h)	3 ± 0.3	4.9 ± 0.8
Incline (%)	0.9 ± 0.9	5.5 ± 1.9

Values are described as mean ± standard deviation. HR: heart rate; BORG: scale of perceived exertion.

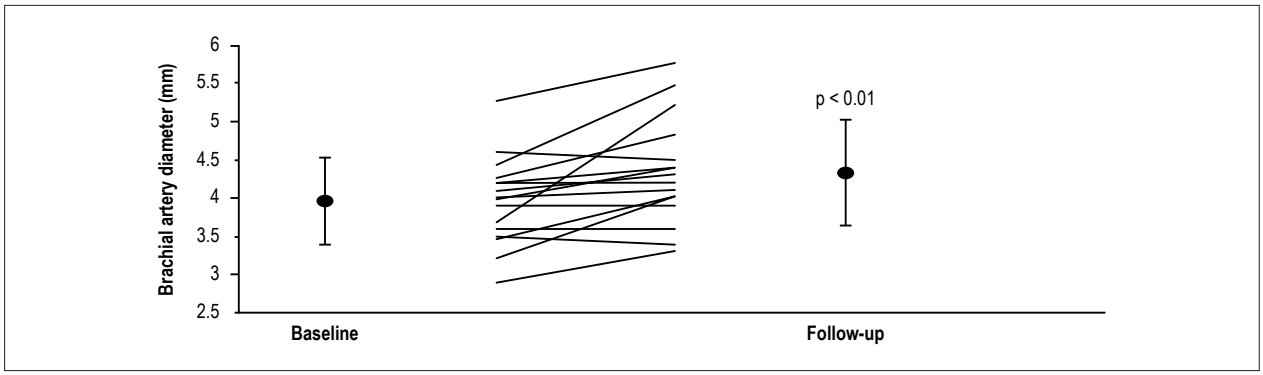

Figure 2 – *Brachial artery diameter pre- and post-high-intensity interval training session. Data are expressed as mean± standard deviation. Lines represent individual values. Probability value indicates within-group significant differences.*

Table 5 – Brachial artery diameters and variations pre- and post-high-intensity interval training session.

Variables	Pre	Post	p
Brachial artery diameter (mm)	3.96 ± 0.57	4.33 ± 0.69	< 0.01
Brachial artery diameter post-hyperemia (mm)	4.19 ± 0.61	4.47 ± 0.66	< 0.05
Absolute FMD (mm)	0.23 ± 0.20	0.13 ± 0.26	0.177
Relative FMD (%)	5.91± 5.20	3.55 ± 6.59	0.162
Brachial artery diameter pre-NTG (mm)	4.11 ± 0.65	4.16 ± 0.68	0.528
Brachial artery diameter post-NTG (mm)	4.57 ± 0.65	4.52 ± 0.64	0.541
Absolute NTG (mm)	0.46 ± 0.17	0.35 ± 0.20	0.106
Relative NTG (%)	11.4 ± 4.4	9.0 ± 5.37	0.117

Values are described as mean ± standard deviation. FMD: flow-mediated dilatation; NTG: nitroglycerin.

Conclusion

One single HIIT session promoted an increase in brachial artery diameter and a reduction in systolic BP, and did not change FMD and diastolic BP 30 minutes after the exercise session.

Author contributions

Conception and design of the research: Lima JB, Silveira AD, Zanini M, Nery RM, Stein R; Acquisition of data: Lima JB, Silveira AD, Saffi MAL, Menezes MG, Piardi DS, Ramm LDCR; Analysis and interpretation of the data: Lima JB, Saffi MAL, Menezes MG, Piardi DS, Ramm LDCR, Stein R; Statistical analysis: Lima JB; Writing of the manuscript: Lima JB, Silveira AD, Stein R; Critical revision of the manuscript for intellectual content: Lima JB, Silveira AD, Saffi MAL, Zanini M, Nery RM, Stein R.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Juliana Beust de Lima, from Universidade Federal do Rio Grande do Sul.

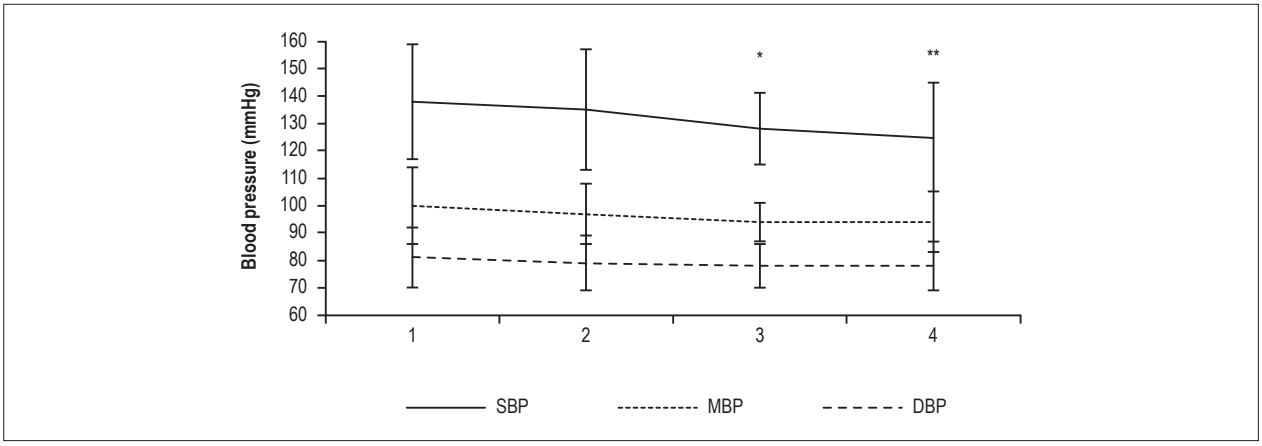

Figure 3 – *Variation of blood pressure pre- and post-high-intensity interval training session. Data are expressed as mean± standard deviation. Lines represent mean values:.1) pre-assessment of endothelial function; 2) immediately before HIIT session; 3) 5 minutes after HIIT session; 4) 30 minutes after HIIT session. SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure. Probability value indicates within-group differences between points 3 and 1, and points 4 and 1 of SBP. *p < 0.05, **p < 0.01.*

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Clínicas de Porto Alegre under the protocol number 130471. 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.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction.N Engl J Med. 2006;355(3):251-9.
2. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016;375(19):1868-77.
3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.
4. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail. 2008;10(2):149–56.
5. WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH,et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16): e240–e327.
6. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction. J Am Coll Cardiol. 2013;62(4):263–71.
7. Lim SL, Lam SPC. Breakthrough in heart failure with preserved ejection fraction: are we there yet? Korean J Intern Med. 2016;31(1):1-14.
8. Haykowsky MJ, Kitzman DW. Exercise physiology in heart failure and preserved ejection fraction. Heart Fail Clin. 2014;10(3):445–52.
9. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56(11):845-54.
10. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006;114(20):2138–47.
11. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol.2012;60(18):1778–86.
12. Matsue Y, Suzuki M, Nagahori W, Ohno M, Matsumura A, Hashimoto Y, et al. Endothelial dysfunction measured by peripheral arterial tonometry predicts prognosis in patients with heart failure with preserved ejection fraction. Int J Cardiol .2013;168(1):36-40.
13. Pandey A, Parashar A, Kumbhani JD, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail. 2015;8(1):33–40.
14. Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. J Appl Physiol. 2015;119(6):726–33.
15. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a JOINT POSITION STATEMENT OF THE EUROPEAN ASSOCIATION FOR CARDIOVASCULAR PREVENTION AND REHABILITATION, THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION, AND THE CANADIAN ASSOCIATION OF CARDIAC REHABILITATION. J Cardiopulm Rehabil Prev. 2012;32(6):327–50.
16. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation .2007;115(24):3086–94.

17. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, et al. High-intensity interval training in patients with Heart Failure With Reduced Ejection Fraction. Circulation 2017;135(9): 839–49

18. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS.The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. Sports Med. 2015;45(5):679-92.

19. Batacan RB, Duncan MJ, Dalbo VJ,Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. Br J Sports Med. 2017;51(6):494-503.

20. Currie KD, Mckelvie RS, Macdonald MJ. Flow-Mediated Dilation Is Acutely Improved after High-Intensity Interval Exercise. Med Sci Sports Exerc 2012;44(11): 2057–64.

21. Currie KD, McKelvie RS, MacDonald MJ. Brachial artery endothelial responses during early recovery from an exercise bout in patients with coronary artery disease. BioMed Res Int. 2014;2014:591918.

22. Ciolac EG, Guimarães GV, D´Àvila VM, Bortolotto LA, Doria EL, Bocchi EA. Acute effects of continuous and interval aerobic exercise on 24-h ambulatory blood pressure in long-term treated hypertensive patients. Int J Cardiol. 2009;133(3):381–7.

23. Carvalho RST de, Pires CMR, Junqueira GC, Freitas D, Marchi-Alves LM. Hypotensive response magnitude and duration in hypertensives: continuous and interval exercise. Arq Bras Cardiol. 2014;104(3):234-41.

24. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction implications for systolic and diastolic reserve limitations. Circulation. 2003;107(5): 714-20.

25. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007; 28(20): 2539–50.

26. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation. 2003;108(9):1146–62.

27. Mason RE, Likar I. A new system of multiple-lead exercise electrocardiography. Am Heart J. 1966; 71(2):196–205.

28. Nery RM, Zanini M, de Lima JB, Bühler RP, da Silveira AD, Stein R. Tai Chi Chuan improves functional capacity after myocardial infarction: A randomized clinical trial. Am Heart J. 2015; 169(6):854-60.

29. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.

30. Maréchaux S, Samson R, van Belle E, Breyne J, de Monte J, Dédrie C, et al. Vascular and microvascular endothelial function in heart failure with preserved ejection fraction. J Card Fail. 2015;22(1):3-11.

31. da Nobrega AC. The subacute effects of exercise: concept, characteristics. Exerc Sport Sci Rev. 2005; 33(2):84-7.

32. Dawson EA, Green DJ, Timothy Cable N, Thijssen DH. Effects of acute exercise on flow-mediated dilatation in healthy humans. J Appl Physiol.2013;115(11):1589–98.

33. Fu TC, Yang NI, Wang CH, Cherng WJ, Chou SL, Pan TL, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. Am J Phys Med Rehabil. 2016;95(1):15-27.

34. Birk GK, Dawson EA, Batterham AM, Atkinson G, Cable T, Thijssen DH, et al. Effects of exercise intensity on flow mediated dilation in healthy humans. Int J Sports Med.2012;34(5):409–14.

35. Umpierre D, Stein R, Vieira PJ, Ribeiro JP. Blunted vascular responses but preserved endothelial vasodilation after submaximal exercise in chronic heart failure. Eur J Cardiovasc Prev Rehabil.2009;16(1):53–9.

36. Guindani G, Umpierre D, Grigoletti SS, Vaz M, Stein R, Ribeiro JP. Blunted local but preserved remote vascular responses after resistance exercise in chronic heart failure. Eur J Prev Cardiol.2012;19(5):972–82.

37. Forjaz CL, Cardoso CG Jr, Rezk CC, Santaella DF, Tinucci T.Postexercise hypotension and hemodynamics: the role of exercise intensity. J Sports Med Phys Fitness. 2004;44(1): 54-62.

38. Quinn TJ. Twenty-four hour, ambulatory blood pressure responses following acute exercise: impact of exercise intensity. J Hum Hypertens.2000;14(9):547-53.

High Intensity Exercises in Heart Failure with Preserved Ejection Fraction

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Short Editorial related to the article: Vasodilation and Reduction of Systolic Blood Pressure after One Session of High-Intensity Interval Training in Patients With Heart Failure with Preserved Ejection Fraction

Introduction

Heart failure with preserved ejection fraction (HFpEF) comprises several pathologies that present with variable degrees of dyspnea, high filling pressures, structural or diastolic alterations and great limitation to exercise.[1] HFpEF can represent up to 50% of cases of hospital admissions due to decompensated heart failure (HF).[2]

Hypertension and obesity are conditions frequently associated with HFpEF and the adequate management of these two pathologies are essential for the treatment of this syndrome. One of the main characteristics of patients with HFpEF is the intolerance to exercise at different degrees and through diverse mechanisms.[3]

Exercises are among the main therapeutic strategies for the treatment of heart failure with reduced ejection fraction (HFrEF) and HFpEF, being important agents in decreasing the morbidity and mortality of these patients.[4-6]

Among the benefits of aerobic training in patients with HFpEF, we can highlight the improvement in endothelial function and arterial stiffness, contributing to the improvement of cardiovascular dynamics and symptoms.[7] The physical training programs offered to patients with HF in cardiac rehabilitation services involve primarily aerobic exercises supplemented by resistant exercises, stretching and, in some cases, respiratory exercises.[1]

Aerobic exercises can be continuous, of moderate intensity or intercalating high and low-intensity efforts. High-intensity interval training (HIIT) is currently one of the most effective methods for improving cardiorespiratory and metabolic function. HIIT involves repeated activities, from short to long ones, of high-intensity exercises combined with periods of active or passive recovery.[8] Kiviniemi et al. have recently reported that HIIT is superior to traditional continuous aerobic training in improving cardiac autonomic function and suggested that the effect verified on post-HIIT autonomic function was related to improved baroreflex modulation and vagal control.[9]

Keywords

Heart Failure; Stroke Volume; Obesity; Exercise; Exercise Therapy; Breating Exercises.

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There are several potential adaptations that explain the positive changes induced by HIIT on the autonomic cardiac function. One of the potential mechanisms related to HIIT-induced improvement in cardiac vagal tone may be angiotensin II, which inhibits cardiac vagal activity. Sedentary or physically inactive individuals have higher plasma renin activity when compared to those who are physically active. Exercise causes angiotensin II suppression, which can, to some extent, mediate the improvement in cardiac vagal tone.[10] Studies have also suggested that HIIT induces increased baroreflex sensitivity and reduces arterial stiffness.[11]

Comments about the current study

In this interesting study, designed for the assessment of the acute effects of a single session of high-intensity interval training, Lima et al.[12] studied post-training changes in blood pressure (BP) and endothelial function in 16 patients with HFpEF. As main results, it was possible to demonstrate a significant increase in the brachial artery diameter with a corresponding reduction in systolic BP. These findings indicate the potential benefit of this type of training for patients with HFpEF, with an improvement in blood pressure levels and, possibly, a beneficial effect on ventricular function.

Although the authors did not find any significant changes in the flow-mediated dilation index, questions have been raised about the real importance and interpretation of this measurement.[13] The BP reduction after the exercise sessions tends to last for hours, acting as powerful adjuvants to the vasodilation effects of antihypertensive drugs, which are commonly used in HFpEF. BP control is among the main goals for symptom improvement in HFpEF, and exercises are crucial to attain this goal and improve diastolic function.[14]

Limitations and conclusions

This experiment used a single training group, without a control group for better definition of the effects and lower chance of bias when assessing the results. Although the number of patients was small, the positive results encourage better designed future researches, with a larger number of individuals to define the role of this training modality in HFpEF. These patients have an expressive limitation to exercises and strategies that improve BP and diastolic function show great potential for benefits in functional class improvement and, likely, in morbimortality reduction.

References

1. Comitê Coordenador da Diretriz de Insuficiência Cardíaca. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539.
2. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47(1):76-84. Erratum in: J Am Coll Cardiol. 2006;47(7):1502.
3. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. Circulation. 2018;137(2):148-61.
4. Piepoli MF, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure. BMJ. 2004;328(7433):189.
5. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1439-50.
6. Edelmann F, Gelbrich G, Düngen HD, Fröhling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol. 2011;58(17):1780-91.
7. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol. 2013;62(7):584-92.
8. Tschakert G, Hofmann P. High-Intensity Intermittent Exercise: Methodological and Physiological Aspects. Int J Sports Physiol Perform. 2013;8:600-610.
9. Kiviniemi A, Tulppo M, Eskelinen J, Savolainen A, Kapanen J, Heinonen I, et al. Cardiac autonomic function and high-intensity interval training in middle-age men. Med Sci Sports Exerc. 2014;46(10):1960-7.
10. Buch AN, Coote JH, Townend JN. Mortality, cardiac vagal control and physical training – What's the link? Exp Physiol 2002;87(4):423-35.
11. Heydari M, Boutcher YN, Boutcher SH. High-intensity intermittent exercise and cardiovascular and autonomic function. Clin Auton Res. 2013;23(1):57-65.
12. Lima JB, Silveira AD, Saffi MAL, Menezes MG, Piardi DS, Ramm LDCR et al. Vasodilation and Reduction of Systolic Blood Pressure after One Session of High-Intensity Interval Training in Patients With Heart Failure with Preserved Ejection Fraction. Arq Bras Cardiol. 2018; 111(5):699-707
13. Atkinson G, Batterham AM. The clinical relevance of the percentage flow-mediated dilation index. Curr Hypertens Rep. 2015;17(2):4.
14. Pearson MJ, Mungovan SF, Smart NA. Effect of exercise on diastolic functional in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev. 2017;22(2):229-42.

Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis

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Abstract

Background: **Recent studies suggest that baseline prolonged PR interval is associated with worse outcome in cardiac resynchronization therapy (CRT). However, a systematic review and meta-analysis of the literature have not been made.**

Objective: **To assess the association between baseline prolonged PR interval and adverse outcomes of CRT by a systematic review of the literature and a meta-analysis.**

Methods: **We comprehensively searched the databases of MEDLINE and EMBASE from inception to March 2017. The included studies were published prospective or retrospective cohort studies that compared all-cause mortality, HF hospitalization, and composite outcome of CRT with baseline prolonged PR (> 200 msec) versus normal PR interval. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate the risk ratios and 95% confidence intervals.**

Results: **Six studies from January 1991 to May 2017 were included in this meta-analysis. All-cause mortality rate is available in four studies involving 17,432 normal PR and 4,278 prolonged PR. Heart failure hospitalization is available in two studies involving 16,152 normal PR and 3,031 prolonged PR. Composite outcome is available in four studies involving 17,001 normal PR and 3,866 prolonged PR. Prolonged PR interval was associated with increased risk of all-cause mortality (pooled risk ratio = 1.34, 95 % confidence interval: 1.08-1.67, $p < 0.01$, $I^2 = 57.0\%$), heart failure hospitalization (pooled risk ratio = 1.30, 95 % confidence interval: 1.16-1.45, $p < 0.01$, $I^2 = 6.6\%$) and composite outcome (pooled risk ratio = 1.21, 95% confidence interval: 1.13-1.30, $p < 0.01$, $I^2 = 0\%$).**

Conclusions: **Our systematic review and meta-analysis support the hypothesis that baseline prolonged PR interval is a predictor of all-cause mortality, heart failure hospitalization, and composite outcome in CRT patients. (Arq Bras Cardiol. 2018; 111(5):710-719)**

Keywords: **Heart Failure/complications; Heart Conduction System/physiopathology; Ventricular Dysfunction/complications; Cardiac Resynchronization/methods; Review; Meta-Analysis.**

Introduction

It has been widely accepted that surface electrocardiogram findings are associated with prognosis in congestive heart failure (HF) patients who have required cardiac resynchronization therapy (CRT), particularly the QRS complex. QRS duration and morphology is a well-established predictor of outcome among patients receiving CRT as well as selection criteria for CRT implantation according to the current guidelines of the American College of Cardiology/American Heart Association/Heart Rhythm Society.[1]

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More recently, baseline PR interval has been invoked as an additional factor that may affect CRT outcomes.[2] A prolonged PR interval is a marker of a ventricular substrate that is less amenable to resynchronization. It also reflects a combination of intrinsic intra-atrial and atrioventricular conduction which impacts diastolic filling time.[2,3] There are no clear evidence and explanation why PR prolongation might contribute to the outcome of CRT patients. Nonetheless, there is controversial evidence in literature regarding the association between baseline PR prolongation and outcomes of HF patients who require CRT implantation. Some studies implied that PR prolongation was associated with higher morbidity and mortality amongst these patients,[2,4-7] while others suggested it is associated with favorable outcomes.[8-10] However, a systematic literature review and meta-analysis of the association between PR interval and CRT outcome have not been made.

We have first conducted a systematic literature review and meta-analysis to comprehensively analyze whether baseline

PR prolongation in comparison with normal PR interval is associated with outcomes in CRT-dependent HF patients by assessing all-cause mortality, HF hospitalization rate, and composite outcome as our interest.

Method

Search strategy

Two investigators (NP and TR) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to January 2017 using a search strategy that included the terms "PR interval" and "cardiac resynchronization therapy" described in supplementary document 1. Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also made.

Inclusion criteria

The eligibility criteria included the following:

(1) Cohort study (prospective or retrospective) reporting incident of all-cause mortality, HF hospitalization, or composite outcome, after the CRT and the corresponding index date for controls.

(2) Relative risk, hazard ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals or sufficient raw data for the calculation were provided.

(3) Participants without PR prolongation were used as controls.

Study eligibility was independently determined by two investigators (NP and TR) and differences were resolved by mutual consensus. A Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies.[11]

Data extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose the outcomes of interest (all-cause mortality, HF hospitalization rate and composite outcome), and average duration of follow-up with confounders that were adjusted and adjusted effect estimates with 95% confidence interval and covariates that were adjusted in the multivariable analysis.

To ensure accuracy, all investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles.

Statistical analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. The extracted studies were excluded from the analysis if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird.[12] The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%–50\%$, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity).[13] A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Meta-regression was performed to explore source of heterogeneity. Publication bias was assessed using funnel plot and Egger's regression test[14] ($p < 0.05$ was considered significant). All data analyses were performed using the Stata/SE 14.1 software from StataCorp LP.

Results

Description of the included studies

Our search strategy yielded 580 potentially relevant articles (82 articles from EMBASE and 498 articles from MEDLINE). After exclusion of 204 duplicated articles, 376 underwent title and abstract review. Three hundred and seventy articles were excluded at this stage since they were not cohort studies, did not report the outcome of interest (incidence of death/HF hospitalization) or were not conducted in patients with CRT, leaving six for full-length article reviews. Therefore, six retrospective cohort studies with 17,432 normal PR and 4,278 prolonged PR patients were included in this meta-analysis. Figure 1 outlines the search and literature review process. The clinical characteristics and summary of the included studies are described in Table 1.

Quality assessment of the included studies

Newcastle-Ottawa scales of the included studies are described in Table 2. The Newcastle-Ottawa scale uses a star system (0 to 9) to evaluate the included studies on three domains: selection, comparability, and outcomes. Higher scores represent higher study quality. Intra-study risks of bias of the included studies are also described in Table 3.

Meta-analysis results

Six studies[2,4,7,8,15,16] from January 1991 to May 2017 were included in this meta-analysis. All-cause mortality rate is available in four studies[2,4,7,16] that involved 17,432 normal PR and 4,278 prolonged PR. All four studies revealed an increased death rate among patients with prolonged PR interval but with of the four achieving statistical significance. The pooled analysis demonstrates a statistically significant increased risk of all-cause mortality in patients with prolonged PR interval compared to participants without prolonged PR interval with the pooled risk ratio of 1.34 (95 % confidence interval: 1.08-1.67, $p < 0.01$). The statistical heterogeneity was substantial with I^2 of 57.0%. Forest plot of this meta-analysis is shown in Figure 2A.

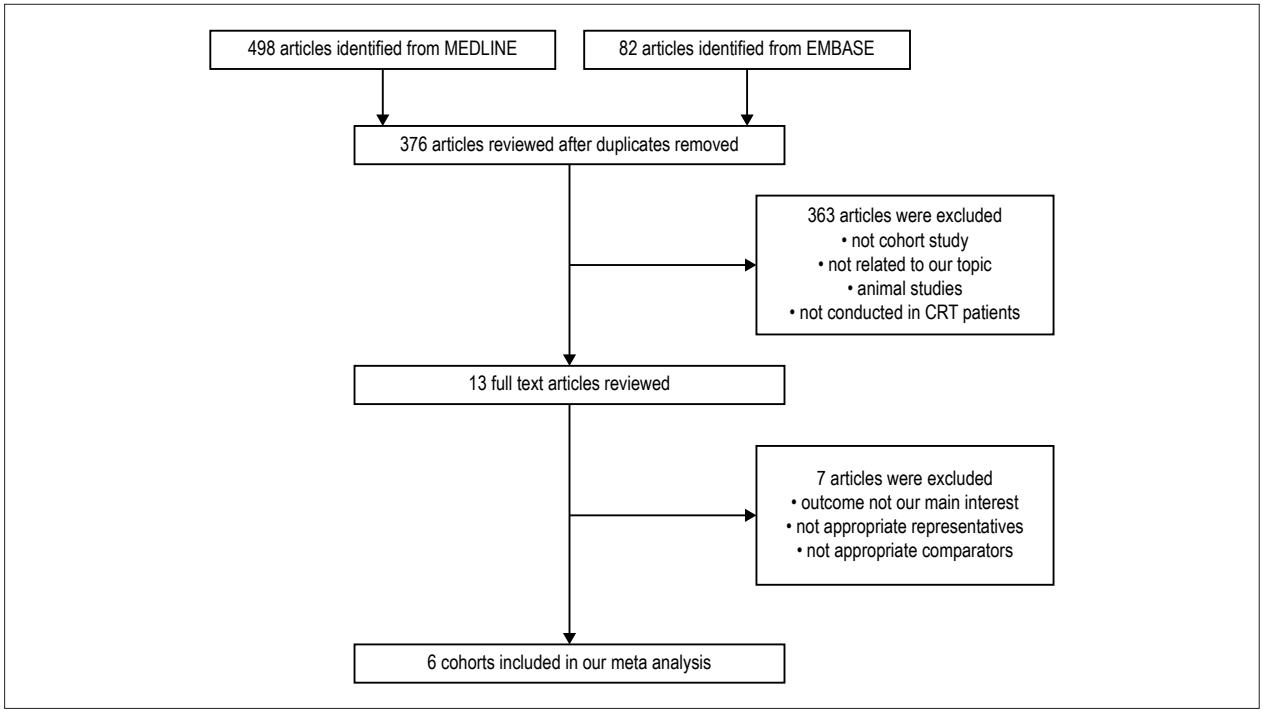

Figure 1 – *Search methodology and selection process.*

HF hospitalization is available in two studies [2, 4] involving 16,152 normal PR and 3,031 prolonged PR. Both studies achieved statistical significance. HF hospitalization pooled risk ratio is 1.30 (95 % confidence interval: 1.16-1.45, $p < 0.01$). The statistical heterogeneity was low with I^2 of 6.6%. Forest plot of this meta-analysis is shown in Figure 2B.

Composite outcome (all-cause mortality and HF hospitalization) is available in four studies[2,4,8,15] involving 17,001 normal PR and 3,866 prolonged PR. All four studies revealed an increased death rate among patients with prolonged PR interval with two achieving statistical significance. In composite outcome, the pooled analysis also demonstrated a statistically significant increased composite outcome in CRT patients with prolonged PR interval compared to participants without prolonged PR interval with the pooled risk ratio of 1.21 (95% confidence interval: 1.13-1.30, $p < 0.01$). The statistical heterogeneity was low with I^2 of 0%. Forest plot of this meta-analysis is shown in Figure 2C.

Sensitivity analysis

To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis by excluding one study at a time. None of the results was significantly altered, indicating that our results were robust (supplementary document 2). However, after exclusion of Freidman et al.,[2] the heterogeneity decreased from 57.0% to 0% (supplementary document 3).

Given moderate heterogeneity ($I^2 = 57.0\%$) among all-cause mortality meta-analysis results, meta-regression (supplementary document 3) showed non-significant changes in all-cause mortality in PR interval > 230 msec compared with PR interval > 200 msec with risk ratio of 0.73 (95% confidence interval: 0.43-1.23, $p = 0.123$).

Publication bias

To investigate potential publication bias, we examined the funnel plot with pseudo 95% confidence limits of the included studies in assessing change in log risk ratio of death or composite outcome (Figure 3). The vertical axis represents study size (standard error) while the horizontal axis represents effect size (log risk ratio). From this plot, bias is present because there is asymmetrical distribution of studies on both sides of the mean. The Egger's test was significant ($p < 0.05$). However, using the trim and fill methods in the random-effects model, there was no difference of the imputed risk ratio and its 95% confidence interval.

Discussion

The evidence provided in this systematic review and meta-analysis shows that a prolonged PR interval is significantly associated with an increased risk for all-cause mortality, composite outcome, and HF hospitalization of patients with CRT.

Prolongation of PR interval, also known as first-degree atrioventricular block, is independently associated with increased risk for mortality and atrial fibrillation in the general population.[17] Even though correlation of PR interval with CRT response was conflicted in previous studies, our meta-analysis confirms the negative effect on clinical outcome in patients with prolonged PR interval. According to the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, around 50% of patients with CRT have prolonged PR interval. In addition, patients with CRT and prolonged PR interval are more likely to have ischemic cardiomyopathy, wider QRS complexes, more

Table 1 – The clinical characteristics and summary of the included studies

First author	Freidman	Januszkiewicz	Kronborg	Olshansky	Lee	Rickard
Country of Origin	USA	USA	Denmark	USA	USA	USA
Year	2016	2015	2010	2012	2014	2017
Study type	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Participants description	Patients who underwent CRT (LVEF ≤ 35 and QRS ≥ 120)	Patients who underwent CRT (LVEF ≤ 35%, QRS > 120, NYHA III, IV)	Patients who underwent CRT	Patients who underwent CRT (LVEF ≤ 35, QRS ≥ 120 and NYHA III, IV)	Patients who underwent CRT (LVEF ≤ 35, QRS ≥ 120 and NYHA III, IV)	Patients who underwent CRT (LVEF ≤ 35, QRS ≥ 120)
Median duration of follow up (Months)	34	30.1	30	15.95	52.4	61.2
Definition of prolonged PR	≥ 230 ms	≥ 200 ms	≥ 200 ms	≥ 200 ms	≥ 200 ms	≥ 200 ms
Number of patients with prolonged PR	2906	125	208	638	204	197
Number of patients with not prolonged PR	15994	158	232	574	199	275
Mean age of patients	75.37	66.00	66.00	65.56	66.72	65.10
confounder adjustment	age, race, QRS, Intraventricular conduction, Non ischemic cardiomyopathy, NYHA, HF duration, eGFR, BUN, SBP	sex, RBBB, Ischemic cardiomyopathy, AF, medications	age, sex, HF aetiology, NYHA, DM, AF, ICD, LVEF	age, sex, NYHA, LVEF, LBBB, QRS, HR, SBP, DBP, ischemic status, comorbidities, medication	age, sex, ischemic cardiomyopathy, RV size, RV dysfunction, NYHA, MR grade, PASP, medication	age, sex, ischemic cardiomyopathy, LVEF, QRS, LBBB, Cr, NYHA

AF: atrial fibrillation; BUN: blood urea nitrogen; HF: heart failure; Cr: creatinine; CRT: cardiac resynchronization therapy; DM: diabetes mellitus; DBP: diastolic blood pressure; eGFR : estimated Glomerular infiltration; HR: heart rate; ICD: implanted cardiac defibrillator; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; RBBB: right bundle branch block; RV: right ventricular; SBP: systolic blood pressure.

Table 2 – Newcastle–Ottawa scales of the included studies

Study	selection				comparability	outcome			
	representativeness	selection of the non-exposed cohort	ascertainment	end point not present at start	Comparability (confounding)	assesment of outcome	follow up duration	adequacy follow-up	total
Freidman	*	*	*	*	**	*	*	*	9
Januszkiewicz	*	*	*	*	**	*	*	*	9
Kronborg	*	*	*	*	**	*	*	*	9
Olshansky	*	*	*	*	**	*		*	8
Ying-Hsiang	*	*	*	*	**	*	*	*	9
Rickard	*	*	*	*	**	*	*	*	9

severe right ventricular dysfunction, and renal diseases.[7,8] The pathophysiology of PR prolongation causing adverse outcomes is explained by decreased ventricular filling time leading to decreased stroke volume. It can also induce ineffective mitral valve closure, causing diastolic mitral valve regurgitation, which is known to be associated with unfavorable outcomes in left ventricular dysfunction.[18] The study results of Gervais et al.[6] show that after CRT placement, there is a marked subsequent shortening of the mean PR interval, which suggests that CRT cures atrioventricular dyssynchrony.[6] However, our result still shows worse outcome among patients with prolonged PR interval compared to normal PR interval. The reasons for PR interval affecting CRT outcome are uncertain. In general, prolonged PR interval reflects either intrinsic intra-atrial or atrioventricular conduction defect. Thus, CRT may facilitate AV synchrony to mitigate diastolic

Table 3 – Intra-study risks of bias of included studies

Study	Clear definition of study population?	Clear definition of outcomes and assessment?	Independent assessment of outcomes? (e.g. by third party)	Sufficient Follow-up duration?	Selective loss during Follow-up?	Limitations identified?
Freidman	Yes	Yes	Yes	Yes	No	Yes
Januszkiewicz	Yes	Yes	No	Yes	No	Yes
Kronborg	Yes	Yes	Yes	Yes	No	Yes
Kutyifa	Yes	Yes	Yes	Yes	No	No
Olshansky	No	Yes	Yes	No	No	Yes
Ying-Hsiang	Yes	Yes	No	Yes	No	Yes

AV valve regurgitation and improve diastolic function.[19] On the other hand, with the presence of intra-atrial conduction disturbance, CRT implantation could have deleterious impact on these patients as it shortens the appropriate PR interval and causes paradoxical effect, leading to worsening heart failure.[20] Alternatively, PR prolongation may simply be a rough marker of "sicker" heart failure patients.[17,21,22]

In current heart failure guidelines, the duration of QRS, the type of bundle branch block and the presence of atrial fibrillation have been utilized as criteria for pacemaker device implantation.[23] Also, CRT has a range of effects which has promoted interest in refining selection criteria for this important therapy. In our analysis, we imply hat the PR interval is a promising prognostic marker in patients with heart failure requiring CRT. Thus, PR interval may also be a valuable adjunctive selection criteria.

As our study has substantial heterogeneity in all cause mortality, we performed sensitivity analysis and found that after exclusion of Freidman et al.,[2] the heterogeneity decreased from 57.0% to 0%. We concluded that the most likely explanation could be from the definition criteria of the recruited studies. Friedman is the only study that defined prolonged PR as more than 230 msec whereas every other study defined prolonged PR as more than 200 msec. Therefore, a meta-regression was conducted to investigate the statistical significance of PR definition affecting the results. However, meta-regression showed non-significant changes in all-cause mortality in PR interval > 230 msec compared with PR interval > 200 msec.

Our study has some limitations. Despite the fact that our funnel plot does not show biased data set, there are only six studies included in the analysis. In addition, PR prolongation is generally defined as PR interval exceeding 200 milliseconds. However, among the six included studies, there is only one study that defines prolonged PR interval as 230 ms and above.[2] Given the total number of subjects, the heterogeneity of sample is small. While there are other possible predictor variables that are not included in this study, they were already analyzed in Rickard et al.[24] Lastly, instead of using cardiac cause-specific mortality, all-cause mortality was used as outcome of interest in the included studies, which might overestimate the total outcome.

Conclusion

In conclusion, among patients requiring CRT, prolonged PR interval is an independent indicator for all-cause mortality, HF hospitalization, and composite outcome. Our result suggests that PR interval should be considered as one of the important predictors of CRT response when addressing risk stratification.

Acknowledgement

We would like to thank Elysse Tom, MD for critical reading.

Author contributions

Conception and design of the research and Statistical analysis: Rattanawong P; Acquisition of data: Prasitlumkum N, Riangwiwat T, Kanjanahattakij N, Chongsathidkiet P; Analysis and interpretation of the data: Rattanawong P, Prasitlumkum N, Riangwiwat T, Kanjanahattakij N, Vutthikraivit W, Chongsathidkiet P; Writing of the manuscript: Prasitlumkum N, Riangwiwat T, Vutthikraivit W; Critical revision of the manuscript for intellectual content: Simpson RJ.

Potential Conflict of Interest

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

Sources of Funding

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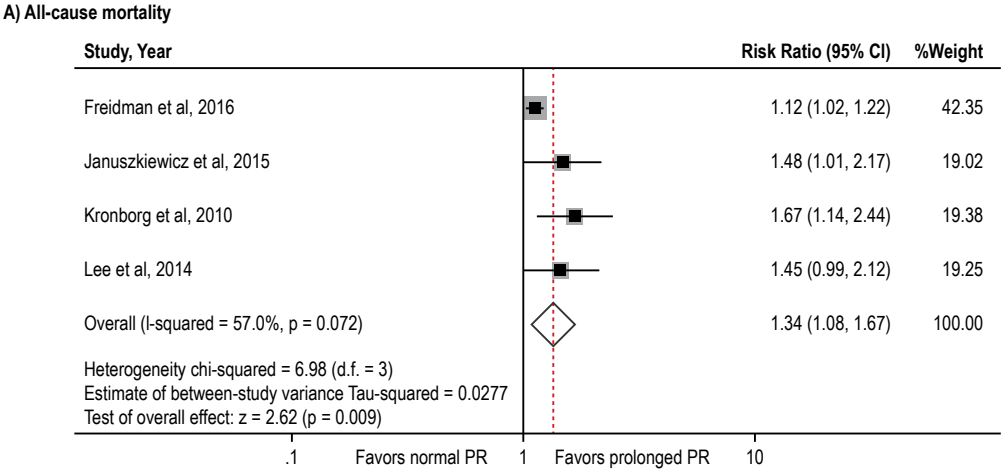
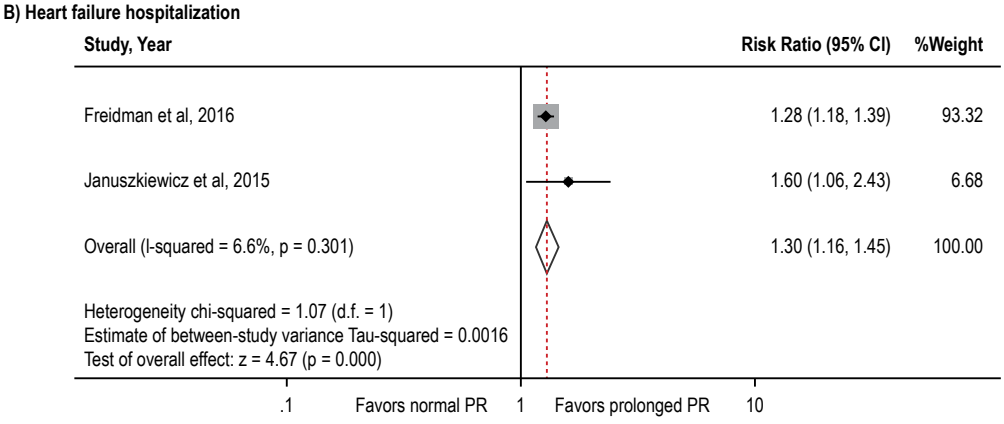
Study Association

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

Ethics approval and consent to participate

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





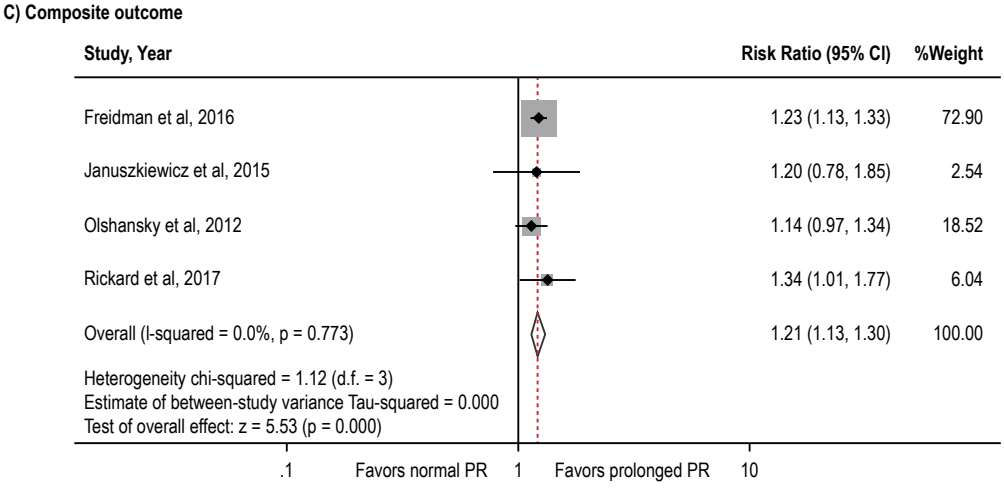


Figure 2 – *Forest plot of the included studies assessing the association between prolonged PR and risk of all-cause mortality (2A), HF hospitalization (2B), and composite outcome (2C).*

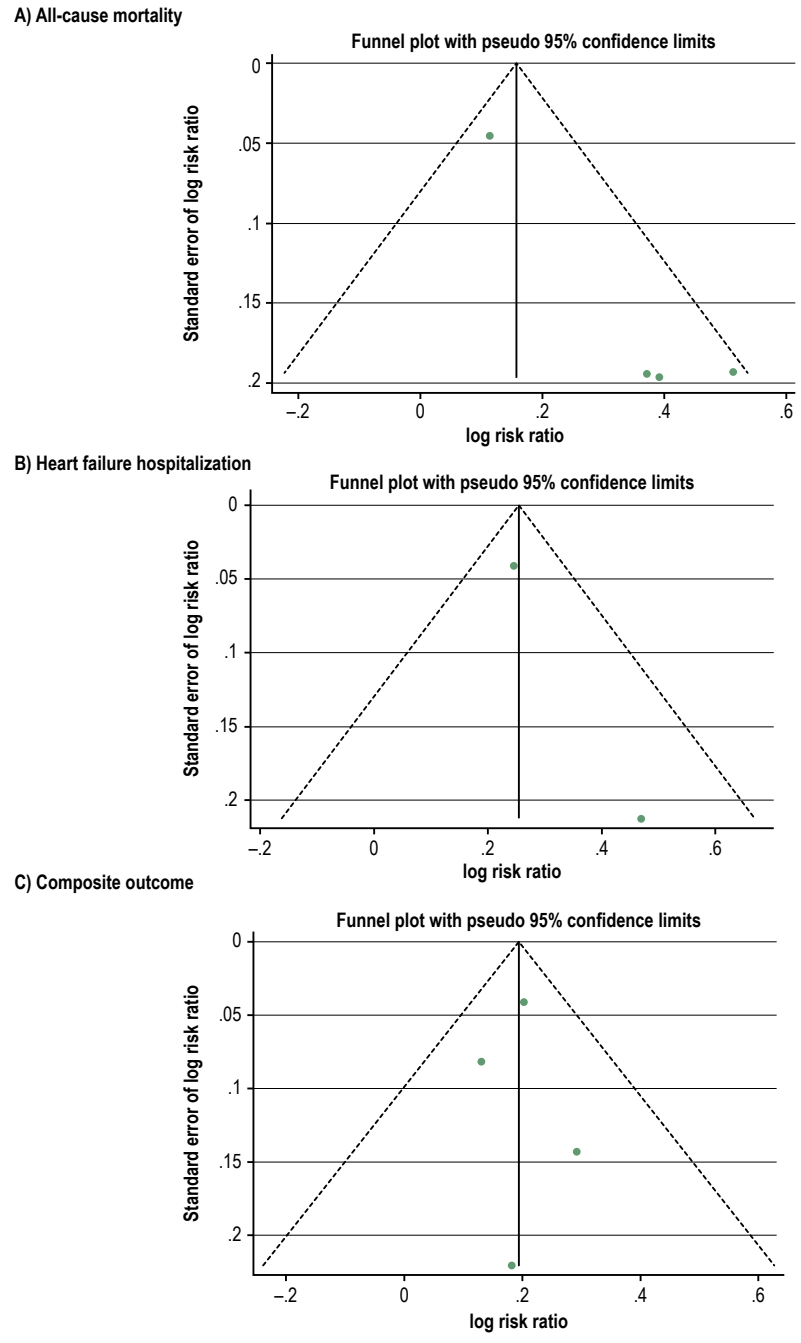


Figure 3 – *Funnel plot of prolonged PR and risk of all-cause mortality (3A), HF hospitalization (3B), and composite outcome (3C). Circles represent the observed published studies.*

References

1. Epstein AE, Di Marco JP, Ellenbogen KA, Estes NA3rd, Freedman RA, Gettes LS, et al. *2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol. 2013;61(3):e6-75.
2. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khalib SM. *Association between a prolonged PR interval and outcomes of cardiac resynchronization therapy: a report from the National Cardiovascular Data Registry.* Circulation, 2016;134(21):1617-28.
3. Waggoner AD, Kalathivetil S, Spence KE, D'avila Roman VG, de las Fuentes L.*Interatrial conduction time and left atrial function in patients with left ventricular systolic dysfunction: effects of cardiac resynchronization therapy.* J Am Soc Echocardiogr. 2009;22(5):472-7.
4. Januszkiewicz L, Vegh E, Borgquist R, Bose A, Sharm A, Orencole M, et al. *Prognostic implication of baseline PR interval in cardiac resynchronization therapy recipients.* Heart Rhythm. 2015;12(11):2256-62.
5. Pires, LA,Abraham WT, Young JB, Johnson KM, MIRACLE-ICD Invesigators. *Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials.* Am Heart J. 2006;151(4):837-43.
6. Gervais R, Leclercg C, Shankar A, Jacobs S,Eiskjaer H, Johannessen A. *Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial.* Eur J Heart Fail, 2009;11(7):699-705.
7. Lee YH, Wu JH, Asirvatham SJ, Del Carppio Munoz F, Webster T, Brooke KL,et al. *Effects of atrioventricular conduction delay on the outcome of cardiac resynchronization therapy.* J Electrocardiol. 2014;47(6):930-5.
8. Olshansky B, Day ID, Sullivan RM, Yong P, Galle E, Steinberg JC. *Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial.* Heart Rhythm. 2012;9(1):34-9.
9. Kutyifa V, Stockburger M, Daubert JP, Holmgrvist F, Olshansky B, Schuger C, et al. *PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy Substudy.* Circ Arrhythm Electrophysiol, 2014;7(4):645-51.
10. Joshi NP, Stopper MM, Beshai JF, Pavri BB. *Impact of baseline PR interval on cardiac resynchronization therapy outcomes in patients with narrow QRS complexes: an analysis of the ReThinQ Trial.* J Interv Card Electrophysiol. 2015; 43(2):145-9.
11. Stang A. *Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.* Eur J Epidemiol. 2010; 25(9):603-5.
12. Der Simonian R,Laird N. *Meta-analysis in clinical trials.* Control Clin Trials. 1986;7(3):177-88.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. *Measuring inconsistency in meta-analyses.* BMJ. 2003;327(7414):557-60.
14. Sterneb JA, Egger M. *Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis.* J Clin Epidemiol. 2001;54(10):1046-55.
15. Rickard J,Karim M, Baranowski B, Cantillon D, Spragg D, Tang WH, et al. *Effect of PR interval prolongation on long-term outcomes in patients with left bundle branch block vs non-left bundle branch block morphologies undergoing cardiac resynchronization therapy.* Heart Rhythm.2017;14(10):1523-8.
16. Kronborg MB, Nielsen JC, Mortensen PT. *Electrocardiographic patterns and long-term clinical outcome in cardiac resynchronization therapy.* Europace. 2010; 12(2):216-22.
17. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Lerry D, et al.*Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block.* JAMA. 2009;301(24):2571-7.
18. Schnittger L, Appleton CP, Hatle LK, Popp RL. *Diastolic mitral and tricuspid regurgitation by Doppler echocardiography in patients with atrioventricular block: new insight into the mechanism of atrioventricular valve closure.* J Am Coll Cardiol. 1998;11(1):83-8.
19. Maloney J, Khoury D, Simmons T, Willkoff B, Morant V, Trohman R. *Effect of atrioventricular synchrony on stroke volume during ventricular tachycardia in man.* Am Heart J. 1992;123(6):1561-8.
20. Auricchio A, Ding J, Spinelli JC, Kramer AP, Salo RW, Hoersch W, et al. *Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay.* J Am Coll Cardiol. 2002;39(7):1163-9.
21. Magnani JW, Wang N, Nelson KP, Connelly S, Deo R, Rodondi N, et al. *Electrocardiographic PR interval and adverse outcomes in older adults: the Health, Aging, and Body Composition study.* Circ Arrhythm Electrophysiol. 2013;6(1):84-90.
22. Marcus GM. *The PR interval and cardiac resynchronization therapy outcomes: considering confounding, mediation, and effect modification.* Heart Rhythm. 2012;9(1):40-1.
23. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. *2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation. 2013;128(16):1810-52.
24. Rickard, J, Michtalik H, Sharma R, Berger Z, Iyoha E, Green AR, et al. *Predictors of response to cardiac resynchronization therapy: A systematic review.* Int J Cardiol. 2016; 225:345-52.

Search strategy and keywords

EMBASE

Searching term:

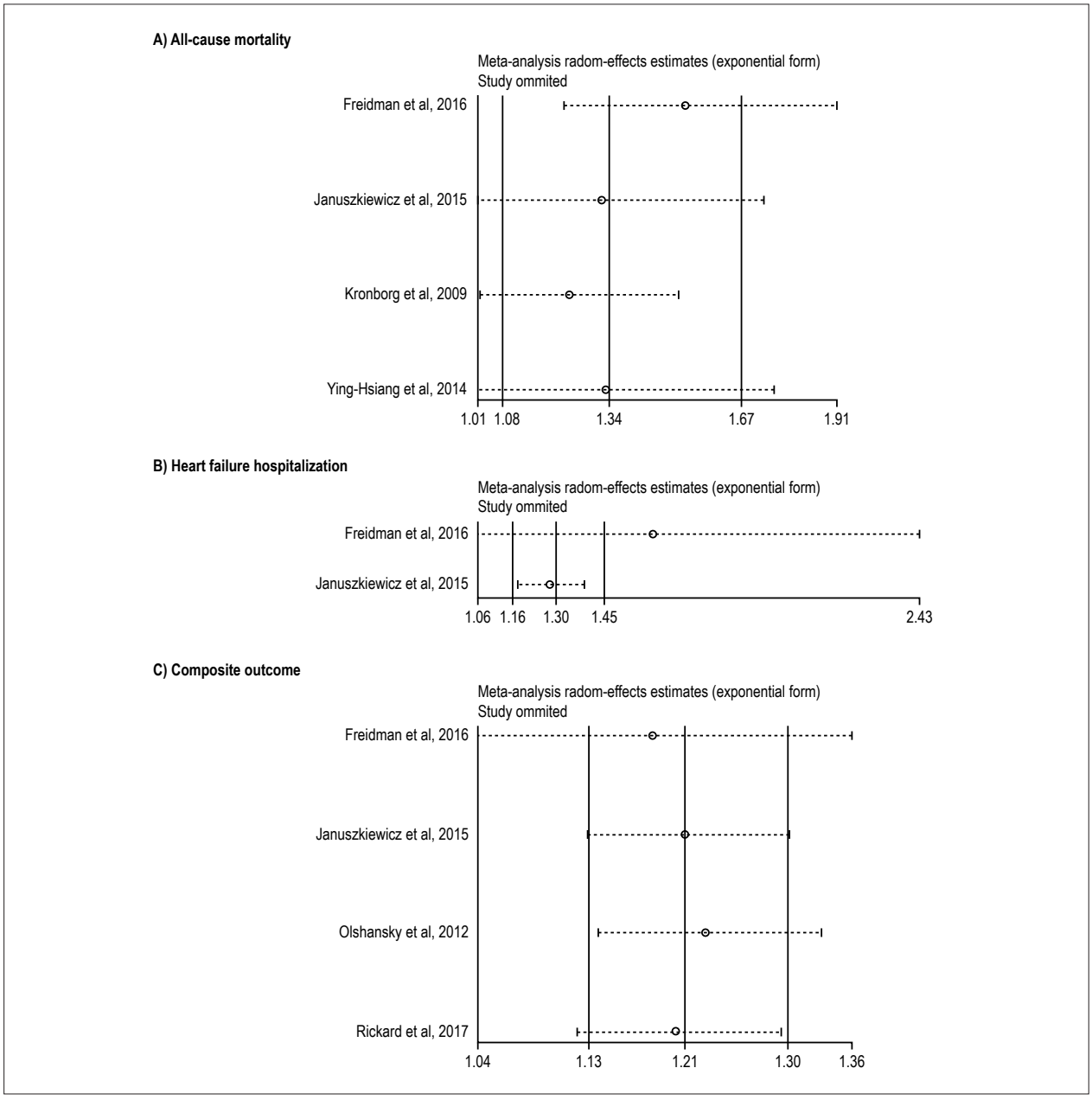
'pr interval' AND 'cardiac resynchronization therapy' AND [humans]/lim AND [english]/lim AND [clinical study]/lim

Pubmed

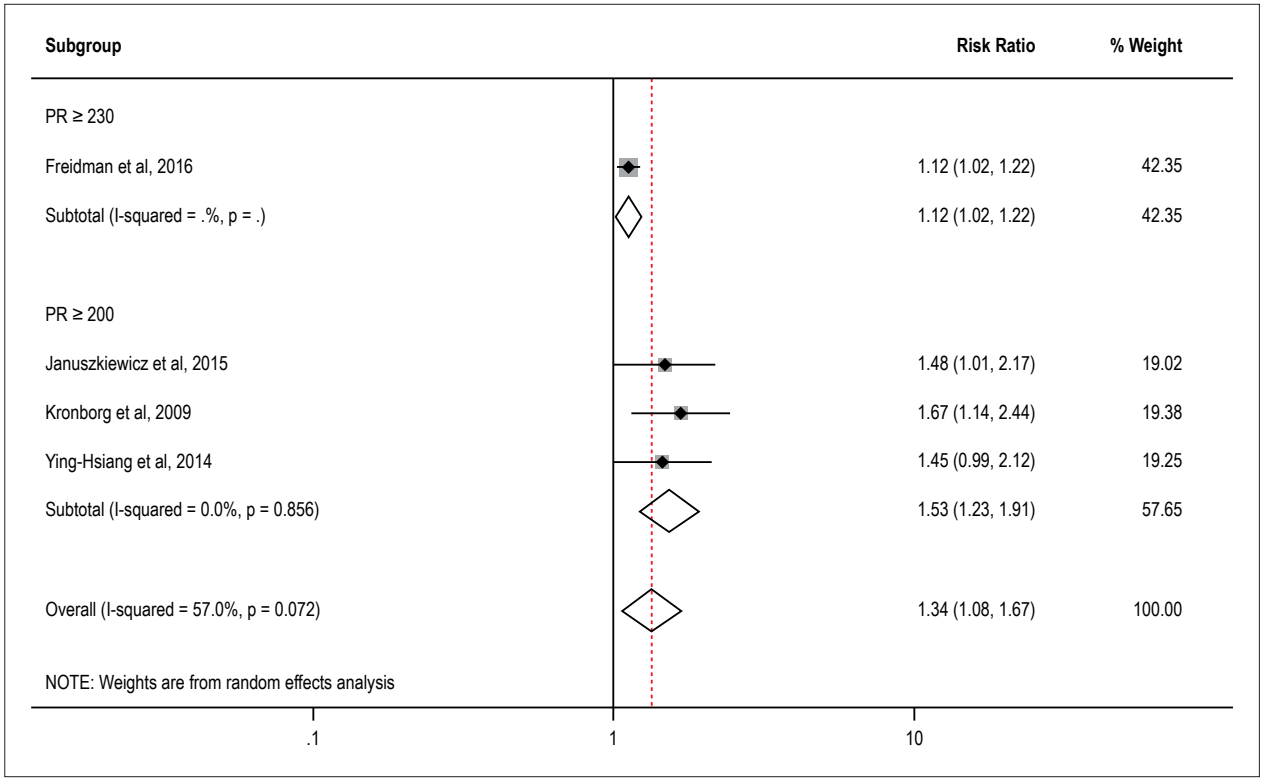
Searching term:

"pr interval"[All Fields] AND "cardiac resynchronization therapy "[All Fields] NOT "case report"[All Fields]

Supplementary Document 1 – Search strategy and keywords



Supplementary Document 2 – *Plot of sensitivity analysis of all-cause mortality (S2A), HF hospitalization (S2B), and composite outcome (S2C).*



Supplementary Document 3 – *Meta-regression of PR definition.*

Can We Consider PR Interval to Screen Patients for Cardiac Resynchronization Therapy?

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Short Editortial related to the article: Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis

The search for response markers to Cardiac Resynchronization Therapy (CRT) remains intensive. Currently, the main criteria for CRT indication are the QRS morphology and the absence of myocardial fibrosis.[1]

The electrocardiogram remains an important tool for selecting CRT candidates, and new parameters, such as the PR interval, are interesting to discriminate the prognosis in this population. On this issue, we have a meta-analysis study[2] concluding that the presence of prolonged PR interval is a marker of poor prognosis at baseline.

In clinical practice, these data may surprise clinicians. The common sense is that it is much easier to make adjustments of the atrioventricular interval to obtain the best hemodynamic response,[3] as well as to ensure a higher rate of effective atriobiventricular resynchronization.[4]

The pathophysiological hypotheses that could justify this worse prognosis remain a challenge for medicine.

However, a critical view of these data is needed. The question of strong clinical interest is "Can the PR interval be used as a selection criterion for CRT indication?"

This doubt cannot be clarified yet, focusing on findings of this systematic review and meta-analysis. The reason is very clear: the analysis did not include a control group with prolonged PR interval in patients not undergoing CRT, to assess its actual benefit.

Therefore, this meta-analysis adds scientific collaboration, but we still have much more to study!

Keywords

Electrocardiology/methods; Heart Failure/complications; Cardiac Resynchronization Therapy; Review.

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DOI: 10.5935/abc.20180224

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
2. Rattanawong P, Prasitlumkum N, Riangwiwat T, Kanjanahattakij N, Vutthikraivit W, Chongsathidkiet P, et al. Baseline prolonged PR interval and outcome of cardiac resynchronization therapy: a systematic review and meta-analysis. Arq Bras Cardiol. 2018; 111(5):710-719
3. Kosmala W, Marwick TH. Meta-analysis of effects of optimization of cardiac resynchronization therapy on left ventricular function, exercise capacity, and quality of life in patients with heart failure. Am J Cardiol. 2014;113(6):988-94.
4. Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. J Am Coll Cardiol 2008;52(15):1239-46.

Arterial Stiffness Use for Early Monitoring of Cardiovascular Adverse Events due to Anthracycline Chemotherapy in Breast Cancer Patients. A Pilot Study

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Abstract

Background: Chemotherapy with doxorubicin and cyclophosphamide, although efficient for treating breast cancer, is associated with cardiovascular complications. Recent studies seek to identify methods that can early detect cardiological and vascular changes as a strategy to decrease the incidence of cardiovascular comorbidities.

Objective: To evaluate the role of arterial stiffness measurement in the monitoring of doxorubicin and cyclophosphamide-induced cardiotoxicity in breast cancer patients.

Methods: Prospective longitudinal study in 24 breast cancer patients undergoing treatment with doxorubicin and cyclophosphamide. Patients underwent an indirect evaluation of arterial stiffness through non-invasive measurement of hemodynamic parameters such as pulse wave velocity with the Mobil-O-Graph® 24H PWA device at three different times of the chemotherapy treatment (pre-chemotherapy, after the first and the fourth cycle). The left ventricular ejection fraction was also evaluated by Doppler echocardiography (pre-chemotherapy and after the fourth chemotherapy cycle). Data were considered significant when $p \leq 0.05$.

Results: Patients had a mean age of 52.33 ± 8.85 years and body mass index of 31 ± 5.87 kg/m². There was no significant difference between the hemodynamic parameters evaluated by the oscillometric method or in the left ventricular ejection fraction in the different evaluated periods.

Conclusion: Evaluations of arterial stiffness by oscillometry and measurement of left ventricular ejection fraction by Doppler echocardiography showed equivalence in the values found, suggesting that the evaluation method of arterial stiffness studied could be used as a marker for cardiovascular adverse events associated with doxorrubicin-based chemotherapy drugs. (Arq Bras Cardiol. 2018; 111(5):721-728)

Keywords: Breast Neoplasms; Vascular Stiffness; Stroke Volume/drug effects; Cardiotoxicity; Doxorubicin/adverse effects; Cyclophosphamide/adverse effects.

Introduction

Breast cancer is the most common cancer among women in Brazil and in the world, second only to non-melanoma skin cancer, accounting for approximately 25% of new cases each year.[1] Advances in cancer therapy have resulted both in the improvement of quality of life and in the increase of cancer patients survival.[2] However, in spite of the evolution in the pharmacological treatment of the different neoplasms, several studies have indicated a significant increase in the occurrence of cardiovascular adverse events, mainly myocardial dysfunction in patients undergoing chemotherapy with cardiotoxic drugs, such as the anthracycline group and, to a lesser extent, cyclophosphamide.[3-5] Chemotherapy regimens using doxorubicin and cyclophosphamide are the most commonly used in the treatment of breast cancer in Brazil.[6] The cardiotoxic potential of these drugs is already established, and it is evaluated mainly by Doppler echocardiography in studies showing an increase in the incidence of Heart Failure (HF) in patients who received these drugs.[7]

The early identification of the appearance of cardiovascular alterations in patients during chemotherapy with drugs considered cardiotoxic could help adjust cancer treatment, with the adoption of preventive, substitutive measures or their interruption, aiming at minimizing cardiovascular adverse events caused by these agents.[7,8]

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Arterial Stiffness (AS) is characterized by the reduction of the arteries elastic properties due to intrinsic structural or functional changes.[9] Aging is a normal evolutionary factor for vascular stiffening, and can be accelerated by several factors, such as diabetes and hypertension.[10]

Several studies have related the increase in AS with the progression of cardiovascular diseases.[3,5,11] The early increase in AS can be estimated mainly through the evaluation of the Pulse Wave Velocity (PWV) obtained from indirect imaging or hemodynamic methods.[3,12,13]

Because cardiovascular changes are observed in some patients on doxorubicin, and AS measurement allows the detection of the onset and progression of cardiovascular disease, this study is warranted because it aims to estimate AS, based on PWV measurement, through oscillometric evaluation of the brachial artery, in patients with breast cancer in the initial phases of chemotherapy with doxorubicin combined with cyclophosphamide (AC regimen). In addition, it proposes to check if there is a correlation between AS and the values of Left Ventricular Ejection Fraction (LVEF), an altered condition in patients with cardiotoxicity due to chemotherapy.

Methods

This is a prospective and longitudinal study with a convenience sample. Twenty-four women aged over 18 years with breast cancer and indication of at least four cycles (every 3 weeks) of adjuvant or neoadjuvant chemotherapy based on the AC regimen (at doses of 75 mg/m^2 for doxorubicin and 600 mg/m^2 for cyclophosphamide in each cycle, totaling 300 mg/m^2 and 2,400 mg/m^2 for doxorubicin and cyclophosphamide, respectively) were followed. The recruitment took place in an Oncology Outpatient Clinic of a High Complexity Unit in Public Oncology of the city of Belo Horizonte (state of Minas Gerais), from July 2016 to December 2017.

The following were excluded: pregnant and lactating women; patients with previous history of chemotherapy or radiotherapy; pre-chemotherapy assessment showing abnormal left ventricular systolic function (LVEF < 50%) evaluated by Doppler echocardiography; history of/or active heart disease; moderate to severe hepatic or renal dysfunction; brain-degenerative diseases requiring caregiver's action; and those in use of other chemotherapeutics other than the AC regimen in the treatment of breast cancer.

Randomization took place in an outpatient basis, under clinical evaluation by a cardiologist with experience in the area. Subsequently, patients underwent an echocardiographic study, according to the methodology proposed by Campos-Filho et al.,[14] to evaluate cardiac parameters that could contraindicate participation in the study and also to monitor the cardiac function at different treatment times of chemotherapy, as suggested by current guidelines.[5,7] Following these procedures, patients were referred for chemotherapy with doxorubicin and cyclophosphamide in the same hospital.

Brachial artery AS measurement was performed using the non-invasive device Mobil-O-Graph® 24h PWA (IEM, Germany) through oscillometric measurements on the upper limb. The device has a device for Blood Pressure (BP) measurement and provides measures of PWV, systolic and central diastolic pressure, and *augmentation index*, which are used as an estimate of AS. This device was validated for use in scientific research by the *European Society of Hypertension*.[13] Measurements were made in the contralateral upper limb on the side affected by the tumor, seeking to exclude the influence of axillary dissection surgery and consequent lymphedema. After measuring the circumference of the limb and choosing the appropriate cuff, the device was positioned similarly to procedures defined by guidelines of cardiology societies.[7] Mobil-O-Graph® 24h PWA is able to offer a number of useful results of the cardiovascular condition of the evaluated patient, because the BP and PWV measurements are correlated with the weight, height and age data previously provided by the HMS Client-Server data management software.

Follow-up chronology was implemented with measurements of hemodynamic parameters by Mobil-O-Graph® 24H PWA at three different times: (1) prior to chemotherapy, when measurements of the hemodynamic parameters through the oscillometric method were taken 15 minutes before the beginning of chemotherapy infusion; (2) post-1chemo, measured up to 30 minutes after intravenous (IV) infusion of the first cycle of the AC regimen; there was a variation of 45 to 90 minutes in the chemotherapy infusion; and (3) post-4chemo, measured up to 30 minutes after IV infusion of the fourth cycle of the AC regimen; the time interval from the start of chemotherapy to its completion was 80 to 90 days.

After 1 week of the fourth chemotherapeutic cycle, the patient underwent a new clinical-cardiological evaluation and an echocardiographic study for LVEF analysis and for comparison with the value before the first cycle.

The results of all the variables that the Mobil-O-Graph® 24H PWA instrument provided were tabulated and submitted to statistical treatment among the three measures of the patients studied.

The protocol of this study is in accordance with the Declaration of Helsinki, having been released by the Research Ethics Committee of the institution, and all the patients evaluated signed the Free Informed Consent Form (FICF).

Statistical analysis

The variables underwent the Shapiro-Wilk normality test and were presented as mean ± Standard Deviation (SD), in case of normality, or as median (Interquartile Distance - DI - which is the difference between the third and the first quartiles). Categorical variables were expressed in frequency. The three measurements provided by the device were expressed as mean ± SD. In the comparison between the three moments (pre-chemotherapy, soon after the first cycle of chemotherapy, and after the fourth cycle), we adopted the analysis of variance for repeated measures, with the sphericity check, or Friedman test. The comparison of measurements between two moments was performed by the Wilcoxon test for paired samples, including post hoc analysis. The analysis was developed in the free software R, version 3.3.2, with a significance level of 5% being adopted.

Results

The sample consisted of 24 women, mean age of 52.33 ± 8.85 years, and mean Body Mass Index (BMI) of 31 ± 5.87 kg/m². Approximately 16.7% of the women were alcoholics, and 20.8% were smokers. More than half of them (58.3%) had hypertension, while 12.5% had type 2 diabetes mellitus (Table 1).

LVEF mean values obtained through transthoracic Doppler echocardiogram before and after the fourth cycle of chemotherapy were 67.8% ± 3% and 66.0% ± 3%, respectively, and showed no significant difference between the two times (Figure 1). We also did not observe differences in hemodynamic variables among the three periods analyzed (pre-chemo, post-1chemo, and post-4chemo - all with $p > 0.05$), in relation to peripheral and central systolic and diastolic BP parameters, mean BP, pulse pressure, heart rate, pulse pressure augmentation, systolic volume, cardiac output, total vascular resistance, cardiac index, augmentation pressure, reflection coefficient and augmentation index (Table 2). PWV, a variable that correlated most with arterial stiffness, did not show a statistically significant difference among the three periods analyzed, with $p = 0.507$ (Figure 2).

Table 1 – Characteristics of the patients evaluated in the sample

Variables	n = 24
Age, years	52,33 ± 8,85
BMI, kg/m²	31 ± 5,87
Smoking	5 (20,8)
Alcoholism	4 (16,7)
Diabetes Mellitus	3 (12,5)
Hypertension	14 (58,3)

Results expressed as mean ± standard deviation or n (%). BMI: body mass index.

Discussion

Since the 1970s, chemotherapy with doxorubicin is known to be related to an increase in the prevalence of HF.[15-17] To a lesser extent, but used in high doses, cyclophosphamide has also been shown to be toxic to the cardiovascular system.[18] Currently, the main guidelines for chemotherapy of the most prevalent types of cancer, especially breast cancer, recommend the combination of these agents.[19,20] Several studies have shown a large increase in the incidence of cardiovascular changes following cancer chemotherapy. Frequently, such changes are only clinically observed months or years after the use of these medications.[2,8,12]

The protocol for adjuvant and neoadjuvant treatment of breast cancer at the institution where the research was performed is based on the doxorubicin and cyclophosphamide regimen. The use of other regimens with taxane and 5-fluorouracil can be applied as an adjuvant and as a neoadjuvant; in our study, we chose not to include patients taking these drugs, because the incidence of HF is lower when compared to anthracyclics (5% to 35% of cases vs. 2% to 10%).[6,7] Also, the number of patients using 5-fluorouracil-doxorubicin-cyclophosphamide, or 5-fluorouracil-epirubicin-cyclophosphamide in the institution is lower when compared to the AC regimen. As the incidence of cardiovascular toxicity with the use of trastuzumab alone is low in prospective clinical studies, ranging from 1% to 4%, commonly reversible if detected early, and with a good response to clinical treatment, we chose to exclude patients on their use.[21,22]

According to data from the World Health Organization (WHO), oncological diseases are currently the second largest cause of death in the world.[23] The continuous therapeutic developments of the last decades allowed an increase in the survival of these patients. The adverse effects caused by chemotherapy, especially in the cardiovascular area, have become an important cause of morbidity and mortality in this population. It is estimated that the mortality rate among oncological patients who develop some

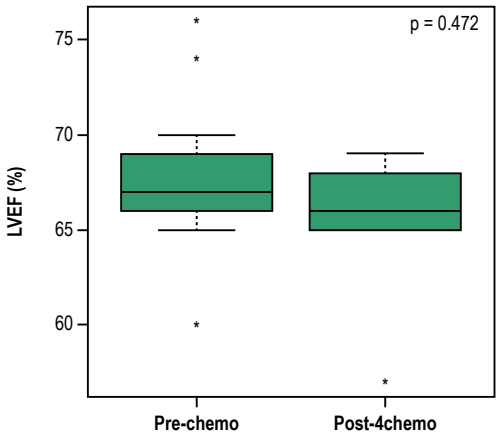

Figure 1 – *Left ventricular ejection fraction (LVEF) values measured by transthoracic Doppler echocardiography in breast cancer patients before (pre-chemo) and after the fourth cycle of chemotherapy (post-4chemo) in the chemotherapy regimen with doxorubicin combined with cyclophosphamide. p values refer to Wilcoxon test.*

Table 2 – Longitudinal evaluation of heart parameters

Hemodynamic variables	Pre-chemo	Post-1chemo	Post-4chemo	p Value
Peripheral SBP, mmHg	125.7 ± 17	123.3 ± 18.2	123.7 ± 8.3	0.244*
Peripheral DBP, mmHg	79.9 ± 14	78.4 ± 10.2	80 ± 11.7	0.988*
Mean blood pressure, mmHg	100.3 ± 11.2	98.6 ± 11.4	100.3 ±10.1	0.879†
PP, mmHg	45.8 ± 12.4	42.5 ± 16.1	43 ±7.6	0.527*
Heart rate, bpm	76.4 ± 18.1	73.9 ± 16.8	78 ±15.7	0.055*
Central SBP, mmHg	117.1 ± 14	115.3± 13.3	116.2± 9.7	0.731†
Central DBP, mmHg	79.7± 10.7	79.5 ± 10.9	81.8 ± 10.7	0.815†
PP^N amplification	1.30 ± 0.11	1.25 ± 0.10	1.28 ± 0.10	0.428†
Stroke volume, mL/m^2	67.4 ± 14.5	68.2 ± 13.5	64.4 ±11.8	0.144†
Cardiac output, L/minute	5.1 ± 0.6	4.9 ± 0.6	5 ± 0.5	0.521†
Total vascular resistance, mmHg/mL	1.2 ± 0.14	1.25 ± 0.16	1.24 ± 0.22	0.675*
Cardiac index, L/min/m^2	2.8 ± 0.3	2.7 ± 0.5	2.7 ± 0.4	0.918*
Augmentation pressure, mmHg	8.8 ± 6.1	7.7 ± 5.1	7.7 ± 3.3	0.110*
Reflection coefficient, %	67.2 ± 7	69.8 ± 6.1	67.6 ± 6.2	0.136†
Augmentation index	26.6 ± 10.8	23.2 ± 11.6	24.4 ± 10.6	0.144†
PWV, m/s	7.61 ± 1.28	7.49 ± 1.20	7.45 ± 1.15	0.507†

*Results expressed as mean ± standard deviation, or median ± difference between the third and first quartiles. For all measured variables, there were three missing data on the measurements after four cycles. *Friedman test; †analysis of variance for repeated measures. Pre-chemo: before chemotherapy; post-1chemo: after the first cycle of chemotherapy; post-4chemo: after the fourth cycle of chemotherapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; PWV: pulse wave velocity.*

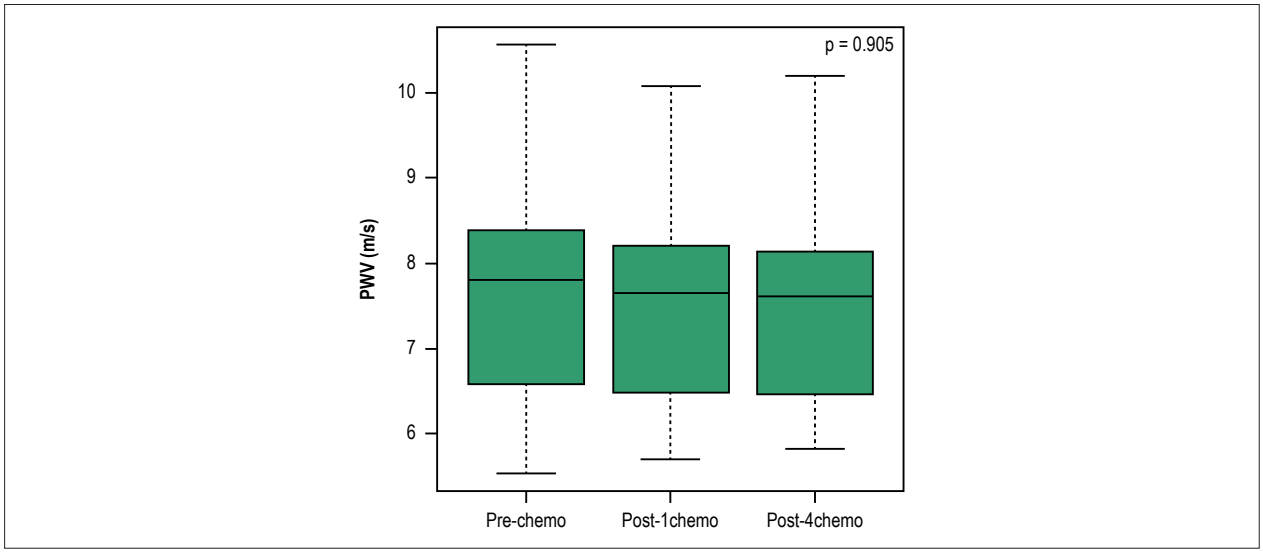

Figure 2 – *Box diagrams for pulse wave velocity (PWV) at the three times assessed: before, after the first cycle of chemotherapy, and after the fourth cycle (pre-chemo, post-1chemo, and post-4chemo). p value refers to analysis of single-factor variance.*

cardiovascular event is high, with values higher than 60% when evaluated within 2 years. With this, cardiovascular disease has become a major cause of morbidity and mortality among cancer survivors.[24,25]

The main mechanism established for the increase in HF secondary to the use of doxorubicin is the direct myocardial damage of these agents (type I cardiotoxicity). The severity of the heart diseases triggered by chemotherapeutic agents seems to depend on the frequency and dose of the medicines administered; on the genetic characteristics; and on other cardiovascular comorbidities previously present.[11,26] The mechanism related to myocardial damage seems to occur due to the production of free radicals from the reduction of the quinone group of B ring in the anthracyclic structure,

leading to the production of superoxide anions and hydrogen peroxide, which saturate the antioxidant systems and react with the cellular structures, mainly in the membranes, causing cytotoxicity.[27] However, recently, some authors have shown that, in addition to already established myocardial dysfunction, vascular alterations resulting from endothelial dysfunction also occur secondary to the use of anthracyclics and can be used as predictors for the cardiovascular toxicity induced by these agents.[5,28] These changes may occur early, [29] and the mechanism proposed for these vascular changes is also related to the production of free radicals, with consequent cell death, or changes in the production of vasoactive endothelial factors.[2,8,30]

Some authors have already proposed the use of clinical tools to assess the vascular status of individuals undergoing antineoplastic therapies with anthracyclic drugs.[3,11,31] These vascular changes could also justify an increase in the incidence of systemic arterial hypertension, atherosclerosis, and thromboembolic events in patients after chemotherapy.[11,32,33] Early detection of dysfunctions in the vascular system is always difficult when non-histochemical methods are used, and it appears to develop from endothelial dysfunction, leading to progressive vascular remodeling.[28] In addition, vascular changes could contribute to the increase of the preload and, consequently, to decrease of the cardiac output. Thus, in addition to direct myocardial damage, vascular alterations could, at least in part, be related to the decrease in LVEF in patients undergoing chemotherapy.

Several studies have tried to find early markers that can predict the occurrence of these changes in patients on chemotherapy with potential cardiovascular toxicity and, consequently, to detect patients at risk.

Currently, LVEF measurement by transthoracic Doppler echocardiogram is considered the main tool to monitor myocardial dysfunction induced by chemotherapy, and is used in several follow-up protocols.[7,34,35] LVEF can also be measured by other techniques. Drafts et al.,[11] in a study involving 53 patients who received anthracyclic chemotherapy, showed that changes in LVEF can be detected within 30 days of the beginning of chemotherapy sessions.[11] However, these authors, in addition to using larger sampling, applied more accurate techniques, involving magnetic resonance imaging for the early detection of changes in ventricular volumes, compared to the classic Doppler echocardiogram routinely used in cancer treatment services and also in our study. Although other studies have shown a reduction in LVEF in patients at different times of treatment with these agents, our study was not able to show a significant reduction in LVEF between the values measured before the beginning of chemotherapy and in the post-4chemo. This fact may be due to the short period of patients follow-up, which does not allow the demonstration of a clinical change through this method - although structural and molecular microalterations have been shown early in this profile of patients, in the first months after treatment.[3,11,12] There are studies suggesting that most cardiovascular alterations occur in the early stage, from the third month after the end of chemotherapy.[2,12] Furthermore, because it is a pilot study, the reduced sampling may have contributed to this result.

The generic term "arterial stiffness" refers to changes in arterial mechanical properties, in response to acute or chronic phenomena, resulting in atherosclerosis and endothelial dysfunction, and correlating with increased cardiovascular morbidity and mortality.[9] Currently, the best way to estimate AS is by measuring the PWV, obtained through the measurement of the time required for a wave formed by vascular distension to travel a certain distance between two points of an arterial segment.[9] Thus, the greater the values of the PWV, the greater the AS. Some techniques do it with imaging tests, such as ultrasound techniques and magnetic resonance imaging with great precision. However, non-invasive devices, coupled with computerized systems, have been increasingly used for AS measurements.[12]

AS has been shown to be an early marker of cardiovascular diseases. A 2010 study showed, for the first time, a significant increase in aortic artery PWV, measured by magnetic resonance imaging, in patients after 4 months of chemotherapy with anthracyclics.[3] In 2013, the same methodology was applied to patients in earlier stages of the same chemotherapy regimen, showing that it is possible to observe changes in PWV only 1 month after the administration of these agents.[11] Despite the relevance of these studies in the predictability of AS changes in patients receiving anthracyclics, they apply methods that demand higher costs and specialized professionals for their technical performance. From 2010 onwards, portable devices appeared that were capable of simple estimation of AS of the brachial artery through oscillometric measurements of the upper limb, providing several hemodynamic data, which may be predictive markers of cardiovascular changes, such as PWV, augmentation index and cardiac index.[13] Since this is an easy-to-use methodology, several studies have evaluated the potential of increased AS as a marker for cardiovascular diseases in various clinical conditions.[36,37] Clinical studies have confirmed the validity of this instrument, which uses several algorithms to obtain hemodynamic variables such as PWV, which is the gold standard for assessing AS.[9,13] With the same equipment, it is possible to measure central BP and other variables, which can be used to estimate arterial stiffness, but they are influenced by pathophysiological conditions, drugs and age, which make them less reliable.[38,39]

Due to the practicality of estimating AS through this method, our study proposed to evaluate the application of this methodology and correlate it with the data obtained by the LVEF through Doppler echocardiogram. The use of this tool could simplify the monitoring of cardiovascular toxicity induced by chemotherapy, since the use of Doppler echocardiography, as is routinely done for this purpose, is a method that requires higher cost, a qualified medical professional, and scheduled appointment at a specific time and place. This difficulty of access could reduce the guarantee of cardiotoxicity monitoring in patients who underwent chemotherapy.

In our study, all patients were monitored by this system at three different times (immediately before and after the first and fourth cycles of chemotherapy). In contrast to what was observed in other studies, which made these measurements early during chemotherapy, mainly by imaging tests,[3,11] we were unable to show any significant statistical difference in the parameters evaluated at different times.

This study used the oscillometric method in the upper limb to show an increase in PWV and other hemodynamic parameters in 53 children with malignant tumors treated with anthracyclics.[29] However, there was no difference in PWV after treatment with anthracyclines for a period of at least 1 year and without evaluation in the early stages of treatment. No other study in the literature that was researched evaluated any immediate changes in hemodynamic parameters shortly after the chemotherapy infusion of the AC regimen. Although we performed this assessment, we did not observe significant changes at this stage of treatment.

Our study showed an agreement between the parameters related to the estimation of AS by the oscillometric method and those observed in the LVEF values obtained from transthoracic Doppler echocardiography, in an early period of administration of chemotherapeutic agents. These data suggest that later studies, with longer follow-up and a larger sample, should test AS estimation through the method described as a practical and accessible tool for cardiovascular monitoring of breast cancer patients undergoing chemotherapy and using drugs with known cardiovascular toxicity potential.

Conclusion

The application of measures of hemodynamic parameters that correlate with arterial stiffness, evaluated by oscillometric method of the upper limb, as well as the values of left ventricular ejection fraction, measured by transthoracic Doppler echocardiogram, was not changed in the early phase of chemotherapy - up to the fourth cycle of chemotherapy - in women with breast cancer on doxorubicin and cyclophosphamide.

Author contributions

Conception and design of the research: Souza CA, Simões R, Malachias MVB, Drummond-Lage AP, Rezende BA; Acquisition of data: Souza CA, Simões R, Oliveira AN, Zogeib JB, Alves B; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Souza CA, Simões R, Borges KBG, Oliveira AN, Zogeib JB, Alves B, Malachias MVB, Drummond-Lage AP, Rezende BA; Statistical analysis and Obtaining financing: Rezende BA; Writing of the manuscript: Souza CA, Simões R, Borges KBG, Oliveira AN, Malachias MVB, Drummond-Lage AP, Rezende BA.

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 Universidade Federal de Minas Gerais (CAAE 38538714.2.0000.5149) under the protocol number 1408811. 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.

References

1. Fayer VA, Guerra MR, Cintra JR, Bustamante-Teixeira MT. Ten-year survival and prognostic factors for breast cancer in the southeast region of Brazil. Rev Bras Epidemiol. 2016;19(4):766-78.
2. Wu AH. Cardiotoxic drugs: clinical monitoring and decision making. Heart. 2008;94(11):1503-9.
3. Chaosuwannakit N, D'Agostino R, Hamilton CA, Lane KS, Ntim WO, Lawrence J, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. J Clin Oncol. 2010;28(1):166-72.
4. Koelwyn GJ, Lewis NC, Ellard SL, Jones LW, Gelinas JC, Rolf JD, et al. Ventricular-arterial coupling in breast cancer patients after treatment with anthracycline-containing adjuvant chemotherapy. Oncologist. 2016;21(2):141-9.
5. Mozos I, Borzak G, Caraba A, Mihaescu R. Arterial stiffness in hematologic malignancies. Onco Targets Ther. 2017 Mar 3;10:1381-8.
6. Brasil. Ministerio da Saúde. Diretrizes diagnósticas e terapêuticas do carcinoma de mama. Brasília; 2018. p.38.
7. Kalil Filho R, Hajjar LA, Bacal F, Hoff PM, Diz MeP, Galas FR, et al; Grupo de Estudos em Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia (GEIC/SBC); Sociedade Brasileira de Oncologia Clínica; Instituto do Coração – Faculdade de Medicina da Universidade de São Paulo; Instituto do Câncer do Estado de São Paulo – Faculdade de Medicina da Universidade de São Paulo. [I Brazilian Guideline for Cardio-Oncology from Sociedade Brasileira de Cardiologia]. Arq Bras Cardiol. 2011;96(2 Suppl 1):1-52.
8. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ET. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. J Am Coll Cardiol. 2017;70(20):2552-65.
9. Mikael LR, Paiva AM, Gomes MM, Sousa AL, Jardim PC, Vitorino PV, et al. Vascular aging and arterial stiffness. Arq Bras Cardiol. 2017;109(3):253-8.
10. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(41):2873-926.
11. Drafts BC, Twomley KM, D'Agostino R, Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging. 2013;6(8):877-85.

12. Jones LM, Stoner L, Brown C, Baldi C, McLaren B. Cardiovascular disease among breast cancer survivors: the call for a clinical vascular health toolbox. Breast Cancer Res Treat. 2013;142(3):645-53.

13. Franssen PM, Imholz BP. Evaluation of the Mobil-O-Graph new generation ABPM device using the ESH criteria. Blood Press Monit. 2010;15(4):229-31.

14. Campos Filho O, Zielinsky P, Ortiz J, Maciel BC, Andrade JL, Mathias W Jr, et al; Brazilian Society of Cardiology. [Guideline for indication and utilization of echocardiography in clinical practice]. Arq Bras Cardiol. 2004;82 Suppl 2:11-34.

15. Bönner F, Fenk R, Kochanek M, Pfister R. [2016 ESC position paper on cancer treatments and cardiovascular toxicity]. Dtsch Med Wochenschr. 2017;142(24):1826-30.

16. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32(2):302-14.

17. Von Hoff DD, Layard MW, Basa P, Davis HL, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-7.

18. Santos GW, Sensenbrenner LL, Burke PJ, Mullins GM, Blas WB, Tutschka PJ, et al. The use of cyclophosphamide for clinical marrow transplantation. Transplant Proc. 1972;4(4):559-64.

19. Mizuno Y, Fuchikami H, Takeda N, Iwai M, Sato K. Efficacy of reduced dose of pegfilgrastim in Japanese breast cancer patients receiving dose-dense doxorubicin and cyclophosphamide therapy. Jpn J Clin Oncol. 2017;47(1):12-7.

20. Shulman LN, Berry DA, Cirrincione CT, Becker HP, Perez EA, O'Regan R, et al. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014;32(22):2311-7.

21. Procter M, Suter TM, de Azambuja E, Dafni U, van Dooren V, Muehlbauer S, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol. 2010;28(21):3422-8.

22. Muss HB, Berry DL, Cirrincione C, Theodoulou M, Mauer A, Cohen H, et al. Standard chemotherapy (CMF or AC) versus capecitabine in early-stage breast cancer (BC) patients aged 65 and older: results of CALGB/CTSU 49907. J Clin Oncol. 2008;26(15_suppl):507.

23. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.

24. Lancellotti P, Anker SD, Donal E, Edvardsen T, Popescu BA, Farmakis D, et al. EACVI/HFA Cardiac Oncology Toxicity Registry in breast cancer patients: rationale, study design, and methodology (EACVI/HFA COT Registry)--EURObservational Research Program of the European Society of Cardiology. Eur Heart J Cardiovasc Imaging. 2015;16(5):466-70.

25. Cadeddu C, Mercurio V, Spallarossa P, Nodari S, Triggiani M, Monte I, et al. Preventing antiblastic drug-related cardiomyopathy: old and new therapeutic strategies. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1:S64-75.

26. Schmitz KH, Prosnitz RG, Schwartz AL, Carver JR. Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. Cancer. 2012;118(8 Suppl):2270-6.

27. A. Velásquez C, González M, Mejía M, Jaramillo N. Cardiotoxicidad inducida por la quimioterapia desde las bases moleculares hasta la perspectiva clínica 2015. Rev Colomb Cardiol. 2016;23(2):104-11.

28. Skrypnyk I, Maslova G, Lymanets T, Gusachenko I. L-arginine is an effective medication for prevention of endothelial dysfunction, a predictor of anthracycline cardiotoxicity in patients with acute leukemia. Exp Oncol. 2017;39(4):308-11.

29. Herceg-Cavrak V, Ahel V, Batinica M, Matec L, Kardos D. Increased arterial stiffness in children treated with anthracyclines for malignant disease. Coll Antropol. 2011;35(2):389-95.

30. Finkelman BS, Putt M, Wang T, Wang L, Narayan H, Domchek S, et al. Arginine-nitric oxide metabolites and cardiac dysfunction in patients with breast cancer. J Am Coll Cardiol. 2017;70(2):152-62.

31. Krystal JI, Reppucci M, Mayr T, Fish JD, Sethna C. Arterial stiffness in childhood cancer survivors. Pediatr Blood Cancer. 2015;62(10):1832-7.

32. Fraeman KH, Nordstrom BL, Luo W, Landis SH, Shantakumar S. Incidence of new-onset hypertension in cancer patients: a retrospective cohort study. Int J Hypertens. 2013;2013:379252.

33. Okur A, Karadeniz C, Özhan Oktar S, Pınarlı FG, Aral A, Oğuz A. Assessment of brachial artery reactivity, carotid intima-media thickness, and adhesion molecules in pediatric solid tumor patients treated with anthracyclines. Pediatr Hematol Oncol. 2016;33(3):178-85.

34. Belham M, Kruger A, Mepham S, Faganello G, Pritchard C. Monitoring left ventricular function in adults receiving anthracycline-containing chemotherapy. Eur J Heart Fail. 2007;9(4):409-14.

35. Gulati G, Zhang KW, Scherrer-Crosbie M, Ky B. Cancer and cardiovascular disease: the use of novel echocardiography measures to predict subsequent cardiotoxicity in breast cancer treated with anthracyclines and trastuzumab. Curr Heart Fail Rep. 2014;11(4):366-73.

36. Feistritzer HJ, Klug G, Reinstadler SJ, Reindl M, Mayr A, Schocke M, et al. Oscillometric analysis compared with cardiac magnetic resonance for the assessment of aortic pulse wave velocity in patients with myocardial infarction. J Hypertens. 2016;34(9):1746-51.

37. Chi C, Yu SK, Auckle R, Argyris AA, Nasothimiou E, Tountas C, et al. Association of left ventricular structural and functional abnormalities with aortic and brachial blood pressure variability in hypertensive patients: the SAFAR study. J Hum Hypertens. 2017;31(10):633-9.

38. van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, et al. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. J Am Coll Cardiol. 2014;63(17):1739-47.

39. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. Hypertension. 2015;66(3):698-722.

Cardiovascular Aggression by Doxorubicin: The Search for Mechanisms

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Short Editorial related to the article: Arterial Stiffness Use for Early Monitoring of Cardiovascular Adverse Events due to Anthracycline Chemotherapy in Breast Cancer Patients. A Pilot Study

Cardio-oncology is an emerging subject in cardiology events and journals. Increased cancer (CA) incidence and survival rates, easier access to health care and the multiplicity of chemotherapy regimens all contribute to the increase in the diagnosis of cardiovascular complications in patients with CA. The increase in CA prevalence and mortality, as well as its cardiovascular complications, is the price that nations pay for the aging of their populations in an oncogenic environment.[1] Therefore, we are faced with an epidemiological problem and major clinical challenges.

The discovery, in the 1960s, in the Adriatic Sea coast, of a red pigment produced by a fungus with great cytotoxic power has changed paradigms and introduced the concept of cure in clinical cancerology.[2] Reports of toxicity previously presented with other chemotherapeutic agents had also been confirmed with the new class of anthracyclines. The novelty was the real possibility of cure. In the risk-benefit evaluation, adverse effects were neglected on behalf of the decision to use it.[3] Warnings on the cardiotoxicity of doxorubicin (DOXO) came with the description of the classic 'von Hoff curve', where the risk of heart failure incidence at cumulative doses above 500 mg/m^2 was demonstrated.[4]

Initially, the mechanism was said to be an oxidative effect of the chemotherapeutic agent. Later, it was demonstrated that DOXO had a blocking effect on topoisomerases II alpha (neoplastic cells) and beta (cardiomyocyte), as well as its consequence to the structure of DNA, which caused cell death.[5] Other mechanisms of cellular aggression did not become clear until recently, when the action on the mechanical properties of cancerous and healthy cells was demonstrated, especially their effect on the cellular membrane.[6]

Today, there is a pertinent criticism about the lack of studies using judicious methodology and satisfactory casuistry in cardio-oncology. Indeed, there is a lack of basic science research addressing the aggression mechanisms in cardiovascular disease in CA patients. The study published in Arq Bras Cardiol[7] investigates the relationships between arterial stiffness and ventricular dysfunction in patients undergoing DOXO and cyclophosphamide.

Theoretically, the cytotoxic impairment of DOXO could affect the endothelium, with consequences to blood pressure variables, secondarily becoming one of the multiple ventricular myocardial aggressions. Actually, there are no significant clinical reports of arterial hypertension in DOXO users, unlike patients undergoing angiogenesis inhibitors that act by blocking one of several endothelial growth pathways.[8,9] The decision to study DOXO is justified by the high prevalence of its use in solid tumors such as breast cancer and hematological tumors.

In the cohort studied, which comprised 24 middle-aged women, high global cardiovascular risk was clearly observed. On average, the women were hypertensive and obese. There was no change in blood pressure variables in left ventricular function according to measurements by pulse wave velocity and two-dimensional echocardiography. The negative result should not be viewed with dismay. We need all the information we can find on these mechanisms. It is urgent to understand the pathophysiology of these cardiovascular aggressions. Only then will we be able to design ethical clinical trials with the highest possibility of results that might interfere with the reduction of cardiovascular lesions and, above all, with the improvement of survival of patients with cancer.

Keywords

Cardiovascular Diseases/complications; Neoplasms; Cardiotoxicity; Doxorubicin; Cyclophosphamida; Drug-Related Side Effects and Adverse Reactions; Vascular Stiffness; Ventricular Dysfunction.

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References

1. Martins WA, Moço ETSM. Cardio-Oncology: the price of aging. Rev Bras Cardiol. 2012;25(3):164-6.
2. Ewer MS, Von Hoff DD, Benjamin RS. A historical perspective of anthracycline cardiotoxicity. Heart Fail Clin. 2011;7(3):363-72.
3. De Vita Jr VT, Chu E. A history of cancer chemotherapy. Cancer Res. 2008;68(21):8643-53.
4. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-7.
5. Sawyer DB. Anthracyclines and heart failure. N Engl J Med. 2013;368(12):1154-6.
6. Fraczkowska K, Bacia M, Przybyło M, Drabika D, Kaczorowska A, Rybka J, et al. Alterations of biomechanics in cancer and normal cells induced by Doxorubicin. Biomed Pharmacother. 2018 Jan;97:1195-203.
7. Souza CA, Simões R, Borges KBG, Oliveira AN, Zogeib JB, Alves B, et al. Uso da rigidez arterial para monitoramento precoce de eventos adversos cardiovasculares por antracíclicos em pacientes com câncer de mama. um estudo piloto. Arq Bras Cardiol. 2018; 111(5):721-728.
8. Rees ML, Khakoo AY. Molecular mechanisms of hypertension and heart failure due to antiangiogenic cancer therapies. Heart Fail Clin. 2011;7(3):299-311.
9. Souza VB, Silva EN, Ribeiro ML, Martins WA. Hypertension in patients with cancer. Arq Bras Cardiol. 2015;104(3):246-52.

Real World of Percutaneous Coronary Interventions in the Public Health System in Rio de Janeiro: How Can It Be Improved?

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Short Editorial related to the article: Up to 15-Year Survival of Men and Women after Percutaneous Coronary Intervention Paid by the Brazilian Public Healthcare System in the State of Rio de Janeiro, 1999-2010

Cardiovascular diseases (CVD) are currently the leading cause of death in Brazil[1] and in the world,[2] with 80% of the cases[3] occurring in low- and middle-income countries. It impacts these countries economies negatively,[4] with reductions in the Gross Domestic Product (GDP), and increases in the burden on already precarious health care systems. The risk factors associated with CVD are largely preventable, and raising awareness[5] and increasing access to primary health care for prevention[6] are key factors for reducing events.

The present study examined mortality rates in patients who underwent percutaneous coronary interventions (PCI) for both stable coronary disease (SCD) and acute coronary syndromes (ACS) in the State of Rio de Janeiro Public Health System (SUS) from 1999 to 2010. It provides us with interesting data regarding mortality outcomes in such patients, dividing them by gender, age groups, and type of intervention (balloon coronary angioplasty, stenting with bare metal stents and primary PCI for STEMI). It has obvious limitations: it is a retrospective populational cohort; its data were extracted from different databases, and the information had to be paired (hospital admissions versus death certificates, which are not in the same dataset); the mortality outcome was death by any cause, and although the authors cite that the cause of death was divided into two groups (cardiovascular death and any other cause), it is not clear which data was used; there is no information regarding comorbidities, single vessel versus multivessel disease, or medications prescribed; and patients with more than one PCI were excluded.[7]

The authors also state that, compared with other studies,[8-10] the present study showed higher mortality rates, attributing that to the difficulties of extrapolating randomized clinical trials (RCT) results to real-world practice. Although external validity of RCTs and generalizability of their results is a known issue,[11] it is also reasonable to consider the precariousness of the Brazilian Public Health Care System (SUS), with restricted access to primary care and preventive medicine, unsteady supply of medication, unavailability of drug-eluting stents, and insufficient secondary and tertiary health care structure. Above all, low socio-economic conditions and education contribute to a scenario where there are many confounding factors to this higher mortality rates. We also have to consider that there is no evidence that PCI for SCD reduces mortality when compared to optimized medical treatment;[8] therefore, perhaps a better primary outcome could be major cardiac and cerebrovascular events (MACCE) rather than death alone, although it is understandable that the lack of a unified registry, with thorough information, makes it virtually impossible.

Finally, it would be interesting to investigate the costs of cardiovascular disease to SUS, and to compare the financial burden of CVD in Brazil to that in other countries.[12]

Besides its limitations, the present study has strong points: a large number of individuals, a long follow-up time, and a real-world setting. It should be used to generate questions rather than providing answers, and it is a big step towards providing better care for our patients in Brazil.

Keywords

Coronary Artery Disease; Percutaneous Coronary Intervention/economics; Mortality; Morbidity; Unified Health System/economics; Epidemiology.

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References

1. Mansur, A P, Favarato, D. Mortalidade por doenças cardiovasculares no Brasil e na região metropolitana de São Paulo: atualização 2011. Arq Bras Cardiol. 2012; 99(2):755-61.
2. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016;4(13):256.
3. Bovet P, Paccaud, F. Cardiovascular disease and the changing face of global public health: a focus on low and middle income countries. Publ Health Rev. 2012;33(2):397-415.
4. World Health Organization.(WHO). Global status report on noncommunicable diseases 2010. Burden:mortality, morbidity and risk factors. Geneva;2010. P.9-31.
5. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310(9):959-68.
6. Joshi R, Jan S, Wu Y, MacMahon S. Global inequalities in access to cardiovascular health care: our greatest challenge. J Am Coll Cardiol. 2008;52(23):1817-25.
7. Souza e Silva CG, Klein CH, Godoy PH, Salis LHA, Souza e Silva NA. Sobrevida em até 15 anos de homens e mulheres após intervenção coronariana percutânea paga pelo Sistema Único de Saúde no Estado do Rio de Janeiro, em 1999-2010. Arq Bras Cardiol. 2018; 111(4):553-561
8. Weaver WD, Reisman MA, Griffin JJ, Buller CE, Leimgruber PP, Henry T, et al. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. Lancet. 2000;355(9222):2199-203.
9. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al; COURAGE Trial Research Group. Optimal medical therapy with or without ICP for stable coronary disease. N Engl J Med. 2007;356(15):1503-16.
10. Sedlis SP, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GB, et al. Effect of ICP on long-term survival in patients with stable ischemic heart disease. N Engl J Med. 2015;373(20):1937-46.
11. Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?". Lancet. 2005;365(9453):82-93.
12. Tarride JE , Lim M, DesMeules M, Luo W, Burke N, O´Reilly D,et al. A review of the cost of cardiovascular disease. Can J Cardiol. 2009;25(6):195-202.

Is it Possible to Easily Identify Metabolically Healthy Obese Women?

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Abstract

Background: Obesity is recognized as a major risk factor for the development of several metabolic complications. However, some obese individuals have a favorable metabolic profile.

Objective: The aim of this study was to identify an easy parameter for recognizing metabolically healthy obese (MHO) women.

Methods: A total of 292 non-diabetic women with a body mass index (BMI) ≥ 30 kg/m² were selected, and 239 composed the final cohort. We classified the participants according to their metabolic state determined by homeostasis model assessment (HOMA) into MHO or metabolically unhealthy obese (MUO). Both groups were compared regarding biochemical, anthropometric, and body composition characteristics.

Results: The average age of the cohort was 43.9 ± 10.9 years and the average BMI was 37.2 ± 5.3 kg/m². In total, 75.7% of the participants were classified as MHO by HOMA. A cutoff of 108.2 cm for waist circumference (WC) identified MHO participants with a sensitivity of 72.4% (95% confidence interval [CI]: 59.8–82.3%), specificity of 66.9% (95% CI: 59.71–73.3%), and negative likelihood ratio of 0.41 (95% CI: 0.36–0.47). Additionally, a visceral adiposity index cutoff value of 99.2 identified MHO women with a sensitivity of 89.7% (95% CI: 79.2–95.2%), specificity of 48.6% (95% CI: 41.4–55.9%), and negative likelihood ratio of 0.21 (95% CI: 0.15–0.30).

Conclusion: Women classified as MHO exhibited smaller WC measurements and lower body fat percentages, as well as lower blood glucose and insulin levels. WC emerged as an easy parameter for identifying MHO women.

Introduction

The prevalence of obesity has increased sharply in recent decades. Between 1980 and 2013, it increased by 27% to affect 2.1 billion adults worldwide. A meta-analysis of 97 studies including over 2.88 million individuals and more than 270,000 deaths concluded that obesity is linked to a significantly higher risk of mortality from all causes, including cardiovascular diseases (CVD), when compared with normal weight.[1] According to recent data, 17% of the Brazilian population over 20 years of age is obese, and women have higher prevalence of diabetes, hypercholesterolemia, and abdominal obesity.[2]

Obesity is recognized as a major risk factor for the development of several metabolic complications. However, some obese individuals have a favorable metabolic profile, characterized by normal homeostasis model assessment (HOMA) index, blood pressure, and lipid profile. These individuals are identified as metabolically healthy obese (MHO),[1] although there is a current lack of consensus on defining MHO. Recent meta-analysis based in 40 studies showed that almost one-third of obese individuals were MHO using the definition based on the cutoffs established by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III) or by those of the International Diabetes Federation (IDF).[3] Among them, we have Pimentel et al.,[4] whose studies on Brazilian women showed that around 70% were considered MHO according to HOMA and NCEP-ATP III criteria for the diagnosis of metabolic syndrome.

We hypothesized that individuals with MUO phenotype have increased abdominal adiposity and insulin resistance. Consequently, this study was conducted to identify an easy parameter for detecting MHO women.

Methods

The sample comprised 239 women recruited in the municipality of São Gonçalo, State of Rio de Janeiro, Brazil. The study was approved by the Research Ethics Committee of the Clementino Fraga Filho University Hospital (Federal University of Rio de Janeiro, Brazil), under certificate number 062/10. All participants signed an informed consent form. The study included women ≥ 20 years of age with a body mass index (BMI) ≥ 30 kg/m². We excluded women who smoked, used drugs or supplements of any kind (including weight loss supplements), were pregnant or nursing, or had pacemakers or metal prostheses (since they would prevent the assessment of body composition by bioimpedance). We also excluded participants who self-reported diagnosis of diabetes mellitus or use of hypoglycemic drugs.

We measured participants' weight using an electronic scale (Welmy, São Paulo, Brazil). Height was measured using a stadiometer and BMI was calculated as the weight in kg divided by the square of the height in meters. We also measured waist circumference (WC) with a tape measure, body composition

Keywords

Cardiovascular Diseases/physiopathology; Metabolic Syndrome; Dyslipidemias; Diabetes Mellitus; Hypertension; Obesity/prevalence; Women.

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with bioelectrical impedance (Biodynamics 450, Seattle, WA, USA), and blood pressure with an aneroid sphygmomanometer (Missouri, Curitiba, Brazil). Finally, in all participants we calculated the waist-to-height ratio (WHtR) in cm/cm. The visceral adiposity index (VAI) was calculated using the following sex-specific formula for women:

$$VAI = \left(\frac{WC}{36.58 + (1.89 \times BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

Blood samples were collected after a 12-hour overnight fast. Serum was obtained by centrifugation of the samples at 4000 rpm for 15 minutes (Excelsa Baby I, Fanem, São Paulo, Brazil). Serum concentrations of glucose, triglycerides, high-density lipoprotein (HDL)-cholesterol, and total cholesterol were determined by the enzymatic method in an automated biochemical analyzer (LabMax 240, Labtest Diagnostica SA, Brazil). Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. Serum insulin was measured by chemiluminescence, and insulin resistance was estimated using the HOMA index.[5] We distributed the HOMA indices in quartiles and classified the participants as metabolically healthy when their indices were within the three lowest quartiles (2.78), based on Pimentel et al.[4]

The data are presented as mean and standard deviation (SD). The normality of the variables was tested using the Kolmogorov-Smirnov test. Intergroup comparisons were performed with the chi-square test for categorical variables and Student's t-test for continuous variables. P values < 0.05 were considered statistically significant. We used receiver operating characteristic (ROC) curves to identify the cutoff points for WC and VAI values. The analyses were carried out with the statistical software SPSS 20.0 (SPSS, Chicago, IL, USA).

Results

We selected 292 women, 53 of whom were excluded after reporting a diagnosis of diabetes mellitus or use of hypoglycemic drugs. The final sample consisted of 239 individuals. A total of 181 participants (75.7%) were classified as MHO according to their HOMA index. The results showed that all anthropometric parameters and VAI were significantly greater in MUO, and that there were fewer hypertensive individuals and higher triglyceride values in the MHO group when compared with the MUO group (Table 1).

Figure 1 shows the values of WC and VAI and their accuracy in identifying MHO women. Both groups presented similar ROC curves; the WC curve had a better negative likelihood ratio to discriminate MHO at a cutoff value of 108.2 cm.

Discussion

Regardless of the criteria used to define the MHO and MUO phenotypes, it is unclear whether MHO individuals have a lower risk of CVD or all-cause mortality when compared with MUO individuals.[6] A systematic review of the 14 studies that focused on the risk of CVD showed that most of the studies failed to demonstrate a significant association between MHO and increased risk of CVD and mortality, although MHO individuals may indeed have a slightly increased risk of CVD when compared with individuals with normal weight.[1,3]

Berezina et al.[7] studied 503 patients with abdominal obesity and concluded that the MHO phenotype was associated with younger age, smaller WC, higher physical activity level, shorter duration of obesity, and presence of the G45G adiponectin genotype.[7] However, the greatest challenge is establishing a cutoff point for WC that can be applied to different obese populations.

In our study, the prevalence of metabolic health was high; approximately 76% of obese individuals were MHO, and these results were influenced by which definition of metabolic health was used. According to those results, increased waist circumference, waist-to-height ratio, fat mass, blood glucose, insulin, triglycerides, VAI, and hypertension were associated with the MUO phenotype, suggesting that the criterion applied could identify individuals with higher CVD risk. This phenotype overlaps the so-called hypertriglyceridemic waist phenotype, associated with atherosclerosis, diabetes, and coronary artery disease.[1,3,6] Also, this higher prevalence of MHO suggests lack of evidence that BMI is a good marker of cardiometabolic risk and that there is a need for the development and validation of other markers that may help to guide diagnosis and treatment of obese individuals.[7]

In a recent study,[8] including 296,535 participants of both sexes from the UK Biobank followed up for an average of 5 years, one standard deviation increase in waist circumference (12.6 cm for women and 11.4 cm for men) was associated with a hazard ratio (HR) of 1.16 (95% CI: 1.13–1.19) for women and 1.10 (95% CI 1.08–1.13) for men for CVD events. In our study, WC had greater measurement values and was an inexpensive and easy tool to apply in a clinical setting in order to discriminate Brazilian women with MHO from those with MUO. Also, WC and VAI identified MHO women with a similar area under the ROC curve.

The VAI was a positive independent indicator of arterial stiffness, measured by brachial-ankle pulse wave velocity in 5,158 individuals over the age of 40 in a cross-sectional study conducted in Nanjing, China.[9] However, VAI is not so easily obtained in clinical practice. It is possible that WC and VAI could be markers of different aspects of MHO. The former is a tool that easily identifies MHO individuals, and the later assesses the effects of obesity on arterial stiffness and transition into an unhealthy state.

Hamer et al.[10] followed up 2,422 men and women for over 8 years as part of the English Longitudinal Study of Ageing. These authors showed that the MHO phenotype is relatively unstable, since 44.5% of MHO individuals transitioned into an unhealthy state, and emphasized that the progress to an unhealthy state was linked with a significant increase in WC.[10] Visceral obesity is associated with pro-inflammatory activity and increased production of adiponectin linked to deterioration of insulin sensitivity, increased risk of diabetes, dyslipidemia, hypertension, atherosclerosis, and higher mortality.[10]

The primary issue is that the number of obese individuals is continually increasing, and it would be unaffordable to treat all of them in the same fashion. When it comes to obese individuals, as a rule, they all exhibit higher WC measures than the values proposed as cutoff points by IDF and NCEP-ATP III.[3] In our study,

Table 1 – Baseline characteristics of the study participants

	All (n = 239)	MHO (n = 181)	MUO (n = 58)	p value*
Age (years)	43.9 ± 10.9	44.0 ± 10.7	43.6 ± 11.7	0.810
Weight (kg)	93.6 ± 16.0	91.5 ± 15.1	100.2 ± 17.0	< 0.001*
BMI (kg/m^2)	37.2 ± 5.3	36.3 ± 4.9	39.7 ± 5.5	< 0.001*
Waist circumference (cm)	107.5 ± 11.6	105.4 ± 10.2	114.3 ± 13.3	< 0.001*
Waist/height ratio	67.9 ± 7.1	66.5 ± 6.2	72.1 ± 8.1	< 0.001*
Fat mass (kg)	39.6 ± 9.2	38.2 ± 8.5	44.1 ± 10.1	< 0.001*
Fat mass (%)	41.9 ± 3.3	41.4 ± 3.4	43.2 ± 2.9	< 0.001*
Lean mass (kg)	54.0 ± 7.7	53.2 ± 7.4	56.2 ± 8.2	0.011*
Blood glucose (mg/dL)	99.0 ± 32.7	94.1 ± 24.2	114.4 ± 48.1	0.003*
Insulin (mg/dL)	8.7 ± 7.0	6.0 ± 3.5	17.4 ± 8.0	< 0.001*
Total cholesterol (mg/dL)	200.2 ± 40.9	198.9 ± 3.9	201.9 ± 41.9	0.607
LDL-c (mg/dL)	128.0 ± 39.8	128.9 ± 39.1	124.8 ± 37.3	0.479
HDL-c (mg/dL)	44.5 ± 9.3	44.7 ± 9.6	42.9 ± 9.4	0.193
Triglycerides (mg/dL)	139.0 ± 75.5	128.4 ± 67.2	170.3 ± 89.3	< 0.001*
VAI	133.5 ± 92.0	119.4 ± 81.8	177.4 ± 107.7	< 0.001*
SBP (mmHg)	124.1 ± 19.8	123.5 ± 20.2	126.1 ± 18.7	0.396
DBP (mmHg)	82.7 ± 10.6	81.6 ± 10.8	82.2 ± 10.1	0.671
Skin color – non-whites % (n)	67.4(161)	71.3(129)	55.2(32)	0.064
Marital status – with partner % (n)	60.7(145)	59.7(108)	63.8(37)	0.944
Education ≤ 11 years % (n)	82.9(198)	82.9(150)	82.7(48)	0.918
Income per capita in reais	658.1 ± 524.4	647.6 ± 496.3	691.1 ± 607.6	0.622
Hypertension % (n)	43.9(105)	38.7(70)	60.3(35)	0.004*
Lipid-lowering drugs % (n)	5.0(12)	5.0(9)	5.2(3)	0.952
Hypothyroidism % (n)	5.9(14)	6.6(12)	3.4(2)	0.369
Physical exercise – Yes % (n)	18.8(45)	19.3(35)	17.2(17)	0.722
Menopause – Yes % (n)	34.6(80)	35.6(62)	31.6(18)	0.577

The values are expressed in mean ± standard deviation or frequency (%/n). BMI: body mass index; VAI: visceral adiposity index; SBP: systolic blood pressure; DBP: diastolic blood pressure. To compare the MHO and MUO groups, we used Student's t-test (for continuous variables) or chi-square test (for categorical variables). P value: statistically significant difference.*

there is a lack of information regarding some other variables that have been used to define MHO, such as production of adiponectin and inflammatory markers. The strengths of this study include the sample size and the study setting. Furthermore, by easily identifying high-risk obese individuals, this study may make lifestyle modification possible.

There has been much interest in the paradoxical findings of individuals considered MHO despite increased adiposity. The major challenge was to determine a single parameter for detecting MHO women, given that there is no consensus in literature and that few studies have been conducted in Brazil. Therefore, our study suggests that waist circumference is an easy parameter for identifying MHO women.

Author contributions

Conception and design of the research and acquisition of data: Scorsatto M, Rosa G, Pimentel AC, Luiz RR, Oliveira GMM; analysis and interpretation of the data: Scorsatto M, Rosa G, Pimentel AC, Oliveira GMM; statistical analysis: Luiz RR; writing of the manuscript: Scorsatto M, Rosa G, Oliveira GMM; critical revision of the manuscript for intellectual contente: Scorsatto M, Rosa G, Luiz RR, Oliveira GMM.

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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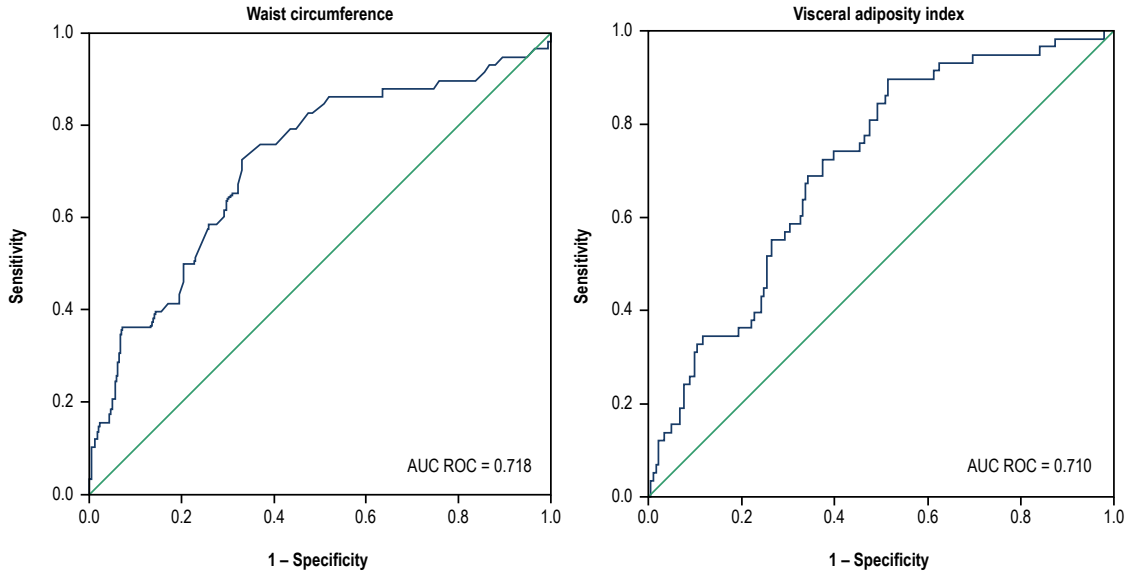

	Sensitivity (%) 95% CI	Specificity (%) 95% CI	AUC (95% CI)	LR (+)	RV (–)
Waist circumference (108.2 cm)	72.4 (59.8–82.3)	66.9 (59.7–73.3)	0.72 (59.7–73.3)	2.18	0.41
Visceral adiposity index (VAI-99.2)	89.7 (79.2–95.2)	48.6 (41.4–55.9)	48.6 (41.4–55.9)	1.75	0.21

Figure 1 – *Accuracy and Receiver operating characteristic (ROC) curves for waist circumference and visceral adiposity index at cutoff values of 108.2 cm and 99.2, respectively. LR, Likelihood ratio; AUC: area under the receiver operating characteristic curve; 95% CI: 95% confidence interval; LR: Likelihood ratio; AUC: area under the receiver operating characteristic curve; 95% CI: 95% confidence interval.*

References

1. Roberson LL, Aneni EC, Maziak W, Agatston A, Feldman T, Rouseff M, et al. Beyond BMI: The "Metabolically healthy obese" phenotype & its association with clinical/ subclinical cardiovascular disease and all-cause mortality – a systematic review. BMC Public Health. 2014 Jan 14;14:14.
2. Ramires EK, Menezes RC, Longo-Silva G, Santos TG, Marinho PM, Silveira JA. Prevalência e fatores associados com a Síndrome Metabólica na população adulta brasileira: pesquisa nacional de saúde – 2013. Arq Bras Cardiol. 2018;110(5):455-66.
3. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis A PRISMA-compliant article. Medicine (Baltimore). 2017;96(47):e8838.
4. Pimentel AC, Scorsatto M, Oliveira GM, Rosa G, Luiz, RR. Characterization of metabolically healthy obese Brazilians and cardiovascular risk prediction. Nutrition. 2015;31(6):827-33.
5. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.
6. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6(9):714-724.
7. Berezina A, Belyaeva O, Berkovich O, Baranova E, Karonova T, Bazhenova E, et al. Prevalence, risk factors, and genetic traits in metabolically healthy and unhealthy obese individuals. Biomed Res Int. 2015; 2015:548734.
8. Iliodromiti S, Celis-Morales CA, Lyall DM, Anderson J, Gray SR, Mackay DF, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. Eur Heart J. 2018;39(17):1514-20.
9. Yang F, Wang G, Wang Z, Sun M, Cao M, Zhu Z, et al. Visceral adiposity index may be a surrogate marker for the assessment of the effects of obesity on arterial stiffness. PLoS One. 2014;9(8):e104365.
10. Hamer M, Bell JA, Sabia S, Batty GD, Kivimäki M. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. Eur J Endocrinol. 2015;173(5):703-8.

Role of miRNAs on the Pathophysiology of Cardiovascular Diseases

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Abstract

MiRNA (or microRNA) is a subclass of non-coding RNAs that is responsible for post-transcriptional gene regulation. It has approximately 22 nucleotides and regulates gene expression in plants and animals at the post-transcriptional level, by the cleavage of a target mRNA or by suppression of its translation. Although many of the processes and mechanisms have not yet been fully elucidated, there is a strong association between miRNA expression and several diseases. It is known that miRNAs are expressed in the cardiovascular system, but their role in cardiovascular diseases (CVDs) has not been clearly established. In this non-systematic review of the literature, we first present the definition of miRNAs and their action at the cellular level. Afterward, we discuss the role of miRNAs as circulating biomarkers of CVDs, and then their role in cardiac remodeling and atherosclerosis. Despite the complexity and challenges, it is crucial to identify deregulated miRNAs in CVDs, as it allows a better understanding of underlying cellular and molecular mechanisms and helps in the development of more accurate diagnostic and prognostic circulating biomarkers, and new therapeutic strategies for different stages of CVDs.

Introduction

Scientific research has been done in attempts to explain the pathophysiology of several diseases for the development of new therapies. In this regard, miRNA (or microRNA) has drawn attention of scientific community as a potential therapeutic target. Since their discovery in 1993,[1] several miRNAs related to biologic processes for their gene-regulatory roles have been cataloged. However, many miRNAs remain to be discovered, which makes them one of the largest classes of gene regulators. To give an idea of the importance of miRNAs, these molecules regulate approximately one third of all gene expression in mammals.[2]

Although many studies have successfully established an association between miRNA expression patterns and several diseases, many mechanisms and processes involved have not been fully elucidated. In diabetes mellitus, for example, results of experimental studies have indicated that specific miRNAs present in pancreatic islets may play a regulatory role in insulin secretion.[3] MiRNA expression may also be visualized in different types of tumors, acting either as tumor suppressors or exerting an opposite role with deleterious effects.[4] Although it is currently known that miRNAs are expressed in the cardiovascular system, their role on the development of cardiovascular diseases (CVDs) still need to be better understood.

In light of this, we conducted a systematic review aimed at summarizing and discussing the findings of the main studies investigating the relationship between miRNAs and CVD. We searched for articles published in the PubMed database (www.ncbi.nlm.nih.gov/pubmed). Original articles written in English, involving humans or animals, were selected using the following MeSH terms – microRNA AND Cardiovascular Diseases, miRNA AND Cardiovascular Diseases.

In this review, we first describe the definition of miRNAs and their actions at the cellular level. Subsequently, we discuss the role of miRNAs as circulating biomarkers, and their role in cardiac remodeling and atherosclerosis.

MiRNA biology

For many years, it was believed that non-coding regions of the genome were "junk", as they did not carry information for protein synthesis. Currently, it is known that most of the eukaryotic transcriptome is composed by noncoding RNAs, which are classified as functional and regulators. Among functional RNAs, there are transfer RNA (tRNA), small nuclear RNA (snRNA) and small nucleolar RNA (snoRNA); major classes of RNAs regulators are miRNAs, small interfering RNAs (siRNAs), piwiRNAs (piRNAs) and long noncoding RNAs (lncRNAs).[5]

Among this wide variety of noncoding RNA classes, much attention has been drawn to miRNAs because of the association between dysregulation of these molecules and development of phenotypic and pathological changes.[6] MiRNAs are defined as single-stranded, small noncoding RNA molecules containing about 22 nucleotides (nt). They function in post-transcriptional regulation of gene expression in plants and animals by means of cleavage of the target messenger RNA (mRNA) or by suppression of mRNA translation.[7] The first miRNA, lin-4, was described in 1993 by the group of Rosalind Lee as a miRNA involved in the larval development of *Caenorhabditis elegans* (*C. elegans*). Lin-4 negatively regulates the level of LIN-14 protein in the first larval stage, decreasing its expression over time.[1]

MiRNA biogenesis starts with the synthesis of a long primary transcript, known as pri-miRNA (~110pb) (Figure 1). Pri-miRNAs are transcribed by RNA polymerase II or III;[8]

Keywords

Cardiovascular Diseases/physiopathology; Cardiovascular Diseases/diagnosis; Cardiovascular Diseases/genetics; Biomarkers/metabolism; Cardiac, Remodeling/genetics; Atherosclerosis; MicroRNAs.

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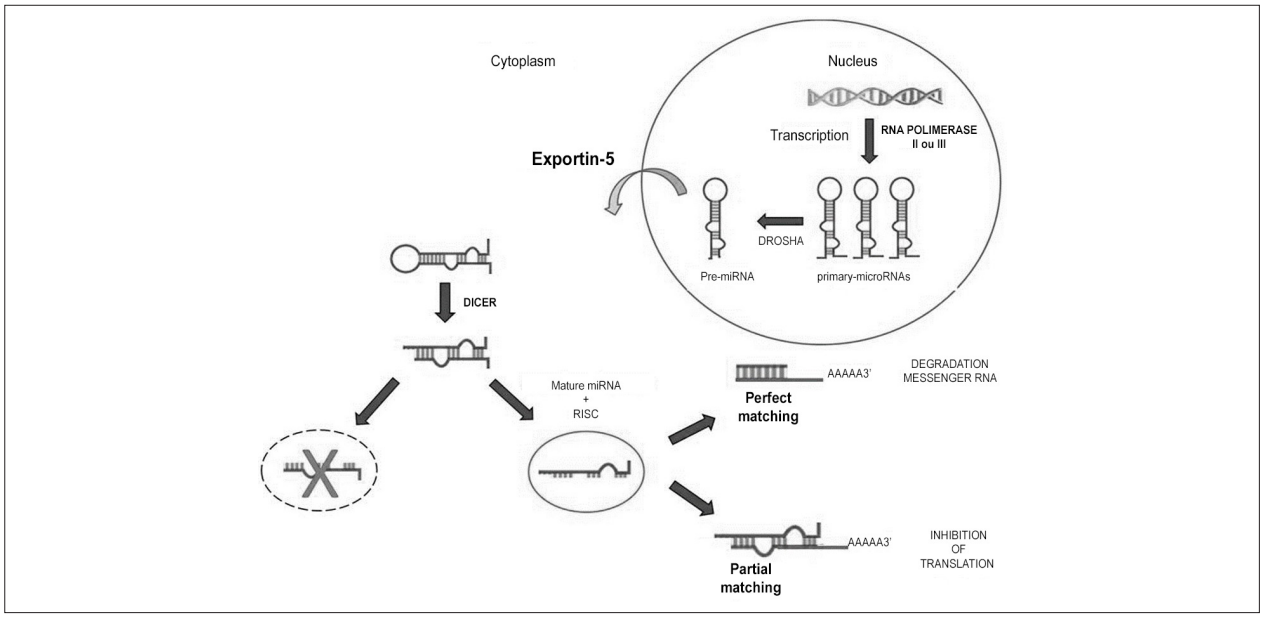

Figure 1 – *Synthesis of miRNA and its action on messenger RNA (mRNA). Hairpin primary-microRNAs are synthesized in the nucleus, converted into pre-miRNA by Drosha enzyme, and exported from the nucleus into the cytoplasm by the Exportin-5 protein. In the cytoplasm, pre-miRNA is recognized by the enzyme Dicer; RNA-induced silencing complex (RISC) binds to a double-stranded RNA (dsRNA), generating mature miRNA. Mature miRNA interacts with the target mRNA, leading to either its degradation or its translation.*

they contain a hairpin structure, essential for its recognition by miRNA processing enzymes. Pri-miRNA is processed into pre-miRNA (~70pb) by the nuclear RNaseIII enzyme Drosha[9] which recognizes and cleaves the ends of the hairpin-shaped small RNA structures.[10]

Following the nuclear processing, each pre-RNA is exported into the cytoplasm by the Exportin-5 protein.[11] Pre-miRNA is recognized by the enzyme Dicer, which cleaves the loop region into a double-stranded RNA (dsRNA:~22pb). This process recruits proteins of the Argonaute protein family to form the RNA-induced silencing complex (RISC).[12] RISC binds to one of the strands of the dsRNA and generates mature miRNA (canonical miR or miR-5p) which is involved in the regulation of a target mRNA.[13] The other strand (miR* or miR-3p) is either degraded or involved in the generation of another RISC, acting in the regulation of another target mRNA.[14]

The perfect matching between miRNA and the three prime untranslated region (3'-UTR) of the target mRNA leads to the cleavage of the mRNA and its transfer to mRNA processing bodies (p-bodies) and subsequent degradation.[15] On the other hand, a partial matching between miRNA and 3'-UTR inhibits translation, which is the main mechanism of action of the miRNAs in mammals.[16] Thus, by translation inhibition, miRNA has a direct effect on translation factors and on poly(A) tail functioning.[17] Although the primary location of miRNAs is cell cytoplasm,[8] some studies have confirmed the entry of these molecules into the circulatory system, possibly resulting from cell lysis.[18]

Therefore, MiRNAs are also found in the circulatory system and several studies have shown its high stability in the extracellular environment. MiRNA degradation in the extracellular milieu could be prevented by its binding to proteins (e.g. lipoproteins) or its encapsulation into microvesicles and exosomes. Thereby, miRNAs can be reliably detected in plasma samples, and suggested as potential biomarkers of CVDs.[19] Since miRNAs are small sequences and do not require perfect matching, a unique miRNA can have tens of target mRNA, and a unique mRNA can be the target of multiple miRNAs, producing a broad regulatory power of genetic expression.[20]

MiRNAs as circulating biomarkers

Circulating levels of miRNAs have been shown to be altered in some CVDs. This fact has aroused interest in using it as a diagnostic and prognostic tool, since circulating miRNAs have high stability and are easily detected. MiRNAs could be used, for example, as biomarkers of heart failure (HF), atrial fibrillation, acute myocardial infarction (AMI) and atherosclerosis, by its detection in blood plasma (Figure 2).

It has been well established that the presence of miR-1 in the blood may be helpful in the detection of AMI. However, its long-term use as a biomarker has not been recommended, since it remains circulating in the blood only for a short period. The short half-life of MiR-1 is probably explained by its direct release from cardiac necrotic tissue into the circulation, not encapsulated in exosomes.[21] In case of heart injury, miRNAs would be released into the blood through exosomes or by cell rupture, associated or not with other molecules. These molecules could protect miRNAs from degradation, prolonging its time in circulation. Besides, the increase in blood flow, changes in pH and release of cytokines can also affect the half-life of circulating miRNAs. For example, it was shown that exogenously added mature miR-1 is rapidly degraded both *in vitro* and *in vivo*.[22]

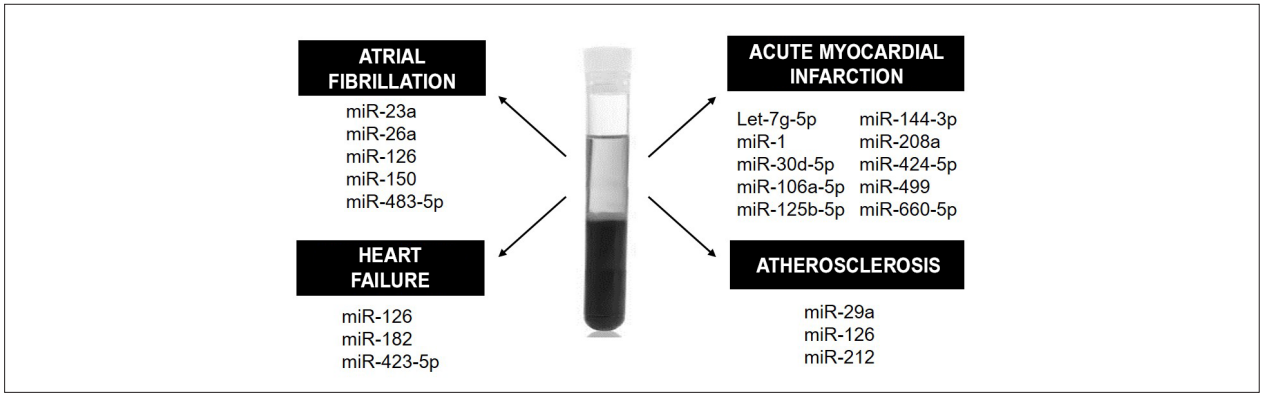

Figure 2 – *Circulating biomarkers. Some of the serum and plasma miRNAs that could be used as diagnostic or prognostic biomarkers in cardiovascular diseases are here illustrated.*

One limitation of the use of circulating miRNA is the lack of normalization of its quantification as compared with tissue miRNA.[23] Despite these limitations, miR-1 is highly sensitive in early identifying AMI.

Several studies have suggested a higher diagnostic accuracy of miR-499 compared with troponin T for AMI.[24,25] MiR-499 has the advantage of being detectable in the blood within the next four hours after the AMI, whereas troponin can be detected only later.[26] Therefore, miR-499 could enhance the accuracy of troponin T in the early diagnosis of AMI. The HUNT study investigated 179 miRNAs in 212 healthy subjects aiming to predict AMI in these individuals. Several circulating miRNAs were significantly different between individuals who suffered from fatal AMI and those who remained healthy during the follow-up period. Logistic regression analysis revealed that five miRNAs (miR-106a-5p, miR-424-5p, let-7g-5p, miR-144-3p and miR-660-5p) composed the best model for predicting AMI, providing 77% correct classification for both genders.[27] Jia et al.[28] showed that miR-30d-5p and -125b-5p also have diagnostic value for AMI, in a study on acute coronary syndrome patients.[28] In an animal model of AMI, serum miR-208a was increased at 4 hours and 24 hours after AMI.[25]

Several studies have been conducted aiming at evaluating prognostic and/or diagnostic value of miRNAs in heart failure (HF), as well as in HF treatment. There is evidence that miRNAs have an important role in both the initiation and progression of HF. Although brain natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are considered the gold standard for HF diagnosis, miRNAs have been exhaustively studied as potential biomarkers. For example, a recent systematic review with meta-analysis showed that miR-423-5p, as associated with atrial natriuretic peptide (ANP) would have a potential diagnostic value for HF detection.[29] In chronic HF, Cakmak et al.[30] showed that miR-182 has a higher prognostic value for cardiovascular mortality, characterized by unexplained sudden death, decompensated HF or hemodynamically significant arrhythmia, as compared with NT-proBNP and high-sensitivity C-reactive protein (CRP) by ROC curve analysis in patients with compensated HF (NYHA II, n = 20) and decompensated HF (NYHA III, n = 22) compared with healthy controls (n = 15).[30] A more comprehensive overview of miRNAs involved in acute and chronic HF can be found in a recent review by Vegter et al.[31]

Studies on atrial fibrillation (AF) patients have shown that patients with stable chronic HF, AF and ejection fraction < 40% show a significant reduction in plasma miR-150 compared with healthy controls.[32] Harling et al.[33] analyzed the plasma obtained at 24 h before myocardial revascularization to evaluate diagnostic accuracy of miRNA in post-operative AF. The authors showed a predictive accuracy of 78%,[33] indicating that miR483-5 is a potential biomarker of post-operative AF. There is evidence that miR-23a and miR-26a could also predict post-operative AF, since their levels are reduced in the postoperative period of patients undergoing coronary bypass artery grafting surgery.[34] Reduced circulating levels of miR-126 is a potential biomarker of the development, progression and severity of AF and HF, according to a study conducted with patients with AF, HF or both.[35] Also, Gorem et al.[36] showed reduced expression of miR-150 in both platelets and serum of patients with chronic systolic HF associated with AF, compared with individuals without AF.[36]

A study[37] reported the synthesis of endothelial cell-derived apoptotic bodies containing high levels of miR-126 in atherosclerotic vascular disease. These molecules triggered the production of the chemokine CXCL12 in recipient vascular cells.[37] Circulating miR-212 has been suggested by Jeong et al.[38] as a biomarker of atherosclerosis, as it improves the prediction of atherosclerosis when combined with hemoglobin A1c, HDL and lipoprotein(a). Elevated plasma miR-29a levels were associated with increased carotid intima-media thickness in atherosclerosis patients.[39]

Cardiac remodeling

Ventricular remodeling is one of the mechanisms involved in the progression of HF and involves cardiomyocyte apoptosis and hypertrophy, interstitial fibrosis caused by collagen deposition, and vascular rarefaction (Figure 3). Despite evidence of an important role of miRNAs on pathologic remodeling, many miRNAs involved in this process remain to be identified. Also, there have been conflicting results on the association of miRNAs with diseases.

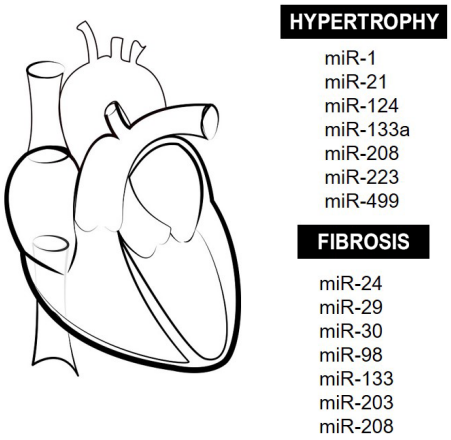

Figure 3 – *Cardiac remodeling and miRNAs. Main miRNAs that modulate cardiac hypertrophy and tissue fibrosis during adverse cardiac remodeling in many diseases are here illustrated.*

MiR-1, -133a, -208a/b and -499 are believed to be specific for cardiac tissue, as they are more abundant in this tissue than in others. These miRNAs are involved in mesodermal precursor differentiation, in transdifferentiation/reprogramming of adult fibroblasts/myofibroblasts into mature cardiomyocytes, and preservation of normal function and survival of cardiomyocytes.[40] In pathologic conditions, dysregulation of cardiac miRNAs may lead to HF progression, combined with arrhythmia, ischemia, ventricular dilatation, fibrosis and tissue necrosis.

Cardiomyocytes

MiR-1 is one of the most abundant miRNAs, responsible for the control of different aspects of differentiation and proliferation of cardiomyocytes. In animals, miR-1 would be involved in the proliferation and differentiation of cardiac cells during cardiogenesis.[41] However, increased expression of miR-1 can cause arrythmia, as it controls cardiac conductance and automaticity by modulating the expression of proteins involved in intracellular calcium regulation.[42] MiR-21 is predominantly expressed in cardiac fibroblasts. Its increased expression was shown to indirectly promote cardiac hypertrophy by stimulating Mitogen Activated Protein (MAP) kinases in an animal model of HF,[43] although there is evidence that increased expression of miR-1 has an anti-hypertrophic role in isolated cardiomyocytes.[44]

Silencing of miR-208 in an animal model of AMI attenuated apoptosis, hypertrophy and fibrosis, promoting improvement in cardiac function.[45] There is evidence that miR-133 protects cardiomyocytes from hypertrophy in neonatal rats. Mechanisms involved in this process include modulation of intracellular calcium concentrations and reduction of mRNA expression into ANP and myosin heavy chain beta MHC-β.[46,47] MiR-223 could suppress hypertrophy by decreasing calcium intracellular concentrations, cardiomyocyte contractility, and phosphorylation of cardiac troponin I (cTNI).[4]

MiR-124 would be involved in cardiac hypertrophy, since its expression is increased in a model of angiotensin II-induced hypertrophy in primary cultured rat neonatal cardiomyocytes, and inhibition of its expression would suppress angiotensin II-induced hypertrophy.[49] In mice, induction of miR-499 expression in the heart caused cellular hypertrophy and cardiac dysfunction due to altered expression of contractile proteins – MYH7B and skeletal muscle actin alpha 1 (ACTA1).[50]

Fibrosis

Connective tissue growth factor (CTGF) is considered a key molecule in the fibrotic process, as it induces the synthesis of extracellular matrix (ECM). Duisters et al.[51] demonstrated that miR-133 and miR-30 regulate CTGF expression.[51] CTGF expression is inversely proportional to the expression of these miRNAs in models of cardiac diseases in rodents (genetic model with hyperactivation of the renin-angiotensin-aldosterone system, cardiac hypertrophy and HF) and in disease-related left ventricular remodeling in biopsy samples of patients with aortic stenosis undergoing valve replacement surgery. Besides, increased expression of miR-133 and miR-30 reduces CTGF expression, resulting in decreased collagen deposition.[51] On the other hand, miR-203 may play a pro-fibrogenic role, since induction of its expression in cultured mouse cardiomyocytes increases the synthesis of CTGF, transforming growth factor beta 1 (TGF-β1) and fibronectin.[52]

Mir-29 also seems to play an important role in ECM remodeling in patients with HF. Mir-29 is preferentially expressed in fibroblasts, in areas surrounding infarcted areas. It would be involved in apoptosis, specially at final stages of HF, reducing collagen expression.[53] In an animal model of infarction, miR-24 expression is reduced, which is correlated with EMC remodeling. MiR-24 expression induced by synthetic precursors inhibits fibrosis, and differentiation and migration of cardiac fibroblasts.[21] MiR-98 seems to have a similar mechanism, since induction of its expression in human cardiac fibroblasts inhibits TGF-β1-induced fibrosis.[54]

Tissue expression profile based on diseases

Ikeda et al.[55] performed a broad analysis of miRNA expression in 67 samples of left ventricular myocardium in ischemic cardiomyopathy, dilated cardiomyopathy and aortic stenosis patients. They found distinct microRNA expression profiles according to different diseases; expression of 13 miRNAs was specific to aortic stenosis, and 8 miRNAs specific to both cardiomyopathies, with no overlapping between both groups.[55] In dilated cardiomyopathy and aortic stenosis, expression of miR-1, -19a and -19b was reduced and miR-214 expression was increased; this was related to cardiac hypertrophy, with no changes in miRNA-133 and -208 expression.[55] Nevertheless, Care et al.[56] showed reduced expression of miRNA-133 in hypertrophic cardiomyopathy and atrial dilation, whereas Yang et al.[57] reported increased expression of miR-1 in ischemic cardiomyopathy.

In the study by Lai et al.,[53] the association of several miRNAs with HF was investigated in biopsy specimens taken from left ventricular apex during cardiac surgery. Increased expression of miR-1, -21, -23, -29, -130, -195 and -199 was found in myocardium of these patients, whereas miR-30, -133 and -208 expression was unchanged. This was associated with higher mRNA expression for caspase-3, type I and type III collagen and TGF.[53]

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the artery walls in response to endothelial injury, especially in medium and large sized elastic vessels, muscular arteries and regions with disturbed laminar blood flow. It is considered the main cause of coronary artery disease, carotid artery disease, stroke and peripheral vascular disease.[58] Several evidences have shown the involvement of miRNAs in the development of atherosclerosis, in both human and animal models. MiRNAs can be categorized into miRNAs involved in endothelial dysfunction, cholesterol homeostasis, development of atherosclerotic plaque, neoangionesis and plaque instability and rupture, as described in Figure 4.

Endothelium

In pigs, endothelial cells from regions susceptible to atherosclerosis (aortic arch and abdominal aortic-renal artery bifurcation) showed reduced expression of miR-10a and -10b. MiR-10a inhibits some pro-inflammatory genes in endothelial cells, including vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, as well as the NF-kB pathway.[59] In rats, miR-181b regulates endothelial cell activation and vascular inflammatory response to NF-kB in the presence of pro-inflammatory stimuli.[60] In human umbilical vein endothelial cells (HUVEC), miR-126, miR-31 and miR-1703p also regulate vascular inflammation by controlling the expression of cell adhesion molecules – VCAM-1, intercellular adhesion molecule-1 (ICAM-1) and E-selectin.[61]

Cholesterol homeostasis

MiR-33a and miR-33b regulate SREBP2 and SREPB1 genes, responsible for cholesterol regulation and fatty acid metabolism, in human and mice cells.[62] Inhibition of miR-33a inhibited atherosclerosis in mice.[63] Inhibition of miR-122 expression, which accounts for 80% of miRNAs expressed in the liver, significantly decreased cholesterol serum levels in mice and non-human primates.[64]

Plaque development

MiR-155 is an important regulator of the immune system and seems to be involved in acute inflammatory response. MiR-155 modulates the development of atherosclerotic plaque, lipid uptake and the inflammatory response of monocytes and macrophages that leads to foam cell formation. Among its mechanism of action, this miRNA acts as a regulator of the negative feedback in oxidized LDL-induced inflammatory response in macrophages and inhibits the release of inflammatory cytokines from macrophages, such as interleukin 6 (IL-6) and IL-8 and tumoral necrosis factor alpha (TNF-α).[65]

In peripheral blood monocytes in humans, miR-125a-5p showed an important role in mediating lipid absorption and reducing the secretion of some inflammatory cytokines (IL-2, IL-6, TNF-α and TGF-β) in macrophages.[66] Oxidized LDL increased the levels of miR-125a-5p, which regulates oxysterol-binding protein-related protein (ORP)-9, hence decreasing the expression of scavenger receptors (CD68) and LOX-1.[66] Similarly, miR-155 reduced oxidized LDL uptake, decreasing the expression of CD36 and LOX-1.[65]

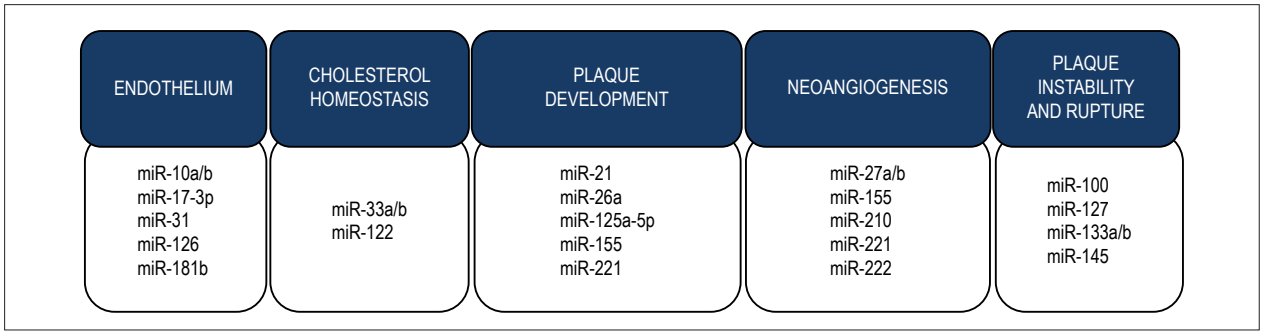

Figure 4 – *Atherosclerosis and miRNAs. Dysregulation of the expression of several miRNAs has been found in different stages of atherosclerosis formation. Some of the miRNAs involved in endothelial dysfunction and inflammation, cholesterol homeostasis, plaque development, neoangiogenesis and plaque instability and rupture are here illustrated.*

Progression of fatty streaks to fibrous cap of an atheroma is mainly caused by proliferation and migration of vascular smooth muscle cells (VSMCs) to the intima. Proliferation and apoptosis of these cells are regulated by TGF-β, which, in turn, is negatively regulated by miR-26a (i.e., miR-26 inhibition promotes VSMC differentiation) in human serum.[67] In addition, both miR-21 and miR-221 also modulate the proliferation of VSMC; miR-221 acts in response to platelet derived growth factor (PDGF). Also, miR-221 negatively regulates p2Kip1, which is critical for induction of cell proliferation mediated by PDGF, whereas c-Kit may be associated with inhibition of VSMC-specific contractile gene transcription by reducing the expression of myocardin, a potent VSMC-specific nuclear coactivator.[68]

Neoangionesis

During the development of atherosclerotic plaque, activated, cholesterol-containing macrophages are responsible for the release of several cytokines, including those involved in neoangiogenesis. MiRNAs involved in this process include miR-221, -222, -155, -27a, -27b and -210. In HUVEC cells, miR-222/221 affect the expression of c-Kit,[69] and miR-222 is involved in vascular remodeling mediated by inflammation.[70] MiR-155 seems to regulate the expression of endothelial nitric oxide synthase (eNOS) and endothelium-dependent vascular relaxation.[71] In a three-dimensional spheroid model, increased expression of miR-27a/b stimulates endothelial cell sprouting, indicating its pro-angiogenic effect, since they target semaphorin 6A, an angiogenesis inhibitor.[72] Finally, miR-210 expression in HUVEC progressively increases in hypoxia and its increased expression in normoxia leads to formation of capillary-like structures by VEGF on Matrigel.[73]

Plaque instability and rupture

Instability and rupture of the fibrous capsule of an atherosclerotic plaque depend on the balance between synthesis and degradation of the ECM by fibroblasts. Plaque rupture is the main mechanism involved in the development of stroke and AMI, and sudden death. Matrix metalloproteinases (MMPs) act in collagen degradation, especially MMP-1, MMP-2, MMP-3 and MMP-9 released by activated macrophages.[74]

MMP-9 is regulated by miR-133a/b, which can also modulate VSMC apoptosis and proliferation in animal models.[75] Cipollone et al.[76] investigated miRNA expression and its correlation with plaque instability in internal carotid artery in humans. Two independent cohorts of atherosclerotic plaques of patients who underwent carotid endarterectomy for extracranial high-grade (>70%) internal carotid artery were collected in two Italian hospitals (n = 15 and n = 38). The plaques were subdivided into 2 groups (symptomatic and asymptomatic plaques) according to the presence or absence of stroke. The authors observed that, among the 41 miRNAs examined, there was increased expression of 5 miRNAs (miNA-100, miRNA-127, miRNA-145, miRNA-133a, and miRNA-133b) in symptomatic compared with asymptomatic plaques.[76] It is worth mentioning that differences in the expression of miRNAs between stable and unstable plaques were not related to differences in conventional risk factors or concomitant therapies, since these variables were well balanced between the two groups. Incubation of HUVECs with miR-133 downregulated the expression of plasminogen activator inhibitor-1 (PAI-1).[76]

Conclusion

Despite all difficulties and challenges, it is crucial to identify dysregulated miRNAs, as it allows a better understanding of cellular and molecular mechanisms involved in CVDs. Studies on tissue and circulating miRNAs could help in the development of more accurate diagnostic and prognostic circulating markers, as well as new therapeutic strategies for different stages of CVDs.

Despite advances in this field, there are still some limitations, for example, in using circulating miRNAs as biomarkers. Molecular processes that control the packing and release of extracellular miRNAs have not been fully elucidated, including mechanisms mediated or not by vesicles. Besides, detection of circulating miRNAs requires high technical skills, which could limit their use in routine laboratory use. Another limiting factor is the omnipresence of miRNAs in the circulation, requiring further investigations to identify its tissue origin.

Author contributions

Conception and design of the research: Fernandes-Santos C; acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual contente: Silva DCP, Carneiro FD, Almeida KC, Fernandes-Santos, C.

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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References

1. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75(5):843-54.
2. Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet. 2006;15(spec1):R17-29.
3. Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, Macdonald PE, et al. A pancreatic islet-specific microRNA regulates insulin secretion. Nature. 2004;432(7014):226-30.
4. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101(9):2999-3004.
5. Zhou X, Zuo Z, Zhou F, Zhao W, Sakaguchi Y, Suzuki T, et al. Profiling sex-specific piRNAs in zebrafish. Genetics. 2010;186(4):1175-85.
6. Chang TC, Mendell JT. MicroRNAs in vertebrate physiology and human disease. Annu Rev Genomics Hum Genet. 2007;8:215-39.
7. Bartel DP, Chen CZ. Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. Nat Rev Genet. 2004;5(5):396-400.
8. Kim VN. MicroRNA biogenesis: coordinated cropping and dicing. Nat Rev Mol Cell Biol. 2005;6(5):376-85.
9. Han J, Lee Y, Yeom KH, Nam JW, Heo I, Rhee JK, et al. Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. Cell. 2006;125(5):887-901.
10. Lee Y, Han J, Yeom KH, Jin H, Kim VN. Drosha in primary microRNA processing. Cold Spring Harb Symp Quant Biol. 2006;71:51-7.
11. Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes Dev. 2003;17(24):3011-6.
12. Kim VN, Han J, Siomi MC. Biogenesis of small RNAs in animals. Nat Rev Mol Cell Biol. 2009;10(2):126-39.
13. Krützfeldt J, Poy MN, Stoffel M. Strategies to determine the biological function of microRNAs. Nat Genet. 2006;38 (Suppl):S14-9.
14. Rand TA, Petersen S, Du F, Wang X. Argonaute2 cleaves the anti-guide strand of siRNA during RISC activation. Cell. 2005;123(4):621-9.
15. Tang G, Reinhart BJ, Bartel DP, Zamore PD. A biochemical framework for RNA silencing in plants. Genes Dev. 2003;17(1):49-63.
16. Zeng Y, Wagner EJ, Cullen BR. Both natural and designed micro RNAs can inhibit the expression of cognate mRNAs when expressed in human cells. Mol Cell. 2002;9(6):1327-33.
17. Gebauer F, Hentze MW. Molecular mechanisms of translational control. Nat Rev Mol Cell Biol. 2004;5(10):827-35.
18. Zhang J, Zhao H, Gao Y, Zhang W. Secretory miRNAs as novel cancer biomarkers. Biochim Biophys Acta. 2012;1826(1):32-43.
19. Muoio DM, Newgard CB. Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. Nat Rev Mol Cell Biol. 2008;9(3):193-205.
20. van Rooij E, Liu N, Olson EN. MicroRNAs flex their muscles. Trends Genet. 2008;24(4):159-66.
21. Wang J, Huang W, Xu R, Nie Y, Cao X, Meng J, et al. MicroRNA-24 regulates cardiac fibrosis after myocardial infarction. J Cell Mol Med. 2012;16(9):2150-60.
22. Cheng Y, Tan N, Yang J, Liu X, Cao X, He P, et al. A translational study of circulating cell-free microRNA-1 in acute myocardial infarction. Clin Sci (Lond). 2010;119(2):87-95.
23. Rao PK, Toyama Y, Chiang HR, Gupta S, Bauer M, Medvid R, et al. Loss of cardiac microRNA-mediated regulation leads to dilated cardiomyopathy and heart failure. Circ Res. 2009;105(6):585-94.
24. Xin Y, Yang C, Han Z. Circulating miR-499 as a potential biomarker for acute myocardial infarction. Ann Transl Med. 2016;v.4.
25. Xiao J, Shen B, Li J, Lv D, Zhao Y, Wang F, et al. Serum microRNA-499 and microRNA-208a as biomarkers of acute myocardial infarction. Int J Clin Exp Med. 2014;7(1):136-41
26. Chen X, Zhang L, Su T, Li H, Huang Q, Wu D, et al. Kinetics of plasma microRNA-499 expression in acute myocardial infarction. J Thorac Dis. 2015;7(5):890-6.
27. Bye A, Røsjø H, Nauman J, Silva GJ, Follestad T, Omland T, et al. Circulating microRNAs predict future fatal myocardial infarction in healthy individuals - The HUNT study. J Mol Cell Cardiol. 2016 Aug;97:162-8.
28. Jia K, Shi P, Han X, Chen T, Tang H, Wang J. Diagnostic value of miR-30d-5p and miR-125b-5p in acute myocardial infarction. Mol Med Rep. 2016;14(1):184-94.
29. Yan H, Ma F, Zhang Y, Wang C, Qiu D, Zhou K, et al. miRNAs as biomarkers for diagnosis of heart failure: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(22):e6825.
30. Cakmak HA, Coskunpinar E, Ikitimur B, Barman HA, Karadag B, Tiryakioglu NO. The prognostic value of circulating microRNAs in heart failure: preliminary results from a genome-wide expression study. J Cardiovasc Med (Hagerstown). 2015;16(6):431-7.
31. Vegter EL, van der Meer P, de Windt LJ, Pinto YM, Voors AA. MicroRNAs in heart failure: from biomarker to target for therapy. Eur J Heart Fail. 2016;18(5):457-68.
32. Lakschevitz F, Aboodi G, Tenenbaum H, Glogauer M. Diabetes and periodontal diseases: interplay and links. Curr Diabetes Rev. 2011;7(6):433-9.
33. Harling L, Lambert J, Ashrafian H, Darzi A, Gooderham NJ, Athanasiou T. Elevated serum microRNA 483-5p levels may predict patients at risk of post-operative atrial fibrillation. Eur J Cardiothorac Surg. 2017;51(1):73-8.
34. Feldman A, Moreira DA, Gun C, Wang HL, Hirata MH, de Freitas Germano J, et al. Analysis of circulating miR-1, miR-23a, and miR-26a in atrial fibrillation patients undergoing coronary bypass artery grafting surgery. Ann Hum Genet. 2017;81(3):99-105.
35. Wei XJ, Han M, Yang FY, Wei GC, Liang ZG, Yao H, et al. Biological significance of miR-126 expression in atrial fibrillation and heart failure. Braz J Med Biol Res. 2015;48(11):983-9.
36. Goren Y, Meiri E, Hogan C, Mitchell H, Lebanony D, Salman N, et al. Relation of reduced expression of MiR-150 in platelets to atrial fibrillation in patients with chronic systolic heart failure. Am J Cardiol. 2014;113(6):976-81.
37. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, et al. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. Sci Signal. 2009;2(100): 81.
38. Jeong HS, Kim JY, Lee SH, Hwang J, Shin JW, Song KS, et al. Synergy of circulating miR-212 with markers for cardiovascular risks to enhance estimation of atherosclerosis presence. PLoS One. 2017;12(5):e0177809.
39. Liu CZ, Zhong Q, Huang YQ. Elevated plasma MiR-29a levels are associated with increased carotid intima-media thickness in atherosclerosis patients. Tohoku J Exp Med. 2017;241(3):183-8.
40. Piubelli C, Meraviglia V, Pompilio G, D'Alessandra Y, Colombo GI, Rossini A. microRNAs and Cardiac Cell Fate. Cells. 2014;3(3):802-23
41. Zhao Y, Samal E, Srivastava D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. Nature. 2005;436(7048):214-20.
42. Carmean CM, Bobe AM, Yu JC, Volden PA, Brady MJ. Refeeding-induced brown adipose tissue glycogen hyper-accumulation in mice is mediated by insulin and catecholamines. PLoS One. 2013;8(7):e67807.

43. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature. 2008;456(7224):980-4

44. Tatsuguchi M, Seok HY, Callis TE, Thomson JM, Chen JF, Newman M, et al. Expression of microRNAs is dynamically regulated during cardiomyocyte hypertrophy. J Mol Cell Cardiol. 2007;42(6):1137-41.

45. Tony H, Meng K, Wu B, Yu A, Zeng Q, Yu K, et al. MicroRNA-208a Dysregulates Apoptosis Genes Expression and Promotes Cardiomyocyte Apoptosis during Ischemia and Its Silencing Improves Cardiac Function after Myocardial Infarction. Mediators Inflamm. 2015;2015 Nov 25:479123.

46. Lee SY, Lee CY, Ham O, Moon JY, Lee J, Seo HH, et al. microRNA-133a attenuates cardiomyocyte hypertrophy by targeting PKCdelta and Gq. Mol Cell Biochem. 2018;439(1-2):105-15

47. Wu Y, Wang YQ, Wang BX. [MicroRNA-133a attenuates isoproterenol-induced neonatal rat cardiomyocyte hypertrophy by downregulating L-type calcium channel alpha1C subunit gene expression.] Zhonghua Xin Xue Guan Bing Za Zhi. 2013;41(6):507-13.

48. Wang YS, Zhou J, Hong K, Cheng XS, Li YG. MicroRNA-223 displays a protective role against cardiomyocyte hypertrophy by targeting cardiac troponin I-interacting kinase. Cell Physiol Biochem. 2015;35(4):1546-56.

49. Bao Q, Chen L, Li J, Zhao M, Wu S, Wu W, et al. Role of microRNA-124 in cardiomyocyte hypertrophy inducedby angiotensin II. Cell Mol Biol (Noisy-le-grand). 2017;63(4):23-27.

50. Shieh JT, Huang Y, Gilmore J, Srivastava D. Elevated miR-499 levels blunt the cardiac stress response. PLoS One. 2011;6(5):e19481

51. Duisters RF, Tijsen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, et al. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circ Res. 2009;104(2):170-8,

52. He Q, Wang CM, Qin JY, Zhang YJ, Xia DS, Chen X, et al. Effect of miR-203 expression on myocardial fibrosis. Eur Rev Med Pharmacol Sci. 2017;21(4):837-42.

53. Lai KB, Sanderson JE, Izzat MB, Yu CM. Micro-RNA and mRNA myocardial tissue expression in biopsy specimen from patients with heart failure. Int J Cardiol. 2015 Nov 15;199:79-83.

54. Cheng R, Dang R, Zhou Y, Ding M, Hua H. MicroRNA-98 inhibits TGF-beta1-induced differentiation and collagen production of cardiac fibroblasts by targeting TGFBR1. Hum Cell. 2017;30(3):192-200.

55. Ikeda S, Kong SW, Lu J, Bisping E, Zhang H, Allen PD, et al. Altered microRNA expression in human heart disease. Physiol Genomics. 2007;31(3):367-73.

56. Carè A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, et al. MicroRNA-133 controls cardiac hypertrophy. Nat Med. 2007;13(5):613-8.

57. Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, et al. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. Nat Med. 2007;13(4):486-91.

58. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). Annu Rev Immunol. 2009;27:165-97.

59. Fang Y, Shi C, Manduchi E, Civelek M, Davies PF. MicroRNA-10a regulation of proinflammatory phenotype in athero-susceptible endothelium in vivo and in vitro. Proc Natl Acad Sci U S A. 2010;107(30):13450-5.

60. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, et al. MicroRNA-181b regulates NF-κB-mediated vascular inflammation. J Clin Invest. 2012;122(6):1973-90.

61. Suárez Y, Wang C, Manes TD, Pober JS. Cutting edge: TNF-induced microRNAs regulate TNF-induced expression of E-selectin and intercellular adhesion molecule-1 on human endothelial cells: feedback control of inflammation. J Immunol. 2010;184(1):21-5.

62. Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, et al. MiR-33 contributes to the regulation of cholesterol homeostasis. Science. 2010;328(5985):1570-3.

63. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, et al. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. J Clin Invest. 2011;121(7):2921-31.

64. Elmén J, Lindow M, Schütz S, Lawrence M, Petri A, Obad S, et al. LNA-mediated microRNA silencing in non-human primates. Nature. 2008;452(7189):896-9.

65. Huang RS, Hu GQ, Lin B, Lin ZY, Sun CC. MicroRNA-155 silencing enhances inflammatory response and lipid uptake in oxidized low-density lipoprotein-stimulated human THP-1 macrophages. J Investig Med. 2010;58(8):961-7.

66. Chen T, Huang Z, Wang L, Wang Y, Wu F, Meng S, et al. MicroRNA-125a-5p partly regulates the inflammatory response, lipid uptake, and ORP9 expression in oxLDL-stimulated monocyte/macrophages. Cardiovasc Res. 2009;83(1):131-9.

67. Leeper NJ, Raiesdana A, Kojima Y, Chun HJ, Azuma J, Maegdefessel L, et al. MicroRNA-26a is a novel regulator of vascular smooth muscle cell function. J Cell Physiol. 2011;226(4):1035-43.

68. Davis BN, Hilyard AC, Nguyen PH, Lagna G, Hata A.. Induction of microRNA-221 by platelet-derived growth factor signaling is critical for modulation of vascular smooth muscle phenotype. J Biol Chem. 2009;284(6):3728-38.

69. Poliseno L, Tuccoli A, Mariani L, Evangelista M, Citti L, Woods K, et al. MicroRNAs modulate the angiogenic properties of HUVECs. Blood. 2006;108(9):3068-71

70. Dentelli P, Rosso A, Orso F, Olgasi C, Taverna D, Brizzi MF. microRNA-222 controls neovascularization by regulating signal transducer and activator of transcription 5A expression. Arterioscler Thromb Vasc Biol. 2010;30(8):1562-8.

71. Sun HX, Zeng DY, Li RT, Pang RP, Yang H, Hu YL, et al. Essential role of microRNA-155 in regulating endothelium-dependent vasorelaxation by targeting endothelial nitric oxide synthase. Hypertension. 2012;60(6):1407-14.

72. Urbich C, Kaluza D, Frömel T, Knau A, Bennewitz K, Boon RA, et al. MicroRNA-27a/b controls endothelial cell repulsion and angiogenesis by targeting semaphorin 6A. Blood. 2012;119(6):1607-16.

73. Bonauer A, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, et al. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. Science. 2009;324(5935):1710-3.

74. Cipollone F, Fazia M, Mezzetti A. Novel determinants of plaque instability. J Thromb Haemost. 2005;3(9):1962-75.

75. Torella D, Iaconetti C, Catalucci D, Ellison GM, Leone A, Waring CD, et al. MicroRNA-133 controls vascular smooth muscle cell phenotypic switch in vitro and vascular remodeling in vivo. Circ Res. 2011;109(8):880-93.

76. Cipollone F, Felicioni L, Sarzani R, Ucchino S, Spigonardo F, Mandolini C, et al. A unique microRNA signature associated with plaque instability in humans. Stroke. 2011;42(9):2556-63.

Flexibilization of Fasting for Laboratory Determination of the Lipid Profile in Brazil: Science or Convenience?

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A statement endorsed by medical specialty associations has been published in our country recommending the flexibilization of fasting before blood drawing for the laboratory determination of the lipid profile encompassing total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) content and the corresponding calculation of non-HDL-cholesterol (TC – HDL-c).[1] It was considered that non-fasting results do not clinically differ from fasting ones, and prospective studies and meta-analyses have consistently demonstrated that non-HDL-C at a non-fasting state would be at least as good as LDL-c in the prediction of CVD. It was also recommended that when TG > 4.52 mmol/L the formula proposed by Martin et al.[2] should be used for LDL-c estimation.

The statement was based on the European Consensus on the matter published by Nordestgaard et al.[3] However, the automatic application of this approach in Brazil deserves deeper consideration, considering the impact that it may cause on patient care. Furthermore, it is far from a consensus among clinical laboratory scientists and professionals in the country, as it became evident during the 44th Brazilian Congress of Clinical Analysis held last June 11-14th, 2017, and the 51st Brazilian Congress of Clinical Pathology and Laboratory Medicine, held last September 26-29th, 2017.

Indeed, a non-fasting non-HDL-c result would be at least equivalent to LDL-c for goal setting.[4] However, a non-fasting LDL-cholesterol, as well as non-fasting non-HDL-c, could be less sensitive for CVD prediction,[5] especially in women.[6] This possible issue ought to be evaluated judiciously and independently in our specific population.

Secondly, it should be noted that the treatment target for non-HDL-c is simply 0.8 mmol/L (30 mg/dL) higher than the respective target for LDL-c.[7] This was set in an empirical manner, considering an average value of 0.8 mmol/L for VLDL-c. Obviously, this is not consistent with reality, especially in a post-prandial state. On the other hand, the treatment target levels for LDL-c are well established, based on large prospective studies for decades of sound scientific work.

Keywords

Fasting; Cholesterol; Lipids; Triglycerides; Cholesterol, LDL; Cholesterol, HDL.

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Third, the main motives for a non-fasting blood draw as suggested by the European consensus[3] and the Brazilian statement[1] seem to be more commercially driven than scientifically. The rationale included an alleged "inconvenience by having to return on a separate visit for a fasting lipid profile…, a laboratory burden due to a large volume of patients coming for tests in the morning…, a burden for clinicians to review and make decisions based on the findings of the lipid profile at a later date…", and a hypothesized improved "patient compliance with lipid testing".

Only the last motivation may have some scientific background but it yet remains to be proved. It also should be noted that blood sample drawing procedures in Brazil are quite different from those practiced in Western Europe and in the USA. In those countries, biological samples are often drawn right after the consultation with the clinician, at the clinic or hospital; the samples are collected at scheduled times by the laboratory logistics and the result is directly reported to the physician. The patients do not even know what a clinical laboratory is; they just know that their blood samples go somewhere to be analyzed by people who they have no idea what their skills and background are. In Brazil, by law, the laboratory results belong to the patients, and non-hospitalized patients often come to the laboratory collection facility, unless a home visit is scheduled, for blood drawing or other biological sample collection days after the first consultation, where they receive adequate instructions regarding the pre-analytical requirements for each requested test. The realities are completely different.

Fourth, precisely derived from the point above, the impact of these recommendations have not yet been evaluated on the patient's behavior regarding the required fasting for *other* laboratory tests. And even worse, we have already observed movements by some corporations indicating that fasting for *any* laboratory test would be no longer necessary. From the technical and scientific point of view, non-fasting blood samples are not suitable for measurement of several analytes that are influenced by meals, such as blood cell counts, hemoglobin, albumin, bilirubin, phosphate, calcium, magnesium, potassium,[8] insulin, growth hormone, glucagon, chloride, urine pH, and also those affected by diurnal variation, such as ACTH, catecholamines, TSH, PTH, renin, aldosterone, ALT, AST, alkaline phosphatase, blood urea nitrogen and iron,[9] to name a few. As it has been said,[10] in clinical laboratory medicine, no sample would be preferred to a bad sample, if one wishes to attain rigorous standards when providing clinicians with reliable laboratory information. The overall impact of the proposed non-fasting blood sample draw on the eventual rejection of the patient's samples has yet to be determined, due to the presence of other requested laboratory tests that need fasting and/or morning draw.

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And fifth, finally, the suggested Martin's formula still uses TG in its calculations, a parameter that has been demonstrated by many authors not to be correlated with LDL-c or TC. Martin et al.[2] have made a huge mathematical effort to achieve a satisfactory result to include TG in the calculation. And most importantly, this equation has to be validated or at least evaluated, in other populations before being universally recommended. For instance, the proposed Martin's formula, as well as ours, was evaluated in comparison to newly proposed formulas for LDL-c estimation in Iran, and the former was demonstrated to not add value to the estimations in a small cohort.[11]

Anyway, LDL-c remains a frequent parameter requested at clinical laboratories in medical routine, and will likely continue to be so, hence precise methods for its estimation are needed when its direct measurement is not available. A simple and accurate equation developed and evaluated in the Brazilian population has already been developed.[12] It should be noted that this equation performs equally well, for instance, in populations from Germany and United Kingdom,[13] but not as well in others, such as in South Africa,[14] Spain,[15] and Thailand.[16] It seems that the debate on which method to use for LDL-c determination, in each particular population of the globe, is more open than defined.[17]

Sadly, history is full of examples demonstrating that when corporate interests meet with poor science, the only losers are science itself, and patient care. It is apparent and worthy of concern that the Brazilian 'consensus' has recommended the use of an equation for LDL-c estimation that was not validated in the local population and was moved by reasons that are driven more by convenience than by rigorous and unbiased science.

Author contributions

Conception and design of the research: Cordova CMM; Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Cordova CMM, Galgowski C; Writing of the manuscript: Galgowski C.

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References

1. Sociedade Brasileira de Patologia Clínica – Medicina Laboratorial. SBPC-ML Necessidade de jejum para coleta de sangue para a realização de exams laboratoriais. [Citado em 2016 dez 10. Disponível em: http://www.sbpc.org.br/upload/conteudo/consenso_jejum_dez2016_final.pdf
2. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013;310(19):2061-8.
3. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) joint consensus initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016;37(25):1944-58.
4. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins. JAMA. 2012;307(12):1302-9. Erratum in: JAMA. 2012;307(18):1915.
5. Mora S, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation. 2008;118(10):993-1001.
6. Mora S, Rifai N, Buring JE, Ridker PM. Comparison of LDL cholesterol concentrations by Friedewald calculation and direct measurement in relation to cardiovascular events in 27,331 women. Clin Chem. 2009;55(5):888-94.
7. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217(1):3-46.
8. Guidi GC, Simundic AM, Salvagno GL, Aquino JL, Lima-Oliveira G. To avoid fasting time, more risk than benefits. Clin Chem Lab Med. 2015;53(10):e261-4.
9. Young DS, Bermes EW Jr. Preanalytical variables and biological variation. In: Burtis CA, Ashwood ER, Bruns DE. (editors). Tietz textbook of clinical chemistry and molecular diagnostics. 4th ed. St Louis: Elsevier; 2006. p. 449-84.
10. Simundic AM, Cornes M, Grankvist K, Lippi G, Nybo M. Standardization of collection requirements for fasting samples: for the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chim Acta. 2014 May 15;432:33-7.
11. Rasouli M, Mokhtari H. Calculation of LDL-cholesterol vs direct homogenous assay. J Clin Lab Anal. 2017;31(3):e22057.
12. de Cordova CM, de Cordova MM. A new accurate, simple formula for LDL cholesterol estimation based on directly measured blood lipids from a large cohort. Ann Clin Biochem. 2013;50(Pt 1):13-9.
13. Sathyapalan T, Atkin SL, Kilpatrick ES. LDL cholesterol variability in patients with Type 2 diabetes taking atorvastatin and simvastatin: a comparison of two formulae for LDL-C estimation. Ann Clin Biochem. 2015;52(Pt 1):180-2.

14. Nigam PK. Calculated low density lipoprotein-cholesterol: Friedewald's formula versus other modified formulas. Int J Life Sci Med Res. 2014;4:25-31.

15. Laserna-Mendieta EJ, Timón-Zapata J. Comparison of the performance of the Brazilian equation for LDL-c estimation with other proposed formulae in a Spanish population. Ann Clin Biochem. 2013;50(Pt 5):501-2.

16. Dansethakul P, Thapanathamchai L, Saichanma S, Worachartcheewan A, Pidetcha P. Determining a new formula for calculating low-density lipoprotein cholesterol: data mining approach. EXCLI J. 2015 Mar 26;14:478-483.

17. Mendes de Cordova CM, de Santa Helena ET, Galgowski C, Figueira VH, Setter GB, Markus MR, et al. Evaluation of a new equation for LDL-c estimation and prediction of death by cardiovascular related events in a German population-based study cohort. Scand J Clin Lab Invest. 2018;78(3):187-96.

Counterpoint: Flexibilization of Fasting for Laboratory Determination of the Lipid Profile in Brazil: Science or Convenience?

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National and international guidelines for the management of dyslipidemias classically recommend measuring lipid profiles after fasting for at least 8 h.[1-3] Lipid targets for assessing cardiovascular risk traditionally rely on plasma total-cholesterol and low-density lipoprotein-cholesterol (LDL-c) levels, with the latter being calculated by the Friedewald equation.[4]

Some imprecision due to low or high triglycerides in calculating LDL-cholesterol may affect cardiovascular risk assessment, the definition of a therapeutic target, and the need to intensify the treatment.[5,6] Accurate results require triglyceride levels below 400 mg/dL, but above 100 mg/dL the calculated LDL-c starts to be underestimated, when compared to ultracentrifugation measurements. Another limitation to the use of the formula is that samples must not contain beta-VLDL, as in the case of type III hyperlipoproteinemia. When one of these conditions are not satisfied, the equation cannot be used due to imprecision.[5-7]

Other lipid parameters, such as apolipoprotein-B and non-high-density lipoprotein-cholesterol (non-HDL-C) reflect the pool of atherogenic lipoproteins and have emerged as good markers to improve cardiovascular risk assessment, and also to guide lipid-lowering therapy.[2,3,8,9] These variables can be used in both the fasting and non-fasting states, and non-fasting lipoproteins are regarded as better atherosclerotic risk predictors, when compared with fasting ones, for they reflect remnant, atherogenic lipoproteins, with higher correlation with cardiovascular risk.[2,3,8,9]

To avoid the interference of triglycerides, direct measurements of LDL-cholesterol have been developed.[10,11] but these techniques lack proper standardization, and were tested in few clinical trials that use LDL-c as target.[12,13]

Since then, many papers, as result of important and broad studies, were carried out comparing fasting and non-fasting lipid parameters, mainly total cholesterol, HDL-c, LDL-c and triglycerides, concluding that non-fasting lipids do not clinically differ from fasting ones, except for triglycerides, that require different reference values for non-fasting state.[14,15]

Here we present a second opinion for what has been stated in the article: *"Flexibilization of fasting for laboratory determination of the lipid profile in Brazil: science or convenience?"*

Our second opinion uses steps for building a scientific statement. The first step is to find an issue of interest to be debated. The second step requires full understanding of what is currently known about what is being explained. This basically deals with scientific publications, citations seeking other scientific papers, and books on the topic. Although it is possible to defer to the scientific consensus, you cannot really have a personal scientific viewpoint on anything without understanding what current research says about it.

Keep in mind that all scientific papers should be found in peer-reviewed well-reputed journals. It is best to approach scientific literature with no prior judgements; however, it can be a difficult task. After reviewing all relevant papers to the matter, it is possible to develop a scientific view and an opinion. If the scientific material collected reaches the same conclusion, it is unlikely that you can hold a different viewpoint at this moment. But, if some papers disagree, there is room for debate and to raise a plausible second opinion, if there is good research supporting this view. High-quality, well-designed studies, with a large number of participants, in the opposite direction of what had been stated, *do* reinforce the validity of a second opinion.

This article will address the interpretation, applications and limitations of a non-fasting lipid profile for daily clinical practice.

First, large observational data, with population-based studies and registries, including 111,048 women, 98,132 men, 12,744 children, and patients with diabetes, in which non-fasting lipid profiles were compared with those obtained under fasting conditions, have demonstrated that the maximal changes in plasma lipids and lipoproteins occurred between 1-6 hrs. after a usual meal. These trials have established that only minor changes occurred in response to habitual food intake in the majority of individuals.[14,16-19] Total cholesterol, LDL-c, remnant cholesterol, varied 8 mg/dL, whereas HDL-c, apolipoprotein A1, apolipoprotein B, and lipoprotein(a) were not affected by fasting/non-fasting status. These data were derived from the Women's Health Study, the Copenhagen General Population Study, the National Health and Nutrition Examination Survey, and the Calgary Laboratory Services in Canada.[14,16-19]

Among all studies, only minor increases in plasma triglycerides and minor decreases in total and LDL cholesterol concentrations were observed, in non-fasting conditions, with no change in HDL cholesterol concentrations. In subjects with diabetes, calculated LDL-c obtained 1-3 hours after a meal decreased 23 mg/dL, and could imply in statin withhold;

Keywords

Dyslipidemias; Cholesterol; Lipids; Triglycerides; Cholesterol, HDL; Cholesterol, LDL; Fasting.

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however, when corrected for albumin, reflecting fluid intake, the difference disappeared, and was attributed to the fluid and *not* to the diet.[20]

Second, we live most of our time in non-fasting state. Non-fasting and fasting lipid concentrations vary similarly over time and are at least equivalent in the prediction of cardiovascular disease. In fact, data from the Calgary Laboratory Services in Canada demonstrated that in ~200,000 men and women, total cholesterol, HDL and LDL-cholesterol did not vary as a function of the period of fasting after the last meal.[17]

Third, reference plasma lipid, lipoprotein, and apolipoprotein concentration values based on desirable concentration cutoff points, do not vary when non-fasting, except for triglycerides, which should be flagged as abnormal in laboratory reports > 175 mg/dL. However, non-fasting triglycerides were better predictors than in the fasting state.[7]

Fourth, the risk of ischemic heart disease and myocardial infarction in 92,285 individuals from the Copenhagen General Population Study recruited from 2003 through 2014, could be predicted by non-fasting lipids (reported in Nordestgaard et al.[7]).

Fifth, a novel method to estimate LDL-C using an adjustable factor for the TG:VLDL-C ratio provided a more accurate guideline risk classification than the Friedewald equation.[21] The authors used a large convenience sample of consecutive clinical lipid profiles obtained from 2009 through 2011 (n = 1,350,908), including children, adolescents, and adults in the United States). The sample was randomly assigned to derivation (n = 900,605) or validation (n = 450,303) data sets. Results closely matched those in the National Health and Nutrition Examination Survey (NHANES). This estimation method provided higher-fidelity estimates than the Friedewald equation. The greatest improvement in concordance occurred when classifying LDL-C lower than 70 mg/dL, especially in patients with high triglyceride levels. Indeed, there is a need for external validation, and assessment of its clinical importance. However, this novel method could be implemented in most laboratory reporting systems with virtually *no* cost.

Finally, what would be the problem to add convenience to science? Postprandial measurements are more practical and provide the patient a greater access to the laboratory, and also can decrease the number of missed working days and medical appointments due to missed tests; blood collection in the postprandial state is safer in several circumstances and help prevent hypoglycemia secondary to the use of insulin in patients with diabetes mellitus, in pregnant women, children, and elderly individuals, reducing complications and increasing adherence to the tests and to medical appointments; flexibilization of fasting for lipid profiling, can bring more comfort to the patient and greater amplitude of schedules in the laboratories, especially in the morning; technological advances in diagnostic methods, can mitigate the interference of sample turbidity when triglycerides are high.[22]

If, fasting is not routinely required for assessing the plasma lipid profile, some recommendations should be made in specific situations: 1) when non-fasting plasma triglyceride concentration exceed 440 mg/dL, consideration should be given to repeating the lipid profile in the fasting state; 2) laboratory reports should flag abnormal values based on desirable concentration cut-off points; 3) life-threatening or extremely high concentrations should trigger an immediate referral to a lipid clinic or to a physician with special interest in lipids.[7,22]

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Izar MCO.

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References

1. Bailie EE. Report from the Laboratory Standardization Panel of the National Cholesterol Education Program: recommendations for improving cholesterol measurement. 1993. Lab Medicine. 1990;21(7):429-35. (NIH Publication N° 93-2964).
2. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217(1):3-46.
3. Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. [V Brazilian guidelines on dyslipidemias and prevention of atherosclerosis]. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20.
4. Friedewald WT, Lavy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.
5. Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial. SBPC. Brazilian Society of Clinical Pathology. Laboratory determination of the lipid profile. [Cited in 2016 Dec 10]. Available from: http://www.sbpc.org.br/upload/conteudo/consenso_jejum_dez2016_final.pdf
6. Faludi AA, Izar MC, Saraiva JF, Chacra AP, Bianco HT, Afiune Neto A, et al. Atualização da Diretriz Brasileira de dislipidemias e prevenção da aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl.1):1-76.
7. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) joint consensus

initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016;37(25):1944-58.

8. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Boren J, Catapano AL, et al; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32(11):1345-61.

9. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-333.

10. Tanno K, Okamura T, Ohsawa M, Onoda T, Itai K, Sakata K, et al. Comparison of low-density lipoprotein cholesterol con- centrations measured by a direct homogeneous assay and by the Friedewald for- mula in a large community population. Clin Chim Acta. 2010;411(21-22):1774-80.

11. Mora S, Rifai N, Buring JE, Ridker PM. Comparison of LDL cholesterol concentra- tions by Friedewald calculation and direct measurement in relation to cardiovascular events in 27,331 women. Clin Chem. 2009;55(5):888-94.

12. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. The effect of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.

13. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins. JAMA. 2012;307(12):1302-9. Erratum in: JAMA. 2012;307(18):1915. JAMA. 2012;307(16):1694.

14. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008;118(20):2047-56.

15. Langsted A, Kamstrup PR, Nordestgaard BG. Lipoprotein(a): fasting and nonfasting levels, inflammation, and cardiovascular risk. Atherosclerosis. 2014;234(1):95-101.

16. Mora S, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation. 2008;118(10):993-1001.

17. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med. 2012;172(22):1707-10.

18. Steiner MJ, Skinner AC, Perrin EM. Fasting might not be necessary before lipid screening: a nationally representative cross-sectional study. Pediatrics. 2011;128(3):463-70.

19. Langsted A, Nordestgaard BG. Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58,434 individuals from the Copenhagen General Population Study. Clin Chem. 2011;57(3):482-9.

20. Simundic AM, Cornes M, Grankvist K, Lippi G, Nybo M. Standardization of collection requirements for fasting samples: for the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chim Acta. 2014 May 15;432:33-7.

21. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013;310(19):2061-8.

22. Scartezini M, Ferreira CE, Izar MC, Bertoluci M, Vencio S, Campana GA, et al. Positioning about the flexibility of fasting for lipid profiling. Arq Bras Cardiol. 2017;108(3):195-7.

Case 6 / 2018 - Percutaneous Occlusion of a Large Ductus Arteriosus in a Low Weight Infant, with Immediate Clinical and Radiographic Improvement

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Clinical Data

The patient was a one-year-old infant with Down syndrome, and heart murmur auscultated from birth. The child had a difficult clinical course due to failure to thrive, tachypnea, poor suckling due to fatigue and repeated respiratory infections, with pulmonary hypersecretion, and was receiving captopril and furosemide.

Physical examination

Regular overall status, tachypneic, acyanotic, with full and wide peripheral pulses. Weight: 8.6 kg, height: 71 cm, blood pressure in the right upper limb: 80 x 40 mmHg, HR: 148 bpm, O_2Sat: 97%. The apex beat was shifted to the left in the precordium, in clear systolic impulse. Continuous "machine-like" murmur, better auscultated at the left sternal border and irradiating to the posterior chest region. Palpable liver two centimeters from the right costal ridge and diffuse rumbles and subcrepitant rales at the lung bases.

Complementary examinations

Electrocardiogram: sinus rhythm (tachycardic), with left shift and left ventricular overload.

Chet x-ray: enlarged cardiac area with a cardiothoracic index of 0.64, marked vascular pedicle enlargement, and increased pulmonary vascular network (Figure 1A).

Echocardiogram: enlargement of the left chambers, significant dilatation of the pulmonary trunk and pulmonary arteries, and presence of a ductus arteriosus with left-to-right shunt, with the smallest diameter estimated at 4 mm.

Clinical diagnosis

Patent ductus arteriosus with significant hemodynamic consequences in an infant with Down syndrome.

Keywords

Infant; Down Syndrome; Heart Defects, Congenital/surgery; Ductus Arteriosus Patent/surgery.

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Differential diagnosis

Other congenital defects should always be recalled in a similar clinical setting such as: defects between the systemic and pulmonary sites, the aortopulmonary window that connects the ascending aorta and the pulmonary trunk, coronary-cavitary fistulas and arteriovenous defects in general, total anomalous pulmonary vein drainage, sinus of Valsalva rupture, and pulmonary atresia with enlarged bronchial arteries or large systemic-pulmonary collateral vessels, which allow pulmonary flow increase.

Conduct

Due to the infant's clinical impact and failure to thrive, the first considered conduct was percutaneous occlusion through interventional catheterization techniques. The procedure was performed through femoral vein and artery puncture, with hemostasis valve 4F to minimize the risk of peripheral vascular lesions. Manometric study disclosed marked pulmonary hypertension (PT = 45/25 mmHg), corresponding to half of the systemic pressure. The left ventricle showed increased end-diastolic volume, but with preserved contractile function. The aortic arch was shifted to the left and there was a large ductus arteriosus (Figure 2A), type A, according to Krichenko classification, with pulmonary extremity measuring 4.0 mm and aortic 8.0 mm, with a very prominent aortic ampulla, measuring 12 mm in diameter. In this case, we chose to use an Amplatzer® ADO-I 10/8 device with complete occlusion of the defect after its implantation (Figure 2B).

The clinical improvement was immediate with disappearance of the continuous murmur, normal breathing and obvious respiratory relief. The chest radiography, approximately 8 hours after the procedure, showed a marked decrease in the cardiac area with a cardiothoracic index of 0.58 (Figure 1B). The patient was discharged after 48 hours of hospitalization.

Comments

After the percutaneous closure of the ductus arteriosus, a marked decrease in pulmonary hyperflow was observed immediately, due to the decreased cardiac volume and smaller vascular pedicle, as shown by the chest X-ray (Figure 1B). Before that, a marked volume overload was observed on the heart and the hemodynamic consequences to the patient with dyspnea and delayed physical development, consequent to the large ductus arteriosus.

It is concluded that the patent ductus arteriosus occlusion should be performed as soon as possible in this clinical

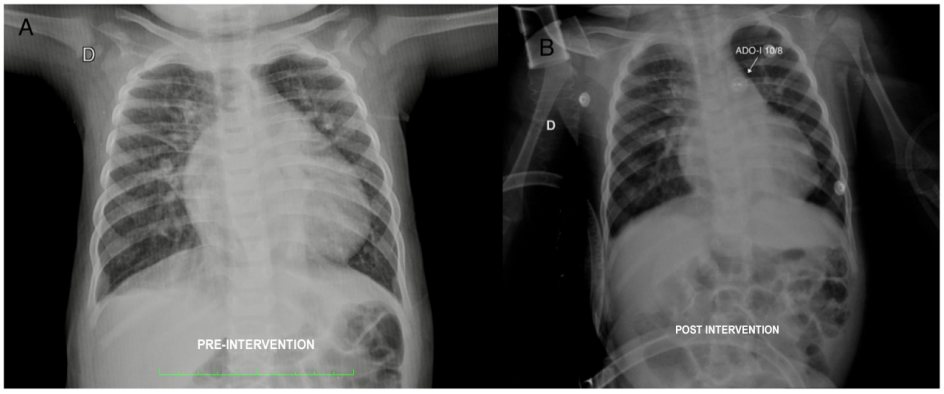

Figure 1 – *A) Pre-intervention chest x-ray. There is an overall increase in the cardiac silhouette, with prominence of the right atrium, left ventricle and vascular pedicle, in addition to the pulmonary vascular network. B) Chest X-ray approximately 8h after occlusion of the defect, showing the significant decrease in the cardiac volume, notably in the right atrium and the vascular pedicle, as well as a decrease in the pulmonary vascular network.*

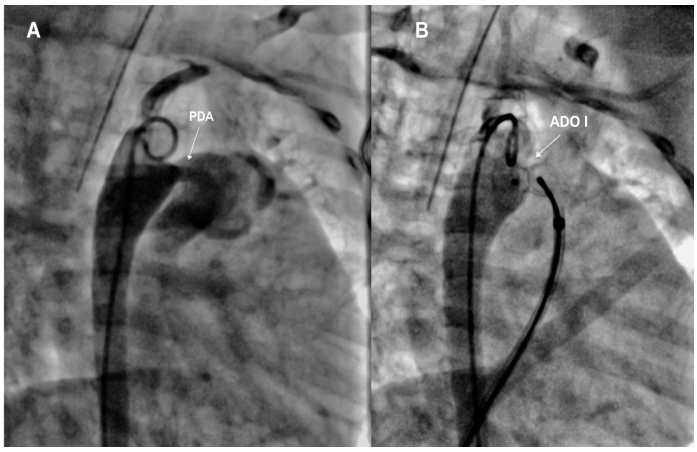

Figure 2 – *A) Angiography of the aorta showing the presence of a large ductus arteriosus with a minimum diameter of 4 mm. B) Implant of Amplatzer® device ADO I-10/8, with complete occlusion of the defect. PDA: patent ductus arteriosus*

situation, considering the several complications that may affect patient evolution, such as frequent respiratory infections, as well as the progression of pulmonary arterial hypertension to Eisenmenger's syndrome.

The occlusion techniques through interventional catheterization are safe and simple, and with catheter profile improvement and the multiple devices available for clinical use, they are currently the first choice techniques for the treatment of young infants and children.[1] Several articles have been published on the experience of several groups showing the practice of occlusion of ductus arteriosus in extremely preterm infants,[2,3] using only venous access and monitoring the implant through echocardiography, thus reserving the surgical technique for special anatomical situations.

References

1. Kang SL, Jivanji S, Mehta C,Tometzki AJ, Derrick G, Yates R, et al. Outcome after transcatheter occlusion of patent ductus arteriosus in infants less than 6Kg: A National Study from United Kingdom and Ireland. Catheter Cardiovasc. Interv. 2017; 90(7):1135-44.
2. Zhou K, Tang J, Hua Y,Shi X, Wang Y, Qiao L, et al. Transcatheter occlusion of patent ductus arteriosus in a preterm infant and review of literatures. Zhonghua Er Ke Za Zhi. 2016; 54 (11): 43-6.
3. Garg G, Garg V, Prakash A. Percutaneous closure of a large patent ductus arteriosus in a preterm newborn weighing 1400g without using arterial sheath: an innovative technique. Cardiol Young. 2018;28(3):494-7.

Rare Presentation of Dercum's Disease in a Child with Abnormalities in Lipoprotein Metabolism

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Adiposis dolorosa, or Dercum's disease, is a subcutaneous accumulation of fat in the body accompanied by intense, chronic, and symmetrical pain, often disabling, and usually not responsive to conventional analgesics. It was first described by Dercum, recognized as a separate disease in 1892,[1] and further reported by White in 1899.[2] Termed in the literature Dercum's disease, Morbus Dercum, *lipomatosis dolorosa*, adiposalgia, *adiposis dolorosa*, and adipose tissue rheumatism, this condition is more prevalent in young women, aged 35 to 50 years, and affects preferably those in the post-menopause phase.[1-3] *Adiposis dolorosa* can also occur in multiple familial lipomatosis, a condition associated with multiple lipomas.[4] Other symptoms and signs include psychiatric (depression, anxiety, sleep disturbances, memory and concentration impairment), cardiovascular (tachycardia), pulmonary (shortness of breath), rheumatological (fatigue, weakness, joint and muscle aches) and gastrointestinal (bloating, constipation) disorders.[3]

Dercum's disease was described as a general disease of the lymphatic system. In 2014, Rasmussen et al.[5] suggested that this is a lymphovascular disorder with abnormalities in the adipose tissue deposition and lymphatic transport, showing that lipomas appeared to be fed and drained by functional lymphatics. In addition, Huang et al.[6] have reinforced the importance of lymphatic system in cholesterol transport, showing the association with ApoA1, HDL formation, and lymphatic transport to the blood for scavenging by the HDL receptor, or scavenger receptor B1.[6]

Although the majority of Dercum's disease cases occurs sporadically, there are reports suggesting an autosomal dominant inheritance, with variable expression. The prevalence and the pathophysiology are also unknown, but inflammation, endocrine, adipose tissue, and nervous system dysfunction, trauma, mechanical pressure on the nerves, are possible etiological conditions.[3-4] Considering the abnormal fat deposition, presence of inflammation, and possible metabolic and lipoprotein abnormalities, an increased risk for atherosclerosis should be expected. Albeit the increased fat mass accumulation in Dercum's disease, it has not been yet reported in association with cardiovascular diseases.[7]

Keywords

Adiposis Dolorosa; Rare Diseases; Inflammation; Lipid Metabolism Disorders; Child; Dyslipidemias.

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Dercum's disease seems to be rare in children, as the disease usually manifests in adulthood. In the present study, we report the rare case of a child with Dercum's disease associated with presence of marked dyslipidemia and inflammation.

An eight-year-old female child presented with lipomatosis in the backbone, with pain, who became resistant to standard pain-relief medications within one year. Magnetic resonance imaging (MRI) of the backbone revealed the presence of multiple diffuse lipomas (Figure 1), reinforcing the suspicion of Dercum's disease.[1,2] Many surgical procedures were performed to remove those lipomas, but abnormal fat deposition and pain progressed over time, with impairment of daily activities, requiring combined analgesic medication, including morphine. Lipomas increased in number and size, affecting the backbone, legs, arms, face, neck, and abdominal wall. Fat deposition also included liver steatosis, confirmed by MRI. The patient is currently 13 years-old with sexual maturity range II (by Tanner staging).

It is believed that this is a variant presentation of Dercum's disease, first classified as a localized nodular form that further became generalized and affected a prepubescent girl. This diagnosis was confirmed after ruling out other pathologies with similar clinical presentation, such as those described by Hansson et al.[3] in 2012.

There were no reports of lipomatosis in any other family member, including parents and siblings.

Laboratory analyses before therapy, to appraise glucose metabolism, lipids and genetic factors revealed hyperinsulinemia (31.8 uU/ml), with normal fasting glucose levels (81 mg/dl) and HbA1c (3.8%), at baseline. Fasting lipid analyses showed low HDL-c (19.3 mg/dl) and Apo A1 (112 mg/dl) concentrations, hypertriglyceridemia (320 mg/dl), hyperbetalipoproteinemia (118 mg/dl), LDL-c in the normal range (108 mg/dl), but with increase in small dense LDL particles (> 40 mg/dl). Her HDL map showed high pre-beta HDL (29 mg/dl; normal < 17 mg/dl), normal alpha 4 HDL (normal< 5.3 mg/dL), high HDL-3 (33mg/dl; normal < 13.5 mg/dl), low HDL 2 (19.3 mg/dl; normal > 45 mg/dl) and HDL-1 (9.5 mg/dl; normal > 29.3 mg/dl), thus showing the incapacity of larger HDL particles formation, with an excess of smaller, less protective particles.

Cholesterol synthesis marker (lathosterol) was below detection level, whereas beta-sitosterol/cholesterol and campesterol/cholesterol ratios were 115 and 149 μmol/mmol of cholesterol (in the normal range). Inflammatory markers, such as high sensitivity-C-reactive protein (13.8 mg/L) and lipoprotein-associated phospholipase A2 (Lp-PLA2, 375ng/ml), were very high.

The child did not present signs of thyroid dysfunction. Sexual and intermediary hormones androstenedione (219 ng/mL),

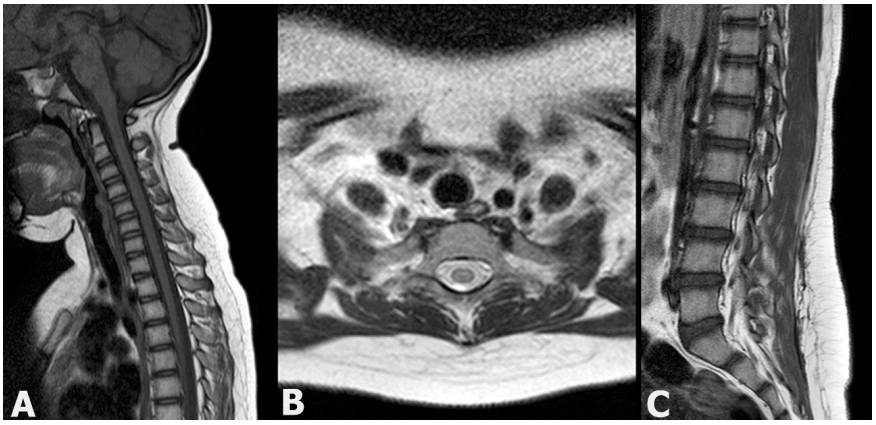

Figure 1 – *Magnetic resonance images acquired in the A) sagital plane (T1-weighted) and in the B) axial plane (T2-weighted) showing diffusely prominent subcutaneous adipose tissue without delineation of margins or signs of an encapsulated lesion. C) Similar findings are observed in the lumbar region on the T1-weighted sagital image, where it is also possible to identify a linear scar, secondary to a previous surgical resection.*

17-hidroxiprogesterone (76 ng/dL), testosterone (124 ng/dL), and estradiol (24.10 pg/mL) were high for her age. Dehydroepiandrosterone-sulphate (28.4 μg/dL) and growth hormone (0.67 ng/mL) were in the normal range.

Normal concentration of N-terminal pro-B-type natriuretic peptide (NT pro-BNP) was observed, reflecting no myocardial dysfunction.

Genetic analysis showed apolipoprotein E genotype E3/E4 and Factor V Leiden -/-, not representing genetic risk factors for cardiovascular disease.

Body composition was evaluated via bioelectrical impedance analysis (BIA 450, Biodynamics Inc, USA), revealing normal levels of water in the body (23.1 L), but high fat mass component (40%), for gender and age.

The therapeutic regimen adopted for the child was metformin 850 mg, atorvastatin 20 mg, losartan 25 mg, hydrochlorothiazide 12,5 mg, gabapentin 300 mg three times a day, fentanyl adhesive 12.5 mcg every 72 h, amitriptyline 50 mg at night for reduction of the neuropathic pain, and morphine 10 mg in exceptional pain crises.

To our knowledge, this is the first report of a case of Dercum's disease affecting a prepubescent child with lipomas in the dorsal region, face and neck, abdominal wall, arms and legs, which are common sites for lipomas seen in patients with Dercum's disease in adulthood.[7] The presentation of lipomas in the backbone can produce a compression of the neural plexus, causing extreme pain, extending to upper and lower limbs, and anterior upper trunk, thus limiting normal daily activities.

The child features a rare presentation of Dercum's disease or *lipomatosis dolorosa* at a young age. The diagnosis of Dercum's disease was based on the differential diagnosis with other lipomatosis, as recently proposed by Hansson et al.[3]

Her parents and siblings did not show any signs of lipomatosis or *lipomatosis dolorosa*, ruling out the diagnosis of familial multiple lipomatosis, as described by Campen et al.[4]

Besides the abnormal fat accumulation, interesting findings observed in the patient were hyperinsulinemia, low HDL-cholesterol, hyperbetalipoprotinemia, with predominance of small-dense LDL and HDL particles, characterizing an insulin resistance state. The HDL map revealed a phenotype of particles associated with increased cardiovascular risk, with low concentration of HDL-2 particles, which are related to cardiovascular protection, and high concentration of the less protective HDL-3 particles.[8] These changes in the HDL particle profile can occur by inherited and acquired factors, or secondary to drugs and vigorous aerobic exercise, and in chronic high alcohol intake. The predominance of small dense LDL is associated with progression of atherosclerosis and is frequent in subjects with multiple risk factors for cardiovascular disease, such as diabetes, obesity, and other insulin resistance states.[9] In patients with lipomatosis, an association with altered activity of lipoprotein lipase (LPL) in the lipomatous tissue, affecting the metabolism of HDL particles, has been also described.[10] However, the authors do not regard LPL activity as the most acceptable mechanism to justify the changes in lipoprotein sub-fractions observed in Dercum's disease. The present study did not assess LPL activity in this patient, and other mechanisms may have affected the remodeling of lipoprotein sub-fractions.

High concentration of inflammatory markers, such as lipoprotein associated phospholipase A2 (Lp-PLA2) and C-reactive protein, are in accordance with a pro-inflammatory state that accompanies these lipomas. Also, small dense LDL particles can interact with Lp-PLA2, thus contributing for the synthesis of products that start the inflammatory signaling cascade by C-reactive protein.[11]

The normal synthesis and absorption of cholesterol, as well as thyroid hormone secretion and Apo E genotype, cannot explain the genesis of these lipomas. It is possible that changes in glucose metabolism in the lipomas, imbalance between lipolysis and lipogenesis, and the need for different lipids and cholesterol for adipocyte hypertrophy could explain lipoma formation,[12] and can be associated with the changes in lipoprotein sub-fractions observed in Dercum's disease.

The child maintains use of the current medication for pain relief; however, there is no evidence of pain reduction in the evolution of Dercum's disease in adults, at least in studies reporting a five-year follow-up. This case remains a challenge for physicians, the patient, and her family, who face difficulties to restore a normal life. Future research is needed to detect the etiology and evolution of Dercum's disease from childhood to adulthood.

Author contributions

Conception and design of the research: Izar MCO, Fonseca HAR, Fonseca FAH; Acquisition of data: Izar MCO, Fonseca HAR, Machado VA, Ferreira CES, Fonseca FAH; Analysis and interpretation of the data: Izar MCO, França CN, Fonseca FAH; Statistical analysis: Izar MCO; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Izar MCO, Fonseca HAR, França CN, Machado VA, Ferreira CES, Fonseca FAH.

Potential Conflict of Interest

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

References

1. Dercum FX. Three cases of a hitherto unclassified affection resembling in its grosser aspects obesity, but associated with special nervous symptoms – adiposis dolorosa. Am J Med Sci. 1892;104(6):521-3.
2. White WH. A case of adiposis dolorosa. Br Med J. 1899;2(2031):1533-4.1
3. Hansson E, Svensson H, Brorson H. Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management. Orphanet J Rare Dis. 2012 Apr 30;7:23.
4. Campen R, Mankin H, Louis DN, Hirano M, Maccollin M. Familial occurrence of adiposis dolorosa. J Am Acad Dermatol. 2001;44(1):132-6.
5. Rasmussen JC, Herbst KL, Aldrich MB, Darne CD, Tan IC, Zhu B, et al. An abnormal lymphatic phenotype is associated with subcutaneous adipose tissue deposits in Dercum's disease. Obesity (Silver Spring). 2014;22(10):2186-92.
6. Huang LH, Elvington A, Randolph GJ. The role of the lymphatic system in cholesterol transport. Front Pharmacol. 2015 Sep 2;6:182.
7. Berntorp E, Berntorp K, Brorson H, Frick K. Liposuction in Dercum's disease: impact on haemostatic factors associated with cardiovascular disease and insulin sensitivity. J Intern Med. 1998;243(3):197-201.
8. Asztalos BF, Tani M, Schaefer EJ. Metabolic and functional relevance of HDL subspecies. Curr Opin Lipidol. 2011;22(3):176-85.
9. Diffenderfer MR, Schaefer EJ. The composition and metabolism of large and small LDL. Curr Opin Lipidol. 2014;25(3):221-6.
10. Enzi G, Favaretto L, Martini S, Fellin R, Baritussio A, Baggio G, et al. Metabolic abnormalities in multiple symmetric lipomatosis: elevated lipoprotein lipase activity in adipose tissue with hyperalphalipoproteinemia. J Lipid Res. 1983; 24(5): 566-574.
11. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.
12. Fagher B, Monti M, Nilsson-Ehle P, Akesson B. Fat-cell heat production, adipose tissue fatty acids, lipoprotein lipase activity and plasma lipoproteins in adiposis dolorosa. Clin Sci (Lond). 1991;81(6):793-8.

How Echocardiographic Deformation Indices Can Distinguish Different Types of Left Ventricular Hypertrophy

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We present cases of athlete's heart, idiopathic HCM, and glycogen storage cardiomyopathy (PRKAG2).

The two non-athlete patients (Pts) underwent genetic studies and myocardial biopsies.

Echocardiography showed moderate to severe LVH in all cases.

Case 1, Figure 1-A, A-3 – Athlete, male, 26, intense exercise practice. Automated function imaging: 2D LV strain bullseye map showing normal Longitudinal Regional Myocardial Deformation (LRMD), despite LVH. GLS (global longitudinal strain) -20.4%.

Case 2, Figure 1-B, B-1, B-2, B-3 – Male, 26, tachycardia and palpitations with myosin essential light chain 3 mutation. LRMD is typically reduced where hypertrophy is more accentuated. GLS -14.0%.

Figure B-1 – Section of RV ventricular myocardium in HCM, demonstrating marked myocyte hypertrophy and disorganization (HE-stained).

Figure B-2 – Gomoritrichrome stain (GS) showing intense fibrosis in extracellular matrix (blue) and cardiomyocyte architecture disarray.

Case 3, Figure 1-C, C-1, C-2, C-3 - Male, 22, palpitations and tachycardia. Genetic analysis found missense mutation, a heterozygous pathogenic variant for PRKAG2 c.905g > A p.(Arg302Gln). LRMD shows deformation levels in a striped pattern. GLS -10.5%.

Keywords

Speckle Tracking; PRKAG2 Mutation; Deformation Indices; Left Ventricular Hypertrophy, Cardiomegaly; Echocardiography/diagnosis.

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Figure C1 - HE-stained RV showing myofiber vacuolization with gross granular glycogen inclusions within vacuoles, without cardiomyocyte architecture disarray.

Figure C2–GS showing intense myofiber vacuolization (white) and extracellular matrix collagen fibers without fibrosis (blue).

STE (speckle tracking echocardiography) differentiates LVH and infiltrative disorders. We tried to instantaneously identify disease-related patterns.

To our knowledge, we present the first pattern in a PRKAG2 mutation Pt bullseye map, differentiated from other causes of LVH.[1] We recommend GLS polar map analysis to improve accuracy in echocardiographic examinations involving moderate LVH. STE can suggest the etiology, critically important to improve therapeutic strategies.

Author contributions

Conception and design of the research, acquisition of data and analysis and interpretation of the data: Pena JLB, Santos WC, Araújo SA, Dias GM, Sternick EB; writing of the manuscript: Pena JLB, Santos WC; critical revision of the manuscript for intellectual contente: Araújo SA, Dias GM, Sternick EB.

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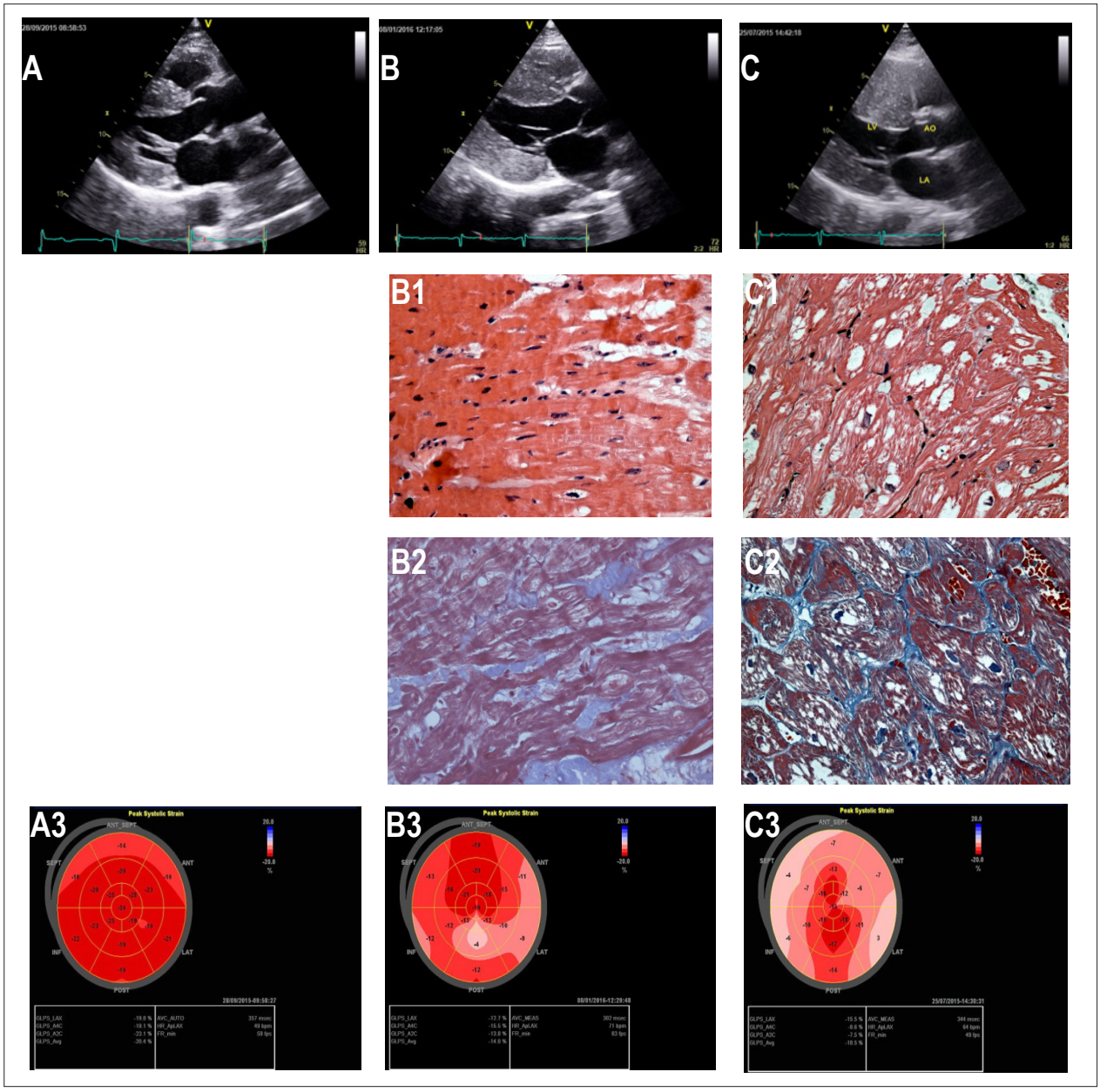

Figure 1 – *Two-dimensional echocardiography (A, B, C), endomyocardial biopsies (B1, B2, C1, C2) and bullseye maps (A3, B3, C3).*

Reference

1. Sternick EB, Oliva A, Gerken LM, Magalhães L, Scarpelli R, Correia FS, et al. Clinical, electrocardiographic, and electrophysiologic characteristics of patients with a fasciculoventricular pathway: the role of PRKAG2 mutation. Heart Rhythm. 2011;8(1):58-64.