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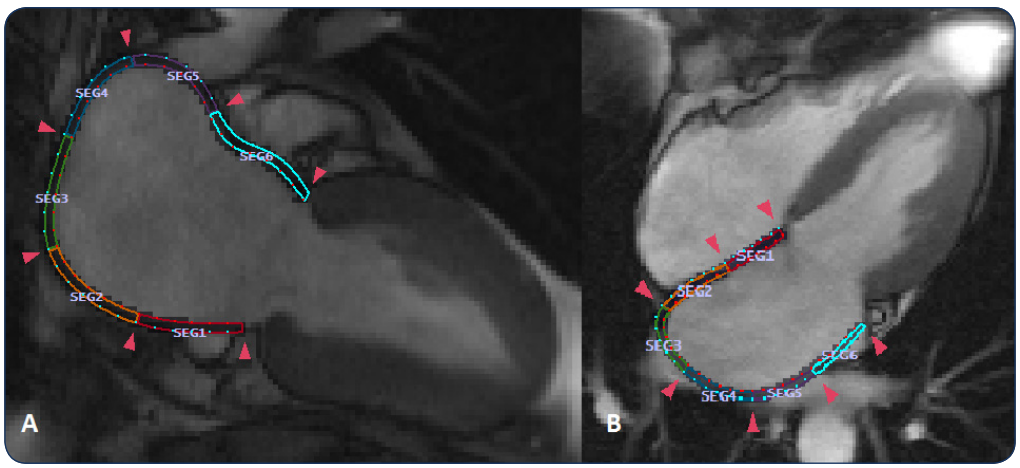

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Editorial

Toward a Patient-Centered, Data-Driven Cardiology

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Beginning in the 1970s and 1980s, the emergence of randomized clinical trials and studies with large cohorts, associated with the development of the methodology for systematic reviews and meta-analyses, triggered a revolution in the way of thinking and performing healthcare practice. Evidence-based medicine (EBM), defined as the integration of the best research evidence with clinical experience and patient values,[1] has become a new paradigm, orienting medical education and specialized publications. One of the principles of EBM was precisely the primacy of information obtained from randomized clinical trials and meta-analyses, which were placed at the top of an evidence hierarchy, valuing quantitative results more than clinical experience and expert opinion. Indeed, it has always been challenging for EBM to integrate empirical evidence with other types of medical knowledge, such as clinical expertise and pathophysiological rationale, or even with the preferences of individual patients.[2]

The use of EBM in clinical practice also runs into the difficulty of finding robust evidence for all subgroups of clinical situations found in the real world, "gray areas" in which no reliable evidence can be obtained from the scientific literature to guide the physician in caring for his patient. Randomized clinical trials are expensive and generally require large study samples and long-term follow-up. There are several situations without evidence, or situations in which the evidence is inconsistent or of poor quality.[3]

In the last two decades, the use of digital technology has invaded daily life worldwide and radically changed the way people live and relate, with a direct impact on healthcare practice. Public and private information systems and administrative record systems in healthcare practice have become ubiquitous and increasingly complex and complete, storing information ranging from diseases of compulsory notification to reasons for hospitalization and cause of death.

Diagnostic equipment has become digital, and electronic medical records began to accumulate the patients' clinical information, prescribed medications, and laboratory tests. Smartphones and digital devices began tracking physical activity or recording an individual's diet, in a myriad of applications and software, including information sharing on social networks. Computational advances also allowed the emergence of bioinformatics, with the attainment of a large volume of genetic information, as well as information about proteins, hormones, and other substances present in the body.

The availability of this huge amount of data and new analytical techniques – big data analytics[4] – opens up new scientific possibilities promising to bring about a real revolution in healthcare practice. Artificial intelligence (AI) areas, such as machine learning and data mining, allow for interactive interpretation and apprehension of the unstructured information available in large databases, recognizing hidden patterns of combination of information that are not obtained with traditional statistical methods.[5] AI-based methods are being increasingly applied to cardiology to diagnose combinations of multiple imaging modalities, biobanks, electronic cohorts remote and on-site clinical sensors for monitoring of chronic pathologies, electronic health records, and genomes and other molecular techniques, among others[6] (Table 1).

The complete sequencing of the genome and exome, already available in multiple centers, and the future sequencing of the proteome, transcriptome, and metabolome may lead to the knowledge of biological differences among individuals, contextualizing the observed phenotypes with their molecular characterization, leading to the modulation of treatment for specific targets, with greater safety and precision, in the so-called precision medicine.[7] This perspective of transformation of how knowledge is generated and applied, from the use of new data sources and analysis methodologies, has the potential to bring a new paradigm to medical and healthcare practice (Table 1).[8-13]

However, the use of this large volume of data by healthcare managers and professionals for planning of actions in healthcare and direct patient care is still a major challenge. Difficulties and risks cannot be underestimated.[14,15] Studies on AI are usually based on observational data obtained from administrative databases or medical records, with the potential for different types of biases and confounding factors. The associations obtained rarely meet the criteria of causality, and well-designed and long-running studies will continue to be necessary for proving hypotheses and defining causality. On the other hand, most algorithms used work with the "black box" principle, without allowing the information user to know the reasons why a diagnosis or recommendation was generated, which can be a problem, especially if the algorithms were designed for a different environment than the one that the user's patient is inserted. Issues regarding information ethics, privacy, and security are still far from being resolved. Matters regarding the cost and cost-effectiveness of healthcare AI projects should be considered early, given

Keywords

Cardiology; Clinical Decision - Making; Patient Centered Care; Evidence-Based Medicine/methods; Access Health Technologies; Artificial Intelligence; Diagnostic Equipment Digital; Machine Learning/trends; Health Manager; Physician Patient Relations.

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Table 1 – Examples of recent studies with artificial intelligence (AI) applications implemented in cardiology[8-13]

Article	Publication	Application of AI in cardiology
Machine learning of three-dimensional right ventricular motion enables outcome prediction in pulmonary hypertension: a cardiac MR imaging study[8]	Dawes TJW et al. MR imaging study Radiology 2017;283(2):381-90	Evaluation of outcomes in pulmonary arterial hypertension based on a highly accurate algorithm derived from nuclear magnetic resonance
Differences in repolarization heterogeneity among heart failure with preserved ejection fraction phenotypic subgroups[9]	Oskouie SK et al Am J Cardiol 2017;120(4):601–6	Identification of phenotypic patterns in heart failure with preserved ejection fraction and unfavorable prognosis
Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram[10]	Attia ZI Nat Med. 2019 Jan;25(1):70-74	AI applied to electrocardiography for identification of patients with left ventricular dysfunction
Artificial intelligence to predict needs for urgent revascularization from 12-lead electrocardiography in emergency patients[11]	Goto S et al PLoS ONE 201914(1):e0210103	Prediction of urgent revascularization in patients with chest pain in the emergency room
Fast and accurate view classification of echocardiograms using deep learning[12]	Madani, A..et al NPJ Digit. Med. 2018 1, 6,.24	Use of AI for interpretation with good accuracy of echocardiograms
Fully automated echocardiogram interpretation in clinical practice feasibility and diagnostic accuracy[13]	Zhang, J. et al. Circulation 2018 138, 1623–35	Automated assessment of echocardiographic measurements comparable to or greater than manual assessment

Table 2 – Premises to guide the future of artificial intelligence (AI) in medicine

• The patient must be considered to be at the center upon implementation of any new technology.
• The incorporation of these new technologies for diagnosis and treatment should occur after robust validation of their clinical efficacy.
• The use of digital tools and decision algorithms by patients should be another option for those patients who feel empowered.
• Cross-disciplinary training will need to be undertaken involving healthcare professionals, engineers, computer scientists, and bioinformaticians, who will minimize the difficulties of implementing the new technology.

Adapted from Topol EJ[16]

the high expenditures in this sector. Topol,[16] in a recent review, emphasized the premises that should guide the future application of AI in healthcare (Table 2).[16]

If greater availability of data and new AI techniques allow for more accurate diagnoses and prognoses, as well as personalized treatments, various aspects of healthcare practice will continue to depend on other dimensions, such as political, economic, and cultural ones, and the ability of healthcare professionals to interact with patients and the community. The issue of unequal access to healthcare is still critical in Brazil and in developing countries, and requires large investments to improve the organization of the healthcare system. Even when healthcare services and evidence-based guidelines are available, for common and relevant conditions such as hypertension and diabetes, the implementation *gap* is gigantic and best practices are not absorbed by healthcare professionals, or recommended measures are not implemented by patients and their families. The implementation science developed in recent decades, proves to be as important as the data science for the recognition of bottlenecks hindering the complete use of preventive and therapeutic measures ensuring benefit to the patients, who may live more and better, benefiting from all available knowledge.[17]

Thus, personalized medicine and AI promise to provide a powerful tool for complex and personalized healthcare data management, which will only be effective if used in the context of the art of caring and the doctor-patient relationship, allowing a new paradigm of medicine based on data but focused on the patient. Physicians and healthcare professionals will be responsible for evaluating and learning the new techniques, expanding the resources available to fully benefit the patients, in terms of not only their physical condition, but also their mental and spiritual conditions, minimizing the suffering that results from the process of illness.[18]

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Effects of Chronic Exposure to Mercury on Angiotensin-Converting Enzyme Activity and Oxidative Stress in Normotensive and Hypertensive Rats

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Abstract

Background: **Mercury's deleterious effects are associated with increased cardiovascular risk.**

Objective: **To determine whether chronic exposure to inorganic mercury increases the activity of angiotensin-converting enzyme and its relationship with oxidative stress in several organs and tissues.**

Methods: **We studied male Wistar and spontaneously hypertensive rats (SHR) (3-month-old) exposed or not to $HgCl_2$ for 30 days. At the end of treatment, we investigated the following: changes in body weight, hemodynamic parameters, angiotensin-converting enzyme (ACE) activity and oxidative stress in the heart, aorta, lung, brain and kidney in hypertensive compared to normotensive animals. A value of $p < 0.05$ was considered significant.**

Results: **Chronic exposure to $HgCl_2$ did not affect weight gain in either group. Systolic blood pressure, measured weekly, did not increase in Wistar rats but showed a small increase in SHR rats. We also observed increases in left ventricular end-diastolic pressure and ACE activity in the plasma and hearts of normotensive rats. In the SHR+Hg group, ACE activity increased in plasma but decreased in kidney, lung, heart, brain and aorta. Oxidative stress was assessed indirectly by malondialdehyde (MDA) production, which increased in Hg-treated rats in both plasma and heart. In the SHR+Hg group, MDA increased in heart and aorta and decreased in lungs and brain.**

Conclusion: **These results suggest that chronic exposure to inorganic mercury aggravates hypertension and produces more expressive changes in ACE activity and oxidative stress in SHRs. Such exposure affects the cardiovascular system, representing a risk factor for the development of cardiovascular disorders in normotensive rats and worsening of pre-existing risks for hypertension. (Arq Bras Cardiol. 2019; 112(4):374-380)**

Keywords: **Mercury Poisoning; Oxidative Stress/radiation effects; Peptidyl-Dipeptidase A; Hypertension; Rats.**

Introduction

Mercury is a toxic metal that causes harmful effects on the cardiovascular system. Blood concentrations levels of 8 ng/mL are found in exposed individuals,[1,2] which might have a relationship with hypertension development.[3]

Several reports showed that mercury induces oxidative stress and might damage several organs and systems.[4-9] In addition, increased mercury exposure has been associated with cardiovascular diseases, such as hypertension, carotid atherosclerosis, myocardial infarction and coronary heart disease.[10,11] Moreover, oxidative stress is reported to be an efficient mechanism for generation of oxidized low-density lipoprotein and subsequently atherosclerosis;[12,13] then, generation of advanced glycation end-products and participation of inflammatory cells take place, sustaining vascular injury.[14]

One of the main harmful actions of mercury is the generation of oxygen free radicals. NADPH oxidase activation and cyclooxygenase (COX) stimulation induced by mercury may trigger the production of reactive oxygen species (ROS).[11,15,16] Moreover, in animal models chronic mercury exposure for 30 days promoted contractility dysfunction in isolated hearts as a result of decreased Na^+-K^+-ATPase (NKA) activity, reduction in sodium/calcium exchanger (NCX) and sarco/endoplasmic reticulum calcium ATPase (SERCA) activity and increased phospholamban (PLB) expression.[17] Although no effects on blood pressure, heart rate or left ventricular systolic pressure have been reported, mercury causes a small increase in left ventricular end-diastolic pressure in rats.[17]

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Additionally, at the vascular level, the vasoconstrictor response to phenylephrine was increased in caudal, mesenteric, coronary arteries and in the rat aorta, effects commonly related to reduced bioavailability of nitric oxide (NO) and increased oxidative stress.[4,18,19] Interacting with NO, superoxide anion ($O_2^{\cdot-}$) forms peroxynitrite, decreasing NO availability for smooth muscle relaxation.[20-22]

We reported that mercury administration increases local angiotensin converting enzyme (ACE) activity,[18] releasing more angiotensin II that enhances the production of free radicals.[23] These results show that mercury pressor effects might depend on angiotensin II generation and are involved in oxidative stress generation. Previous studies showed that mercury could increase local ACE activity and oxidative stress with subsequent oxidative damage in several organs and systems,[5,11,24-27] but the *in vivo* effects of mercury chronic exposure on cardiovascular activity are not yet completely understood.

Moreover, investigations on mercury effects have been mainly focused on the cardiovascular systems of normotensive animals. However, little information exists about the chronic effects of low doses of inorganic mercury regarding ACE activity in organs and tissues of normotensive and hypertensive animals. To investigate such effects, increased mercury levels were induced to produce blood level concentrations similar to those of exposed individuals. Therefore, we aimed to determine whether chronic exposure to inorganic mercury increases the activity of ACE and the relationship of such exposure with oxidative stress on heart, aorta, lung, brain and kidney in hypertensive compared to normotensive animals.

Methods

Animals

Three-month-old male normotensive Wistar rats and SHRs (spontaneously hypertensive rats) were obtained from the Federal University of Espirito Santo breeding laboratories. During treatment, rats were housed at a constant room temperature, humidity, and 12:12-h light-dark cycle. Rats had free access to tap water and were fed with standard *chow ad libitum*. All experiments were conducted in compliance with the guidelines for biomedical research as stated by Conselho Nacional de Controle de Experimentação Animal-CONCEA, and in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institute of Health. The protocols were approved by the Ethics Committee of Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Brazil (CEUA-EMESCAM 003/2007). Wistar rats and SHRs were divided into four groups: control Wistar rats (n = 6) and SHRs (n = 9) treated with vehicle (saline solution, *im*), and Wistar rats (n = 8) and SHRs (n = 9) treated with mercury chloride ($HgCl_2$) for 30 days (1st dose 4.6 μg/kg, subsequent dose 0.07 μg/kg/day, *im* to cover daily loss). We used the model described by Wiggers et al.[4] to reach blood level concentrations (7,97 ng/ml) similar to those of exposed individuals.

Blood pressure measurements

Indirect systolic blood pressure was measured at both the beginning and the end of the treatment using tail-cuff plethysmography (IITC Life Science Inc.). For this measurement, conscious rats were restrained for 5–10 min in a warm and quiet room and were conditioned to numerous cuff inflation-deflation cycles by a trained operator. Subsequently, systolic blood pressure was measured, and the mean of three measurements was recorded.

Hemodynamic parameter measurements

At the end of treatment, control and $HgCl_2$-treated rats (n = 26) were anaesthetized with urethane (1.2 g/kg, Sigma, St Louis, MO, USA), and the carotid artery and jugular vein were cannulated. A polyethylene catheter (PE50/*Clay-Adams*) filled with heparinized saline (50 U/mL) was introduced into the carotid artery to measure systolic blood pressure (SBP) and diastolic blood pressure (DBP). The carotid artery catheter was introduced into the left ventricle, and the jugular vein cannula was advanced into the right ventricular chamber to measure the left and right ventricular systolic pressures (LVSP and RVSP) and their positive and negative time derivatives (+dP/dt and - dP/dt, respectively) along with the left and right ventricular end-diastolic pressures (LVEDP and RVEDP). Recordings were performed over 30 min with a pressure transducer (TSD 104A-Biopac) and with an interface and software for computer data collection (MP100A, Biopac System, Inc., Santa Barbara, CA, USA). Heart rate (HR) was determined in the interbeat intervals.

Measurement of malondialdehyde (MDA) production. Levels of MDA in plasma, heart, aorta, brain, kidney and lung were measured using a modified thiobarbituric acid (TBA) assay.[28] Plasma and tissue samples were mixed with 20% trichloroacetic acid in 0.6 M HCl (1:1, v/v), and tubes were kept on ice for 20 min to precipitate plasma components to avoid possible interferences. Samples were centrifuged at 1500 x g for 15 minutes before adding TBA (120 mM in Tris 260 mM, pH 7) to the supernatant in a proportion of 1:5 (v/v); then, the mixture was boiled at 97°C for 30 min. Spectrophotometric measurements at 535 nm were taken at 20° C.

ACE activity assay

ACE activity was measured in plasma, heart, aorta, brain, kidney and lung using a fluorometric method adapted from Friedland and Silverstein.[29] Briefly, triplicate tissue and plasma samples (3 μL) were incubated for 15-90 minutes at 37°C with 40 μL of assay buffer containing the ACE substrate 5 mM Hip-His-Leu (Sigma). The reaction was stopped by the addition of 190 μL of 0.35 M HCl. The generated product, His-Leu, was measured fluorometrically following 10 min of incubation with 100 μL of 2% o-Phthalaldehyde in methanol. Fluorescence measurements were taken at 37°C in a FLUOstar Optima plate reader (BMG Labtech, Offenburg, Germany) with 350 nm excitation and 520 nm emission filters. The fluorescence plate reader was controlled using the FLUOstar Optima Software. Black 96-Well polystyrene microplates (Biogen Cientifica, Madrid, Spain) were used. A calibration curve with ACE from the rabbit lung (Sigma) was included in each plate.

Data analysis and statistics

The results are expressed as the mean ± SD. All parameters were tested for normality using the one-sample Kolmogorov-

Smirnov test. Differences were analysed using one-way ANOVA, followed by a *post hoc* Tukey *test* (GraphPad Prism Software, San Diego, CA). A p value < 0.05 was considered significant.

Results

At 30 days of mercury treatment, Wistar controls, Wistar treated rats, and treated and untreated SHRs had similar body weights, although the SHRs had lower body weights when compared with Wistar rats (Table 1).

Table 1 also shows that several organs, including the brain, heart, kidney and lungs, presented similar weights, normalized by body weight, which did not change after mercury treatment.

Indirect SBP measured at day zero in awake rats showed that SHRs had a higher mean arterial pressure compared with Wistar rats (Table 2). However, at the end of the treatment, mercury produced a significant increment of blood pressure only in $HgCl_2$-treated SHR rats (Table 2).

Arterial blood pressures, ventricular pressures and their respective derivatives, and HR measurements in anaesthetized rats were not different between groups (Table 3), but the LVEDP increased after Hg treatment in the Wistar group, as previously reported.[17]

It has been reported in animal and human studies that mercury increases free radical production leading to an oxidative stress.[4,24,30,31] We then evaluated the oxidant state in the blood and in several other tissues by measuring MDA levels (Table 4). MDA plasma levels were greater in mercury-treated than in untreated Wistar rats but did not change in SHRs. Mercury treatment increased MDA levels in the heart in both Wistar and SHRs. In the aorta, different from plasma, MDA levels were increased in mercury-treated SHRs but not in Wistar rats. For brain and lungs, no changes were observed for MDA levels in mercury-treated Wistar rats, but a reduction occurred in SHRs. For kidneys, mercury treatment reduced MDA levels in both Wistar and SHR mercury-treated groups.

Since angiotensin II is reported to increase ROS and mercury increases ACE,[32,33] we investigated whether ACE activity was altered after 30 days of mercury treatment in Wistar and SHR groups. Table 5 shows that plasma ACE levels increased in both groups after mercury treatment. In the hearts of Wistar rats, mercury induced a slight ACE activity increment, but no changes were observed in the aorta, lungs, brain or kidneys. However, in mercury-treated SHRs, ACE activity was reduced in the heart, aorta, lungs, brain and kidneys. Interestingly, ACE activity was higher in the heart, aorta and kidneys and lower in plasma of SHR controls compared with Wistar controls.

Discussion

The results presented here suggest that Wistar rats and SHRs, submitted to chronic exposure to inorganic mercury for 30 days, have blood concentrations similar to exposed individuals.[1,2] In addition, $HgCl_2$-treated SHR, but not Wistar rats have increased blood pressure at the end of treatment. The intervention also influenced ACE activity and oxidative stress, by increasing or decreasing them, mainly in SHRs.

Previous reports showed that changes resulting from chronic exposure to mercury have been focused on its toxic effects on the cardiovascular system and the associations with hypertension, carotid atherosclerosis, myocardial infarction and coronary heart disease.[9,10,34] Mercury exposure, both acute and chronic, affects the heart and endothelial function, reducing NO bioavailability and increasing ACE and NADPH activities.[15,18,19] Moreover, studies in rats showed that body weight gain and arterial pressure were not affected when chronic exposure was performed,[4,17] suggesting that this treatment was not sufficient, in either amount or time, to produce changes. Our results reproduced those findings, showing no changes in body weight gain; additionally, similar behaviour was observed for the heart, brain, kidneys and lung, reinforcing the suggestion that this treatment is not sufficient to produce these changes, although cardiovascular function began to be affected.

Regarding the hemodynamic evaluation, no changes were observed in the left or right ventricle in Wistar rats or SHRs. Only an increment of LVEDP was observed in normotensive rats treated with mercury, indicating some deleterious effects of mercury on ventricular function.[35] Right ventricular pressures were investigated because of our previous report showing that under acute mercury exposure (0.5 mg/kg), there was an increase in right ventricular systolic pressure because of pulmonary hypertension,[3,36-39] which was not observed with chronic treatment in the present study. The fact that lung ACE activity was unaffected in both Wistar groups, although slightly reduced in $HgCl_2$-treated SHRs might explain why the right ventricular pressures remained unchanged.

Table 1 – Body Weight (BW), Brain/BW, Heart/BW, Kidney/BW, Lung/BW, Adrenals/BW, Spleen/PC and Liver/PC from $HgCl_2$-treated and non-treated Wistar rats and spontaneously hypertensive rats (SHRs)

	Wistar Control n = 6	Wistar $HgCl_2$-treated n = 8	SHR Control n = 9	SHR $HgCl_2$-treated n = 9
Body weight (BW) (g)	399 ± 58.3	384 ± 18.1	216 ± 20.1*†	222 ± 14.4*†
Brain/BW (mg/g)	4.58 ± 0.7	4.69 ± 0.5	7.48 ± 0.7*†	7.41 ± 0.5*†
Heart/BW (mg/g)	3.06 ± 0.6	3.43 ± 0.2	3.77 ± 0.2	3.81± 0.2
Kidney/BW (mg/g)	6.44 ± 1.7	6.53 ± 0.5	6.78 ± 0.3	6.80 ± 0.6
Lung/BW (mg/g)	3.97 ± 1.5	4.53 ± 0.6	6.48 ± 1.2*†	7.91 ± 1.2*†

*Results represent mean ± SD; n: number of animals used. One-way ANOVA, post hoc Tukey's. *p < 0.05 compared with the Wistar control and † p < 0.05 compared with $HgCl_2$: treated Wistar rats.*

Table 2 – Values of systolic blood pressure (SBP in mmHg) measured by tail plethysmography in Wistar rats and spontaneously hypertensive rats (SHRs) before and after treatment for 30 days with $HgCl_2$.

	Wistar CT n = 5	Wistar Hg n = 5	SHR CT n = 5	SHR Hg n = 5
SBP – Day 0 (mmHg)	123 ± 13	131 ± 15	205 ± 15	198 ± 22
SBP – Day 7 (mmHg)	119 ± 4	132 ± 9	221 ± 18	197 ± 18
SBP – Day 14 (mmHg)	115 ± 10	135 ± 9	219 ± 9	199 ± 29
SBP – Day 21 (mmHg)	132 ± 17	142 ± 14	200 ± 13	199 ± 9
SBP – Day 30 (mmHg)	117 ± 6	143 ± 11	220 ± 21	232 ± 19#

Results represent the mean ± SD; n: number of animals used. One-way ANOVA, post hoc Tukey's for all groups. #p < 0.05 vs. SHR treated with mercury at day 0

Table 3 – Hemodynamic parameters from untreated and mercury ($HgCl_2$)-treated Wistar rats and spontaneously hypertensive rats (SHRs)

	Wistar Control n = 6	Wistar $HgCl_2$-treated n = 7	SHR Control n = 6	SHR $HgCl_2$-treated n = 7
SBP (mmHg)	105 ± 10	97 ± 11	105 ± 7	113 ± 8
DBP (mmHg)	71 ± 10	67 ± 11	58 ± 5	68 ± 11
HR (bpm)	324 ± 88	325 ± 58	343 ± 32	341 ± 34
LVSP (mmHg)	114 ± 20	107 ± 16	117 ± 22	112 ± 8
LVEDP (mmHg)	0.256 ± 1	3.31 ± 1*	1.11 ± 0.2	0.493 ± 0.5
+dP/dt LV (mmHg/s)	8627 ± 3378	8500 ± 2419	7360 ± 1854	7001 ± 1921
-dP/dt LV	-6270 ± 1232	-6249 ± 1234	-7169 ± 1173	-6524 ± 1131
RVSP (mmHg)	32 ± 10	29 ± 5	29 ± 5	33 ± 5
RVEDP (mmHg)	-1.080 ± 1	1.10 ± 2	-0.472 ± 1	0.459 ± 0.3
+dP/dt RV (mmHg/s)	3339 ± 2202	1758 ± 435	2776 ± 1056	2171 ± 405
– dP/dt RV (mmHg/s)	-2560 ± 1553	-1387 ± 469	-1833 ± 478	-1695 ± 368

*Changes in systolic (SBP) and diastolic (DBP) pressure, heart rate (HR), left and right ventricle systolic pressure (LVSP, RVSP), left and right ventricle end diastolic pressure (LVEDP, RVEDP) and positive (+dP/dt) and negative first-time derivatives (-dP/dt) from the left and right ventricles of Control and $HgCl_2$-treated rats. The results represent the mean ± SD. n-Number of animals used. One-way ANOVA, post hoc Tukey's. *p < 0.05 vs Wistar Control.*

The reduction of NO bioavailability is a hallmark resulting from the increase in ROS generation contributing to the development of cardiovascular diseases such as atherosclerosis and hypertension.[10,11,34] The interaction of superoxide anion with NO generates peroxynitrite that decreases NO bioavailability increasing vascular reactivity.[20-22] In fact, our previous studies have associated mercury exposure with increased oxidative stress and the reduction of NO bioavailability.[15,19] In addition, it has been shown that an increase of the local ACE activity could increase NADPH oxidase activity[16 40] and ROS in the aortas of normotensive and SHRs. Therefore, we investigated whether mercury effects alter the renin-angiotensin system and oxidative stress in the organs and tissues of hypertensive and normotensive rats. The increase in ACE activity induced by mercury could lead to increased activity of NADPH oxidase, which could, in turn, increase the release of ROS, generating an oxidative stress, as observed in this study.

Considering that both Hg and increased ACE activity can induce oxidative stress, we should observe a correlation between the amount of oxidative stress and ACE activity measured by MDA. An interesting aspect is that ACE activity levels and MDA concentrations showed similar behavior in plasma and organs investigated. Also, it is of note that both ACE activity and MDA concentrations showed more expressive changes in $HgCl_2$-treated SHRs. Similarly, inorganic mercury treatment aggravated hypertension in SHRs, suggesting that a pre-existing hypertensive condition enhances inorganic mercury action.

ROS are damped in the plasma of all locations where they are produced, and consequently, it is expected an increase in MDA. We have shown that plasma ACE activity increases after acute exposure to low mercury concentrations and reduces after exposure to high concentrations.[18,39] However, we might speculate that in the SHR group, when exposed to mercury, tissues that produce more ROS, such as the aorta, lung and kidney, ACE activity is reduced. Similarly, in the brain tissue, which concentrates mercury, ACE activity also decreased. LVEDP increments in Wistar rats could be explained by the local increase in ACE activity and oxidative stress in the heart. These two factors might explain the small, but significant increase in LVEDP, probably induced by a calcium overload.

Although we cannot give a proper explanation for all the events, it can be suggested that mercury, even at concentrations that do not affect arterial pressure and weight gain in normotensive rats, affects ACE activity and oxidative stress. However, in hypertensive animals, inorganic mercury actions were more expressive. These findings give rise to questions that are not addressed by our results: can exposure to mercury inhibit ACE activity in situations where it is already increased? Does ACE activity in different organs

Table 4 – Malondialdehyde (MDA) (mM/mg of protein) concentrations in plasma, heart, aorta, lung, brain and kidney of untreated and Mercury ($HgCl_2$)-treated Wistar rats and spontaneously hypertensive rats (SHRs)

	Wistar Control n = 6	Wistar $HgCl_2$-treated n = 6	SHR Control n = 6	SHR $HgCl_2$-treated n = 7
Plasma	0.93 ± 0.15	1.28 ± 0.44*	0.89 ± 0.22	0.92 ± 0.05
Heart	0.22 ± 0.03	0.28 ± 0.03*	0.45 ± 0.05	0.55 ± 0.05$^{\&}$
Aorta	0.13 ± 0.03	0.12 ± 0.05	0.96 ± 0.27	1.51 ± 0.37$^{\&}$
Lung	0.18 ± 0.05	0.14 ± 0.03	0.21 ± 0.03	0.12 ± 0.03$^{\&}$
Brain	0.13 ± 0.03	0.09 ± 0.03	0.54 ± 0.07	0.34 ± 0.03$^{\&}$
Kidney	0.38 ± 0.07	0.14 ± 0.03*	0.96 ± 0.07	0.51 ± 0.03$^{\&}$

*Values are expressed in mM/mg of protein (MDA). The results represent the mean ± SD. N-Number of animals used. One-way ANOVA, post hoc Tukey's. *p < 0.05 vs Wistar Control and $^{\&}$p < 0.05 vs SHR Control.*

Table 5 – Angiotensin converting enzyme (ACE) activity levels in plasma, heart, aorta, lung, brain and kidney of untreated and Mercury ($HgCl_2$)-treated Wistar rats and spontaneously hypertensive rats (SHRs)

	Wistar Control n = 6	Wistar $HgCl_2$-treated n = 6	SHR Control n = 6	SHR $HgCl_2$-treated n = 6
Plasma	187 ± 39.2	235 ± 34.3*	114 ± 27.9*	163 ± 38.7$^{\&}$
Heart	3.4 ± 0.5	4.1 ± 0.3*	17.9 ± 2.7*	14.8 ± 1.4$^{\&}$
Aorta	213 ± 53.9	221 ± 61.3	670 ± 39.9*	535 ± 47.0$^{\&}$
Lung	95 ± 6.1	99.4 ± 11.3	87.6 ± 5.4	75.1 ± 9.8$^{\&}$
Brain	46.4 ± 7.9	42.6 ± 9.9	40.3 ± 5.6	27.8 ± 4.4$^{\&}$
Kidney	47.8 ± 16.2	45.4 ± 14.2	80.0 ± 15.4*	61.4 ± 6.9$^{\&}$

*Values are expressed in nmol/mL/min/mg of protein in tissues and in nmol/mL of plasma/min in plasma (ACE). Results represent the mean ± SD. N-Number of animals used. One-way ANOVA, post hoc Tukey's. *p < 0.05 vs Wistar Control and $^{\&}$p < 0.05 vs SHR Control.*

depend on mercury concentration in each of them? Would a pre-existing cardiovascular disorder be aggravated by exposure to inorganic mercury? These questions can be considered limitations of our study, and issues for further studies.

Conclusions

Results described here allow us to affirm that chronic exposure to inorganic mercury, similarly to that we previously reported, produces blood concentrations compatible with those found in exposed humans, and do represent a cardiovascular risk factor. Such exposure influenced ACE activity, increased oxidative stress and promoted hypertension in SHRs (which had a higher blood pressure increment compared with untreated SHRs), as well as increased the LVEDP in Wistar rats. This controlled exposure affected the cardiovascular system, produced more expressive changes of ACE activity and oxidative stress in SHRs representing a risk factor for the development of cardiovascular disorders in normotensive rats and a contributing factor to pre-existing risks in high blood pressure condition.

Author contributions

Conception and design of the research: Vassallo DV, Simões MR, Giuberti K, Stefanon I; acquisition of data: Giuberti K, Azevedo BF, Ribeiro Junior RF; analysis and interpretation of the data and statistical analysis: Vassallo DV, Simões MR, Giuberti K, Azevedo BF, Ribeiro Junior RF, Salaices M, Stefanon I; obtaining funding: Vassallo DV, Salaices M; writing of the manuscript: Vassallo DV, Simões MR; critical revision of the manuscript for intellectual content: Vassallo DV, Simões MR, Salaices M, Stefanon I.

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 on Animal Experiments of the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória under the protocol number CEUA-EMESCAM 003/2007.

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Alterations Resulting From Exposure to Mercury in Normotensive and Hypertensive Rats

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Short Editorial related to the article: Effects of Chronic Exposure to Mercury on Angiotensin-Converting Enzyme Activity and Oxidative Stress in Normotensive and Hypertensive Rats

Mercury is a chemical element still widely used in industrial processes and present in many appliances used daily by the population. However, mercury can be extremely toxic to our body and lead to the development of several diseases such as blindness, deafness, intellectual disability, paralysis, cancer, renal dysfunction, and it can also induce cardiac alterations.[1,2]

Studies have shown that exposure to mercury can cause changes in the cardiovascular system, such as systemic arterial hypertension, coronary dysfunction, cardiac arrhythmia, and increase the risk of myocardial infarction.[3,4] In humans, high blood mercury levels were correlated with increased systolic and diastolic blood pressure.[5]

Mercury interference can also be observed in several enzymatic, amino acid and antioxidant reactions (N-acetyl-L-cysteine, alpha-lipoic acid, L-glutathione), reducing oxidative defense and increasing free radicals with consequent increase of oxidative stress. It is also possible that mercury may lead to mitochondrial dysfunction, causing glutathione depletion and rise on lipid peroxidation.[6]

The study by Vassallo et al.[7] investigated if the chronic exposure to inorganic mercury increases the activity of the angiotensin converting enzyme (ACE) and its relation with oxidative stress in various organs and tissues from hypertensive and normotensive rats. Few studies have evaluated the chronic effects of low doses of inorganic mercury on the ACE activity in organs and tissues of normotensive and hypertensive animals.

The experimental model used by the author was the spontaneously hypertensive rat (SHR), which exhibits hypertension similar to human hypertension and has been widely used in several studies for analysis of cardiovascular and biochemical alterations.[7-9]

The hemodynamic evaluation performed in the study by Vassallo et al.[7] showed that chronic exposure to mercury increased blood pressure in hypertensive animals and left ventricular end-diastolic pressure in normotensive animals. The biometry of the animals demonstrates that hypertensive rats have lower body weight than normotensive animals, data similar to those are found in the literature.[9,10] The ratio of the brain and lungs normalized by body weight have significantly higher values in hypertensive animals. The weight ratio of the lungs normalized by body weight has been used as a marker of heart failure.[11] However, exposure to mercury did not cause biometric changes, except for those resulting from the hypertension factor.

Another interesting result shown by Vassallo et al.[7] was that the concentration of malondialdehyde (MDA) in normotensive animals treated with mercury had higher values in the plasma and the heart, and reduction was reduced in the kidneys. In hypertensive animals treated with mercury, the MDA concentration values are increased in the heart and aorta, and they are reduced in the lungs, brain and kidneys.

The ACE activity in Wistar animals treated with mercury presented higher values only in plasma and heart. Hypertensive animals treated with mercury presented higher values only in plasma and reduced values in the heart, aorta, lungs, brain and kidneys.

Therefore, exposure to mercury caused more significant changes in ACE activity and oxidative stress in SHR rats, determining specific alterations in each organ evaluated and representing a cardiovascular risk factor. The treatment of the animals with mercury exhibited at the end of the experimental period levels similar to those observed in humans exposed to the metal.[12]

However, some questions related to the changes in ACE activity and oxidative stress caused by exposure to mercury are still unclear. More studies are needed to clarify, for example, whether mercury exposure could inhibit ACE activity in situations where it is already elevated, or whether preexisting cardiovascular disease would be aggravated by exposure to mercury.

Keywords

Hypertension; Rats; Mercury Poisoning; Oxidative Stress; Peptidyl-Dipeptidase A; Heart Failure.

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A Proposed Inflammatory Score of Circulating Cytokines/ Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters

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Abstract

Background: **There is evidence that subclinical systemic inflammation is present in resistant hypertension (RHTN).**

Objective: **The aim of the study was to develop an integrated measure of circulating cytokines/adipokines involved in the pathophysiology of RHTN.**

Methods: **RHTN (n = 112) and mild to moderate hypertensive (HTN) subjects (n=112) were studied in a cross-sectional design. Plasma cytokines/adipokines (TNF-alpha, interleukins [IL]-6, -8, -10, leptin and adiponectin) values were divided into tertiles, to which a score ranging from 1 (lowest tertile) to 3 (highest tertile) was assigned. The inflammatory score (IS) of each subject was the sum of each pro-inflammatory cytokine scores from which anti-inflammatory cytokines (adiponectin and IL-10) scores were subtracted. The level of significance accepted was alpha = 0.05.**

Results: **IS was higher in RHTN subjects compared with HTN subjects [4 (2-6) vs. 3 (2-5); p = 0.02, respectively]. IS positively correlated with body fat parameters, such as body mass index (r = 0.40; p < 0.001), waist circumference (r = 0.30; p < 0.001) and fat mass assessed by bioelectrical impedance analysis (r = 0.31; p < 0.001) in all hypertensive subjects. Logistic regression analyses revealed that IS was an independent predictor of RHTN (OR = 1.20; p = 0.02), independent of age, gender and race, although it did not remain significant after adjustment for body fat parameters.**

Conclusion: **A state of subclinical inflammation defined by an IS including TNF-alpha, IL-6, IL-8, IL-10, leptin and adiponectin is associated with obese RHTN. In addition, this score correlates with obesity parameters, independently of hypertensive status. The IS may be used for the evaluation of conditions involving low-grade inflammation, such as obesity-related RHTN. Indeed, it also highlights the strong relationship between obesity and inflammatory process. (Arq Bras Cardiol. 2019; 112(4):383-389)**

Keywords: **Hypertension/physiopathology; Obesity; Inflammation; Cytokines; Adipokines; Probability; Risk Factors**

Introduction

Inflammation is an important pathophysiological factor underlying hypertension, obesity, and metabolic syndrome. Overweight and obese status include a higher prevalence of hypertension and maladaptive consequences including cardiorenal and metabolic disorders. Excess visceral fat is a source of cytokines, that creates an inflammatory-oxidative stress cascade contributing to insulin resistance (IR), endothelial dysfunction, vascular stiffening, and sodium retention in the kidney.[1,2] The combined presence of obesity and IR also contributes to overactivation of both sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system.[3] Ultimately, these disarrangements can lead to the occurrence of resistance to antihypertensive treatment.[4]

Our research group have explored inflammatory cytokines – the anti-inflammatory adiponectin and interleukin 10 and the pro-inflammatory leptin, tumor necrosis factor-alpha (TNF-α), and interleukins 6 (IL-6) – in resistant hypertension (RHTN) associating them to the lack of blood pressure (BP) control and vascular-renal damage.[5-7] In addition, low-grade chronic inflammation, estimated by high C-reactive protein levels, was able to predict major fatal and nonfatal cardiovascular outcomes, and cardiac remodeling in this high-risk population.[8-10]

Adiponectin has an anti-inflammatory role and directly stimulates the production of nitric oxide (NO) in endothelial cells via phosphorylation of endothelial

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NO synthase.[10] It down regulates TNF-α production from macrophage by inhibiting nuclear transcription factor NF-kappa B.[11,12] On the other hand, IL-6 inhibits adiponectin expression and secretion in 3T3-L1 adipocytes *in vitro*.[13] Additionally TNF-α increases the secretion of leptin,[14] which in turn stimulates the SNS.[15] Since cytokines and adipokines have interconnected roles, we aimed with this study (1) to develop an integrated measure of several circulating cytokines/adipokines among subjects with RHTN and mild to moderate hypertension (HTN), and (2) to assess the potential impact of this inflammatory score (IS) on resistance to antihypertensive treatment.

Population and methods

A convenience sample of 112 subjects diagnosed with RHTN attending the Specialized Outpatient Clinic in RHTN of the University of Campinas (UNICAMP, Campinas, Brazil) and 112 HTN attending the Hypertension Clinic of Valinhos (Valinhos, Brazil) were consecutively enrolled in this cross-sectional study. RHTN was defined according to American Heart Association Statement as either (1) the subjects whose BP levels remain above goal (≥ 140/90 mmHg) despite concurrent use of three or more antihypertensive drugs of different classes, or (2) those with controlled BP levels using four or more antihypertensive medication. Ideally, one of the agents should be a diuretic, and all agents should be prescribed at optimal doses.[16] Patients with controlled BP using three or less antihypertensive drugs, or not yet controlled using two or less of these medications were classified as having HTN (grade 1 and grade 2 hypertension).[17]

A 6-month period follow-up for screening and exclusion of secondary causes of hypertension was performed to guarantee a precise diagnosis for HTN and "true" RHTN. The exclusion criteria were compounded with renal artery stenosis, coarctation of the aorta, pheochromocytoma, primary hyperaldosteronism (aldosterone to renin ratio > 20 $ng.dL^{-1}$ per $ng.mL^{-1}.h^{-1}$), Cushing syndrome, obstructive sleep apnea-hypopnea syndrome (patients with previous polysomnographic diagnosis, or classified as high risk by the Berlin questionnaire). This period also included pill count to exclude the lack of BP control due to poor medication adherence,[18] and ambulatory BP monitoring (ABPM) to exclude white coat hypertension. We also excluded patients with symptomatic ischemic heart disease, impaired renal function, chronic kidney disease (creatinine clearance < 30 $mL/min/1.73m^2$) and liver disease (medical history, and platelet and transaminase levels). Inclusion criterion was age over 18 years old.

Blood pressure measurements

Office systolic BP (SBP) and diastolic BP (DBP) were assessed by a trained health professional according to the European Society of Hypertension guidelines for the management of arterial hypertension.[17] We used a validated digital sphygmomanometer (HEM-907XL, OMRON Healthcare Inc., Bannockburn, IL, USA). Ambulatory BP measurement was performed using an automatic oscillometric monitor (Spacelabs90207, SpacelabsInc, Redmon, WA, USA). Patients were instructed to maintain normal daily activities and record their 24-hour activities in a personal diary.

Body composition

The body composition was determined by the Bioimpedance Analyser 450 device (Biodynamics Corporation, Seattle, WA, USA) to assess fat-free mass and fat mass (FM). Briefly, the method is based on tetrapolar bioelectrical impedance (electrodes on feet and hands) to estimate mass and fluid compartments of the body. The measurements were performed after an 8-hour fast, and patients were instructed to avoid physical activity and smoking prior to the exam.

Biochemical tests

Blood samples were collected at morning after an 8-hour fast from patients in the sitting position. Plasma levels of aldosterone and renin were measured by radioimmunoassay (Immunotech SAS, Marseille, France), while the cytokines and adipokines – TNF-alpha, IL-6, IL-8, IL-10, leptin and adiponectin – were measured using enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, USA), according to the manufacturer's instructions. Creatinine clearance was calculated from 24h-urine creatinine level, urine flow rate, and plasma creatinine concentration as the removal rate per minute divided by plasma creatinine concentration.

Statistical analyses

Continuous variables were expressed as mean and standard deviation or median (1st and 3rd quartiles), according to data distribution assessed by the Kolmogorov–Smirnov test. Unpaired Student's t-test or the Mann Whitney test was applied to compare continuous data between the RHTN and HT. Categorical variables were presented in frequencies and percentages compared by chi-square or Fisher's exact test. Pearson or Spearman tests was used to assess correlation of continuous data. Multiple logistic regression analyses were performed to evaluate the association of IS with resistance to antihypertensive treatment, adjusting for potential confounders.

For IS calculation, the values of plasma cytokine/adipokine (TNF-alpha, IL-6, -8, -10, leptin and adiponectin) were divided into tertiles, and a score ranging from 1 (lowest tertile) to 3 (highest tertile) was assigned to them. The IS was considered as the sum of each pro-inflammatory cytokine score (TNF-alpha, IL-6, IL-8 and leptin) from which adiponectin and IL-10 – both anti-inflammatory cytokines – scores were subtracted for each subject.

The analyses were performed using the software SigmaPlot (version 12, Systat Software, Inc., San Jose, CA USA, www.systatsoftware.com) and GraphPad Prism (version 7.00 for Windows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com). The level of significance accepted was alpha 0.05.

Results

General characteristics of both hypertensive groups are described in Table 1. Body fat parameters (body mass index - BMI, waist circumference - WC and FM) revealed to be increased in the RHTN subjects, as well as lipid profile, glycated hemoglobin and aldosterone levels compared to their counterparts. Compared with HTN, RHTN individuals used

Table 1 – Clinical and biochemical characteristics of patients with mild-to-moderate hypertension (HTN) and patients with resistant hypertension (RHTN)

	HTN (n = 112)	RHTN (n = 112)	p-value
Age (years)	66 ± 10	58 ± 10	< 0.001
Female, n (%)	63 (56)	78 (70)	0.27
Black, n (%)	13 (12)	55 (49)	< 0.001
BMI (Kg/m^2)	27(25-31)	31(27-35)	< 0.001
WC (cm)	94 ± 12	101 ± 14	0.003
FFM (Kg)	53 (46-62)	55 (49-64)	0.11
FM (Kg)	20 (15-27)	26 (20-35)	< 0.001
Office SBP (mmHg)	139 (131-149)	149 (134-163)	< 0.001
Office DBP (mmHg)	82 (77-85)	85 (78-92)	0.03
ABPM SBP (mmHg)	126 (118-134)	130 (118-144)	0.03
ABPM DBP (mmHg)	75 (70-81)	75 (70-86)	0.22
HR (bpm)	67 (61-75)	67 (58-75)	0.35
Glucose (mg/dL)	97 (90-107)	101 (90-126)	0.09
HbA1C (%)	6.0 (5.7-6.4)	6.3 (5.9-7.3)	0.03
Cholesterol (mg/dL)	165 (136-187)	181 (150-209)	0.001
LDL-c (mg/dL)	88 (64-109)	97 (77-125)	0.004
HDL-c (mg/dL)	48 (41-56)	46 (38-54)	0.31
Triglycerides (mg/dL)	108 (80-150)	126 (93-185)	0.02
Urea (mg/dL)	34 (27-43)	35 (27-44)	0.52
Creatinine (mg/dL)	0.95 (0.79-1.10)	0.94 (0.80-1.18)	0.19
Renin (pg/mL)	29 (14-73)	25 (12-72)	0.39
Aldosterone (pg/mL)	68 (41-111)	92 (56-176)	0.006
Creat. Clear (mL/min/1.73m^2)	75 (58-93)	81 (61-97)	0.89

Values are expressed as mean ± standard deviation or median (1st, 3rd quartiles), according to data distribution. BMI: body mass index; WC: waist circumference; FFM: fat-free mass; FM: fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABPM: ambulatory blood pressure monitoring; HR: heart rate; HbA1C: glycated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Creat Clear: creatinine clearance.

a greater number of antiplatelet drugs and almost all classes of antihypertensive agents, except for angiotensin II receptor blockers (ARBs). On the other hand, a greater number of HTN subjects were taking statins (Table 2).

IS was higher in the RHTN compared to HTN group [4 (2-6) *vs.* 3 (2-5); p = 0.02, respectively – Figure 1]. Curiously, IS positively correlated with BMI (r = 0.40; p < 0.001), WC (r = 0.30; p < 0.001) and FM (r = 0.31; p < 0.001) in all hypertensive subjects.

Finally, the independent logistic regression models revealed that IS was associated with the presence of RHTN (Odds ratio (OR) = 1.20; p = 0.02), independently of age, gender and race, although it was no longer significant after the adjustments for the body fat parameters studied (Table 3).

Discussion

Our study revealed that the integrated measure of pro-inflammatory and anti-inflammatory cytokines/adipokines scores was associated with the occurrence of RHTN. The IS arises as a strong factor related to body fat parameters, suggesting the relevance of subclinical inflammation in obesity condition regardless of the hypertension degree.

Recent findings from our group have suggested that inflammatory process underlies the pathophysiology of RHTN and its related comorbidities like diabetes, obesity and metabolic syndrome. Altered levels of cytokines and adipokines, such as IL-10, IL-1 beta, adiponectin and leptin, were found in RHTN subjects compared to their controls.[5,7,19] Hyperleptinemia and hypoadiponectinemia were associated with the lack of BP control,[5,19] as well as target organ damage – arterial stiffness and microalbuminuria – in this high-risk population.[6] Obese diabetic RHTN subjects showed lower levels of adiponectin combined with a greater autonomic dysfunction (characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system) than non-diabetic patients.[20]

Recently, we have found a huge prevalence of metabolic syndrome in these RHTN subjects (73%), which may explain the high IS. Interestingly, the HTN group also showed a considerable prevalence of the syndrome (60%),[21] which might justify the worsening of their score in our present study.

Table 2 – Medications used by subjects with mild-to-moderate hypertension (HTN) and subjects with resistant hypertension (RHTN)

	HTN (n = 112)	RHTN (n = 112)	p-value
Antihypertensive drugs			
Number of classes	2 (2-3)	4 (4-5)	< 0.001
Diuretics, n (%)	70 (63)	108 (96)	0.02
ACEIs, n (%)	20 (18)	43 (38)	0.02
ARBs, n (%)	81 (72)	61 (54)	0.01
CCBs, n (%)	53 (47)	94 (84)	< 0.001
Beta-blockers, n (%)	14 (13)	79 (71)	< 0.001
Central α-agonists, n (%)	01 (01)	31 (28)	< 0.001
Statins, n (%)	84 (75)	60 (54)	0.001
Glucose-lowering drugs, n (%)	42 (38)	57 (51)	0.06
Antiplateletdrugs, n (%)	20 (18)	65 (58)	< 0.001

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers.

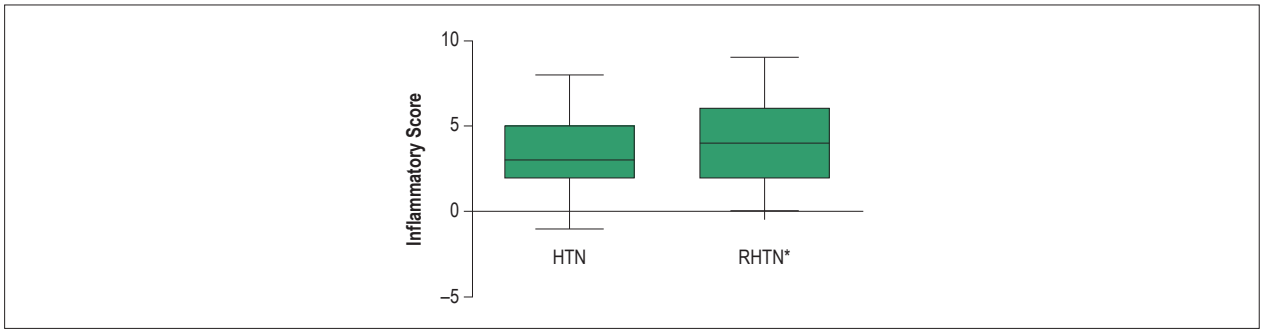

Figure 1 – *Inflammatory score calculated between subjects with mild-to-moderate hypertension (HTN) and resistant hypertension (RHTN) (3 [2-5] vs. 4 [2-6], p = 0.02, respectively). IS of each subject was the sum of each pro-inflammatory cytokine score (TNF-alpha, interleukins (IL) -6, -8, -10) from which the scores of anti-inflammatory cytokines (adiponectin and IL-10) were subtracted; *p < 0.05 vs. HTN*

In addition, the HTN group was older than the RHTN group, and hence an increased IS could be attributed to age.[22]

Experimental studies share similar findings of the role of inflammation on hypertension. Researchers have investigated changes in the systolic pressure of spontaneously hypertensive rats (SHR) treated with infliximab – a TNF-alpha-neutralizing agent.[23] This study revealed cardiovascular benefits of inhibiting this cytokine in SHR with the reduction of both systolic BP and cardiac remodeling. The authors suggested a vasodilation dependent-mechanism in which the infliximab effect is able to induce the NO synthesis.[23] Interestingly, a recent study[24] described a new pathway of hypertension linked to an immune-inflammatory-oxidative stress cascade. Kirabo et al.[24] demonstrated that an angiotensin II–infused mice model increased reactive oxygen species in dendritic cells releasing pro-inflammatory cytokines (IL-6, IL-1 beta, and IL-23), which in turn promoted T cell proliferation featuring a pro-inflammatory phenotype. Ultimately, these mechanisms led to hypertension, suggesting new potential targets to treat hypertension.[24] Our results revealed that the IS – already investigated in type 2 diabetes[25] – was able to address in a single measure a great variety of mechanistically aligned cytokines/adipokines, involved in the pathophysiology of RHTN. Therefore, this approach could enhance estimation of the relation between the low-grade inflammation and high-risk populations such as the obese subjects with RHTN studied in this work.

It is well recognized that obesity, characterized by chronic activation of the immune system and inflammatory pathways, is a critical factor contributing to IR and type 2 diabetes, both comorbidities quite often presented in subjects with RHTN. In this context, many studies have supported this relationship. Esposito et al.[26] found that weight loss and lifestyle changes decreased vascular inflammatory markers, such as IL-6, IL-18, and C-reactive protein, whereas adiponectin levels increased significantly in obese women. Similar effects of reducing levels of TNF-alpha were found in response to these interventions.[27] Overweight and obesity have been suggested to cause microvascular dysfunction characterized by (1) impaired insulin sensitivity, (2) SNS activation and (3) increased vascular peripheral resistance. Along with this, changes in adipokines secretion leading to increased levels of free fatty acids and inflammatory mediators have also

Table 3 – Independent multiple logistic regressions to evaluate the association of the inflammatory score with the presence of resistant hypertension

	OR (95%CI)	p-value
Model 1		
IS	1.20 (1.02-1.38)	0.02
Model 2		
IS	1.10 (0.92-1.28)	0.35
BMI (Kg/m^2)	1.12 (1.05-1.20)	< 0.01
Model 3		
IS	0.97 (0.80-1.18)	0.73
WC (cm)	1.04 (1.01-1.07)	0.01
Model 4		
IS	1.00 (0.84-1.19)	0.96
FM (Kg)	1.08 (1.04-1.13)	<0.01

All models were adjusted for age, gender and race. IS: inflammatory score; BMI: body mass index; WC: waist circumference; FM: fat mass.

been suggested to be involved.[28-30] Interestingly, impaired microvascular function in obese subjects was normalized one year after a gastric bypass surgery, and it was also associated with BP reduction.[31] Elevated levels of free fatty acids lead to endothelial dysfunction by reducing the production of NO, and increasing endothelin-1 vasoconstrictor tone and the release of pro-inflammatory cytokines[32] – which is an early hypertension-related factor associated with future cardiovascular events.[33,34]

Our findings showed that the association of IS and RHTN was abolished when the influence of body fat parameters was considered. Moreover, the IS was no longer significant after exclusion of obese subjects from both groups (data not shown). Our proposed score revealed its high dependence on obesity in the RHTN population, although this is expected since it is well-known these subjects are predominantly obese/overweight, as we found in our study – prevalence of 88%. Accordingly, the IS may reflect the inflammatory process underlying RHTN in an obesity-dependent manner, with the potential to be a clinical prognosis tool providing cardiovascular risk stratification in these obese subjects. On the other hand, we recognized that the design of this study is not sufficient to infer a temporal or cause-effect relationships. We also suggest that once obesity is established and hypertension is manifested, high BP may also contribute to further activation of inflammatory process. Thus, a vicious circle is created with both conditions – hypertension and obesity – that reinforces each other through inflammatory pathways.

Pharmacological or non-pharmacological treatments may affect inflammatory cytokines/adipokines. Studies have indicated that simvastatin reduces plasma levels of TNF-alpha and IL-6.[35,36] Antihypertensive drugs such as candesartan,[37] enalapril,[38] and mineralocorticoid receptor antagonist have also been shown to reverse proinflammatory cytokines.[39] Indeed, exercise and lifestyle modification reduced IL-8 levels in subjects with the metabolic syndrome,[40] while significantly increased adiponectin levels in obese patients.[26] Nevertheless, although these potential sources of variability may be present, they probably did not affect our findings since RHTN subjects had a high IS even though they used a greater number of antihypertensive agents. The use of individualized care also justifies the lack of standard therapy, and due to ethical issues, our subjects could not be assessed withdrawing the drugs. Finally, in a perspective of therapy approach, anti-inflammatory drugs or anticytokine molecules targeting the immune system, such as minocycline, can be attractive and of great interest in clinical setting to treat hypertension and prevent its cardiovascular complications, as supported by previous works.[41-43]

Some limitations should be mentioned. Since the population studied in this study is a convenience sample, with no sample size calculation, we recognize that our findings may not reflect the characteristics of the general population. Bias may also be present by comparing populations from different centers. It is worth mentioning that inflammatory process is quite complex and to measure its mediators is even more challenging since (i) it presents high costs, (ii) is still unavailable in clinical practice, and (iii) cutoff values may have heterogeneous profiles, which make the reproducibility more difficult. Even though, testing specificity and sensitivity in different populations are mandatory in order to guarantee a reliable score. Finally, this proposed score may change if the number of pro-inflammatory cytokines and/or anti-inflammatory cytokines changes.

Conclusion

In conclusion, our findings suggest that the IS, addressing many circulating cytokines/adipokines, may provide clinically important information to complement cardiovascular risk stratification in obese RHTN subjects. Moreover, our proposed score seems to be highly dependent on obesity-related hypertension. It is necessary to validate this score in larger populations in order to allow its use safely in clinical practice.

Author contributions

Conception and design of the research and writing of the manuscript: de Faria AP; acquisition of data: de Faria AP, Ritter AMV; analysis and interpretation of the data and critical

revision of the manuscript for intellectual content: de Faria AP, Ritter AMV, Gasparetti CS, Corrêa NB, Brunelli V, Almeida A, Pires NF, Modolo R, Moreno Junior H; statistical analysis: de Faria AP, Modolo R; obtaining funding: de Faria AP, Ritter AMV, Moreno Junior H.

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 Faculdade de Ciências Médicas da Universidade Estadual de Campinas under the protocol number 188.161/2013; CAAE: 11189712.8.0000.5404. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Biomarker-based Inflammatory Score in Obese Patients with Resistant Hypertension

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Short Editorial relate to the article: Proposed Inflammatory Score of Circulating Cytokines/Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters

Resistant arterial hypertension (RAH) is defined, according to the American Heart Association Scientific Position of 2018,[1] as well as observed in the I Brazilian Position of RAH in 2012,[2] when an individual's blood pressure (BP) remains elevated above the blood pressure target, in spite of the use of three antihypertensive drugs of different therapeutic classes, commonly a long-acting dihydropyridine slow-calcium-channel antagonist drug; a renin-angiotensin-aldosterone system (RAAS) blocker, which may be an angiotensin II converting-enzyme inhibitor or angiotensin II AT_1 receptor blocker; and an appropriate diuretic, all administered at the maximum doses or at the highest possible tolerated doses, and in accordance with the prescribed administration intervals. These patients are considered to be at greater risk of cardiovascular and renal morbidity and mortality;[3] more likely to have adverse events in response to drug therapy, usually dose-related; a secondary cause of hypertension should be ruled out in this group of individuals, because its prevalence is significantly higher than in the nonresistant hypertensive population.[1,2] The controlled RAH is also currently recognized as that in which patients using four or more medications reached the blood pressure target; and refractory AH, an entity that has a different pathophysiology from RAH, when even the four drugs are not enough to control it.[4] According to this new classification, patients with pseudohypertension should be excluded, that is, it is mandatory for diagnostic confirmation to verify adherence and tolerance to medication; to rule out white-coat hypertension; and thus, it is crucial to perform systematized blood pressure measurements outside the office environment through Ambulatory BP Monitoring (ABPM) or Home BP Measurement (HBPM); and finally, the use of a correct and reliable BP measurement technique.[1,2,4,5]

Even in primary AH, the existence of a systemic inflammatory process, albeit a subclinical one, is recognized and this condition has been identified with higher intensity in cardiovascular and renal diseases, such as RAH and chronic kidney disease.[6] Specifically in the case of RAH, which is a multifactorial and polygenic entity, often associated with metabolic diseases that occur with insulin resistance, such as diabetes and obesity, inflammatory processes promoted by mediators may be involved, leading to the important endothelial dysfunction of the microvasculature and increased oxidative stress.[7]

Biomarkers, in turn, are quantifiable characteristics of the biological processes that can be measured with accuracy and reproducibility and may or may not correlate with clinical symptoms.[8]

In recent years, the search for these mediators that may be involved in the prediction, initiation, development, diagnosis, progression and follow-up of AH therapeutic efficacy has been intense and of great value, as the amount of knowledge increases.

Even in Brazil, a recent study has shown that patients with severe and uncontrolled AH have associated microvascular dysfunction, as well as high levels of C-reactive protein and endothelin (in patients not using statins).[9]

The article, "*A Proposed Inflammatory Score of Circulating Cytokines/Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters*" published in this issue,[10] brings good news about the role of inflammatory cytokines and adipokines (TNF-α, IL-6, IL-8, IL-10, leptin and adiponectin) that may be implicated in the pathophysiology of RAH. Based on the measurement of these biomarkers, it was possible to construct an inflammatory score that correlated more with the presence of overweight and obesity than with hypertension itself. The reason for these findings is possibly the production of these substances by the visceral adipose tissue, which becomes resistant to insulin and leptin causing immune responses that, in turn, activate inflammatory, prothrombotic and vasoconstriction cascades with sympathetic nervous system hyperactivity, sodium retention and RAAS activation, thus, occurring simultaneously with AH treatment resistance.[11,12]

The interest in the measurement of biomarkers can be very useful to understand all the variables of the hypertension phenomenon, particularly regarding its pathogenesis.[7] It should be considered, however, that these measurements are not yet routinely available in clinical practice, not even in specialized AH centers, as they are expensive, have their use still restricted to research; have not been tested yet in a large scale survey from an epidemiological point of view; and require technical expertise so that their results are reliable. Understanding their roles, degrees of accuracy and reproducibility, as well as the correlation with cardiovascular and renal outcomes, is a task that still depends on future studies.

Despite the aforementioned difficulties, one can say we are moving towards the measurement of these biomarkers in a systematic way, as they gain more credibility and availability. Based on that, the construction of scores can help in the detection of situations of incipient inflammation, where it would be possible to perform early risk stratification with consequent timely interventions.

Keywords

Hypertension/physiopathology; Obesity; Hypertension/adverse effects; CitoKyines; AdipoKynes; Biomarkers, Pharmacological.

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Therefore, it is expected we can better understand the pathophysiology of resistant hypertension in the presence of obesity and the biological phenomena that culminate in oxidative stress, inflammation and endothelial microvascular dysfunction. The study published in this issue contributes qualitatively to this understanding.

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Prevalence of Lens Opacity in Interventional Cardiologists and Professional Working in the Hemodynamics in Brazil

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Abstract

Background: **Posterior subcapsular cataract is a tissue reaction commonly found among professionals exposed to ionizing radiation.**

Objective: **To assess the prevalence of cataract in professionals working in hemodynamics in Brazil.**

Methods: **Professionals exposed to ionizing radiation (group 1, G1) underwent slit lamp examination with a biomicroscope for lens examination and compared with non-exposed subjects (group 2, G2). Ophthalmologic findings were described and classified by opacity degree and localization using the Lens Opacities Classification System III. Both groups answered a questionnaire on work and health conditions to investigate the presence of risk factors for cataract. The level of significance was set at 5% ($p < 0.05$).**

Results: **A total of 112 volunteers of G1, mean age of 44.95 (±10.23) years, and 88 volunteers of G2, mean age of 48.07 (±12.18) years were evaluated; 75.2% of G1 and 85.2% of G2 were physicians. Statistical analysis between G1 and G2 showed a prevalence of posterior subcapsular cataract of 13% and 2% in G1 and G2, respectively (0.0081). Considering physicians only, 38% of G1 and 15% of G2 had cataract, with the prevalence of posterior subcapsular cataract of 13% and 3%, respectively ($p = 0.0176$). Among non-physicians, no difference was found in the prevalence of cataract (by types).**

Conclusions: **Cataract was more prevalent in professionals exposed to ionizing radiation, with posterior subcapsular cataract the most frequent finding. (Arq Bras Cardiol. 2019; 112(4):392-399)**

Keywords: **Cataract/surgery; Radiation,Ionizing; Cardiologists; Hemodynamics; Occupational Risks; Radiation,Protection.**

Introduction

In the last years, due to considerable increase in the complexity of diagnostic and therapeutic procedures in cardiology, radiology and interventional neurology, health professionals have been increasingly exposed to ionizing radiation. This has been particularly seen in some areas, including interventional cardiology.[1] With the development of new therapeutic devices and adjuvant therapy, cardiologists have been involved in even more complex and longer procedures, requiring longer exposure to ionizing radiation.[2]

Routine, continuous exposure to radiation may cause deleterious effects on human body by direct or indirect effect on the cells, causing physiological and/or functional damage to the organs. For any radiation dosage, there is the risk of neoplasm and cell death, with a direct relationship between the dose and the risk.[3,4]

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The lens is one of the most sensitive tissues to ionizing radiation. Studies have suggested a significant risk of changes in the lens in populations exposed to low radiation doses. These populations include patients undergoing computed tomography,[5] astronauts,[6,7] radiologic technologists,[8] patients undergoing radiotherapy,[9] atomic bombing survivors,[10,11] and Chernobyl survivors.[12,13] The most common change in the lens reported in these studies was lens opacity classified as posterior subcapsular cataract (PSC).[14] Considering health professionals, studies have shown higher prevalence of this type of cataract among individuals working in interventional radiology.[15-18]

In 2011, the International Commission for Radiological Protection (ICRP) revised radiation threshold levels that may cause lens damage, and reduced the occupational dose limits, aiming to reduce the incidence of cataract induced by radiation among health professionals.[19]

During last years, interventional cardiology has exponentially increased in Brazil; however, so far, there is no data available on the prevalence of lens opacity among exposed professionals. Therefore, the aim of the present study was to evaluate the prevalence of cataract in interventional cardiologists (ICs) and professionals working in hemodynamics and possible factors that could minimize the risk.

Methods

Subjects

Eligible participants were recruited at health conferences health. Inclusion criteria were conference attendance and signing of the consent form. Exclusion criteria were – previous ocular surgeries, including cataract, glaucoma, refractive and retina surgeries; chronic use of ocular topical medication; diabetes mellitus; chronic use of corticosteroids and systemic arterial hypertension.

Logistics

All individuals included in the study were volunteers who self-referred to the investigators expressing their willingness to participate in the study. The investigators built an exhibition stand at two medical conferences, so that the attendees had easy, fast access to it.

The individuals included in the study were allocated into one of two groups – exposed to ionizing radiation (G1) and not exposed to ionizing radiation (G2). G1 was composed of ICs and health professionals in the field of cardiac hemodynamics from several regions of Brazil, who attended the annual congress of the Latin American Society of Interventional Cardiology (SOLACI) and the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI) that was held in Rio de Janeiro on June 08th-10th, 2016. G2 was composed of cardiologists not exposed to ionizing radiation, attending the annual congress of the Brazilian Society of Cardiology held in Fortaleza on September 23rd-25th, 2016.

Clinical assessment and ophthalmologic examination

All participants were interviewed by one of the investigators who used a detailed questionnaire on demographic data, occupational practices that may be subjected to radiation exposure (use of radiation protection devices, number of years of work, types of procedures performed, among others) and coexisting diseases.

Ophthalmologic examination was performed using slit lamp examination by two experienced ophthalmologists, after the instillation of topical ocular medication (mydriacyl), which allows examination of the whole lens. The findings were described and classified by opacity pattern and degree according to the *Lens Opacities Classification System III* (LOCS III).[20] It consists of the classification of lens opacity by its pattern as cortical, nuclear, and posterior subcapsular, and by its severity as grade 1-6.

Statistical analysis

A convenience sample was used in the study. Continuous variables were described as mean and standard deviation or median. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to test the normality of data distribution. Categorical variables were compared by the chi-square test. When more than 20% of the cells had expected frequency lower than 5, we used the Fisher's exact test (2 x 2 table) or the likelihood ratio test. The level of significance was set at 5% ($p < 0.05$). The SPSS (*Statistical Package for the Social Sciences)* version 19.0 was used of the analysis.

Results

A total of 278 volunteers agreed to participate in the study, 156 in the radiation-exposed group (G1) and 122 in the non-exposed group (G2). Forty-four volunteers of G1 and 34 of G2 were excluded, and thus 112 participants in G1 and 88 in G2 were included (Figure 1). Mean age was 44.95 ± 10.23 years in the G1 and 48.07 ±12.18 years in the G2 ($p = 0.0264$). Sociodemographic data are described in Table 1.

Regarding the ophthalmologic findings, 37 volunteers (33%) in G1 and only 14 (16%) in G2 had some degree of lens opacity ($p = 0.0058$). When analyzed by the type of cataract, no difference was found in the frequency of cortical cataract, with 15 individuals in G1 (13%) and 8 in G2 (9%) ($p = 0.3438$). However, PSC cataract was significantly more frequent in G1 ($n = 14$, 13%) than in G2 ($n = 2$, 2%) ($p = 0.0081$). Lens opacity in cortical + subcapsular was found in 28 volunteers in G1 (25%) and 10 in G2 (11%) ($p = 0.0147$).

Analysis by occupational category showed a mean age of 46.76 ± 9.99 years among ICs and 48.75 ± 12.32 in the control group, with no difference between the groups ($p = 0.1358$). Lens opacity was found in 32 ICs (38%) and 11 clinical cardiologists (CCs) (15%) ($p = 0.0011$). PSC cataract was found in 11 ICs (13%) and 2 CCs (3%) ($p = 0.0176$). The presence of cortical cataract + subcapsular cataract was found in 28% of ICs ($n = 24$) and 9% of CCs ($n = 7$) ($p = 0.0025$). No statistically significant difference was found in the frequency of cortical cataract (15% versus 7%, $p = 0.0848$).

In the group of non-physicians exposed to radiation, 5 participants showed some degree of lens opacity (18%), which was also detected in 3 control non-physicians (23%) ($p = 0.7357$). Subcapsular cataract was found in 3 radiation-exposed non-physicians, and in none control non-physicians ($p = 0.2114$).

Regarding the eye affected, cataract in the left eye was more common, with SCP cataract observed in 50% of the exposed individuals, whereas cataract in the right eye was identified in 14% of exposed participants. Cataract in both eyes was affected in 36% of these individuals. Cortical cataract was also more frequent in the left eye (46% of exposed subjects), whereas the right eye was affected in 27% of the cases.

In the control group, no eye was more prevalent than the other in the cases of cataract, with similar frequency in both eyes as well as cataract type – cortical and subcapsular – both bilateral in 60% of cases.

Most ICs reported to perform 50 procedures per month (38.1%) and from 50 to 100 procedures (43.7%) per month. Eighty-two percent of the ICs reported to perform diagnostic procedures within 30 minutes, using from four to six X-ray energy projections (46.5%) and 15 frames per second (70.9%). For therapeutic procedures, 66.1% of ICs reported that the procedures lasted 30-60 minutes, with delivery of x-ray energy in pulses (rather than in a continuous dose).

The number of years of work in hemodynamics was not a statistically significant determinant for the occurrence of

Table 1 – Sociodemographic data of the volunteers

		G1	G2
Age (mean)		44.95 (±10.23)	48.07 (±12.18)
Age range	<36	28 (21.9%)	18 (20.5%)
	36-45	45 (35.4%)	14 (15.9%)
	46-55	37 (32.7%)	29 (33%)
	56-65	10 (8.8%)	22 (25%)
	>66	4 (3.5%)	5 (5.7%)
Sex	Female	24 (21.4%)	14 (15.9%)
	Male	88 (78.6%)	74 (84.1%)
Region	Middle-west	7 (6.4%)	10 (11.4%)
	North	6 (5.5%)	5 (5.7%)
	Northeast	20 (18.2%)	22 (25%)
	South	11 (10%)	11 (12.5%)
	Southeast	66 (60%)	40 (45.6%)
Occupation	Nurse	21 (18.6%)	1 (1.1%)
	Physician	85 (75.2%)	75 (85.2%)
	Nurse technician or nursing assistant	3 (3.1%)	11 (12.5%)
	Technician or technologist	3 (2.7%)	1 (1.1%)
Total		112	88

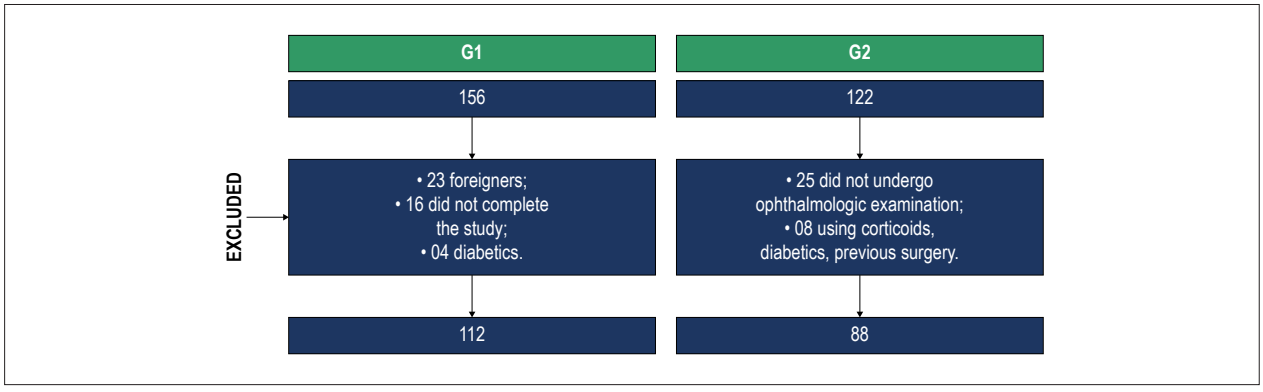

Figure 1 – *Flowchart of the study.*

lens opacity; 62% of the professionals reported less than 20 years of work years, and half of them reported between 5 and 10 years of work in the field. Although we did not find a correlation between damage and work experience time, lens opacity could occur early in those with lower time of work experience. This reinforces the importance of the use of personal and collective protective devices.

Results of the use of personal and collective protective devices reported by the physicians are described in Figures 3,4 and 5.

Regarding the use of lead glasses (with or without lateral protection) 40% of the radiation-exposed volunteers reported to be regular users, although this result did not show a statistically significant correlation with the frequency of lens opacity. The same was observed with the routine use of lead shielding, reported by approximately 30% of the professionals. The reasons for the low frequency of routine use of protective devices, reported by participants, are graphically illustrated in Figures 1-3, such as – ergonomic discomfort, unavailability of protective device, among others.

Discussion

ICs and other professionals that work in hemodynamics are routinely exposed to ionizing radiation and hence at higher risk for the deleterious effects of this exposure. Eye lens are one of the most sensitive organs to continuous radiation exposure. Many studies in several countries have shown a higher prevalence of cataract in professionals exposed to

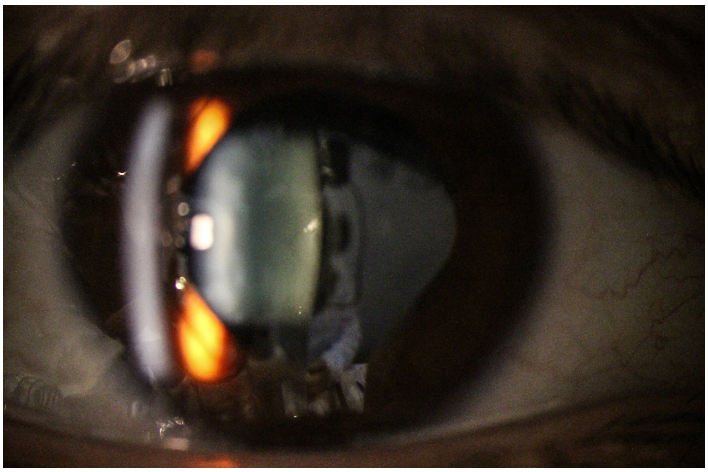

Figure 2 – *Subcapsular cataract in a young interventional cardiologist.*

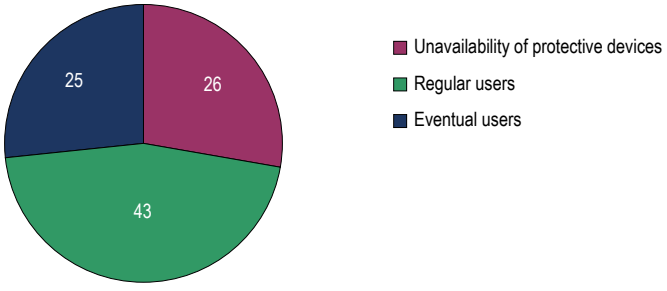

Figure 3 – *Frequency (%) of use of lead shields placed laterally to the fluoroscopy table by interventionists (n = xx).*

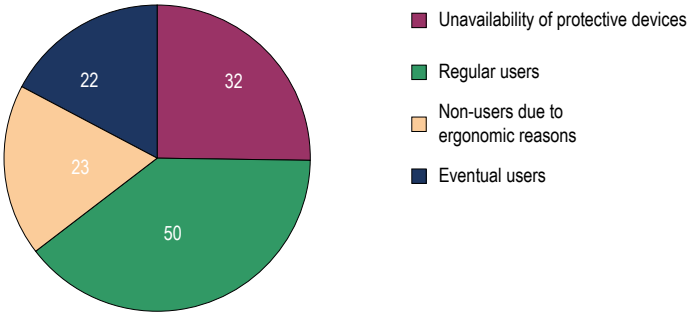

Figure 4 – *Frequency (%) of use of lead glasses by interventionists (n = xx).*

radiation, with the PSC type more frequently correlated with ionizing radiation.[21-23]

The increase in the prevalence of cataract was identified with the increase in radiation doses and previously reported in literature review studies. Uncertainties about a radiation threshold that could induce lens opacity still exist. The latency period between irradiation and development of lens opacity is uncertain.[24]

The LOCS III grading system is considered relevant in these types of studies and have been used to compare recent data obtained from occupationally exposed individuals and atomic bomb survivors.[24]

In Brazil, interventional cardiology has played a prominent, internationally recognized role. Nevertheless, so far, there is no study on the prevalence of cataract among professionals or even in several areas of interventional

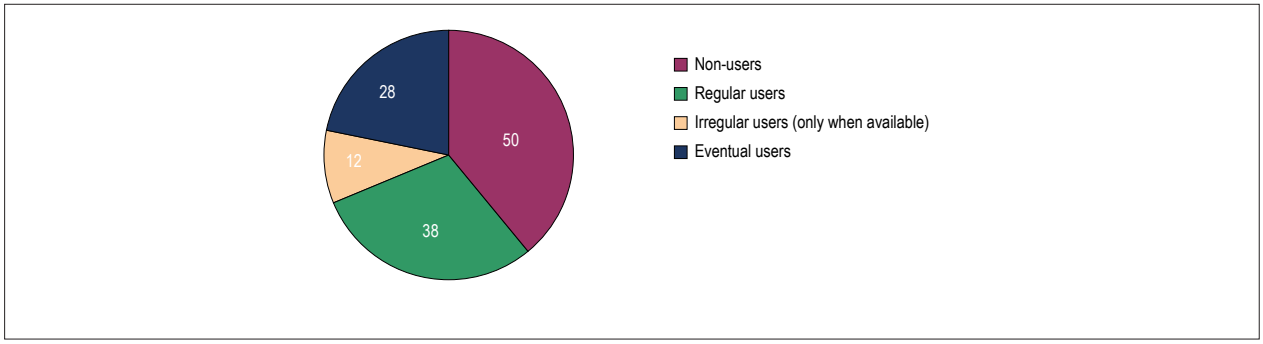

Figure 5 – *Frequency (%) of use of suspended radiation protection by interventionists (n = xx).*

radiology. The present study aims at filling this gap, providing nationwide information on the theme.

Our findings showed that interventional cardiology professionals have significantly more lens changes than non-exposed individuals (p = 0.0058), although the non-exposed groups were significantly older. Sucapsular cataract was more frequent in the exposed group (p = 0.0081) than in controls, confirming previously published results.[18,21,23]

The other types of cataract (cortical and nuclear), when separately analyzed, were not prevalent in the exposed group, corroborating results from previous studies.[23] On the other hand, the prevalence of subcapsular + cortical cataract was higher in the exposed than in control group.

Our findings showed a higher prevalence of cataract in the left eye than in the right eye among participants. This was also reported in previous studies showing that, during interventional procedures, the left side of the brain receives higher doses of radiation, due to positioning of the professional during the tests.[25,26]

Analysis by occupational category highlighted a higher prevalence of lens opacity, of any type, in the exposed group (38% of ICs) and in clinicians that were not exposed to radiation (15%). PSC cataract, a lens opacity related to radiation exposure, was found in 13% of ICs and in only 3% of clinicians.

Elmaraezy et al.,[27] in a metanalysis recently published, found a cataract prevalence, of any type, of 36% among ICs, similar to our results. In this same meta-analysis, all studies included reported a significant prevalence of subcapsular cataract in ICs, with no difference between the prevalence of cortical and nuclear opacity.

In the French O'CLOC study (Occupational Cataracts and Lens Opacities in interventional Cardiology), Jacob et al.[21] found a prevalence of 17% of PSC in ICs and of 5% in the control group, similar to our findings.[21] It is worth pointing out that, in the O'CLOC study, the control group was composed of non-physicians, differently from our study, in which radiation-exposed physicians were compared with medical cardiologists (non-interventionists), similar in number and age, but not exposed to ionizing radiation.

Vañó et al.[18] found a significant prevalence of PSC cataract among interventional catheterization professionals – physicians, nurses and technicians. We did not find a significantly greater prevalence of cataract in radiation-exposed non-physicians when compared with the control group. This can be mainly explained by the small number of non-physicians included in the study (25% nurses and 3% nursing assistants), professional categories and years of work in catheterization laboratory.

Professional activity measured in years of work and number of procedures performed annually can be predictors of increased risk of damage, as we tend to associate them with increased cumulative dose. However, we should consider that the use of protective devices and the ability of professionals in performing the procedures may significantly change these cumulative doses. Some authors have shown that there is no clear relationship between the incidence of lens opacity and number of procedures, as in the study by Jacob et al.[21] in which the number of procedures varied from 50 to 1,267, with a mean of 542 ± 312 procedures per year. In their study,[21] the risk for cataract was lower in regular users of lead glasses as compared with irregular users, without statistical significance though.[21]

In our study, only 40% of the radiation-exposed volunteers reported to wear lead glasses on a regular basis, which make our sample size (considering both exposed and non-exposed groups) even smaller. Besides, variables such as age, work experience, number of procedures performed, lead shielding, among others make it difficult to establish any association between the regular use of protective device and the findings. Also, there are no data regarding occupational dose. Studies have highlighted the importance of the accuracy of dosimetry measurements in clinical practice to determine correlations of radiation doses and effects.[28,29] In the present study, we could not estimate the radiation dose received by the participants exposed. Also, by interview of participants, we found that only 63.8% of them used personal radiation dosimeters over the lead (chest) aprons for their own control, although this device is the most reliable way to measure cumulative radiation over a month, and its usage is regulated by current radiation protection legislation.[30,31]

Variations in individual doses recorded in dosimeters can help in the understanding of conditions associated with increased doses and establishment of safer conditions during the procedures. Safety promotion, by means of reduction of radiation doses delivered to the patient and the staff, is a responsibility of the operator. Fluoroscopy and cinefluorography time should be controlled, as well as the total cumulative dose for the patient (air kerma) should be monitored and registered at the end of the test, For dose reduction, adequate collimation and use of virtual collimation are essential, in addition to other factors, including virtual expansion and geometric adjustments may affect the

distribution of scattered radiation. The use of mobile radiation shields, including suspended radiation protection and lead shields placed laterally to the fluoroscopy table, are relevant strategies to reduce individual radiation doses, and should be used regardless of gantry angulations. The adoption of angiography device in cardiovascular procedures in terms of radiologic protection was summarized in a recent study that describes all adjustments necessary to minimize the radiation doses delivered to patients and professionals.[32]

Although the use of protective lead glasses was recognized as important protective devices by radiation-exposed volunteers, the reason for their low frequency of use, according to them was mainly their "weight" and "difficult adjustment to the face". Thus, ergonomic improvements should be made to encourage the use of protective lead glasses on a routine basis.

Evidence of early occurrence of lens opacity has been discussed in the scientific community; however, the fact that participants have received a radiation dose lower than the occupational threshold (mean of 5 years, 20 mSy/year) can be attributed to the fact that they did not use personal protective apparatus regularly.[18]

Despite the consistent findings of our study, some limitations should be noted. There are some uncertainties regarding the use of personal and collective protective devices that cannot be measured, since these data were obtained by interview. Nevertheless, despite the uncertainties of dose estimates using a radiation dosimeter, an effective control of the doses enables the correlation of dose and tissue damage. In our study, this correlation could not be evaluated since information on individual occupation dose were not available.

Conclusions

In the present study, we detected early occurrence of lens opacity in Brazilian interventional cardiologists, who attended the annual congress of the SOLACI/SBHCI.

The questionnaire administered by interview allowed us to obtain information about the current use of radiation protective devices and to detect the need for strategies that reinforce the importance of fostering a culture of radiologic protection among professionals exposed to radiation.

Acknowledgment

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Author contributions

Conception and design of the research: Barbosa AHP, Medeiros RB; acquisition of data: Barbosa AHP, Medeiros RB, Corpa AMR, Higa FS, Souza MT, Barbosa PL, Moreira AC; analysis and interpretation of the data: Barbosa AHP, Medeiros RB, Corpa AMR, Higa FS; statistical analysis: Barbosa AHP; obtaining funding: Barbosa AHP, Lemke VMG, Cantarelli MJC; writing of the manuscript: Barbosa AHP, Medeiros RB, Corpa AMR, Cantarelli MJC; critical revision of the manuscript for intellectual content: Barbosa AHP, Medeiros RB, Quadros AS, Cantarelli MJC.

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 Unifesp/EPM under the protocol number 1.550.372. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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The Radiological Exposure from the Perspective of the Interventional Cardiologist

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Short Editorial related to the article: Prevalence of Lens Opacity in Interventional Cardiologists and Professional Working in the Hemodynamics in Brazil

The interventional cardiology represents an area in constant development and it has advanced considerably in the treatment of both congenital and acquired cardiovascular diseases. It has a safe and effective role in the correction of septal and shunt[1] congenital abnormalities, valve diseases, especially the percutaneous treatment of the aortic stenosis in patients with high or intermediate[2,3] surgical risk and, more recently, it has also moved towards the mitral and tricuspid apparatuses.[4,5]

The percutaneous coronary intervention has stood out in the treatment of lesions of the left main coronary artery and multivessel coronary artery disease**,** in the absence of high anatomical complexity,[6] reaching now the frontier of chronic occlusions with consistent results.[7]

The technical challenges impose greater risks to the occupational health of those involved in the daily routine of a cardiac catheterization laboratory, especially the interventional cardiologists. Beyond musculoskeletal or orthopedic abnormalities, related to wearable plumbing aprons, current evidence suggests that the extended radiological exposure would cause a fourfold and a half greater risk of cancer and a nine fold greater risk of cataract among these professionals.[8] Besides, chronic low doses of ionizing radiation could promote changes in the endothelial cellular biology, resulting in vascular damage, subclinical atherosclerosis and a greater prevalence of cardiovascular disease.[9]

In the present issue of the *Arquivos Brasileiros de Cardiologia*, Barbosa AHP et al.,[10] describe, in a pioneering way, the deleterious effects of the radiological exposure in a voluntary sample of interventional cardiologists, with nationwide representativity. In the exposed group, the prevalence of subcapsular posterior cataract, the most frequent variant found in this scenario, was 13%, compared to 2% in the control group (p=0.0081), in consonance with the findings from the international literature. In an alarming way, the authors report a lower than the desired and recommended frequency of the use of adjustable positioning shields, such as suspended screen and lead strips positioned at the side of the examination table, as well as protective goggles. The implementation of such preventive actions has proved to reduce radiological exposure to the operators.[11]

The risks inherent in the chronic exposure to the ionizing radiation certainly characterize a topic of extreme relevance and it is necessary to take them into account in the professional quality standards that guide the speciality, as well as in the employment relations. Individually, how many professionals would abdicate this area of medicine because of this hazard? As an inference to this questioning, we have witnessed a recent paradigm shift in relation to the vascular access in the performance of coronary artery invasive procedures, with the preferential choice for the radial technique in lieu of the femoral one. This strategy has benefitted the patients, with the reduction of the complications regarding the site of the arterial puncture, the rate of major bleeding as well as morbidity and mortality, but at the cost of a greater and proved radiological exposure to the operator.[12]

May the interventional cardiologists have the last word.

Keywords

Cardiology, Interventional/trends; Heart, Defects, Congenital; Percutaneous Coronay Intervention; Cardiovascular Diseases/prevention and control; Radiation Exposure/adverse effects.

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Comparative Analysis between Transferred and Self-Referred STEMI Patients Undergoing Primary Angioplasty

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Abstract

Background: Studies have shown the benefits of rapid reperfusion therapy in acute myocardial infarction. However, there are still delays during transport of patients to primary angioplasty.

Objective: To evaluate whether there is a difference in total ischemic time between patients transferred from other hospitals compared to self-referred patients in our institution.

Methods: Historical cohort study including patients with acute myocardial infarction treated between April 2014 and September 2015. Patients were divided into transferred patients (group A) and self-referred patients (group B). Clinical characteristics of the patients were obtained from our electronic database and the transfer time was estimated based on the time the e-mail requesting patient's transference was received by the emergency department.

Results: The sample included 621 patients, 215 in group A and 406 in group B. Population characteristics were similar in both groups. Time from symptom onset to arrival at the emergency department was significantly longer in group A (385 minutes vs. 307 minutes for group B, $p < 0.001$) with a transfer delay of 147 minutes. There was a significant relationship between the travel distance and increased transport time ($R = 0.55$, $p < 0.001$). However, no difference in mortality was found between the groups.

Conclusion: In patients transferred from other cities for treatment of infarction, transfer time was longer than that recommended, especially in longer travel distances. (Arq Bras Cardiol. 2019; 112(4):402-407)

Keywords: ST Elevation Myocardial Infarction/complications; Angioplasty, Balloon, Coronary/methods; Myocardial Reperfusion/methods; Fibrinolytic Agents; Intensive Care Units.

Introduction

For patients presented within 12 hours of ST-segment elevation acute myocardial infarction (STEMI), reperfusion therapy with thrombolytic agent or percutaneous transluminal coronary angioplasty (PTCA) should be provided as early as possible.[1] A shorter time-to-treatment in infarcted patients is associated with greater myocardial salvage and has a positive effect on ventricular function and mortality.[2,3]

PTCA is the therapy of choice for coronary reperfusion, if initiated within 90 minutes from AMI diagnosis or 120 minutes for patients referred for PTCA at another center.[4,5] Nevertheless, some factors contribute to increasing time-to-treatment: a) unawareness of AMI-related signs and symptoms by the patients; b) unawareness of the benefits of a rapid reperfusion therapy; c) lack of healthcare facilities adequately equipped to early detect patients with STEMI; d) delay in defining the most appropriate reperfusion therapy and patient transportation delay.[6]

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For example, in hospitals for less complex cases, PTCA is not available, and the use of thrombolytic therapy or the transfer of patients to more specialized hospitals cause a delay in AMI treatment.

In many countries, an integrated care system for STEMI is already available.[7] Strategies aimed at reducing the time to STEMI diagnosis and treatment are needed. However, data on inter-hospital transfer of patients in Brazil are scarce. The present study aimed at determining whether there are differences in total ischemic time between patients referred from other hospitals and those who self-referred, based on current guidelines' recommendations.[8-10]

Methods

Study design

This was a historical cohort study.

Characteristics of inter-hospital transfer of patients

The normal procedure for accepting a patient's transfer for treatment of STEMI involves the receipt of an electrocardiography report (ECG) confirming the diagnosis of STEMI (previously by fax, and recently by e-mail). This would avoid costs in the health system with incorrect diagnosis and unnecessary referral to the emergency department.

Subjects

Patients with diagnosis of STEMI registered in the database of the Institute of Cardiology of the University Foundation of Cardiology (IC-FUC) were assessed and allocated to one of two groups – Group A, patients whose names and electrocardiographic results were listed in the electronic mailbox of the emergency department, confirming the approximate time of contact and indicating the place of origin – and Group B, self-referred patients (all others).

Transfer time (min) was calculated by subtracting the time and the day the message (containing ECG result attached) was received from the time and day patients were admitted to the emergency department (according to medical records).

Ethical consideration

The study was registered at the research unit of the IC-FUC and approved by the local ethics committee.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range, as appropriate. Categorical variables were presented as absolute number and percentage and compared by the chi-square test and Z-test. Continuous variables were analyzed using Student's t-test for independent samples or the Wilcoxon-Mann-Whitney test, as appropriate. Normality was tested by the D'Agostino-Pearson test. Our database was constructed using Microsoft Excel 2010 software and then transferred to the IBM Statistical Package for the Social Sciences (SPSS) version 19.0.0. The SPSS software version 18.0 was used for statistical analysis. Two-tailed p-values < 0.05 were considered statistically significant.

Results

E-mail messages received by the emergency department of the IC-FUC between April 2014 and September 2015 were reviewed. ECG results showing ST-segment elevation and identification data of patients were cross-checked with data registered in the AMI database of the hospital.

During the study period, 2,532 pieces of information were excluded – 68 messages in which patients' names could not be identified, 869 ECG results of patients with non-STEMI, 381 duplicate messages, 23 "unknown hard error" messages, 491 tomography reports, 408 internal messages, and 292 ECG results of patients with STEMI that had not been referred from other hospitals or patients not registered in the AMI database.

Final sample was composed of 621 patients, 215 transferred patients (group A) and 406 self-referred (group B).

Table 1 describes characteristics of groups A and B. Both groups had similar risk factors.

Figure 1 depicts mean variation in the time elapsed from symptom onset to arrival at emergency department (delta T) and the travel distance of patients, depending on the place of origin.

Mean delta T of all patients was 334 minutes. Mean delta T of patients transferred by emergency medical services of the Secretariat of Health (group A) was 385 minutes, with a delay in transfer time of 147 minutes. Mean delta T of group B was 307 minutes (Figure 2).

Figure 3 shows a scatter plot of delta T and travel distance, with a good correlation coefficient between these variables ($R = 0.55$ and $p < 0.001$). Despite that, the graphs shows a number of cities with shorter travel distances but higher transfer times (plots above diagonal), and cities with longer travel distances but shorter transfer time (plots below diagonal).

Despite the statistical difference in transfer time, no difference in mortality was observed between the groups.

Discussion

Treatment of STEMI is considered a medical emergency, with significant mortality even in well renowned centers.[11] The main objective of the therapy is restoration of blood flow in the culprit vessel. This is achieved by administration of fibrinolytic agents to dissolve intracoronary thrombus, or by PTCA, with percutaneous recanalization of the infarct artery with or without stent implantation. In the present study, we demonstrated the difference in delta T between STEMI patients referred for PTCA and self-referred STEMI patients to the emergency department of the IC-FUC

The finding that transferred patients have longer ischemia time and a longer time to coronary reperfusion therapy is not a surprise, since in these cases there are delays in contacting

Table 1 – Characteristics of patients referred from other hospitals (group A) and self-referred patients (group B). Porto Alegre, RS, Brazil

Variable	Group A (n = 215)	Group B (n = 406)	p
Age, years*	58 (28-87)	60 (18-98)	0.50
Male sex†	145 (67)	283 (69)	0.67
Risk factors†			
Hypertension	128 (59)	251 (61)	0.69
Smoking	148 (68)	249 (61)	0.10
Dyslipidemia	67 (31)	132 (32)	0.86
Diabetes	55 (25)	96 (23)	0.64
Family history	45 (20)	109 (26)	0.11

** Data presented as median and interquartile range; † Absolute and relative frequency.*

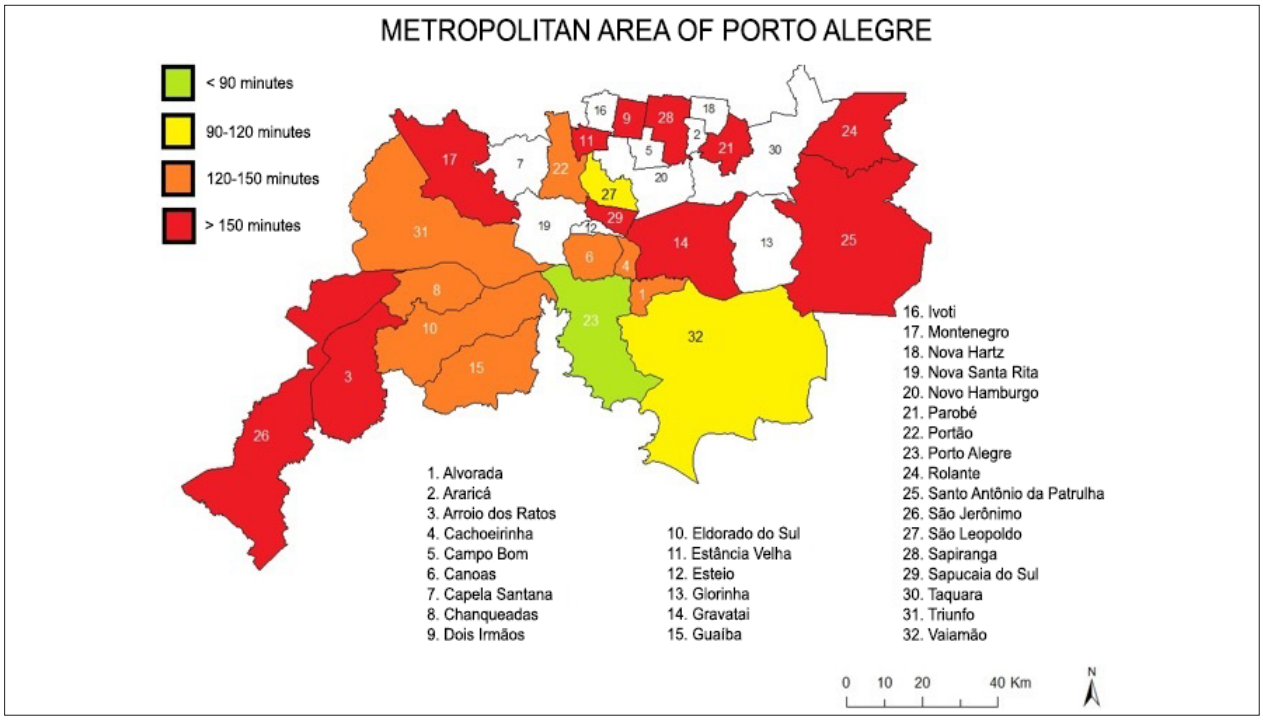

Figure 1 – *Map of the metropolitan area of Porto Alegre, illustrating the regions by names and mean patient transport time to the Institute of Cardiology, University Foundation of Cardiology (IC-FUC).*

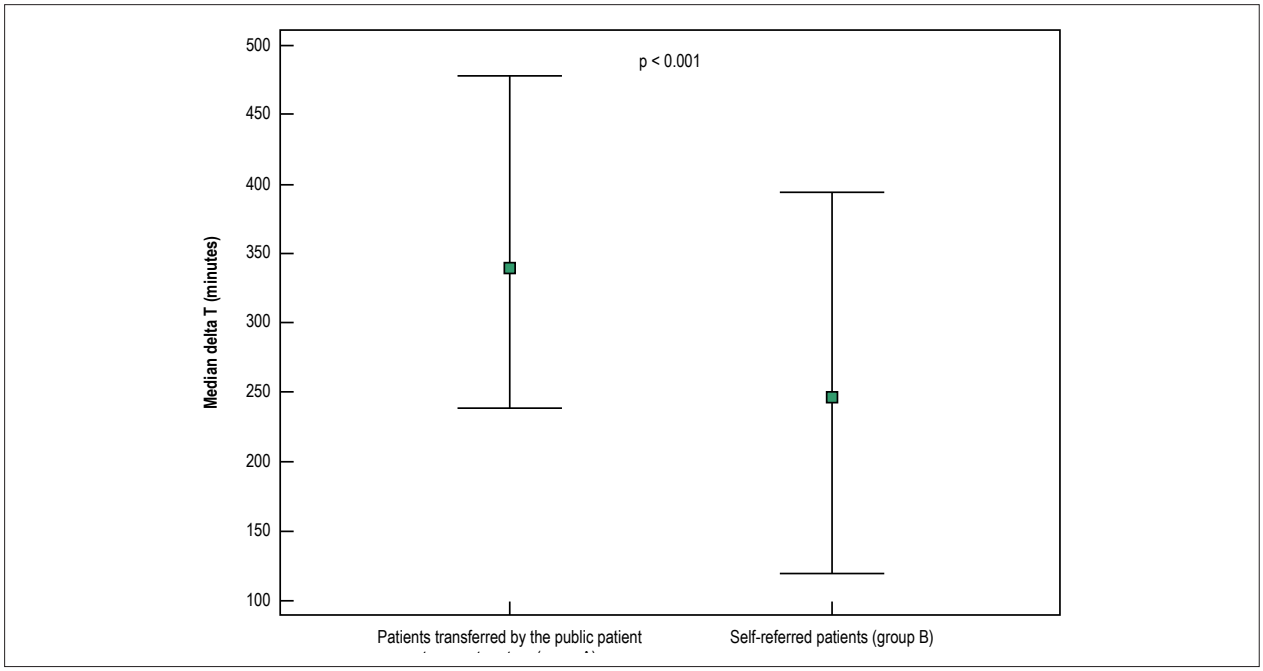

Figure 2 – *Comparison of median delta T between patients transferred from other institutions and self-referred patients.*

medical and transport services, in obtaining authorization from the emergency medical services for ambulance services and in patients' transportation itself.

According to the Brazilian guidelines, PTCA is the preferred option for coronary reperfusion, if initiated within 90 minutes from diagnosis of STEMI or within 120 minutes in case of patients referred for therapy at other centers.[8] It is worth pointing out that, in patients treated with PTCA, for each 30 minutes of delay, relative risk for mortality increases 7.5%.[12]

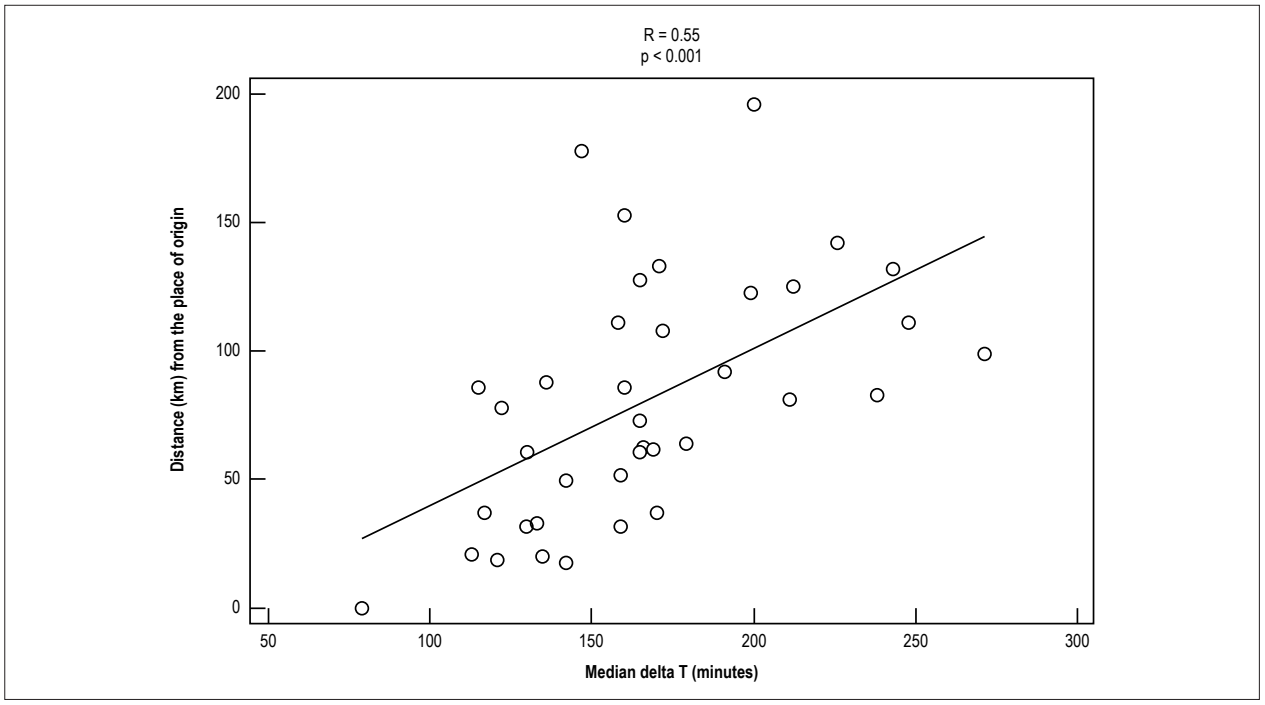

Figure 3 – *Correlation between distance from the place of origin and mean delta T (minutes).*

In a time period lower than 2 hours, primary PTCA was superior to fibrinolytic therapy in terms of severe adverse effects (death, stroke and reinfarction;[13] event rates were 8.5% vs 14.2%, respectively; p = 0.02).

The benefit of transferring STEMI patients for PTCA on in-hospital mortality, compared with onsite fibrinolytic therapy, decreased as transfer time increased. In-hospital mortality was 2.7%, 3.6% and 5.7% in PTCA group and 7.4%, 5.5% and 6.1% in fibrinolytic therapy group for delays of 0-60 minutes, 60-90 minutes and longer than 90 minutes, respectively.[14]

In our study, mean transfer time was 141 minutes, with wide variation according to patients' place of origin. In the cities of Porto Alegre, Viamão and São Leopoldo, transfer time was shorter than 120 minutes. In all other cities, however, it was longer than recommended, reducing the benefits of the immediate transport of patients for primary angioplasty.

Figure 1 more clearly illustrates the relationship between travel distance and prolonged transfer time. White areas in the map correspond to cities where no transfer of STEMI patients for primary angioplasty was registered. Therefore, patients from these areas were not included for analysis, although it is likely that their transfer times were similar to those in the cities nearby, and higher than predicted.

An arm of the GRACE study with 3,959 patients compared fibrinolytic therapy with primary angioplasty, and showed a door-to-needle time of 35 minutes and door-to-balloon time of 78 minutes. Treatment delays were associated with an increase in 6-month mortality for both therapies. For each 10-min delay in door-to-needle, mortality increased by 0.30% for patients who underwent thrombolysis, and 0.18% for those who underwent primary PCI.[15]

In patients with chest pain treated within 3 hours of symptom onset, no difference in mortality was observed between PTCA and fibrinolysis (7.2% *vs*. 7.4%). Nevertheless, in those treated between 3–12 h after symptom onset, mortality significantly increased in fibrinolysis group compared with PTCA (6.0% vs. 15.3%).[16]

In centers without catheterization facilities, i.e., when patient transfer is required, thrombolysis should be performed, since, if carried out within 3 hours of STEMI, both angioplasty and thrombolytic therapy have similar benefit on mortality. Besides, between 3 hours and 12 hours of pain onset, in places where transfer time is expected to be longer than ideal transfer time, thrombolysis should be strongly considered.

For calculation of the total ischemic time, one should consider the delay in seeking medical care, the time until AMI diagnosis, delays in patients' transfer to the catheterization laboratory, and internal delays of the referral system, from patients' enrollment to the opening of the infarct-related artery. In a previous study performed in our institution, the mean time from symptom onset to hospital admission was 90 minutes during business hours and 133 minutes outside this period.[17]

Limitations of the study

Despite the quantitative nature of delta T, this variable can be difficult to be evaluated, resulting in measurement errors. In addition, since this study consisted in a database review, there are potential biases, inherent to this type of analysis.

Conclusion

The present study shows that AMI patients transferred from other institutions have prolonged ischemic time, exceeding that recommended by the Brazilians guidelines. However, ischemic time varied largely between the cities, in a direct proportion to the distance covered. These findings can help health managers in identifying how to improve patient transport system, leading to earlier reperfusion therapy and mortality reduction.

Author contributions

Conception and design of the research: Balk M. Acquisition of data: Balk M, Gomes HB. Statistical analysis: Saffi MAL, Leiria TLL. Writing of the manuscript: Saffi MAL, Leiria TLL. Critical revision of the manuscript for intellectual content: Gomes HB, Quadros AS, Leiria TLL.

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 Instituto de Cardiologia - Fundação Universitária de Cardiologia (IC/FUC), under the protocol number 5565/18. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Time is Muscle

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Short Editorial related to the article: Comparative Analysis between Transferred and Self-Referred STEMI Patients Undergoing Primary Angioplasty

Before the 80's, the treatment of patients with *ST-segment elevation myocardial infarction* (STEMI) had as main goals the control of pain, arrhythmia and reduction of cardiac work, aiming to limit the extent of myocardial necrosis. These measures were partially effective, but the morbidity and mortality of *acute myocardial infarction* (AMI) remained high.[1]

From the findings of Dewood,[2] angiographically showing the presence of coronary occlusion by a thrombus in the culprit artery of the STEMI, strategies of reperfusion have emerged both thrombolytic therapy and primary percutaneous transluminal coronary angioplasty (PCI). The treatment of STEMI changes from contemplation to intervention.

About 50 years ago, Eugene Braunwald proposed a revolutionary hypothesis: time is muscle. It was demonstrated that the severity and extent of myocardial ischemic injury resulting from coronary occlusion could be radically altered by an adequate intervention as late as 3 hours after the coronary occlusion.[3]

The best strategy for obtaining coronary reperfusion has been a constant topic of discussion over the last decades, essentially harmed by the mistaken competitive analysis between the possibilities of getting vessel opening. Most of the time it ignores the already very well defined and clear in the World guidelines; the best strategy is that it is available within well-established deadlines, being indifferent in the first 2 hours of pain.

In a publication by Balk et al.,[4] in this edition, the authors, in a retrospective analysis of a database, comparatively analyzed the total ischemia times among patients undergoing primary PCI transferred from other hospitals (Group A = 406) compared to those who sought the service spontaneously (Group B = 215).

Even if you consider this is a retrospective study with database information, there are very important potential biases. Among these, it was highlighted that 292 patients with electrocardiogram (ECG) tracings with ST-segment elevation were not transferred or were not included in the database. How many of these would have undergone thrombolysis at the site, transferred to another center, or died while waiting? Were they the most serious?

Keywords

ST Elevation Myocardial Infarction/physiopathology; Myocardial Infarction/mortality; Myocardial Infarction/therapy; Myocardial Infarction/diagnosis; Time Factors; Survival Rate; Thrombolytic Therapy; Angioplasty.

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The subject is of great relevance and the global guidelines establish that it adopts the beneficial strategy within the limit window of transfer to primary PCI of at most 120 minutes.[5-7] In the article there is no report regarding thrombolysis in the first place of care. The average time delay for all patients in the study was 334 minutes. The average duration of symptoms of the patients transferred with emergency medical contact via the Health Department (Group A) was 385 minutes, with a delay due to the transport of 147 minutes. The average duration of symptoms of patients in group B was 307 minutes, reflecting real-world values far from those described in clinical trials.

Several non-PCI-capable hospitals are transferring patients with STEMI to a supposed primary PCI without a transport protocol that ensures timely time. The medical act is transferred to another institution and many patients come into the sad statistic of "lost chance" of reperfusion, in which many do not receive and others are treated outside the ideal time window for the best result, a fact found in the world records in which Brazil collaborates.[8]

The decision of the best strategy at the first place of care, in which the limitations of treatment and delays in the transfer were respected, had momentum with the technology for sending ECG tracings and teleconsulting. There are examples of success in the world and in Brazil[9-13] that demonstrated a reduction in mortality and greater preservation of myocardium in pre-hospital reperfusion by emphasizing the organisation of a pre-established regional network for fast transfers allowing the choice of the best treatment.

The pharmaco-invasive strategy comes as a proposal for situations where there is no guarantee of adequate transfer times and for the period outside the routine hours of the referral center for primary angioplasty. It has as great merit to offer the two therapies to the patient. Those without time for adequate transference would receive the thrombolytic therapy in the first place of care, following a pre-established protocol, and with more time would be transferred to PCI-capable center to complement the treatment with the approach of guilty artery. The STREAM[14] study demonstrated benefit and safety being this strategy adopted by the last European guideline.[15]

I agree with the authors' conclusion that their results may serve as an aid to health system managers to identify opportunities to improve but as a whole. In primary care, identifying risk groups, promoting prevention and educating for early recognition of anginous pain; In the first care sites adopt myocardial infarction protocols, when necessary with teleconsultancy, with the strategy that respects the deadlines and clinical profile, with a transfer structure (EMS) for transfer to PCI-capable centre for the most serious cases, to rescue intervention, and for therapeutic complementation in the pharmaco-invasive line. It would be the Unified National Health System (SUS) full. The winnings will be all.

The myocardium thanks.

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Efficacy, Safety, and Performance of Isolated Left vs. Right Ventricular Pacing in Patients with Bradyarrhythmias: A Randomized Controlled Trial

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Abstract

Background: Considering the potential deleterious effects of right ventricular (RV) pacing, the hypothesis of this study is that isolated left ventricular (LV) pacing through the coronary sinus is safe and may provide better clinical and echocardiographic benefits to patients with bradyarrhythmias and normal ventricular function requiring heart rate correction alone.

Objective: To assess the safety, efficacy, and effects of LV pacing using an active-fixation coronary sinus lead in comparison with RV pacing, in patients eligible for conventional pacemaker (PM) implantation.

Methods: Randomized, controlled, and single-blinded clinical trial in adult patients submitted to PM implantation due to bradyarrhythmias and systolic ventricular function ≥ 0.40. Randomization (RV vs. LV) occurred before PM implantation. The main results of the study were procedural success, safety, and efficacy. Secondary results were clinical and echocardiographic changes. Chi-squared test, Fisher's exact test and Student's t-test were used, considering a significance level of 5%.

Results: From June 2012 to January 2014, 91 patients were included, 36 in the RV Group and 55 in the LV Group. Baseline characteristics of patients in both groups were similar. PM implantation was performed successfully and without any complications in all patients in the RV group. Of the 55 patients initially allocated into the LV group, active-fixation coronary sinus lead implantation was not possible in 20 (36.4%) patients. The most frequent complication was phrenic nerve stimulation, detected in 9 (25.7%) patients in the LV group. During the follow-up period, there were no hospitalizations due to heart failure. Reductions of more than 10% in left ventricular ejection fraction were observed in 23.5% of patients in the RV group and 20.6% of those in the LV group (p = 0.767). Tissue Doppler analysis showed that 91.2% of subjects in the RV group and 68.8% of those in the LV group had interventricular dyssynchrony (p = 0.022).

Conclusion: The procedural success rate of LV implant was low, and the safety of the procedure was influenced mainly by the high rate of phrenic nerve stimulation in the postoperative period. (Arq Bras Cardiol. 2019; 112(4):410-421)

Keywords: Cardiac Pacing, Artificial; Bradycardia; Arrhythmias, Cardiac; Pacemaker, Artificial; Ventricular remodeling.

Introduction

Artificial cardiac pacing is the only treatment for acquired atrioventricular blocks.[1-3] Conventional pacemakers (PM), which stimulate the right ventricle (RV), via unicameral or atrioventricular pacing, have been the most widely used devices to treat these bradyarrhythmias.[1-4] Owing to its proven effectiveness in reducing symptoms caused by low cerebral and systemic blood flow, as well as its increased survival rate, this clinical indication represents 55.1% and 83.4% of all implants performed in the United States of America and Brazil, respectively.[5,6]

Nevertheless, deleterious effects of chronic right ventricular pacing have been described. Examples include proarrhythmic mechanisms, intra- or interventricular electromechanical dyssynchrony, and ventricular remodeling, which may lead to heart failure refractory to drug treatment.[7-14] Changing the mode of pacing from RV to biventricular has been reported to reverse these events.[15-20]

Isolated atrial synchronous left ventricular pacing has been used for the correction of cardiac dyssynchrony in patients with severe left ventricular dysfunction and left bundle branch block, with results similar to those obtained by atriobiventricular pacing.[21-25] There is, however, no evidence to date that the use of isolated left ventricular pacing, in comparison with right ventricular pacing, may reduce the rate of ventricular remodeling in patients with acquired atrioventricular blocks, regardless of the presence or absence of previous left ventricular dysfunction.

Notwithstanding the possible clinical-functional benefits that may be expected from the use of left ventricular pacing, in comparison with right ventricular pacing, there are other factors that may influence this comparison, especially those related to the operating technique and its complications. The technique of implanting PM with endocardial RV pacing is well established and its results and complications have long been known. On the other hand, implants in the left ventricle

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(LV), via epicardial or transvenous access, presents specificities both with regard to the anesthetic technique and the skills required to perform them, either via thoracotomy or coronary sinus catheterization.[26-32] Among these aspects, the viability of using coronary sinus tributary veins in individuals with normal or slightly enlarged heart is still unknown, notwithstanding the significant experience already achieved with this means of access in patients with cardiomegaly and an accentuated increase in the left ventricular cavity.

In view of this concern regarding the deleterious effects of chronic right ventricular pacing, the hypothesis of the present study was that the use of an active-fixation coronary sinus lead will allow for safe isolated left ventricular pacing for patients with atrioventricular blocks who are indicated for conventional PM implantation.

Objectives

The objective of the present study was to evaluate the safety, efficacy, and effects of left ventricular pacing, using an active-fixation coronary sinus lead (*Medtronic Attain StarFix® Model 4195 OTW*),[33] in comparison with right ventricular pacing in patients who were indicated for conventional PM implantation and who had normal or slightly altered left ventricular function, with the aim of determining:

- The procedural success rate of coronary sinus lead implantation;
- The safety and efficacy of left ventricular pacing;
- Cardiac synchrony and the occurrence of remodeling and left ventricular dysfunction.

Methods

Study design

This is a randomized controlled clinical trial that compared the use of right ventricular pacing (RV Group) with relation to unifocal left ventricular pacing (LV Group) in patients with bradyarrhythmias.

This study was performed in a high complexity cardiology hospital. It received approval from the Institution's Research Ethics Committee. All participants signed an informed consent form. This study was registered at *ClinicalTrials.gov*.

Study Population

Adult subjects who met the following criteria were considered eligible for the study: (1) Indication of initial implantation of a definitive conventional PM by the transvenous technique; (2) Systolic ventricular function ≥ 0.40; (3) Agreement to participate in the study.

Individuals who presented at least one of the following criteria were not included in the study: (1) Impediment of venous access through tributaries of the superior vena cava due to: uncorrected intracardiac defects, absence of venous access, tricuspid valve prosthesis, or need for radiotherapy in the thorax; (2) > 85 years of age; (3) Pregnancy in progress; (4) Contraindication for use of iodinated contrast during the surgical procedure (serum creatine ≥ 3.0 mg/dL).

Patients were consecutively selected from those with indication for conventional PM implantation. After the indication of surgical treatment, the individuals who fulfilled the eligibility criteria were submitted to a preoperative evaluation, consisting of medical history, clinical, laboratory and echocardiographic assessment. (Figure 1)

Composition of study groups

Before the surgical procedure, patients were allocated into two groups in a random distribution list generated by a computer: (1) composed of patients who were submitted to conventional RV lead implantation; (2) LV Group: composed of patients who received implantation of an active-fixation coronary sinus lead in the LV.

The random distribution list was generated by the computer program *Statistical Analysis System* (SAS), with a 2:1 ratio of LV implants. To guarantee a balanced distribution of patients, we opted for block randomization, generating a list with blocks of 10 to allocate patients into the two study groups.

Allocation was performed by means of sealed, opaque envelopes, which were numbered sequentially. Patient allocation always occurred the night before the surgical procedure, following adequate assessment of the study's eligibility criteria. The process of preparing and sealing the envelopes was performed by an independent individual who was not involved in any other steps of the study.

Blinding of all patients and the investigator responsible for assessing the study results was guaranteed during all phases of the study. Due to the surgical intervention protocol, it was not possible to blind the surgical staff and the team responsible for the PM evaluations and programming.

Study interventions

The two main interventions performed during this study were conventional right ventricular (RV Group) and left ventricular (LV Group) implantations. The surgical procedure for PM implantation was always performed through the transvenous route, in accordance with our institution's routine practice.

In patients allocated into the RV Group, the *Medtronic CapSureFix Novus® 5076-58* lead was preferably implanted in the middle portion of the interventricular septum, always under indirect vision using fluoroscopy. When it was not possible to obtain adequate fixation, stimulation, or sensitivity in the mid-septum position, the ventricular lead was implanted in the apical septum or the outlet septum.

In patients allocated into the LV Group, a *Medtronic 6228 CTH* deflectable catheter was introduced into the coronary sinus, serving as a guide for the introduction of a *Medtronic Attain 6227 DEF* deflectable guide catheter. When the latter was introduced into the coronary sinus, coronary sinus phlebography was performed in a left anterior oblique position at 30 degrees, with the aid of a *Medtronic Attain 6215* balloon catheter and non-ionic iodized contrast medium (*Iodixanol*, VisipaqueTM). When the radiological anatomy of the coronary sinus and its tributary veins was defined, a *Medtronic Attain StarFix® Model 4195 OTW* unipolar lead was introduced

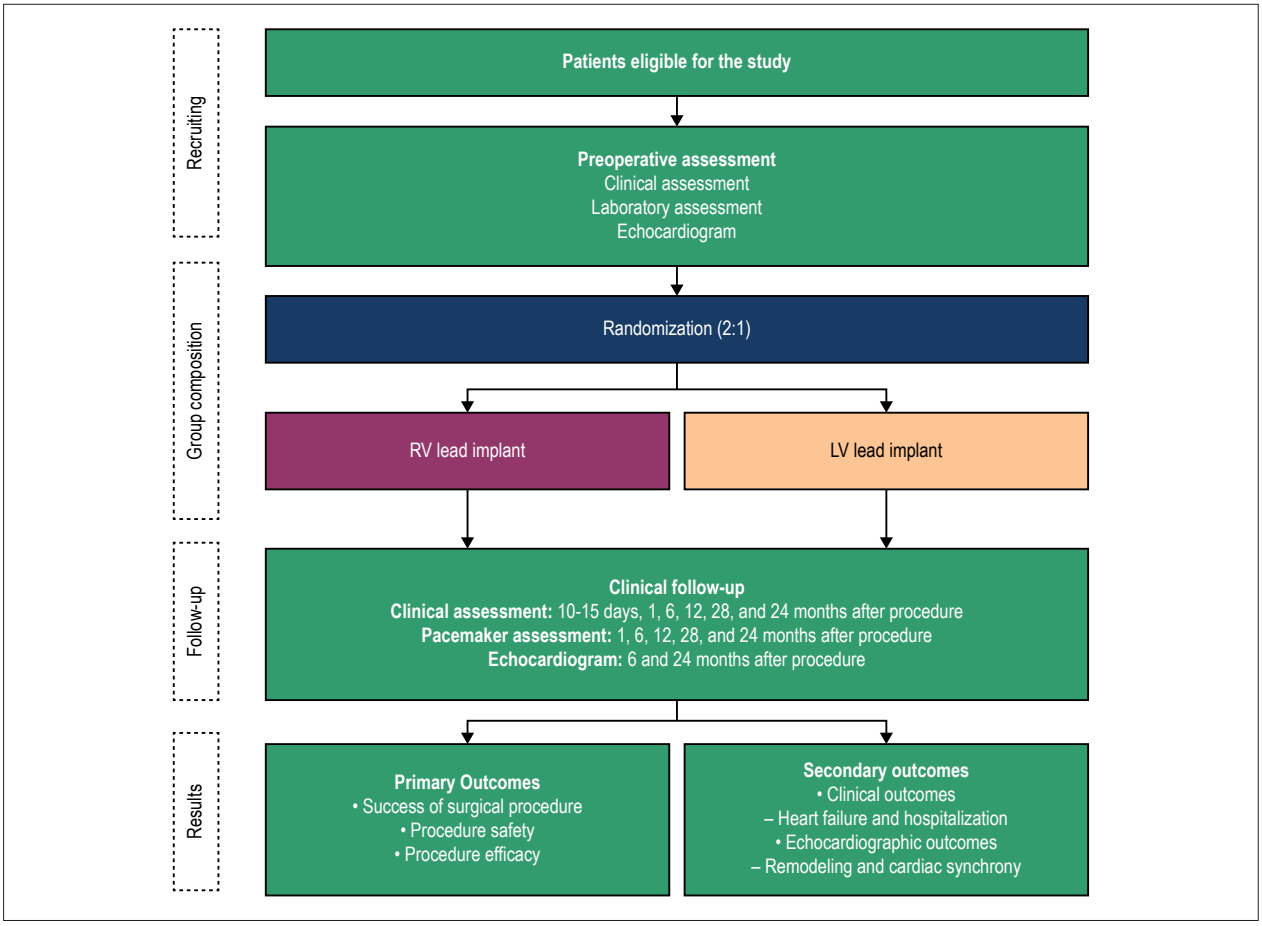

Figure 1 – *Diagram showing the main phases of the study. LV: left ventricle; RV: right ventricle.*

into one of the veins of the lateral or posterolateral wall (Figure 2). When it was not possible to use the veins of the lateral or posterolateral wall due to inadequate stimulation or sensitivity, phrenic stimulation, or lack of lead stability, the diagonal vein was used; placement in the anterior or posterior interventricular sulci was not permitted.

Exclusion of patients when implant through the coronary sinus was not feasible

This study excluded all patients allocated into the LV Group in whom it was not possible to implant the lead in coronary veins. After the surgical team determined that implantation in the LV was not possible, the *Medtronic Attain StarFix® Model 4195 OTW* lead was removed and a new *Medtronic CapSureFix Novus® 5076-58* was implanted in the RV. After the procedure, the patients were excluded from the study.

Study outcomes

This study's primary outcomes include: (1) The proposed procedure was successful, defined by coronary sinus catheterization with lead implant in the posterior or lateral LV wall; (2) Procedure safety, defined by the absence of surgical complications during the study period (24 months); (3) Procedure efficacy, defined by the maintenance of chronic stimulation thresholds at < 2.5 V with 0.4 ms during the study period (24 months).

Secondary outcomes were clinical evolutions and echocardiographic changes, such as: (1) Alteration of left ventricular function, defined by the reduction of at least 10% of the ejection fraction in the examination performed at the end of the study; (2) LV positive remodeling, defined by a 15% increase in the systolic diameter of the cardiac chamber. (3) Ventricular dyssynchrony, defined by the presence of intra-or interventricular electromechanical delay in the examination performed at the end of the study.

Sample size calculation

The calculation of this study's sample size was based on the average occurrence rate of the primary outcomes according to the description in the literature, considering an alpha error of 5% and a statistical power of 80%. With respect to operative outcomes, we found procedural success, efficacy, and safety rates in 99% and 91% of the patients who underwent lead implantation in the RV and the LV, respectively.[1,2,28] The sample size required for finding an equivalence between the two techniques was estimated at 188 patients in the LV Group and 94 in the RV Group, with a total of 282 cases.

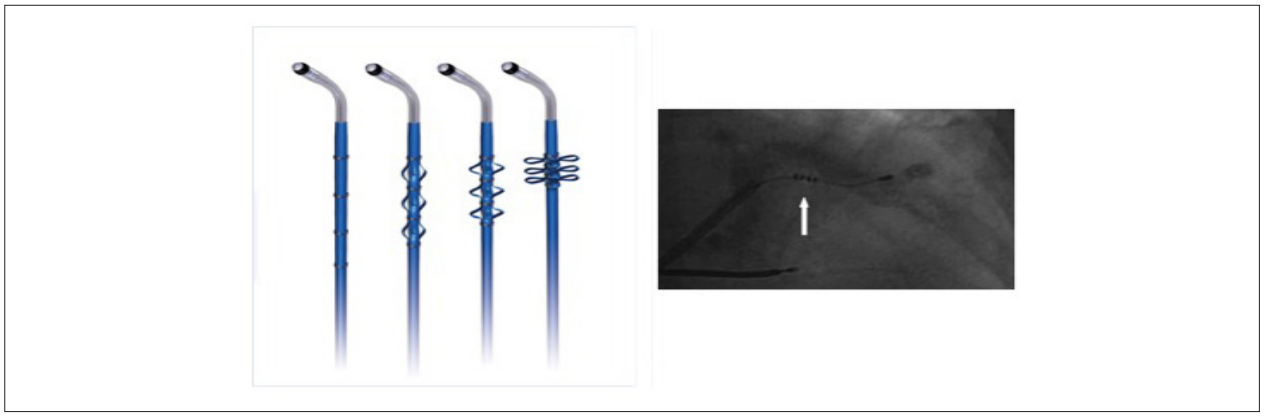

Figure 2 – *View of the active-fixation coronary sinus lead (Medtronic Attain StarFix® Model 4195 OTW).*

Electronic data collection and management

Demographic, clinical, surgical, and echocardiographic data were collected and stored in an electronic database developed in REDCap (*Research Electronic Data Capture*) System,[34,35] which is hosted on our institution's server.

Statistical analysis

The data registered in the REDCap System were exported in the form of Excel spreadsheets (Microsoft Excel) and analyzed by the *Statistical Package for the Social Sciences* (SPSS), version 17.0.

All variables were initially analyzed descriptively. For quantitative variables, this analysis was done by observing the minimum and maximum values, the averages, and standard deviations. Absolute and relative frequencies were calculated for all qualitative variables.

We used unpaired Student's *t*-test to compare averages between groups; when the normality assumption of the data was rejected, the variable was evaluated by logarithmic transformation. The chi-squared test or Fisher's exact test was used to test homogeneity between proportions. We used Analysis of Variance with repeated measures to compare groups throughout the evaluations.

Data analysis was performed according to the intention-to-treat principle. The level of significance for statistical tests was set at 5%.

Results

Participants

In the period between June 2012 and January 2014, 417 patients were indicated for conventional PM implantation due to bradyarrhythmias and were, thus, potential candidates for participation in this study. Of these, 91 were included in the study (Figure 3).

Patient inclusion was prematurely interrupted by a consensual decision made by the study's monitoring committee due to problems related to safety of using the *Medtronic Attain StarFix® Model 4195 OTW* lead. Following this decision, no other participants were included. Nonetheless, clinical follow-up continued until the last patient, who was included in January 2014, had completed 24 months of postoperative follow-up. The premature interruption of this study occurred due to difficulties in obtaining adequate left ventricular pacing conditions with the operating technique defined in the research protocol, on the part of the study population.

Demographic and basic clinical characteristics

The population included in this study was composed of 71 individuals who participated in all phases of the study. There was a slight predominance of females (52.1%), as well as individuals who self-identified as white (69.0%). At the moment of inclusion, average age was 66.5 ± 11.2 years, varying from 24 to 85 years of age. Demographic and clinical characteristics were similar in both groups, except for the presence of Chagas disease, which was more common in the LV Group (Table 1).

Characteristics of the operation

Atrioventricular PM were implanted in 95.8% of individuals studied. Single-chamber ventricular pacing was indicated in 3 (4.2%) patients as a consequence of permanent atrial fibrillation. Details regarding surgical procedures performed on patients in the RV and LV Groups are shown in Table 2.

Data comparison related to the operations performed to implant the devices used in this study revealed significant differences between the groups. Time spent implanting left ventricular leads was, on average, 32.4 minutes greater than RV lead implant. Moreover, the total duration of the procedure was also longer, lasting, on average, 36.3 minutes more in patients in the LV Group.

The approach used to introduce the leads also differed significantly between the two groups. In patients allocated to the LV Group, cephalic vein dissection, either isolated or in association with one puncture in the subclavian vein, was more frequent. The analysis in Table 2 shows that two punctures of the subclavian vein was the preferred technique for the patients in the RV Group ($p = 0.002$).

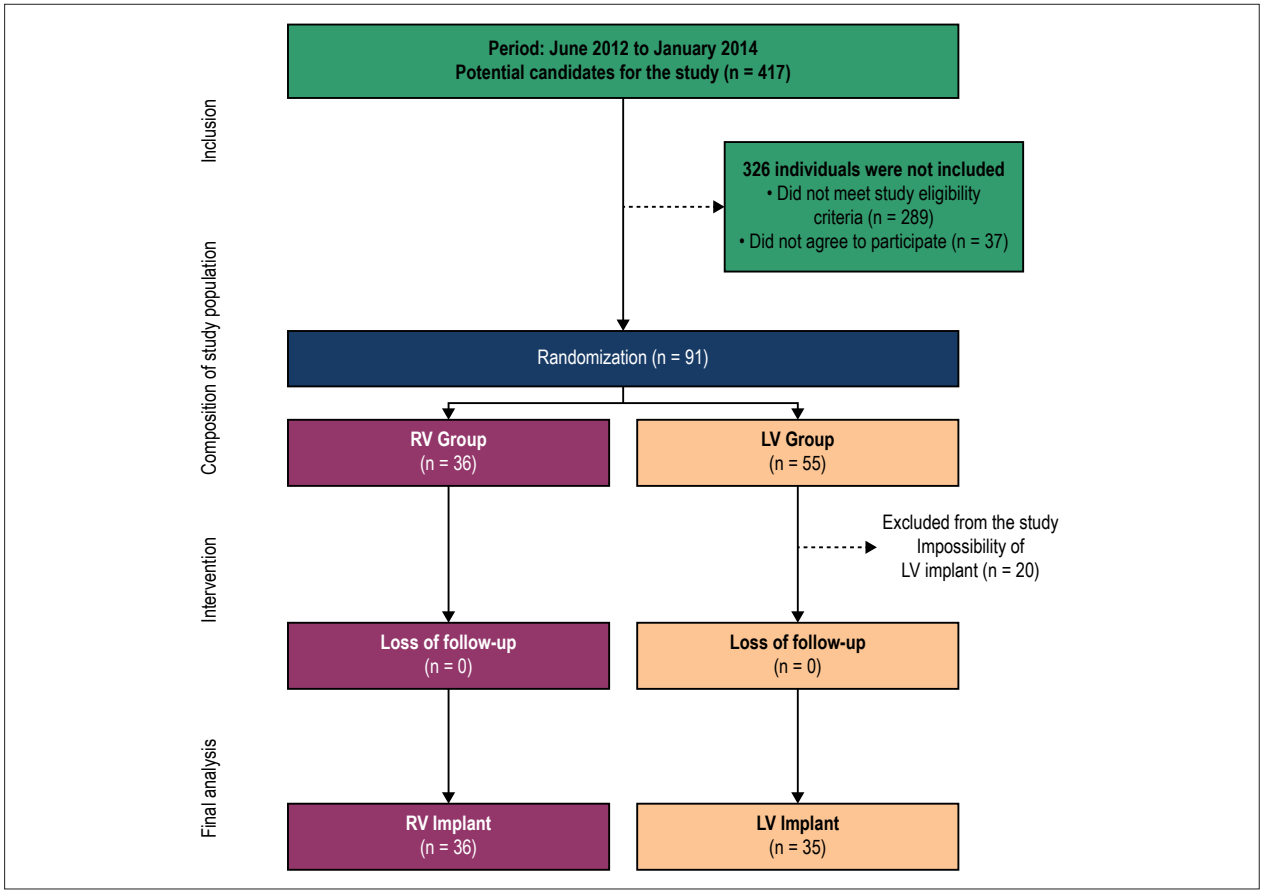

Figure 3 – *Composition of the study population. LV: left ventricle; RV: right ventricle.*

Primary study outcomes

Success of the proposed surgical procedure

In all patients in the RV Group, PM implantation was successfully performed without any intercurrences. In the LV Group, on the other hand, it was not possible to implant the lead in coronary veins in 20 (36.4%) of the of the 55 patients initially allocated.

The most frequent cause of failure to implant the LV lead was undesired phrenic nerve stimulation in regions that could be stimulated through the LV free wall. This problem occurred in 12 patients, representing 60% of all causes of LV implant failure. Coronary sinus cannulation difficulties (n = 3), inability to access coronary veins (n = 5), and unstable positioning (n = 2) prevented the use of left ventricular pacing in the other cases of failure to use the coronary sinus.

Surgical procedure safety

Postoperative complications were detected only in the LV Group. The most frequent complication was phrenic stimulation, observed in 9 (25.7%) patients.

During the clinical follow-up period, 4 (11.4%) patients in the LV Group underwent reoperation. There were 1 case of LV lead fracture (358 days after the initial implant) and 3 (8.6%) cases of phrenic stimulation which could not be resolved by reprogramming (42, 55, and 70 days after the initial procedure). In all 4 cases, the surgical procedure was performed successfully and without complications. The surgical team, however, decided to perform new lead implants in the RV, leading to a crossover of patients from the LV Group to the RV Group.

Surgical procedure efficacy

Once the previously mentioned complications were corrected, stimulation and sensitivity were considered adequate in all phases of the study in 100% of the patients in the RV Group and 31 (88.6%) patients in the LV Group (Table 3). Of the 4 patients who presented ventricular stimulation thresholds above those considered adequate in this study, 2 cases occurred intraoperatively (acute phase); 1 patient presented alterations in the stimulation threshold during months 6, 12, 18, and 24 of clinical follow-up and 1 presented alterations in months 18 and 24 of clinical follow-up.

Secondary study outcomes

Clinical outcomes

There were two deaths in the study, both in patients in the RV Group. The declared causes were acute myocardial infarction, 13.2 months after implantation, and septic shock due to pneumonia, 20.9 months after implantation.

Table 1 – Demographic and clinical characteristic of study participants

Characteristics	Total (n = 71)	LV Group (n = 35)	RV Group (n= 36)	p
Female sex, n (%)	37 (52.1)	19 (54.3)	18 (50.0)	0.717(1)
Age (years), average ± SD	66.5 ± 11.2	68.4 ± 9.2	64.8 ± 12.8	0.179(2)
White race, n (%)	49 (69.0)	24 (68.6)	25 (69.4)	0.936(1)
Functional Class (NYHA), n (%)				
I	22 (31.0)	12 (34.3)	10 (27.8)	
II	33 (46.5)	15 (42.9)	18 (50.0)	0.544(1)
III	14 (19.7)	8 (22.9)	6 (16.7)	
IV	2 (2.8)	-	2 (5.6)	
Structural cardiac disease, n (%)				
None	52 (73.2)	25 (71.4)	27 (75.0)	
Chagas disease	12 (16.9)	9 (25.7)	3 (8.3)	0.063(3)
Ischemic heart disease	6 (8.5)	1 (2.9)	5 (13.9)	
Hypertrophic cardiomyopathy	1 (1.4)	-	1 (2.8)	
Associated comorbidities				
None	2 (2.8)	1 (2.9)	1 (2.8)	1.000(3)
Hypertension	59 (83.1)	28 (80.0)	31 (86.2)	0.492(1)
Chagas disease	8 (11.3)	5 (14.3)	3 (8.3)	0.710(3)
Diabetes	19 (26.8)	10 (28.6)	9 (25.0)	0.734(1)
Dyslipidemia	23 (32.4)	10 (28.6)	13 (36.1)	0.497(1)
Cardiovascular medications, n (%)				
None	4 (5.6)	2 (5.7)	2 (5.6)	1.000(3)
ACEI/ARB	52 (73.2)	28 (80.0)	24 (66.7)	0.204(1)
Diuretics	29 (40.8)	12 (34.3)	17 (47.2)	0.267(1)
Betablockers	8 (11.3)	6 (17.1)	2 (8.3)	0.151(3)
QRS duration prior to implant > 120 ms, n (%)	53 (74.6)	26 (74.3)	27 (75.0)	0.944(1)
LV ejection fraction, average ± SD	59.9 ± 6.8	61.1 ± 4.4	58.1 ± 8.4	0.069(2)
LV final systolic volume, average ± SD	42.1 ± 16.1	39.5 ± 15.4	44.8 ± 16.5	0.168(2)
LV final diastolic volume, average ± SD	100.7 ± 24.7	97.1 ± 27.2	104.3 ±21.7	0.223(2)
BNP, average ± SD	83.2 ± 111.8	72.3 ± 77.6	93.8 ±137.6	0.482(2)
TNF alpha, average ± SD	50.7 ± 186.6	74.9 ± 265.1	27.2 ± 13.5	0.388(2)
IL6, average ± SD	11.3 ± 16.0	9.1 ± 12.4	13.4 ± 18.8	0.092(2)

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; LV: left ventricle; NYHA: New York Heart Association; RV: right ventricle; SD: standard devition. (1) Chi-squared test; (2) Unpaired Student's t-test; (3) Fisher's exact test.

There were no hospitalizations due to heart failure during the study's follow-up period. At the end of the first month of observation, 100% of the patients in the RV Group and 97.1% in the LV Group were oligosymptomatic, being classified as in functional class (FC) I or II. The analysis of Figure 4 shows that there was no difference in behavior between the groups throughout the follow-up period. Few patients presented symptoms with minor exertion and were classified as FC III. No cases were classified as FC IV.

Echocardiographic results

The echocardiographic studies performed at the baseline and at month 24 of follow-up showed that there was left ventricular remodeling and changes in ejection fraction over time in both groups. They also showed the presence of differences in the mechanics of the two ventricles resulting from right or left ventricular pacing.

The analysis in Table 3 makes it possible to observe that: (1) a reduction of more than 10% in LV ejection fraction was observed in 23.5% of the patients in the RV group and in 20.6% of the LV Group (p = 0.767); (2) an increase of more than 15% in final systolic volume was observed in 27.3% of the individuals in the RV Group and 29.4% in the LV Group (p = 0.846), and that both outcomes occurred at the same time in 32.3% of the RV Group and 35.3% of the LV Group (p = 0.798).

Table 2 – Operation data of study participants

Characteristics	Total (n = 71)	LV Group (n = 35)	RV Group (n= 36)	p
Pacemaker type, n (%)				
Single-chamber	3 (4.2)	2 (5.7)	1 (2.8)	0.614(3)
Dual-chamber	68 (95.8)	33 (94.3)	35 (97.2)	
Lead implant access				
Subclavian vein puncture	44 (62.0)	16 (45.7)	28 (77.8)	
Cephalic vein dissection	6 (8.5)	2 (5.7)	4 (11.1)	0.002(3)
Both	21 (29.6)	17 (48.6)	4 (11.1)	
Duration of ventricular lead positioning				
Average ± SD (minutes)	22.2 ± 21.4	38.5 ± 19.8	6.4 ± 3.6	< 0.001(2)
Variation (minutes)	2 - 119	8 - 119	2 - 15	
Total procedure duration				
Average ± SD (minutes)	84.8 ± 29.9	103.3 ± 27.9	66.9 ± 19.0	< 0.001(2)
Variation (minutes)	34 - 167	45 - 167	34 - 113	
RV pacing site, n (%)				
Apex	-	-	4 (11.1)	
Septum	-	-	32 (88.9)	NA
LV pacing site, n (%)				
Anterolateral	-	6 (17.1)	-	
Lateral	-	26 (74.3)	-	NA
Posterolateral	-	3 (8.6)	-	

LV: left ventricle; NA: not applicable; RV: right ventricle; SD: standard deviation. (2) Unpaired Student's t-test; (3) Fisher's exact test.

Table 3 – Echocardiographic outcomes, derived from the comparison between the baseline echocardiogram and the echocardiogram performed at the 24-month follow-up visit

Echocardiographic outcomes	LV Group (n = 34)	RV Group (n = 34)	p
LVEF			
10% reduction	7 (20.6%)	8 (23.5%)	0.767(1)
Without 10% reduction	27 (79.4%)	26 (76.5%)	
FSVLV			
15% increase	10 (29.4%)	9 (27.3%)	0.846(1)
Without 15% increase	24 (70.6%)	24 (72.7%)	
Alteration of LVEF and/or FSVLV			
Present	12 (35.3%)	11 (32.3%)	0.798(1)
Absent	22 (64.7%)	23 (67.7%)	
Intraventricular dyssynchrony			
Delay ≥ 65 ms	14 (43.7%)	19 (55.9%)	0.324(1)
Delay < 65 ms	18 (56.3%)	15 (44.1%)	
Interventricular dyssynchrony			
Delay ≥ 100 ms	22 (68.7%)	31 (91.2%)	0.022(1)
Delay < 100 ms	10 (31.3%)	3 (8.8%)	

LVESV: left ventricular end-systolic volume; LV: left ventricle; LVEF: left ventricle ejection fraction; RV: right ventricle. (1) Chi-squared test.

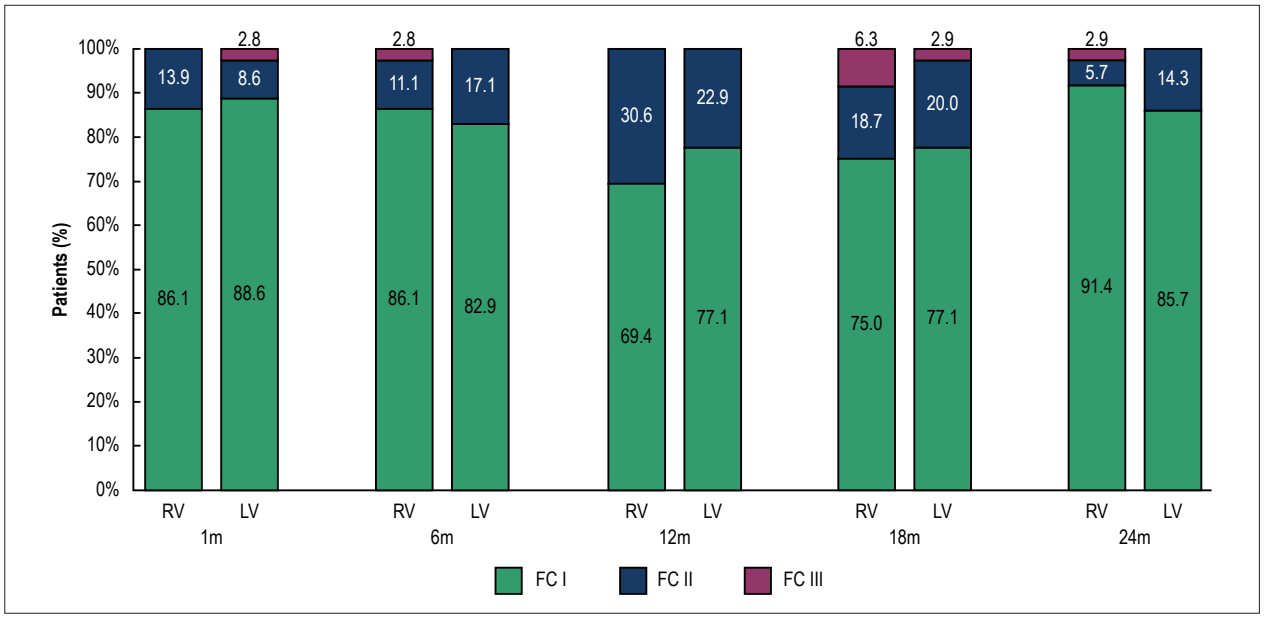

Figure 4 – *Behavior of Functional Classification of Heart Failure (NYHA) during assessment in the clinical follow-up phase. FC: functional class; LV: left ventricle; RV: right ventricle.*

According to the criteria defined for the present study, tissue Doppler analysis showed that 55.9% of the individuals in the RV Group and 43.7% of those in the LV Group had left ventricular intraventricular dyssynchrony (p = 0.324). This method also detected that 91.2% and 68.7% of patients in the RV and LV groups, respectively, had interventricular dyssynchrony (p = 0.022).

Discussion

The present study was the first designed with the specific purpose of comparing the clinical and functional effects of left ventricular pacing to those of right ventricular pacing in patients with advanced atrioventricular conduction block, as well as evaluating the feasibility of using coronary sinus as a safe alternative for the artificial pacemaker dependent patients on this type of therapy.

Considering the evidence that there are deleterious effects related to right ventricular pacing in patients with advanced atrioventricular blocks who have preserved ventricular function at the time of first PM implantation[7-14] and the fact that new transvenous techniques for implanting leads in the LV are being developed, we judge that it is important to evaluate whether there are clinical and functional differences that justify changing from the classic form of endocardial right ventricular pacing to LV pacing, as well as whether the routine use of left ventricular pacing through the coronary sinus is technically feasible in patients with atrioventricular blocks.

There were difficulties in patient inclusion in the study, mainly due to the high rate of chronic renal dysfunction in individuals with acquired atrioventricular block and due to the urgency of treating bradycardia, which made it difficult to perform fundamental tests for selection and inclusion of patients into the study. The main reason why only 91 patients were included was the monitoring committee's decision to interrupt the study, owing to problems related to the safety of the *Medtronic Attain StarFix® Model 4195 OTW* lead in the present study project. In more than a third of individuals allocated for LV implant, it was not possible to obtain safe conditions for artificial pacing of patients who were dependent on this type of therapy. In this manner, in 20 of the 55 patients allocated into the LV Group, after unsuccessfully attempting the left ventricular implant through the coronary sinus, the surgical team decided to perform the implant in the RV. Despite the fact that, at the end of the operation, these 20 patients received the lead in the RV, they were excluded from the phase which compared results regarding pacing effectiveness and clinical and functional effects. On the other hand, regarding safety analysis, the failure to obtain safe conditions for LV pacing in 36.4% of cases was decisive to the conclusion that the *Medtronic Attain StarFix® Model 4195 OTW* lead, notwithstanding its utility in patients undergoing biventricular implantation for cardiac resynchronization, is not an adequate option for unifocal ventricular pacing in patients dependent on PM.

The most frequent reason that left ventricular pacing failed in the patients of the present study was phrenic nerve stimulation. Although this complication is reported in 2–37% of patients with severe left ventricular dysfunction,[31-33,36] in the present study it occurred in 12 patients, which represents the main cause of failure to implant in the LV. Nevertheless, 25.7% of patients presented phrenic nerve stimulation in the postoperative period. We believe that the small epicardial surface of the LV lateral wall, in patients with preserved ventricular function, when compared to the epicardial area of patients with severe dysfunction, caused the regions where the left ventricular lead was implanted to be very close to the phrenic nerve. The association of this condition with the unipolar configuration of the *StarFix.* lead implicated an absence of alternatives for correcting the

phrenic nerve stimulation, with the exception of reducing the stimulation energy. Reducing the stimulation energy, in turn, prevented an adequate safety margin from being maintained in patients pacemaker dependent patients.

Notwithstanding the premature interruption of the study, the results observed regarding ventricular pacing safety and effectiveness assessments were sufficient to reach strong conclusions.

Analysis of the intraoperative parameters of ventricular leads showed that the stimulation threshold, impedance, and sensitivity for QRS complexes showed significant differences between the groups. With the exception of two cases in the LV Group, the values obtained for both RV and LV stimulation were within the range considered ideal for safe ventricular pacing.

Even though the postoperative complication rate was expressively higher in the LV Group, undesired phrenic nerve stimulation was the most common complication, occurring in 9 of the 35 patients in this group. Of these, 3 cases required surgical correction due to the impossibility of resolving the problem by reprogramming the energy. A fourth patient required reoperation due to a fracture of the *StarFix* lead conductor. In these 4 cases, the medical team decided to implant a new lead in the RV, which resulted in 4 cases of crossover in the study.

Based on the criteria established in the study, efficacy, stimulation and sensitivity parameters were considered adequate in all evaluations perfomed for all patients of the RV group. In the LV Group, however, only 31 of the 35 patients studied presented adequate ventricular pacing conditions in all phases of the study. In 2 patients, the parameters did not meet the conditions established as adequate by the study during the intraoperative phase, but there was improvement in the stimulation conditions during the postoperative period. In 2 other cases, failure began to occur in month from the 6th and 18th months of follow-up.

The premature interruption of the study compromised the analysis of secondary results, as the sample size calculation had defined that 282 research subjects would be included in the study, 188 patients in the LV Group and 94 in the RV Group.

During the study's follow-up period, there were no hospitalizations owing to heart failure. On the other hand, we observed the occurrence of left ventricular remodeling and reduction of left ventricular ejection fraction when comparing the echocardiogram performed at the baseline with that obtained at month 24 of follow-up. Although the rate of patients whose LV ejection fraction worsened was higher in patients in the RV Group (23.5% vs. 20.6%), the number of individuals included in the study did not allow the sample to be analyzed regarding this result. The rate of ventricular remodeling was slightly higher in patients in the LV Group (29.4% vs. 27.3%).

Analysis of cardiac synchrony showed that there was an important difference between LV wall activation time in patients in the RV Group more frequently than in the LV Group (55.9% vs. 43.8%). Similarly, patients in the RV Group more frequently showed delays in activation between the RV and LV (91.2% vs. 68.8%). Notwithstanding the small number of patients evaluated, the difference in the occurrence rate of interventricular dyssynchrony between groups was statistically significant ($p = 0.022$).

Study limitations

Although the study met its primary objectives, there are some inevitable limitations. The main limitation is related to the premature interruption of the study which made it impossible to reach the sample size necessary for evaluating clinical and echocardiographic outcomes. Additionally, a small number of individuals with LV ejection fraction between 0.40 and 0.50 were included; these individuals would possibly have had greater chances of suffering the deleterious effects of RV pacing. This notwithstanding, the safety and efficacy results refer exclusively to the use of unipolar leads, which no longer represent state-of-the-art LV pacing through the coronary sinus, given that the last 3 years have seen the development of quadripolar leads that facilitate positioning with ideal stimulation in a location far from the phrenic nerve.[36,37]

Regardless of the methodological problems occurred, it was possible to observe that interventricular synchrony was shown to be significantly better in patients with LV pacing. This perspective opens doors for future studies to be conducted using quadripolar leads with the aim of preventing the deleterious effects of conventional ventricular pacing.

Conclusions

The routine use of isolated left ventricular pacing pacemaker dependent patients with the use of a *Medtronic Attain StarFix® Model 4195 OTW* lead through the coronary sinus was shown to be impractical given the low rates of procedural success, safety, and efficacy.

The comparison of the clinical and echocardiographic effects of left ventricular pacing with those of right ventricular pacing was not possible owing to the low level of cases studied, even though interventricular synchrony was shown to be significantly better in patients with LV pacing.

Author contributions

Conception and design of the research, analysis and interpretation of the data and writing of the manuscript: Crevelari ES, da Silva KR, Costa R; acquisition of data: Crevelari ES, Albertini CMM, Vieira MLC; obtaining funding: Costa R; critical revision of the manuscript for intellectual content: Crevelari ES, da Silva KR, Albertini CMM, Vieira MLC, Martinelli Filho M, 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 00610412,2,0000,0068 (Plataforma Brasil CAAE). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Ventricular Pacing of Conventional Pacemakers in the Era of CRT

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Short Editorial related to the article: Efficacy, Safety, and Performance of Isolated Left vs. Right Ventricular Pacing in Patients with Bradyarrhythmias: A Randomized Controlled Trial

With the advent of cardiac resynchronization therapy (CRT), and the awareness of the impairment of ventricular systolic function caused by intraventricular conduction disorders, especially left bundle branch block, after more than 50 years of routine use, conventional right univentricular artificial cardiac pacing, particularly in its classical site – the apical region – is now being questioned. In fact, conventional right univentricular pacing usually generates a large QRS (often greater than 150 ms), with electrocardiographic pattern of left bundle branch block – more significant signs for the diagnosis of ventricular dyssynchrony that may require CRT.[1]

Some studies have shown impairment of right univentricular pacing in patients with pacemakers compared to normal ventricular activation,[2-4] which prompted the development of algorithms of minimal ventricular pacing, favoring exclusive atrial pacing in currently available dual-chamber pacemakers, which have shown some benefits. However, when the reestablishment of heart rate requires ventricular pacing (in cases of AV blocks), these algorithms cannot be used. Other studies have shown deterioration of ventricular systolic function after initiation of right univentricular pacing.[5,6] In order to minimize any impairment of right univentricular pacing in cases where it is necessary, multiple pacing sites have been tried:[7] (outflow tract, mid-septal, inferior-septal, etc.) and, although no further evidence has been achieved, today, mid-septal pacing is the most commonly method in conventional pacemaker implants, to the detriment of apical pacing.

Special Hisian pacing presents good results[8] and has been shown to be the best site of univentricular pacing in terms of activation synchrony. However, some problems, such as: high pacing thresholds, low endocavitary potentials, oversensing of atrial potential, and implantation difficulties at this site, still need to be considered for this type of ventricular pacing to be routinely used in patients with recommendation of pacemaker.

Exclusive left ventricular pacing has been proposed as an alternative to CRT in patients with CHF requiring ventricular pacing,[9] and did not deliver any considerable benefits in these patients. The manuscript "Efficacy, Safety, and Performance of Left vs. Right Ventricular Pacing in Patients with Bradyarrhythmias: A Randomized Clinical Trial"[10] is a well-designed original study that compared these two types of pacing in patients with preserved cardiac function and recommendation for conventional pacemaker. The findings of that study showed low success rate and safety in the implantation of LV electrode via the coronary sinus, contradicting the initial assumption and questioning the appropriateness of proposing left ventricular pacing via the coronary sinus as an option for conventional endocardial right ventricular pacing in patients with recommendation of pacemaker. These findings, however, have been impaired by the small number of patients included and the use of a electrode for LV pacing, which is highly associated with low-performance and complication, not reproducing much better results in the literature for this type of procedure.[11,12]

Although it is contested, especially in patients with cardiac systolic dysfunction, where some guidelines recommend that preference should be given to biventricular pacing,[1] right univentricular pacing persists and is routinely used in patients with recommendation of conventional pacemakers who have preserved ventricular function, and there is no consensus as to the best site of pacing. However, preference is given to the septal region.

Keywords

Cardiac Pacing,Artificial/methods; Bradycardia; Arrhythmias,Cardiac; Pacemaker, Artificial/utilization; Remodeling Atrial.

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Women with Polycystic Ovarian Syndrome Exhibit Reduced Baroreflex Sensitivity That May Be Associated with Increased Body Fat

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Abstract

Background: **Polycystic ovarian syndrome (PCOS) women have a high prevalence of obesity and alterations in cardiovascular autonomic control, mainly modifications in heart rate variability (HRV) autonomic modulation. However, there are few studies about other autonomic control parameters, such as blood pressure variability (BPV) and baroreflex sensitivity (BRS). In addition, there are still doubts about the obesity real contribution in altering autonomic control in these women.**

Objective: **To investigate BPV and BRS autonomic modulation alterations in PCOS women, as well as, to evaluate whether these alterations are due PCOS or increased body fat.**

Methods: **We studied 30 eutrophic volunteers [body mass index (BMI) < 25 kg/m^2] without PCOS (control group) and 60 volunteers with PCOS divided into: eutrophic (BMI < 25 kg/m^2, N = 30) and obese women (BMI > 30 kg/m^2, N = 30). All volunteers were submitted to anthropometric evaluation, hemodynamic and cardiorespiratory parameters record at rest and during physical exercise, analysis of HRV, BPV and spontaneous BRS. The differences in p less than 5% ($p < 0.05$) were considered statistically significant.**

Results: **Related to eutrophics groups, there were no differences in autonomic parameters evaluated. The comparison between the PCOS groups showed that both PCOS groups did not differ in the BPV analysis. Although, the obese PCOS group presented lower values of spontaneous BRS and HRV, in low frequency and high frequency oscillations in absolute units.**

Conclusion: **Our results suggest that obesity did little to alter HRV in women with PCOS, but it may influence the spontaneous BRS. (Arq Bras Cardiol. 2019; 112(4):424-429)**

Keywords: **Obesity; Hypertension; Polycystic Ovary Syndrome/physiopathology; Adiposity; Body Fat Distribution; Autonomic Nervous System; Heart Rate.**

Introduction

Women with polycystic ovarian syndrome (PCOS) frequently present cardiovascular autonomic control impairments, mainly characterized by a cardiac autonomic imbalance in determining heart rate variability (HRV).[1-4] This imbalance is an important cardiovascular diseases risk predictor.[5-7] The autonomic impairment causes are still not well established. Some studies suggest that they are result of hormonal and metabolic disorders due PCOS, such as insulin resistance increased.[2,3,8] On the other hand, it is possible that they are simply due body fat percentage increase, which triggers series of systemic alterations, including metabolic and cardiovascular, that affect the cardiac autonomic control.[4,9,10]

Another important aspect is that only HRV is frequently investigated in these women, and we know little about PCOS effects on others autonomic parameters, such as baroreflex sensitivity (BRS) and blood pressure variability (BPV). More specifically, there are no studies associating PCOS to BPV, and in BRS case, studies are incipient. On this, only one study was performed and found no differences.[11] However, this study only addressed obese PCOS and non-PCOS women, which limited further findings.

Therefore, the aim of the present study was to evaluate spontaneous BRS and BPV in eutrophic PCOS women and to investigate the contribution of obesity to these autonomic parameters in these women.

Methods

Participants

With a convenience sample, ninety volunteers aged between 18 and 39 years were included, 30 non PCOS women, considered as a control group, and 60 PCOS women, according to Rotterdam consensus,[12] were subdivided according to the body mass index (BMI): eutrophic group (30 women) and obese group (30 women). All of them were sedentary, did not

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use any medication, and were screened at the outpatient clinic of the Gynecology and Obstetrics Clinic of Clinical Hospital of Ribeirao Preto Medical School (HC-FMRP/USP).

Polycystic ovary syndrome diagnostic

Transvaginal pelvic ultrasound was performed with the Voluson 730 Expert Machine (GE Medical Systems, ZIPF, Austria) to analysis the cysts presence or absence. The ovarian volume and follicles number/size were evaluated, and to calculate ovarian volume the prolate ellipsoid formula (depth x width x length x 0.5) was used.[13]

In addition, laboratory tests for serum total testosterone, androstenedione, sex hormone binding globulin and free androgen, prolactin, 17-hydroxyprogesterone and thyrotropin dosed to diagnose exclusion causes. Blood samples were collected during the follicular phase in women with regular ovulatory cycles and at any time in those with irregular cycles. All the above examinations were performed at the Gynecology Laboratory of HC-FMRP, between 07h00 and 09h00 a.m. after a previous 12-hour fast.

Ergospirometric test

The peak oxygen uptake (VO_{2peak}) was assessed by a submaximal exercise test on a treadmill (Super ATL Millenium®, Inbramed/Inbrasport, Brazil) using the Modificated Bruce protocol. The analysis of exhaled gases (VO_2 and VCO_2) was performed using a metabolic device (UltimaTM CardiO^2, Medical Graphics Corp., USA).

Anthropometric parameters

Body weight and height were obtained using an analogue scale with an altimeter (Welmy), while the body mass index (BMI) values were obtained using the formula W/H^2, where W is the weight in kilograms and H is the height of the subject in meters. Body composition was evaluated using the bioelectrical impedance method (Quantum BIA 101; Q-RJL Systems, Clinton Township, Michigan, USA). The groups were subdivided by their BMI, where the eutrophic groups had BMI < 25 kg/m^2 and the obese group had BMI > 30 kg/m^2.[14]

Analysis of the heart rate variability and blood pressure variability

The spectral analysis of HRV was recorded between 09h00 and 10h00 a.m. according to the following protocol: after remaining in a supine rest position on orthostatic bed for 20 min, the volunteers were passively placed in an inclined position (75° angle) for an additional 10 min. HRV for supine and inclined positions (that is, the tilt test) was recorded using an electrocardiogram (AD Instruments, Sydney, Australia), and a time series of RR interval (RRi) was obtained.

The HRV was obtained using the RRi from electrocardiographic record (ECG), through the modified MC5 shunt at a sampling frequency of 1000Hz. The BPV data values were obtained from the systolic arterial pressure (SAP) recorded beat-to-beat by means of digital plethysmography recording equipment, FINOMETER (Finometer Pro, Finapress Medical System, Amsterdam, Netherland). The room temperature was kept at 21ºC, the ambient light and the noise were controlled, to prevent any interference with recording of data.

The BPV and HRV analyses were performed using custom computer software (CardioSeries v2.0, http://sites.google.com/site/cardioseries). The values of the RRi and SAP intervals were redesigned in 3 Hz cubic spline interpolation, to normalize the time interval between the beats. The series of interpolated RRi and SAP follow the Welch Protocol;[15] they have been divided into half-overlapping sets of 256 data points, overlapping 50%. The stationary segment was visually inspected and those with artifacts or transients were excluded. Each RRi and SAP stationary segment were submitted to spectral analysis by Fast Fourier Transform (FFT), after Hanning window. The RRi specters were integrated in low frequency (LF; 0.04 - 0.15 Hz) and high frequency (HF; 0.15 - 0.5 Hz) bands and the results are expressed in absolute (ms^2) and normalized units (nu), while the SAP specters were integrated only in low frequency band (LF; 0,04 – 0,15Hz) and the results are expressed in absolute units (mmHg^2).

The HRV normalized values were obtained by calculating the percentage of LF and HF power related to the total power of spectrum minus the very low-frequency band (VLF; < 0.2 Hz).[16,17] In addition, normalization procedure was performed to minimize variations of total power in the absolute value of LF and HF.[18] To assess the sympathovagal balance, LF/HF ratio of RRi variability was also calculated.[19]

Spontaneous baroreflex sensitivity

The BRS was assessed in time-domain using the sequence technique, as described by Di Rienzo et al.,[20] The computer software CardioSeries v2.4 scanned beat-to-beat time series of RRi and SAP values searching for sequences of at least 3 consecutive beats in which; progressive increases in SAP were followed by progressive increases in RRi (up sequence) and progressive decreases in SAP were followed by progressive decreases in RRi (down sequence), with a correlation coefficient (r) between RRi and SAP values higher than 0.8. The mean slope of the linear regression line between the SAP and RRi values of each sequence found determined spontaneous BRS.

Statistical analysis

In a comparison between two groups the Student's t-test and in comparison of three groups the one ways variance analysis (ANOVA ONE WAY) were performed. The Shapiro-Wilk test was used to verify de the dates normality; when the distribution was not normal, non-parametric tests were used, the Mann-Whitney test to compare between two groups, and in comparison of three groups, the Kruskal-Wallis test. When the variables had a normal distribution, they were described as mean (± standard deviation), and which had non-parametric distribution they were described as median (± interquartile range). The differences in p were less than 5% ($p < 0.05$) were considered statistically significant. All statistical tests were performed with Sigma Stat 3.5 software (Systat Software Inc., San Jose, CA, USA).

Results

The volunteer's anthropometric characteristics and hemodynamic parameters are in Table 1. The obese PCOS group had higher BMI, weight and body fat percentage than the other groups. On the other hand, VO_{2peak} was lower in the obese PCOS group. In relation to blood pressure, the obese group had higher values of diastolic blood pressure and mean blood pressure compared to the control and eutrophic PCOS groups.

Table 2 presents the spectral analysis of HRV and BPV results during rest of all groups studied. The HRV analysis at rest shows the obese PCOS group had lower variance. In addition, the control groups and eutrophic PCOS presented higher LF and HF oscillations in absolute values than the obese PCOS group. There were no differences between the groups in BPV analysis.

The results of BRS analysis obtained during rest in all groups studied, control, eutrophic PCOS and obese PCOS, are seen in Table 3, that show at rest the obese PCOS group presented lower spontaneous BRS than the others groups. In addition, it is important to note that the control group demonstrated a higher baroreflex effectiveness index.

Discussion

The present study mainly findings were, at rest the obese PCOS group had lower HRV and BRS than the other two groups, BPV was similar across groups.

Regarding hemodynamic values, PCOS obese group showed the highest values of systolic, diastolic and mean blood pressure compared to other groups, despite the fact that all subjects were normotensive; some studies had also show a relation with body fat increase and increase BP values.[9,10,21,22] To VO_{2peak}, the obese PCOS group had the lowest value, similarity to literature, which some authors found a negative correlation between obesity and VO2peak.[21,22]

There are few studies in the literature about obesity and PCOS, which are contradictory, some point to this association as a negative factor in HRV,[3,4] although others report that there is no association between weight gain and PCOS.[11,23] In this sense, the lower HRV found in the obese PCOS group in the present study suggests that this change is due to obesity. The literature indicates that the obesity mechanisms may be associated with a reduced sympathetic system response in the postsynaptic region since they had found in presynaptic cleft a high sympathetic activity represented by high concentration of noradrenaline.[24,25] In addition, a recent study carried out in our laboratory showed low frequency (LF) and high frequency (HF) bands differences, in absolute and normalized units, in healthy and sedentary women with normal BMI, overweight and obesity, they verified that the obese group had lower LF and HF oscillations.[10]

Regarding BRS, the eutrophic PCOS and control groups presented similar values, agreeing with Lambert, 2015, in which the groups had similar BMI and BRS values. In relation to the obese PCOS group, it had the lowest values in all BRS parameters than the others two eutrophic groups, suggesting that obesity may be responsible for a reduction in BRS. In this sense, a study comparing BRS in women divided by BMI indicates a BRS reduction with gain weight, observed by the BRS gain value, in this way, the BRS decrease might correlate to weight increase.[26] However, it is known that BRS is also influenced by many other factors like insulin resistance, blood glucose, sodium sensibility, genetic markers and ovarian hormones.[27,28] In the present study, neither of these other factors were measuring. Thereby it is possible to suggest that obesity may influenced in BRS values, as observed in another study,[26] although further studies are needed to confirm these findings in PCOS women.

Table 1 – Hemodynamic characteristics and values among healthy women and women with polycystic ovary syndrome (PCOS), subdivided into eutrophic PCOS (BMI < 25 kg/m²) and obese PCOS (BMI > 30 kg/m²)

	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
Characteristics					
Age, years	31.2 ± 6.6	28.5 ± 5.2	30.2 ± 5.3	0.053	0.107
Heights, meters	1.64 ± 5.0	1.62 ± 5.8	1.62 ± 7.9	0.102	0.649
Weight, kg	64 ± 10	60.6 ± 5.7	90.3 ± 10.9*†	0.09	< 0.001
BMI, kg/m²	23.5 ± 3	22.9 ± 1.6	33.9 ± 2.4*†	0.494	< 0.001
Body fat percentage, %	25.6 ±3.6	26.4 ± 3.4	44.3 ± 3.3*†	0.325	< 0.001
VO_{2peak}, L/min/kg	35.5 ± 3.3	31.9 ± 3.9	25.3 ± 3.3*†	0.05	< 0.001
Hemodynamics Values					
HR (bpm)	76 ± 2.6	74.6 ± 2	77 ± 2	0.764	0.416
SBP (mmHg)	105 ± 8.9	101 ± 11.8	111 ± 9.5†	0.057	< 0.001
DBP (mmHg)	70 ± 10.3	66 ± 9.6	76 ± 7.4*†	0.05	< 0.001
MBP (mmHg)	84 ± 9	80 ± 9.8	90 ± 7.5*†	0.05	< 0.001

Values expressed as means ± SD: standard deviation; m: Meters; Kg: kilogram; BMI: body mass index; VO_{2peak}: volume of oxygen consumed at the peak of exercise; L/min/Kg: liters per minutes per kilo; HR: heart rate; bpm: beat per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; mmHg: millimeters of mercury; statistical difference when p < 0.05; (*) vs. Control; (†) vs. eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Table 2 – Parameters of the spectral analysis of the heart rate variability analysis calculated from the time series RR intervals and systolic arterial pressure variability calculated by the pulse beat-to-heart rate interval obtained between women without and with polycystic ovaries syndrome (PCOS) divided according to the body mass index eutrophic < 25 kg/m² and obese > 30 kg/m²

	Rest				
	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
HR variability					
RRi, ms	872 ± 31	879 ± 20.6	812 ± 18.5†	0.961	0.049
Variance, ms²	2389 ± 310	2654 ± 341	1851 ± 405*†	0.971	0.010
LF, ms²	697 ± 105	720 ± 93	413 ± 80*†	0.855	0.002
LF, un	40.3 ± 3.8	45.5 ± 3.5	46.4 ± 2.9	0.350	0.850
HF, ms²	1134 ± 188	1180 ± 229	968 ± 204*†	0.502	0.014
HF, un	59.6 ± 3.8	54.4 ± 3.5	53.4 ± 2.9	0.350	0.850
LF/HF Ratio	0.79 ± 0.1	0.92 ± 0.1	0.94 ± 0.1	0.474	0.99
BP variability					
Variance, mmHg²	22.9 ± 4.3	24.9 ± 2.2	21 ± 2	0.168	0.052
LF, mmHg²	6.7 ± 1.4	7.6 ± 0.8	5.7 ± 0.7	0.196	0.054

Values expressed as means ± SD: standard deviation; HR: heart rate; RRi: interval between R waves on the electrocardiogram; nu: normalized units; ms²: milliseconds squared; LF: low frequency band; HF: high frequency band; BP: blood pressure; significant difference p < 0.05; (*) vs rest control, (†) vs. rest eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Table 3 – Parameters of the baroreflex analysis by the calculated sequence series of RR intervals obtained between women with and without polycystic ovary syndrome (PCOS) divided according to the body mass index eutrophic < 25 kg/m² and obese > 30 kg/m²

	Rest				
	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
Baroreflex Sensitivity					
Ramp numbers	85 ± 40.7	84.3 ± 39.8	93.7 ± 42.4	0.853	0.379
BEI	0.74 ± 0.13	0.63 ± 0.12*	0.58 ± 0.15*	0.005	0.225
UP, ms/mmHg	15.1 ± 6	18 ± 11	11.7 ± 6.7 *†	0.738	0.008
DOWN, ms/mmHg	16.5 ± 5.6	18.3 ± 8.8	12.7 ± 7.5 *†	0.738	0.004
GAIN, ms/mmHg	16.1 ± 5.5	18.3 ± 9.3	12.3 ± 7.2 *†	0.687	0.003

Values expressed as means ± SD: standard deviation; BEI: baroreflex efficacy index; GAIN: total gain; DOWN: hypotensive responses associated with tachycardia responses; UP: hypertensive responses associated with bradycardic responses; significant difference p < 0.05; (*) vs rest Control, (†) vs rest eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Finally, in relation to BPV similarity were found between the studied groups, there are few information since there are no studies in the literature about the behaviour of BPV in PCOS women, the studies found are associated with cardiovascular diseases, unrelated to PCOS.[29-31] Although, PCOS women have a greater predisposition to develop cardiovascular diseases, the present study population were healthy and did not use medication, suggesting that PCOS does not alter the BPV. In addition, the obese PCOS group also did not present differences in relation to eutrophic groups. The studies found on BPV and obesity are contradictory, some suggest an increase[24,32] while others point out a reduction of BPV.[33] However, both suggest that the baroreflex could justify these changes. Meanwhile, in our study, although the obese PCOS group presented a decrease in BRS, the BPV, apparently, was not affected. In this way, we need more studies to elucidate these findings.

Study limitations

The present study had some limitations, as insulin, glucose and inflammatory markers dosages absence, which could contribute to results discussion; another limitation was HRV and BPV measure only in supine position. It is possible that during an autonomic provocation test, as in tilt test, we could find different responses in autonomic modulation between the studied groups. However, it is important to note that the study limitations do not invalidate the main findings in supine position and its clinical implications.

Conclusion

Although PCOS is an endocrine-metabolic disease that causes several body changes, it does not alter the autonomic cardiovascular control. However, the association with obesity resulted in a decrease in BRS values, and attenuated the HRV values. Suggesting that obesity may play a role in change hemodynamics parameters and cardiovascular autonomic control. However, further studies should be conducted to investigate the effects of metabolic and hormonal changes in these women and the association of these changes with cardiovascular autonomic control.

Author contributions

Conception and design of the research: Philbois SV, Souza HCD; acquisition of data: Philbois SV, Facioli TP, Felix ACS; analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Philbois SV, Gastaldi AC, Souza HCD; statistical analysis: Philbois SV, Facioli TP; obtaining funding: Souza HCD; writing of the manuscript: Gastaldi AC, Souza HCD.

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 das Clínicas de Ribeirão Preto e da Faculdade de Medicina de Ribeirão Preto under the protocol number 11487/2014. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Polycystic Ovary Syndrome and Cardiovascular Diseases: Still an Open Door

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Short Editorial related to the article: Women with Polycystic Ovarian Syndrome Exhibit Reduced Baroreflex Sensitivity That May Be Associated with Increased Body Fat

This issue of the Brazilian Archives of Cardiology (ABC Cardiol) brings the article "Women with Polycystic Ovarian Syndrome Exhibit Reduced Baroreflex Sensitivity That May Be Associated with Increased Body Fat", by Philbois, SV et al., which draws attention to this clinical condition that is so prevalent in our country and its many aspects related to cardiometabolism, neuroregulation and cardiovascular risk.[1]

The Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age,[2] with an estimated prevalence of 6 to 10% in this population.[3] According to the Rotterdam criteria, PCOS is diagnosed in the presence of at least two of the three criteria: menstrual disorders or amenorrhea with chronic lack of ovulation, clinical and/or biochemical characteristics of hyperandrogenism and the presence of polycystic ovaries on ultrasonography after exclusion of other endocrine disorders.[4] Overall, SOP has been considered a reproductive disorder; however, it also represents a significantly increased risk for cardiometabolic disorders.[2] The impact on reproduction is predominant during the reproductive years, while cardiometabolic alterations become more important in the later stages of a woman's life.[2]

Women with PCOS are at increased risk of obesity, arterial hypertension, glucose intolerance, dyslipidemia and obstructive sleep apnea.[5] Obesity is present in approximately 50%,[4] whereas insulin resistance occurs in 60% to 95% of them,[6] leading to glucose intolerance in 31% to 35%[7] and type 2 diabetes mellitus in 7.5% to 20%[8] of these women. However, dyslipidemia is the most common metabolic abnormality in PCOS, generally presenting with the phenotype exhibiting low levels of high-density lipoprotein (HDL) and high levels of triglycerides, consistent with insulin resistance, also presenting with increased insulin resistance and low-density lipoprotein (LDL) cholesterol levels.[7,8]

The prevalence of non-alcoholic fatty liver disease and obstructive sleep apnea are also high in women with PCOS. Even after controlling for body mass index (BMI), women with PCOS are still 30-fold more likely to have sleep-disordered breathing.[9,10]

Keywords

Polycystic Ovary Syndrome; Cardiovascular Diseases/physiopatholog; Obesity/metabolism; Autonomic Nervous System/abnormalities; Baroreflex.

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Sub-clinical markers of cardiovascular disease, such as increased carotid artery intima-media thickness,[11] increased calcification of the coronary arteries,[12] and higher serum concentrations of C-reactive protein[13] have also been associated with PCOS.

There is evidence that the autonomic nervous system (ANS) plays an important role in ovarian physiology regulation.[14] It is estimated that increased sympathetic activity in women with PCOS may be associated with their hormonal and metabolic characteristics.[15] Although autonomic dysfunction is considered a predictor of cardiovascular events and mortality,[16] there is limited evidence of alterations in this pathophysiological parameter among women with PCOS.

A study showed that rats with estrogen-induced polycystic ovaries showed high uptake of norepinephrine, and a high degree of the neurotransmitter release with ovarian electrical stimulation.[17] Yildirir et al. analyzed heart rate variation (HRV) in women with PCOS, demonstrating a significant increase in the low-frequency spectrum component and a decrease in the high-frequency component in relation to the control group.[18] Tekin et al. showed a decrease in heart rate and blood pressure recovery after exertion in comparison to controls.[19] Drag et al. demonstrated dysfunction of the sympathetic and parasympathetic components of ANS in women with PCOS using electromyography.[20] The authors found no association between weight gain as measured by BMI and alterations in skin sympathetic response tests and R-R interval variation, parameter of the parasympathetic response, attributing to hyperandrogenism and insulin resistance the probable cause of the dysfunction.[20] Using the HRV spectral analysis, the study by Philbois SV et al., published in this issue of ABC Cardiol, found no alterations in autonomic cardiovascular control in women with PCOS.[1] However, the authors correlated the decline in baroreflex sensitivity, an important measure of autonomic cardiovascular function, as well as the attenuation of HRV values, with the increase of body fat in women with PCOS.[1]

Although the results of the studies are conflicting, it can be concluded that insulin resistance, hyperandrogenism and obesity may result in autonomic dysfunction in PCOS.[1,17-21] This autonomic dysregulation is recognized as a factor of worse prognosis,[16,22] in addition to the set of metabolic[5-8] clinical,[9,10] and structural alterations[11-13] related to the syndrome when determining a higher cardiovascular risk. Despite all these demonstrations of subclinical dysfunction, there is still a lack of conclusive, long-term follow-up studies in these women, aiming to demonstrate definitive evidence of increased cardiovascular clinical outcomes associated with PCOS.[23]

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Retrospective Analysis of Risk Factors for Related Complications of Chemical Ablation on Hypertrophic Obstructive Cardiomyopathy

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Abstract

Background: **The analysis of risk factors for predicting related complications has not been reported to date.**

Objective: **This study aims to investigate the risk factors of related complications of percutaneous transluminal septal myocardial ablation (PTSMA) for hypertrophic obstructive cardiomyopathy (HOCM) retrospectively.**

Method: **Clinical data, and one-year follow-up results of patients with HOCM, who underwent PTSMA between January 2000 and July 2013 in the Department of Cardiology, Liaoning Province People's Hospital, Liaoning Province, China, were retrospectively analyzed to determine risk factors for operative complications with multiple logistic regression analysis. All p values are two-sided, with values of $p < 0.05$ being considered statistically significant.**

Results: **Among 319 patients with HOCM, PTSMA was performed in 224 patients (120 males and 104 females, mean age was 48.20 ± 14.34 years old). The incidence of PTSMA procedure-related complications was 36.23% (66/224), which included three cardiac deaths, two cardiac shocks, one ST-segment elevated myocardial infarction, two ventricular fibrillations, 20 third-degree atrioventricular (AV) blocks (four patients were implanted with a permanent pacemaker (PPM)), 32 complete right bundle branch blocks, two complete left bundle branch blocks, and four puncture-related complications. After multivariate logistic regression analysis, it was found that age, gender, coronary artery diseases, diabetes, heart rate, cardiac function on admission, the number of septal ablations, and the volume of alcohol were not independent risk factors correlated to the whole complications, except for hypertension (OR: 4.856; 95% CI: 1.732-13.609). Early experience appears to be associated with the occurrence of complications.**

Conclusion: **Hypertension was an independent risk factor for PTSMA procedure-related complications. It might be much safer and more efficient if PTSMA procedures are restricted to experienced centers, according to the analysis results for the learning curve. (Arq Bras Cardiol. 2019; 112(4):432-438)**

Keywords: **Cardiomyopathy, Hypertrophic/prevention and control; Myocardial, Percutaneous Transluminal Septal Myocardial Ablation (PTSMA); Ventricular Dysfunction Left/complications.**

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is defined as primary myocardial hypertrophy with dynamic left ventricular outflow tract (LVOT) obstruction and diastolic dysfunction of left ventricle (LV). HOCM, which induces symptoms of angina, dyspnea and syncope, is a genetically determined disorder caused by mutations in genes encoding sarcomeric contractile proteins.[1] Myectomy has been proven to be capable of improving short- and middle-term survival in patients with HOCM with severe drug refractory symptoms.[2,3] With the development of techniques and equipment for percutaneous coronary intervention, percutaneous transluminal septal myocardial ablation (PTSMA) has become an alternative to myectomy with a decade history.[4,5] However, despite the advances in the judgment of indication, operating skill, optimal medical treatment and the management of complications, PTSMA-related complications remain high during the perioperative period. The most common complication is right bundle branch block. The most significant complications include high-degree conduction block needing PPM, acute myocardial infarction, cardiac shock, cardiac death, puncture site complications.[6-8] Unfortunately, only predictors for long follow-up outcome have ever been analyzed.[7,9] The analysis of risk factors for predicting related complications have not been reported to date. In this report, we attempted to identify risk factors related to PTSMA procedure complications by conducting a retrospective review of 319 HOCM patients.

Methods

The study population comprised 319 patients with HOCM, who were referred to the Cardiology Department of Liaoning Provincial People's Hospital of China, and considered septal reduction therapy with PTSMA between

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January 2000 and July 2013. Among these 319 patients, 258 met the inclusion criteria for septal reduction therapy with resting left ventricular outflow tract gradient (LVOTG) ≥ 30 mmHg or exercise-induced LVOTG ≥ 50 mmHg.[9] The diagnostic criteria for HOCM were end-diastolic wall thickness >15 mm, and a non-dilated LV with an ejection fraction (EF) of ≥ 50%.[10] Exclusion criteria were hypertrophy from other causes (n = 17), history of myocardial infarction (n = 10), and prior intervention with PTSMA (n = 7) or septal myectomy (n = 0). Patients with coronary artery disease (CAD) (coronary artery stenosis ≥ 50% evaluated at coronary angiography) without myocardial infarction, mild or moderate valvular heart disease unrelated to HOCM, and patients on antihypertensive therapy were not excluded.

Diabetes was defined according to the guidelines.[11] Hypertension was defined as either a systolic or diastolic elevation of blood pressure (>140/90 mmHg) or ongoing antihypertensive therapy. Hypercholesterolemia was defined as a total cholesterol level >5.0 mmol/L, or current treatment with lipid-lowering medications. The present study complied with the Declaration of Helsinki. The Local Ethics Committee of the Liaoning Province Hospital approved the study protocol, and all patients provided an informed consent.

Echocardiography

Before and during the procedure, and at follow-up, all patients underwent transthoracic echocardiography using a Hewlett-Packard Sonos 1500 (Hewlett-Packard Co., Andover, Massachusetts, USA) echocardiograph with an interfaced 2.5-MHz transducer. The following parameters were measured: intra-ventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, and end-systolic and end-diastolic dimensions from the minor axis M-mode of the LV obtained from a 2-dimensional standard left parasternal view. LVOTG was measured by a continuous-wave Doppler probe positioned at the cardiac apex. EF was automatically calculated.

Dobutamine stress echocardiography

Dobutamine was administered using an infusion pump at a starting rate of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with increments of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every three minutes to a maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ if necessary. The stress-induced echocardiography endpoint is the end of the eighth stage of the dobutamine protocol, or following chest pain, dyspnea, a drop in arterial pressure of 20 mmHg or more, and an ST-segment shift of 1 mm or more.

Cardiac catheterization, gradient determination and ablation procedure

The right femoral and right radial arteries, as well as the right femoral vein, were cannulated using the standard Judkins technique. After an intravenous bolus of 100-150 U/kg of heparin, a 6F temporary pacemaker lead was placed in the right ventricle, a 6F pigtail catheter was positioned in the left ventricular apex, and a 6F Judkins guiding catheter was placed in the left coronary artery. The resting LVOTG was determined by simultaneous pressure recording. Provocation after premature ventricular contraction caused by the pigtail catheter (Terumo, Japan) was performed if necessary. The adequate septal branch was identified on the coronary angiogram; after that, a 0.014-inch guide wire (Bmw; Bebi Inc., India) was inserted into the septal branch. Then, an over-the-wire balloon catheter (1.5/2.0/2.5 mm in diameter, 10/20 mm in length; Medtronic, USA) was placed in the proximal part of the septal branch. After balloon inflation at 2-6 atm, the correct balloon position was determined by injection of the contrast medium *via* the guiding catheter into the left coronary artery, and by injection through the balloon catheter shaft into the septal branch. In order to determine the target septal branch, probationary balloon inflation and/or myocardial contrast echocardiography (MCE) was performed. When sufficient decrease in LVOTG was observed through probationary balloon inflation, the septal branch was identified as the target. MCE was routinely performed according to routine methods.[12] When the target septal branch was determined, after intravenous administration of 5 mg of diamorphine, 1-2 ml of absolute alcohol was slowly injected through the balloon catheter shaft. Ten minutes later, the balloon was deflated and the contrast medium was injected *via* the guiding catheter to ascertain that the septal branch was completely blocked. Patients were monitored in the Coronary Care Unit for three days after removal of the vascular sheaths. After 48 hours, when the patient appeared to have normal cardiac conduction, the temporary pacemaker was removed. If high-grade AV conduction disturbances were observed during the following days, PPM implantation was offered. Patients were discharged and followed at our outpatient clinics.

Complications

Complications during PTSMA procedures and in-hospital monitoring were registered. The events were acute heart failure, cardiac shock, cardiac death and arrhythmic events (bradycardia, asystole, sustained and non-sustained ventricular tachycardia, and ventricular fibrillation). Coronary artery complications were coronary dissection, coronary perforation, acute myocardial infarction, acute pericardial effusion, pericardial tamponade, and alcohol displacement. Bundle branch block and AV block including advanced heart block, which lead to PPM implantation, were registered. Advanced heart block was defined as bifascicular block, and second- or third-degree AV block. Asystole due to third-degree AV block was classified as third-degree AV block (i.e. advanced heart block). Puncture related complications were also included for the final analysis.

Patient follow-up

Patients were carefully monitored in the Coronary Care Unit for at least three days after the procedure, and back-up pacing was continued *via* the femoral vein when necessary. In-hospital assessment was performed for all clinical outcomes, including hemorrhagic and vascular complications (femoral artery pseudoaneurysm and puncture hematoma were also included for analysis). After discharge, monthly clinical follow-up examinations were conducted on an outpatient basis, in order to monitor the occurrence of adverse events. Examinations through catheterization were not routinely performed, and were only conducted when residual or recurrent symptoms were observed after discharge. PTSMA was repeated when necessary. A failed outcome after PTSMA was defined as the need for

re-intervention due to the absence of clinical improvement, or recurrence of symptoms, and significant LVOTG. To analyze the influence of the learning curve in relation to PTSMA complications, patients were separated into three chronological groups (early experience: from 2000 to 2004; intermediate experience: from 2005 to 2009; late experience: from 2010 to 2013) according to their experience with PTSMA.

Statistical analysis

All data analysis was performed with the SPSS System (version 19.0; SPSS Inc., Chicago, IL, USA).One-Sample Kolmogorov-Smirnov test, and Levene's test had been used to test the normality distribution and variances equality of data. Data with normal distribution were expressed as mean ± standard deviation (SD). Differences between groups were analyzed for statistical significance using the unpaired Student's t-test. Frequency was compared using Chi-squared (X^2) test. Multivariate stepwise logistic regression was used to select independent variables. A p-value < 0.05 (2-tailed) was considered statistically significant.

Results

A total of 224 subjects, who were between 9-82 years old, were included into this study for final analysis (Figure 1). The detailed patients' demographic and echocardiographic characteristics were shown in Table 1.

Acute results

Changes to hemodynamic results during the intervention

An 82 year-old patient died during the injection of alcohol for acute pericardial tamponade. A mean of 1.17 ± 0.45 (range: 1-2) septal branches were occluded by injection of 2.07 ± 0.89 ml (range: 0.5-3.0 ml) of alcohol. A reduction in LVOTG was achieved for all patients. The mean systolic pressure difference in LVOTG at rest decreased from 67.91 ± 37.23 to 16.24 ± 19.13 (p < 0.01). The post premature gradient was reduced from 119.42 ± 38.44 to 40.83 ± 22.61 (p < 0.01).

Improvement of clinical course

All patients complained of marked chest pain during alcohol injection, and a feeling of discomfort in the left thorax lasted up to 30 hours (10-30 hours). Clinical symptoms greatly improved in 190 patients (85%). Differences in New York Heart Association functional class (from 1.08 ± 0.36 to 1.01 ± 0.09) were not statistically significant.

Complications

Two patients developed ventricular fibrillation after alcohol injection, and sinus rhythm was restored by 200 J of defibrillation. Two patients had cardiac shock due to the prolonged occlusion of the septal arteries. One case of thrombosis in the left anterior descending artery during the PTSMA procedure was observed. The patient was successfully treated, and coronary flows were normalized. Temporary right bundle branch block and left bundle branch block occurred in 32 patients and two patients, respectively. Furthermore, 20 patients developed a third-degree AV block, but only four patients developed a complete AV block, requiring PPM implantation. Puncture related complications occurred in four patients (femoral artery pseudoaneurysm in two patients and puncture hematoma in two patients), which were successfully treated with compression bandage.

One-year noninvasive follow-up

None of the patients were lost to follow-up. No other complications or severe major adverse cardiac events

Table 1 – Clinical characteristic of 224 patients with hypertrophic obstructive cardiomyopathy (HOCM) on admission

	Patients on admission (n = 224)
Age (years)	48.20 ± 14.34
Male/female	120/104
New York Heart Association functional class	1.08 ± 0.36
CAD	13
Hypertension	47
DM	3
Stroke	1/
HR (beats/min)	70.92 ± 11.66
LVOTD (mm)	9.38 ± 2.52
EF	0.65 ± 0.07

CAD: coronary artery disease; DM: diabetes mellitus; HR: heart rate; LVOTD: left ventricular outflow tract diameter; EF: ejection fraction.

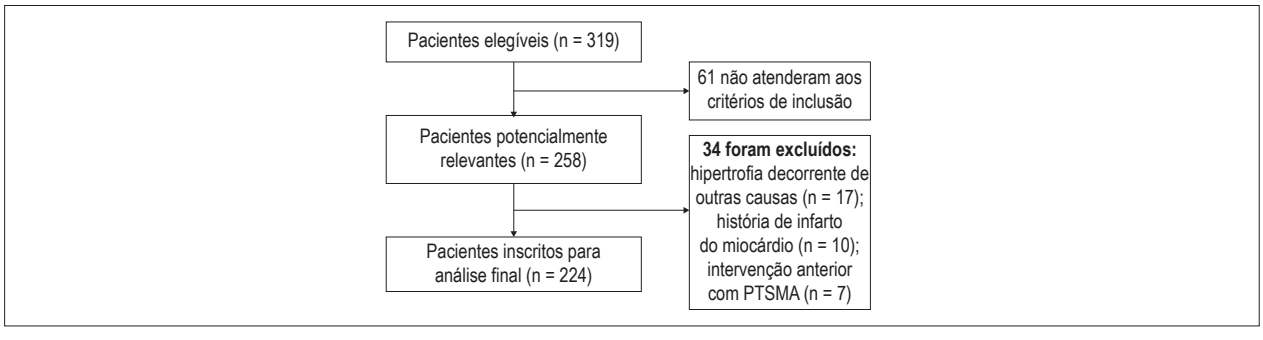

Figure 1 – *Flow diagram of the patients selection.*

occurred during the clinical follow-up, except that PTSMA was successfully performed again in one patient for recurrent angina pectoris.

The univariate analysis of risk factors for PTSMA-related complications is shown in Table 2. Age, female gender, alcohol volume, the number of septal ablations, comorbidities with CAD, hypertension, and diabetes mellitus (DM) were associated with increased occurrence of complications. Results of the multiple logistic regression analysis are presented in Table 3. In multiple logistic models, except for hypertension (OR: 4.856; 95% CI: 1.732-13.609), age, gender, alcohol volume, the number of septal ablation, comorbidities with CAD, and DM were not potential risk factors for predicting PTSMA-related complications.

Table 4 shows the comparisons of clinical characteristics between patients with and without history of hypertension. Female patients appeared to have more cardiovascular risk factors such as hypertension, aging, DM, and history of heart failure in the present study.

As listed in Table 5, patients were chronologically divided into three groups according to their experience with PTSMA. In addition, in-hospital complications were more frequent in patients who underwent PTSMA procedures in the early stage (from 2000 to 2004), and less often in patients who unerwent PTSMA procedures later and in experienced time periods (2010-2013) ($p = 0.022$).

Discussion

PTSMA is a nonsurgical technique to reduce septal mass by producing a septal infarction using the catheter techniques reported by Sigwart.[4] Permanent septal necrosis is created through the injection of alcohol in the septal branches that supply the myocardium and are responsible for LVOT obstruction induced by abnormal structure and function. This effectively reduces the pressure gradients in patients with HOCM. This technique has the advantage of micro-trauma and high success rate, as well as low mortality (0–1.8%).[13,14] In the present cohort, a successful reduction in LVOTG was achieved in the majority of patients during the procedure (85%) (at rest: from 67.91 ± 37.23 to 16.24 ± 19.13 mmHg, $p < 0.01$; post premature beat: 119.42 ± 38.44 to 40.83 ± 22.61 mmHg, $p < 0.01$) and at discharge (96%).

However, the occurrence of PTSMA procedure-related complications was notable. In the present study, 14.35% (32/223) of patients had transient complete bundle branch block (32/223), and 0.90% (2/223) of patients had complete left bundle branch block. This phenomenon was consistent with a previous report.[15] The right bundle is usually supplied by proximal septal perforators. Thus, PTMSA frequently leads to complete right bundle branch block. Furthermore, septal myectomy causes complete left bundle branch block in most patients. This is the reason why PTMSA caused more complete right bundle branch and less complete left bundle branch block in our study. Not more than 10% of patients had a high-degree AV block. However, PPM was only performed in four patients (1.79%), which was superior when compared with other PTSMA centers (46% and 38%).[16,17] Serious complications were not uncommon. Except for patient's death from acute tamponade during the procedure, the most significant complication of the procedure was heart block,[9] which led to the deaths of two patients in our study. One patient had acute severe left ventricular dysfunction during the procedure, while the other patient had heart failure during monitoring in Coronary Care Unit. In addition, reports of in-hospital ventricular fibrillation in relation to PTSMA have attracted considerable attention.[18,19] We found two (0.89%) cases of in-hospital ventricular fibrillation. According to our experience, careful monitoring was indispensable to reducing cardiac adverse events caused by ventricular arrhythmia. As for other serious nonfatal complications, acute myocardial infarction, which was caused by the spill of alcohol into the left anterior descending coronary artery, occurred in one patient. However, no coronary dissection and nonfatal cardiac tamponade occurred.

Table 2 – Univariate analysis of risk factors for related complications of PTSMA

	Complications (n=66)	No Complications (n=158)	p value
Age (years)	51.27 ± 14.13	46.91 ± 14.28	0.038
Male/female	27/39	92/66	0.000
New York Heart Association functional class	1.10 ± 0.40	1.08 ± 0.33	0.566
CAD	5	8	0.000
Hypertension	19	27	0.000
DM	3	0	0.000
Stroke	1	0	0.122
HR (beats/min)	71.55 ± 11.92	71.08 ± 12.29	0.792
LVOTD (mm)	9.13 ± 2.64	9.33 ± 2.54	0.604
EF	0.63 ± 0.13	0.66 ± 0.08	0.506
Alcohol volume	2.14 ± 0.88	1.85 ± 0.91	0.023
Number of ablation septal	1.19 ± 0.43	1.07 ± 0.27	0.034

CAD: coronary artery disease; DM: diabetes mellitus; HR: heart rate; LVOTD: left ventricular outflow tract diameter; EF: ejection fraction.

Table 3 – Multivariate logistic regression for potential risk factors for PTSMA complications

	p value	Odds ratio	CI
Age (years)	0.767	0.995	0.959-1.031
Male	0.198	0.527	0.198-1.399
CAD	0.761	0.761	0.132-4.407
Hypertension	0.003	4.856	1.732-13.609
DM	0.176	6.620	0.428-12.527
Alcohol volume	0.385	0.757	0.403-1.420
Number of ablation septal	0.436	0.682	0.370-2.253

CAD: coronary artery disease; DM: diabetes mellitus.

Table 4 – Comparisons of clinical and echocardiographic characteristics between patients with and without hypertension

	Hypertension (n = 46)	No hypertension (n = 178)	p value
Age	58.13 ± 10.10**	45.23 ± 13.95	0.000
Female	28**	75	0.025
DM	3**	0	0.007
CAD	5	8	0.000
History of heart failure	7*	8	0.010
LVOTD (mm)	9.56 ± 2.76	9.24 ± 2.62	0.480
HR (beats/min)	70.57 ± 11.13	71.37 ± 12.46	0.692
EF	0.63 ± 0.07	0.65 ± 0.07	0.113

CAD: coronary artery disease; DM: diabetes mellitus; HR: heart rate; LVOTD: left ventricular outflow tract diameter; EF: ejection fraction.

Table 5 – In hospital complications and late interventional failure according to experience

	Early experience (n = 75)	Intermediate experience (n = 93)	Late experience (n = 56)	p value
Events	31	22	13	0.022
No events	44	71	43	

Patients' demographic characteristics should be the potential risks for PTSMA procedure complications. However, according to a previous report,[18] none of the studied baseline echocardiographic, clinical and PTSMA-related characteristics were useful in predicting the PTSMA success rate and its complications. A report on nine-year follow-up results from the SZEGED study revealed that coronary flow velocity reserve (CFR) was an independent predictor of cardiovascular event-free survival for patients with HOCM.[13] However, CFR was estimated by transesophageal echocardiography, which is inconvenient in clinical practice. In the univariate analysis of our study, age, gender, alcohol volume, the number of septal ablations, comorbidities with CAD, hypertension and DM appeared to be associated with the increased occurrence of complications. However, only hypertension, and not the other characteristics, was shown to be a potential factor for predicting complications (OR: 4.856; 95% CI: 1.732-13.609) after multivariate logistic regression analysis. Patients with hypertension were older, showed more significant changes in the echocardiogram, presented with more comorbidities (Table 4). We might present a hypothesis that patients with hypertension had lower cardiac reserve function due to more cardiovascular risks in this cohort. Hence, this might be the reason why hypertension could be a potential risk factor for PTSMA complications.

It is well-known that clinical experience influences the results of a procedure. Similar to results observed from percutaneous coronary interventions,[20] a high-volume load for operators and institutions has been proven to be associated with better procedural outcomes. The importance of a learning curve for PTSMA was confirmed in our study, because a high incidence of late PTSMA failure was noted in the early experience group of patients, whereas this number was significantly reduced with higher experience. At a frequency of approximately 16 treated patients per year, the incidence of late PTSMA complication has been reduced from 41.33%

to 23.21%, which was not different from that in other experienced centers.[7,21] Therefore, PTSMA procedures might be safer and more efficient in experienced centers.

Limitations

There were several important limitations in the present study. (1) One of the most important limitations was that only a limited number of HOCM patients were examined. (2) In this study, these PTSMA procedures were elected based on the preferences of patients and the physician. Therefore, patients were not consecutively enrolled. If the patient was an older person, or had significant comorbidity conditions, PTSMA was not that strongly suggested. For older patients, especially those with concomitant disease and without enough insurance, medication or a less aggressive approach of PTSMA might be a better or the only choice, even with the incomplete elimination of LVOT obstruction. (3) The decision regarding the target septal artery was taken based on available angiographic images, as well as the assistance of MCE. However, we still could not rule out that more targeted imaging might have yielded more anatomically correct values.

Conclusion

In summary, PTSMA was effective in reducing LVOTG in HOCM patients. Hypertension was the only independent risk factor for PTSMA procedure-related complications after multivariate logistic regression analysis. In addition, PTSMA procedures might be safer and more efficient in experienced centers, according to the analysis result for the learning curve.

Author contributions

Conception and design of the research, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Cheng-Yang L; Acquisition of data and Analysis and interpretation of the data: Cheng-Yang L and Yun-Qi S.

Potential Conflict of Interest

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

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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 Hospital da Província de Liaoning. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Septal Ablation in Obstructive Hypertrophic Cardiomyopathy (oHCM)

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Short Editorial related to the article: Retrospective Analysis of Risk Factors for Related Complications of Chemical Ablation on Hypertrophic Obstructive Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with a prevalence of 1 case in 500 individuals.[1] The disease is very heterogeneous regarding its phenotype, being the main cause of sudden death in athletes who they die in competitions.[1,2] Fortunately, most patients are asymptomatic or have few symptoms and will have a life expectancy very close to the individuals without the disease.[2] However, some patients will develop symptoms such as angina, dyspnea, palpitations, syncope and even sudden death, usually caused by ventricular arrhythmia. Approximately 2/3 of patients with HCM have a significant left ventricular outflow tract (LVOT) gradient at rest or during drug or physical exertion provocation tests.[3] The presence of a significant gradient, mainly at rest, characterizes obstructive hypertrophic cardiomyopathy (OHCM) and the presence of the gradient is related to greater symptom intensity and a higher risk of death.[1-3]

The standard treatment of symptomatic patients comprise the use of drugs such as beta-blockers and/or calcium channel blockers, which decrease the gradient and improve angina, diastolic function and increase tolerance to physical exertion.[1-3] Between 5 and 10% of patients with OHCM are refractory to pharmacological treatment and should be considered for invasive treatment: surgical myomectomy (SM) or septal ablation (SA) (alcoholization) with the aim of reducing septal muscle mass and relieve LVOT obstruction.[4,5] Since its introduction in 1995 by Sigwart et al.,[5] SA has become an alternative to surgical treatment (which was considered the gold standard treatment for patients with OHCM and refractory to clinical treatment). After the introduction of SA, because it was found to be attractive to the patient and to the physician, a rapid and progressive increase in the number of performed procedures was observed, especially in the European countries, which quickly surpassed the number of surgeries performed annually worldwide and with results in the short and medium term that were similar to the results obtained with surgical procedures in centers of excellence, according to data from patient cohorts, registries and meta-analyses,[6,7] since there are no randomized trials comparing the two forms of intervention. But despite the significant increase in the number of SA performed and after two decades of experience, some controversy remains about the choice of invasive procedure (SA or SM?).[4,8-11]

As it has more than 4 decades of experience, consistent results in the longer term and it is more effective in reducing the gradient (eliminates the gradient in >90% of the cases), the European guideline recommends surgery (septal myomectomy) performed in specialized centers (mortality rate <2.0% and rate of complications <5%) as the procedure of choice (degree of recommendation Ia and evidence level B) and SA as an alternative, with degree of recommendation IIa and evidence level **C** for selected patients, with contraindication to surgery or at high surgical risk or even in cases of myomectomy failure.[9]

It is worth noting that the determinant factor for having good results with both procedures is the experience of centers, which must be measured by more than 50 procedures performed per year and more than 20 procedures performed by the operator (surgeon or interventional cardiologist), seeking to attain mortality rates <2% and complication rates <5%.[10,11]

In this issue, Li et al.[12] report the experience of a single center in China with SA for treatment of symptomatic OHCM. The author shows the results of the procedure in 224 patients, performed according to the preference of the patient and/or the attending physician, over a period of 13 years and after the 1-year follow-up, they retrospectively analyzed the risk factors for complications related to the procedure (in-hospital phase). The rate of complications related to the procedure was 36.23%, including 4 deaths, 3 cardiogenic shocks, 6 episodes of ventricular fibrillation, 1 myocardial infarction, 20 advanced AV blocks and 4 permanent pacemaker implants, plus 28 minor complications. At the multivariate analysis, only arterial hypertension stood out as a strong complication predictor. The rate of severe complications reported by the author is very high when compared to those of large series, in specialized centers and with a high volume of procedures.[4,6-8,13]

In the study by Li et al.,[12] it becomes clear that one of the factors associated with high complication rates may have been the relatively low number of procedures per year, the inclusion of older patients with comorbidities, and the inclusion of 46 hypertensive patients, who usually have a sigmoid, less thick interventricular septum; moreover, the hypertrophy may be secondary to hypertension and not necessarily observed in patients with OHCM, in addition to worsening diastolic function and being accompanied by comorbidities such as diabetes, coronary disease and atrial fibrillation.

In the large series that evaluated complications, factors related to the experience of the center and the operator and also to patient selection for SA always stand out as predictors

Keywords

Cardiomyopathy, Hypertrophic/physiopathology; Cardiomyopathy, Hypertrophic/therapy; Heart Septum/pathology; Heart Septum/drug effects; Ethanol/administration & dosage; Blood Pressure.

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of low rates of complications, especially age, comorbidities, preexisting bundle branch blocks, as well as anatomical and functional factors as determinants of complications and also of the success rate of the procedure.[13]

When selecting the patients for invasive treatment, one must ascertain the actual refractoriness of the clinical treatment (present in 5% of the patients in our center), evaluate the presence and impact of comorbidities, perform a careful assessment of the gradient, especially the resting gradient, since we do not know the actual influence of the inotropic stimulus on the genesis of the symptoms and the risk of death. The resting gradient should be >30 mmHg or ideally >50 mmHg; the basal septum thickness >15 mm or ideally >18 mm; one should determine that the gradient is in the outflow tract and not the mid-ventricular portion (10-15% of cases), the presence of the anterior systolic movement of the mitral leaflet, degree and mechanism of mitral regurgitation, anatomy of the papillary muscle and, mainly, the anatomy of the dominant septal artery, collateral dependence, source of collateral, risk of remote infarction, and, finally, technical factors with appropriate material, balloon test to verify whether there is a gradient reduction, amount of alcohol to be injected and procedure monitoring with contrast echocardiogram to prevent large infarctions.[1,3,4,13]

When choosing the type of invasive procedure, SM or SA, in addition to careful patient selection, one has to consider very thoroughly the fact that even symptomatic patients have an annual risk of death <3%. Thus, the availability of specialized centers and operators with experience in both procedures is mandatory, as both invasive procedures have only been shown to date to have an impact and reduce symptoms and improve quality of life, and none has shown to be capable of reducing the risk of sudden death, which is a major concern, especially in younger patients.[8,13] "We must always remember that the most important thing is to "treat the patient, not just the gradient."

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Intra-Atrial Dyssynchrony Using Cardiac Magnetic Resonance to Quantify Tissue Remodeling in Patients with Atrial Fibrillation

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Abstract

Background: **Recent studies suggest that left atrial (LA) late gadolinium enhancement (LGE) can quantify the underlying tissue remodeling that harbors atrial fibrillation (AF). However, quantification of LA-LGE requires labor-intensive magnetic resonance imaging acquisition and postprocessing at experienced centers. LA intra-atrial dyssynchrony assessment is an emerging imaging technique that predicts AF recurrence after catheter ablation. We hypothesized that 1) LA intra-atrial dyssynchrony is associated with LA-LGE in patients with AF and 2) LA intra-atrial dyssynchrony is greater in patients with persistent AF than in those with paroxysmal AF.**

Method: **We conducted a cross-sectional study comparing LA intra-atrial dyssynchrony and LA-LGE in 146 patients with a history of AF (60.0 ± 10.0 years, 30.1% nonparoxysmal AF) who underwent pre-AF ablation cardiac magnetic resonance (CMR) in sinus rhythm. Using tissue-tracking CMR, we measured the LA longitudinal strain in two- and four-chamber views. We defined intra-atrial dyssynchrony as the standard deviation (SD) of the time to peak longitudinal strain (SD-TPS, in %) and the SD of the time to the peak pre-atrial contraction strain corrected by the cycle length ($SD\text{-}TPS_{preA}$, in %). We used the image intensity ratio (IIR) to quantify LA-LGE.**

Results: **Intra-atrial dyssynchrony analysis took 5 ± 9 minutes per case. Multivariable analysis showed that LA intra-atrial dyssynchrony was independently associated with LA-LGE. In addition, LA intra-atrial dyssynchrony was significantly greater in patients with persistent AF than those with paroxysmal AF. In contrast, there was no significant difference in LA-LGE between patients with persistent and paroxysmal AF. LA intra-atrial dyssynchrony showed excellent reproducibility and its analysis was less time-consuming (5 ± 9 minutes) than the LA-LGE (60 ± 20 minutes).**

Conclusion: **LA Intra-atrial dyssynchrony is a quick and reproducible index that is independently associated with LA-LGE to reflect the underlying tissue remodeling. (Arq Bras Cardiol. 2019; 112(4):441-450)**

Keywords: **Heart Atria; Atrial Fibrillation; Diagnostic Imaging; Echocardiography/methods; Magnetic Resonance Spectroscopy.**

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia[1] and an independent predictor of stroke[2] and dementia.[3] The cornerstone treatment for drug-refractory AF is invasive catheter ablation with pulmonary vein isolation (PVI), but the rate of recurrence after PVI is relatively high.[4] Preprocedural assessment of left atrial (LA) late gadolinium enhancement (LGE) is a predictor of AF recurrence after PVI.[5,6] LA-LGE can be considered as a surrogate for the underlying tissue remodeling represented by fibrotic replacement that promotes AF. Although LA-LGE has a potential to improve the clinical outcomes of PVI by refining patient selection, its major limitation is the requirement of labor-intensive magnetic resonance imaging (MRI) acquisition and postprocessing, which are not always compatible with clinical workflow. In addition, LA-LGE requires intravenous contrast administration, which is contraindicated in subgroups of PVI candidates, such as individuals with renal failure or allergic reactions to gadolinium-based contrast materials. As a result, LA-LGE is not part of the standard clinical practice, except at experienced centers.[7]

Recently, we demonstrated that preprocedural assessment of LA intra-atrial dyssynchrony predicts AF recurrence after PVI.[8] The assessment utilizes a tissue-tracking technology that can be applied to any routinely acquired cine MRI, which does not require intravenous contrast administration.[9] It is simple and quick, only based on two long-axis views (two-chamber and four-chamber views) of routine cine MRI. Because the LA structure and function reflect the underlying tissue fibrosis,[10] it is possible that LA intra-atrial dyssynchrony serves as a surrogate for LA-LGE.

In this study, we hypothesized that LA intra-atrial dyssynchrony is associated with LA-LGE in patients with AF. In addition, we further hypothesized that LA intra-atrial dyssynchrony is greater in patients with persistent AF than

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in those with paroxysmal AF. To test these hypotheses, we conducted a cross-sectional study to evaluate LA intra-atrial dyssynchrony and LA-LGE in patients with either paroxysmal or persistent AF. We also quantified the amount of time required for the postprocessing, and the inter-reader and intra-reader reproducibility of LA intra-atrial dyssynchrony.

Methods

Study population

The study included 146 consecutive patients with symptomatic, drug-refractory AF referred for catheter ablation at the Johns Hopkins Hospital between June 2010 and December 2015 who underwent pre-procedural cardiac magnetic resonance (CMR). Patients with prior AF ablation or surgical procedure in the LA were excluded. Based on Heart Rhythm Society most recent guidelines, paroxysmal AF was defined as AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF is defined as continuous AF that is sustained beyond 7 days.[7] Patients in AF at the time of CMR were also excluded. The protocol was approved by the Institutional Review Board of The Johns Hopkins Hospital, and all the patients provided written informed consent.

CMR protocol

CMR was performed with a 1.5-Tesla scanner (Avanto; Siemens Medical Systems, Erlangen, Germany), a 6-channel phased-array body coil in combination with a 6-channel spine matrix coil. Electrocardiogram (ECG)-gated, breath-holding cine CMR images were acquired in the long-axis two- and four-chamber views by true fast imaging with steady-state precession (TrueFISP) sequence with the following parameters: TE/TR 3.0/1.5 ms; flip angle 78°; in-plane pixel size 1.5×1.5 mm^2; slice thickness 8 mm; slice spacing 2 mm; 30 frames per ECG R-R interval with a temporal resolution of 20-40 ms. The patients also underwent respiratory-navigated, ECG-gated LGE for quantification of LA fibrosis (Figure 3). LGE images were acquired within 15-25 minutes following the injection of gadopentetate dimeglumine (0.2 mmol/kg; Bayer Healthcare Pharmaceuticals, Montville, NJ, USA) using a fat-saturated 3D inversion recovery-prepared fast spoiled gradient-recalled echo sequence with the following parameters: TE/TR 1.52/3.8 ms; flip angle 10°; in-plane pixel size 1.3×1.3 mm^2; slice thickness 2.0 mm. The trigger time for three-dimensional (3D) LGE images was optimized to acquire imaging data during LA diastole as determined by the cine CMR images. The optimal inversion time was determined by an inversion time scout scan (median 270 ms, range 240-290 ms) to maximize nulling of the LA myocardium. The image intensity ratio (IIR)[11] was measured to quantify LA-LGE using QMass MR (version 7.2; Medis Medical Imaging Systems bv, Leiden, the Netherlands) on axial images from 3D axial image data. Briefly, IIR is a signal intensity of LA-LGE normalized by the mean signal intensity of the LA blood pool. The IIR threshold of 1.22 that corresponds to bipolar voltage 0.3 mV on intracardiac electrogram was used to define myocardial fibrosis.[12,13] Preprocedural CMR scans were acquired within a range of 15–25 minutes (mean 18.8 ± 2.4 minutes).

Magnetic resonance imaging Analysis

Left atrial intra-atrial dyssynchrony

Multimodality Tissue Tracking software (MTT, version 6.1, Toshiba, Japan) was used to quantify the LA longitudinal strains and strain rates in two-chamber and four-chamber views. The accuracy and reproducibility of MTT have been validated previously.[9,14] Briefly, an experienced operator, blinded to the type of AF, defined the LA endocardial and epicardial borders at the LA end diastole (Figure 1). The confluence of the pulmonary veins and LA appendage were excluded as appropriate. The software automatically propagates endocardial/epicardial borders over the entire cardiac cycle using a template matching algorithm.[14] Finally, the operator verified the quality of the tracking generated by MTT. The software automatically divides the LA into six equal-length segments in each of the two- and four-chamber views, creating a total of 12 segments (Figure 1). Longitudinal strain and strain rate were calculated within each of the 12 segments (Figure 2). Based on those curves, we defined five indices of LA intra-atrial dyssynchrony as follows:[15,16]

- SD-time to peak strain (SD-TPS): Standard deviation of the time to peak longitudinal strain in 12 segments. This index quantifies intra-atrial dyssynchrony of the LA reservoir function.
- SD-time to peak pre-atrial contraction strain (SD-TPS_{preA}): Standard deviation of the time to the peak pre-atrial contraction strain in 12 segments. This index quantifies intra-atrial dyssynchrony of the LA reservoir and conduit function.

A higher value of each index reflects a greater degree of intra-atrial dyssynchrony. We also presente the values of LA dyssynchrony as percentage (SD, %) of R-R' interval. A similar assessment of LA dyssynchrony has been published and validated before using 3D echocardiography against standard two-dimensional (2D) echocardiography, in a population of individuals with paroxysmal and persistent AF against healthy subjects.[17,18] Out of a total of 1,752 segments, 34 (1.94%) were excluded from analysis because these segments lacked well-defined peaks in the strain/strain rate curves. A total of 22 subjects had at least one segment that was not analyzable, of whom 15 were in the persistent AF group and 7 were in the paroxysmal AF group ($p = 0.02$).

LA function

LA functional analysis was described previously.[16] The LA longitudinal strain and strain rate were calculated by averaging strain values in all 12 segments obtained in long-axis two- and four-chamber views. A positive and negative strain value indicates stretch and shortening, respectively, with respect to the reference configuration at the ventricular end diastole, defined as the peak of R wave on surface ECG. Maximum LA longitudinal strain (S_{max}) and pre-atrial contraction strain (S_{preA}) were identified from the strain curve (Figure 2); the strain rates in left ventricular (LV) systole (SR_s), LV early diastole (SR_e), and LA contraction (SR_a) were obtained from the strain rate curve. The LA volume curve was generated by the biplane modified

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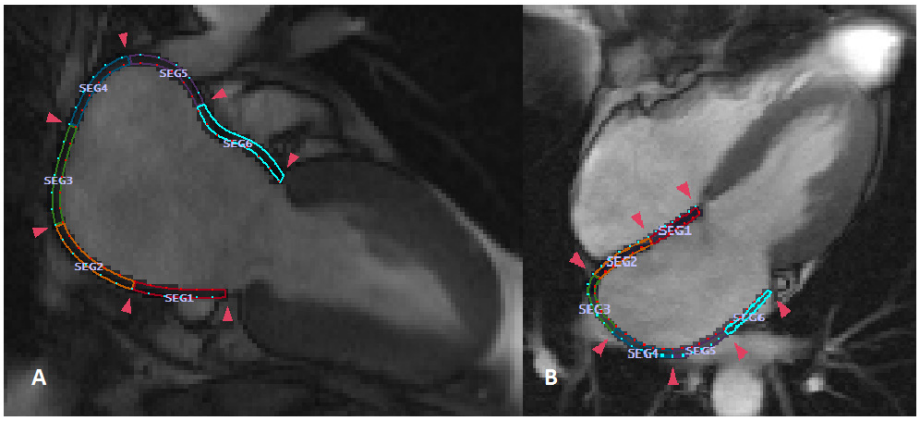

Figure 1 – *Quantification of left atrial regional function using cine cardiac magnetic resonance. The figures show a total of 12 color-coded segments within the left atrium. A: Two-chamber view with six equal-length segments; B: Four-chamber view with six equal-length segments.*

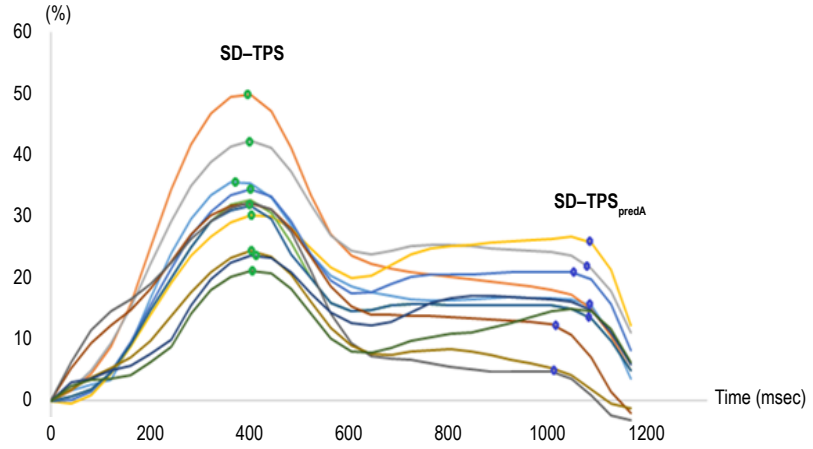

Figure 2 – *Strain curves of all 12 segments. Green dots, standard deviation of the time to peak strain (SD-TPS) of each segment; Blue dots, standard deviation of the time to peak pre-atrial strain (SD-TPS$_{preA}$) of each segment.*

Simpson's method, which was validated using the area-length method[19-21] and the maximum LA volume (V_{max}), pre-atrial contraction LA volume (V_{preA}), and minimum LA volume (V_{min}) were extracted. All LA volumes were normalized by body surface area based on the Haycock's formula.[22] The LA emptying fractions (EF) were calculated as follows: LA total EF = (V_{max} - V_{min}) × 100% / V_{max}; LA passive EF = (V_{max} - V_{preA}) × 100% / V_{max}; and LA active EF = (V_{preA} - V_{min}) × 100% / V_{preA}.

Ablation Protocol

PVI catheter ablation of AF was performed using an electroanatomic mapping system with an image integration module (CARTO and CARTOMERGE®, Biosense Webster, Irvine, CA, USA) to merge preprocedural CMR. The electrical isolation of the pulmonary veins was confirmed by a circular multipolar electrode mapping catheter (Lasso, Biosense Webster, Irvine, CA, USA). In cases of persistent AF, the ablation procedure usually included complementary ablation strategies. Ablation was performed with either an open-irrigated radiofrequency ablation catheter with or without force sensing, or a cryoballoon ablation catheter.

Reproducibility

Intra-reader reproducibility was established by one reader who performed analysis of the 15 studies twice, with an interval of 7 days between the two analyses. Inter-reader reproducibility was assessed by two readers who analyzed the same 15 cases. The second reader was blinded regarding the results of the first reader.

Statistical analysis

Data are presented as mean ± SD for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and percentages for categorical variables. Comparison between groups was performed using Student's *t* test, chi-square test, and, Fisher's exact test, as appropriate. Multivariable linear regression

analysis and Pearson's correlation were also used to examine the relationship between LA intra-atrial dyssynchrony and LA-LGE. Four linear regression models are presented: Model 1 (unadjusted), Model 2 (adjusted for the following clinical characteristics: age, sex, type of AF, body mass index [BMI], history of heart failure, hypertension, and obstructive sleep apnea), and Model 3 (Model 2+ V_{min} and S_{max}). Indices of LA intra-atrial dyssynchrony and LA-LGE were log-transformed due to non-normal distribution. We also evaluated the possibility of interaction between LA intra-atrial dyssynchrony and AF type. Pearson's correlation coefficient was categorized with the following correlations: poor, 0; slight, 0.01-0.20; fair, 0.21-0.40; moderate, 0.41-0.60; good, 0.61-0.80, and excellent, 0.81-1.00. In a subset of randomly selected participants (n = 15), a Bland-Altman analysis was performed to quantify intraobserver and interobserver reproducibility and inter-study reproducibility(21)(22) [23, 24]. Moreover, the intraclass correlation coefficient (ICC) with a two-way random model was evaluated, in which agreement was categorized as follows: ICC, < 0.40, poor; ICC 0.40-0.75, fair to good; and ICC > 0.75, excellent. The statistical computations were performed using Stata, version 12.0 (StataCorp LLC, College Station, TX, USA).

Results

Clinical

A total of 146 patients were included in the final analysis, and their clinical characteristics are summarized in Table 1. There were 61 (29.3%) female patients, and the mean age was 60.0 ± 10.0 years. A total of 102 patients (69.8%) had paroxysmal AF at the time of the procedure. Patients with paroxysmal and persistent AF were similar in terms of clinical baseline characteristics and medication usage, as demonstrated in Table 1; 4 of 44 patients (9.1%) in the persistent group and 2 of 102 patients (2.0%) in the paroxysmal group underwent cardioversion within 3-4 weeks prior to CMR (p = 0.158).

Left atrial function, intra-atrial dyssynchrony, and atrial fibrillation type

Patients with persistent AF had lower total LA emptying fraction (LAEF), active LAEF, SR, SR_e, SR_a, and left ventricular ejection fraction (LVEF) than those with paroxysmal AF (Table 2). In addition, SD-TPS was significantly higher in patients with persistent AF than in those with paroxysmal AF (median 3.6% *versus* 2.9 %, respectively, p = 0.036). $SD\text{-}TPS_{preA}$ was not significantly different between the AF types (4.6% *versus* 3.7%, respectively, p = 0.227) (Table 2). The dyssynchrony analysis was performed in a consistent manner in all cases and took 5 ± 9 minutes per case. There was no difference in the amount of time required for the dyssynchrony analysis between the AF types (p = 0.35).

LA Dyssynchrony and LA-LGE

There was no significant difference in the extent of LA fibrosis quantified by LGE between the AF types (11.6 [6-17.6]% of LA surface *versus* 13.8 [7.6-28.4] % of LA surface in the paroxysmal and persistent AF groups, respectively, p = 0.061). In Model 1, log-transformed SD-TPS and $SD\text{-}TPS_{preA}$ were associated with the LA degree of log-transformed LA-LGE enhancement (Table 3). After adjusting for age, sex, BMI, AF type, history of heart failure,

Table 1 – Baseline characteristics

	Overall (n = 146)	Paroxysmal AF (n = 102)	Persistent AF (n = 44)	p
Clinical				
Age, years	60.0 ± 10.0	60.0 ± 10.1	59.7±9.8	0.906
Body mass index, kg/m^2	28.4 ± 5.5	28.0 ± 5.4	29.9 ± 5.3	0.073
Male, n (%)	102 (70.0)	74 (72.5)	28 (63.3)	0.134
Heart failure, n (%)	14 (9.6)	8 (7.8)	6 (13.6)	0.082
Coronary artery disease/vascular disease, n (%)	12 (8.2)	10 (9.8)	2 (4.5)	0.536
Diabetes, n (%)	15 (15.4)	12 (11.8)	3 (6.8)	0.704
Hypertension, n (%)	60 (41.1)	42 (41.2)	18 (40.9)	0.154
History of stroke/TIA, n (%)	9 (6.2)	8 (7.8)	1 (2.3)	0.351
$CHA_2DS_2\text{-}VAS_c$	1.60 ± 1.5	1.5 ± 1.6	1.6 ± 1.2	0.942
Obstructive sleep apnea, n (%)	23 (15.8)	17 (16.7)	6 (13.6)	0.796
Ablation strategy (cryoablation), n (%)	34 (23.3)	28 (27.5)	6 (13.6)	0.324
Medication				
ACEI/ARBS, n (%)	37 (25.3)	24 (23.5)	13 (29.5)	0.389
Beta-blockers, n (%)	81 (56.3)	62 (60.8)	19 (43.2)	0.788
Calcium-channel blockers, n (%)	33 (22.9)	26 (25.5)	7 (15.9)	0.637
Number of antiarrhythmic drugs	1.2 ± 0.8	1.2 ± 0.8	1.4 ± 0.7	0.108

Data are presented as mean ± standard deviation, n (%), or median. AF: atrial fibrillation; TIA: transient ischemic attack; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; $CHA_2DS_2\text{-}VAS_c$: score for stroke risk assessment in atrial fibrillation.

Table 2 – Left atrial (LA) functional parameters by groups

	Paroxysmal AF (n = 102)		Persistent AF (n = 44)		p
	Mean	95% CI	Mean	95% CI	
LA structure					
Minimum LA volume index, mm^3/m^2	19.0 ± 7.8	18.5 – 21.4	23.0 ± 10.1	19.5 – 26.5	0.062
Maximum LA volume index, mm^3/m^2	38.8 ± 10.5	36.8 – 40.8	39.6 ± 11.7	35.6 – 43.7	0.691
LA Function					
Total LAEF, %	49.5 ± 10.0	47.6 – 51.4	44.0 ± 12.6	39.6 – 48.3	0.008
Passive LAEF, %	22.9 ± 7.3	21.6 – 24.3	20.7 ± 8.3	17.8 – 23.5	0.128
Active LAEF, %	34.6 ± 10.8	32.5 – 36.6	29.5 ± 14.1	24.6 – 34.3	0.026
S_{max}, %	28.9 ± 8.9	27.2 – 30.5	26.0 ± 11.8	22.0 – 30.1	0.132
SR	1.1 ± 0.4	1.1 – 1.2	1.1 ± 0.5	0.9 – 1.3	0.347
SR_e	-1.1 ± 0.5	-1.2 – -1.0	-0.8 ± 0.4	-1.0 – -0.7	0.010
SR_a	-1.4 ± 0.5	-1.5 – -1.3	-1.1 ± 0.6	-1.3 – -0.9	0.011
LVEF, %	58.4 ± 6.0	57.0 – 59.8	53.4 ± 10.3	49.4 – 57.4	0.004
	Median	**IQR**	**Median**	**IQR**	**p**
Dyssynchrony					
Mean TPS, ms	397.8	374.5 - 420.2	403.5	369.9 - 429.0	0.538
SD-TPS, %	2.9	2.1 – 3.9	3.6	2.3 – 4.9	0.036
Log - SD-TPS, %	1.0	0.7 – 1.4	1.1	0.8 – 1.6	0.036
Mean SD-TPS_{preA}, ms	795.3	692.4 - 884.9	846.7	760.6 - 967.4	0.046
SD-TPS_{preA}, %	4.6	3.0 – 8.6	3.7	2.9 – 5.4	0.227
Log - SD-TPS_{preA}, %	1.5	1.1 – 2.2	1.3	1.1 – 1.7	0.177
LGE extent (% LA surface)	11.6	6.0 – 17.6	13.8	7.6 – 28.4	0.061
Log LGE extent (% LA surface)	2.4	1.8 – 2.9	2.6	2.0 – 3.3	0.061

Data are presented as median (interquartile range [IQR]) or mean ± standard deviation (SD). CI: confidence interval; LAEF: LA emptying fraction; S_{max}: maximum longitudinal LA strain; SR: peak longitudinal strain rate; SR_e: early diastolic strain rate; SR_a: late diastolic strain rate; LVEF: left ventricular ejection fraction; TPS: time to peak strain; TPS_{preA}: time to peak pre-atrial contraction strain; LGE: late gadolinium enhancement.

Table 3 – Univariable and multivariable analyses

	Model 1 Unadjusted		Model 2 Clinical variables		Model 3 Model 2 + Vmin + Smax	
	β	p	β	p	β	p
Log SD-TPS, %	0.66	< 0.001	0.57	0.001	0.60	0.001
Log SD-TPS_{preA}, %	0.19	0.034	0.21	0.020	0.18	0.045

Model 2, adjusted for age, sex, type of atrial fibrillation, body mass index, history of cardiac failure, hypertension, obstructive sleep apnea. Model 3, covariables included in Model 2 in addition to minimum left atrial volume and maximum longitudinal strain. V_{min}: minimum left atrial volume; S_{max}: maximum longitudinal strain; SD: standard deviation; TPS: time to peak strain; TPS_{preA}: time to peak pre-atrial contraction strain.

obstructive sleep apnea, hypertension, V_{min}, and S_{max}, both indices SD-TPS and SD-TPS_{preA} remained significantly associated with LA-LGE (SD-TPS, β: 0.60, p = 0.001; SD-TPS_{preA}, β: 0.18, p = 0.045) (Table 3). Figure 4 displays the relationship between LA-LGE and LA intra-atrial dyssynchrony. There was no significant multiplicative interaction between AF type and LA intra-atrial dyssynchrony (interaction term for SD-TPS: 0.008, p = 0.258 and SD-TPS_{preA}: 0.003, p = 0.158). The LA-LGE analysis was performed in a consistent manner in all cases and took 60 ± 20 minutes per case, also depending on the image quality.

Dyssynchrony: inter-reader and intra-reader reproducibility

Interobserver and intraobserver variabilities of LA analysis for the MTT method were assessed in 15 randomly select subjects (Table 4, Figure 5). All parameters showed excellent intraobserver reproducibility (ICC 0.86 and 0.85 for SD-TPS and SD-TPS_{preA} respectively, p < 0.001) (Figure 5) without significant systematic bias. In addition, both parameters showed good to excellent interobserver reproducibility (ICC 0.86 and 0.74 for SD-TPS and SD-TPS_{preA}, respectively, p < 0.001) (Figure 5).

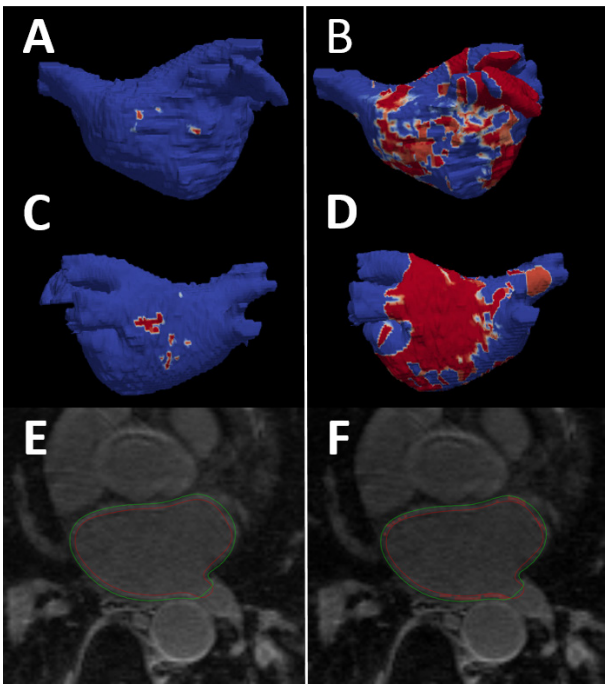

Figure 3 – *Left atrial (LA) late gadolinium enhancement cardiac magnetic resonance (CMR). A – B: anterior LA shell view with areas of enhancement (red). C – D: posterior LA shell view with areas of enhancement (red). E - F: quantification of LA enhancement by CMR using image intensity ratio (IIR). Left side (A, C, and E), individual with low enhancement – right side (B, D, and F), individual with high enhancement.*

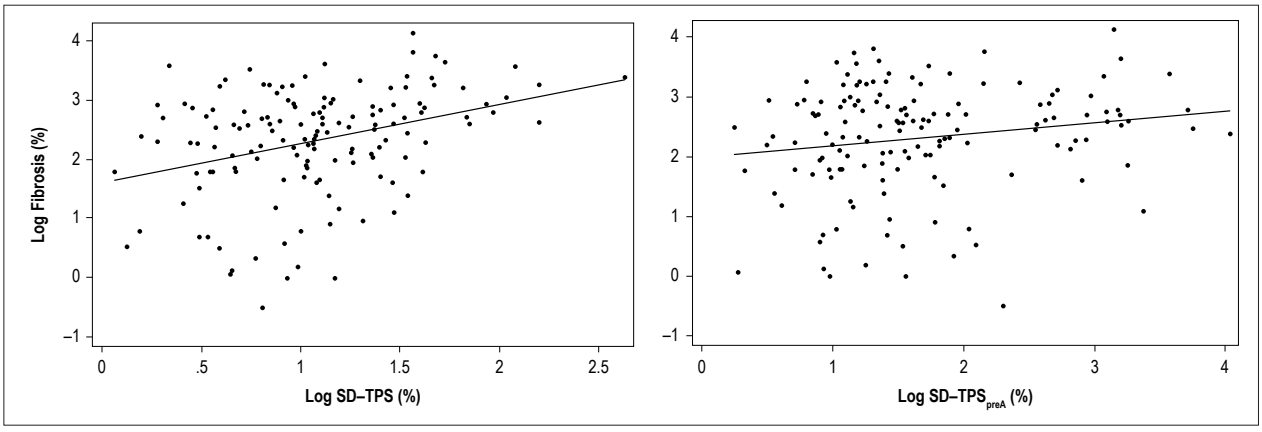

Figure 4 – *Association between left atrial (LA) intra-atrial dyssynchrony and LA late gadolinium enhancement (LA-LGE). A, regression between LA-LGE and the standard deviation of the time to peak strain (SD-TPS); B, regression between LA-LGE and the standard deviation of the time to peak pre-atrial strain (SD-TPS$_{preA}$). Blue line, linear regression line. Log: logarithmically transformed variables; SD: standard deviation.*

Discussion

The main findings are summarized as follows: 1) LA intra-atrial dyssynchrony was independently associated with LA-LGE, 2) LA intra-atrial dyssynchrony was significantly greater in patients with persistent AF than in those with paroxysmal AF, 3) LA intra-atrial dyssynchrony is a reproducible index, and 4) LA intra-atrial dyssynchrony analysis is less time-consuming than LA-LGE.

LA-LGE and dyssynchrony

Our multivariable analysis showed that LA intra-atrial dyssynchrony is associated with LA-LGE after adjusting for clinical risk factors including the AF type. This finding serves as evidence to the potential use of LA intra-atrial dyssynchrony as a surrogate for LA-LGE. In addition, our analysis showed that patients with persistent AF had significantly greater LA intra-atrial dyssynchrony than those with paroxysmal AF. In contrast, there

Table 4 – Inter-reader and intra-reader reproducibility of the left atrial measurements. Results are reported as mean ± standard deviation

	Inter-reader	ICC	p
LA parameter	Difference (mean ± SD)		
SD-TPS, %	-0.05 ± 0.21	0.86	< 0.001
$SD\text{-}TPS_{preA}$, %	-0.09 ± 0.83	0.74	< 0.001
	Intra-reader	ICC	p
LA parameter	Difference (mean ± SD)		
SD-TPS, %	0 ± 0.25	0.86	< 0.001
$SD\text{-}TPS_{preA}$, %	-0.03 ± 0.73	0.85	< 0.001

LA: left atrial; SD: standard deviation; ICC: intraclass correlation coefficient; TPS: time to peak strain; TPS_{preA}: time to peak pre-atrial contraction strain.

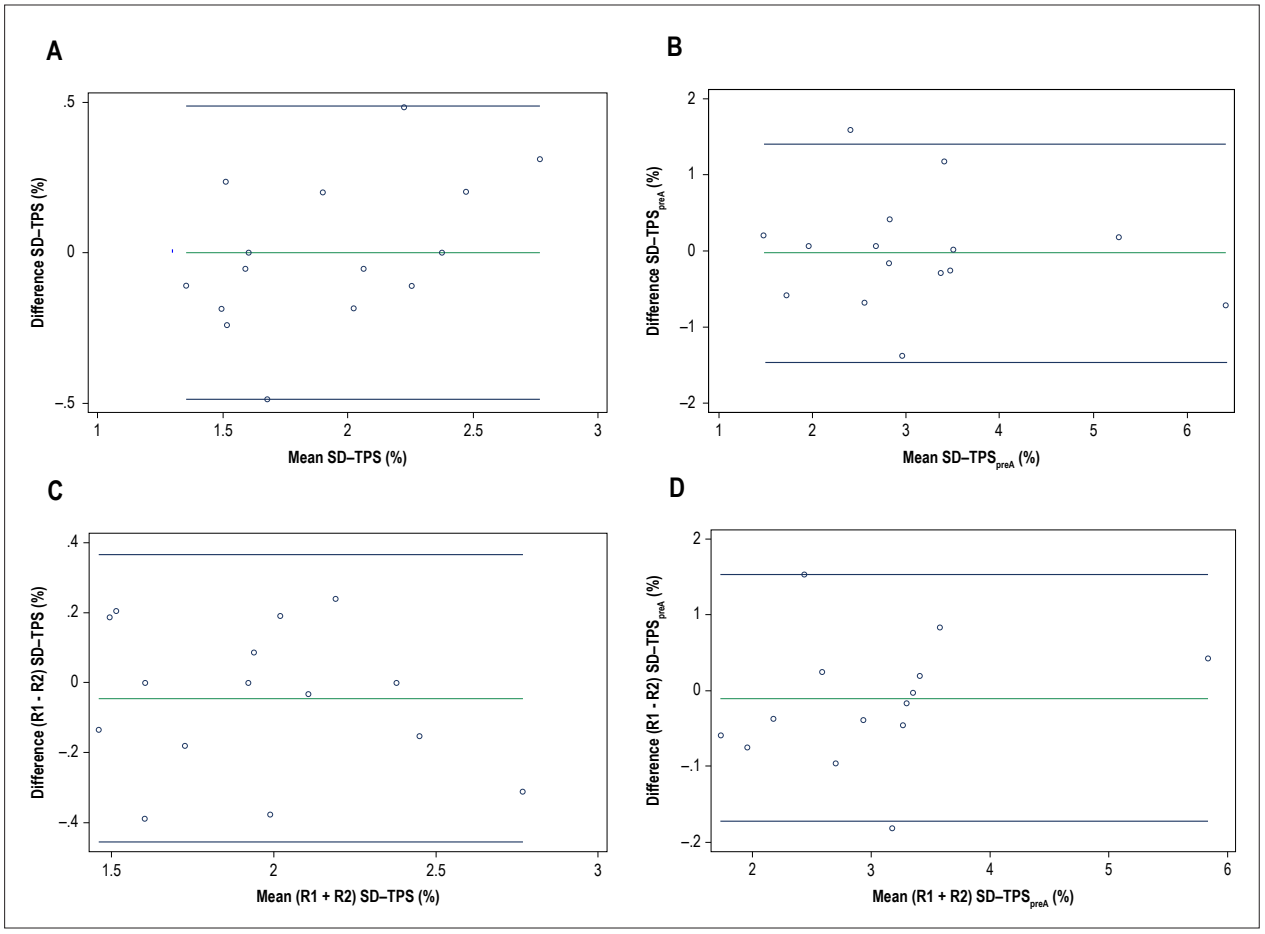

Figure 5 – *Intra-reader and inter-reader reproducibility – Bland-Altman plot. A, standard deviation of the time to peak strain (SD-TPS) intra-reader reproducibility. B, standard deviation of the time to peak pre-atrial strain ($SD\text{-}TPS_{preA}$) intra-reader reproducibility. C, SD-TPS inter-reader reproducibility. D, $SD\text{-}TPS_{preA}$ inter-reader reproducibility. R1: first reader; R2: second reader.*

was no significant difference in LA-LGE between patients with persistent and paroxysmal AF, although there was a trend for a larger extent of LA-LGE with persistent AF. A possible explanation to account for these results is that intra-atrial dyssynchrony likely reflects subtle changes in atrial architecture that could generate AF but is not captured by LGE or other indices of LA function. In fact, mechanical dyssynchrony was a more specific marker of AF recurrence after AF ablation when compared to LA scar and function (8). Technical difficulties associated with LA-LGE acquisition and processing may also account for the finding. For example, the thin wall of the LA (~3 mm) poses a challenge to the spatial resolution of CMR. In addition, only a small fraction of intravenously administered contrast perfuses the LA wall because the vast majority perfuses the ventricles

via the coronary arteries. Our result also showed that the LA intra-atrial dyssynchrony analysis is less time-consuming (5 ± 9 minutes) than LA-LGE (60 ± 20 minutes). This finding suggests that the implementation of LA intra-atrial dyssynchrony analysis in routine clinical practice would not significantly impede the clinical workflow of preprocedural assessment. The possibility that cardioversion-induced atrial stunning could have confounded our findings is low because: 1) cardioversion was performed in only a minority of patients in both groups and 2) there was no significant difference in the fraction of patients who underwent cardioversion between both groups.

LA dyssynchrony reproducibility

Our results showed excellent intra-reader reproducibility of LA intra-atrial dyssynchrony, with ICC ranging from 0.74 to 0.86 for SD-TPS, and 0.85 to 0.95 for SD-TPS_{preA}, with the mean difference of 0 and -0.03, respectively (Table 4, Figure 5). The inter-reader reproducibility was also excellent to good, with ICC ranging from 0.86 for SD-TPS and 0.74 for SD-TPS_{preA}, with the mean difference of -0.05 and -0.09, respectively (Table 4, Figure 5). Both intra-reader and inter-reader reproducibility were similar to the values described in studies using 2D and 3D echocardiography.[17]

Limitations

This study accounts for a single-center, retrospective, cross-sectional analysis of patients referred for PVI to treat drug-refractory AF in a tertiary center. Therefore, there is a non-negligible chance of selection bias. For the dyssynchrony analysis, we used only two- and four-chamber cine CMR, which was included in a routine image-acquisition protocol. Therefore, it is possible that our analysis underestimated the degree of dyssynchrony by missing regions that were not covered by those two views. Since the strain was 2D and was obtained only in the in-plane direction, the strain values may have been underestimated compared with those in 3D strains. Besides, the CMR temporal resolution may also explain our lower values of dyssynchrony compared to echocardiography.[17] There is a chance of underestimation of dyssynchrony due to spontaneous restoration of sinus rhythm a few weeks before the CMR. However, we believe that this fact would happen more often in individuals with paroxysmal AF; thus, our findings may have underestimated the real difference in dyssynchrony between individuals with paroxysmal and persistent AF by underestimating the dyssynchrony in the paroxysmal group. Finally, we had to exclude subjects who were not in sinus rhythm by the time of the cine image acquisition, which could be a limitation for the application of our method in subjects with persistent AF.

Conclusions

LA intra-atrial dyssynchrony is significantly associated with LA-LGE independent of traditional cardiovascular risk factors or LA structure and function. Moreover, LA intra-atrial dyssynchrony was greater in individuals with persistent AF than in those with paroxysmal AF, whereas LA-LGE was not significantly different between the two AF types. LA intra-atrial dyssynchrony is a reproducible index to quantify LA remodeling and is less time-consuming than LA-LGE. Intra-atrial dyssynchrony can be used as a surrogate for the underlying tissue remodeling in patients with AF.

Author contributions

Conception and design of the research: Ciuffo LA, Lima J, Ashikaga H; Acquisition of data na Statistical analysis: Ciuffo LA; Analysis and interpretation of the data: Ciuffo LA, Tao S; Obtaining financing: Ashikaga H; Writing of the manuscript: Ciuffo LA, Ashikaga H; Critical revision of the manuscript for intellectual content: Lima J, Balouch M, Tao S, Nazarian S, Marine JE, Calkins H, Ashikaga H, Vasconcellos HD, Spragg DD, Berger RD.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Johns Hopkins IRB under the protocol number CIR0004531. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Quantification of Left Atrial Tissue Remodeling Using Intra-Atrial Dyssynchrony by Cardiac Magnetic Resonance Imaging

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Short Editorial related to the article: Intra-Atrial Dyssynchrony Using Cardiac Magnetic Resonance to Quantify Tissue Remodeling in Patients with Atrial Fibrillation

Morphological and functional characteristics of the left atrium (LA) play a key role in the pathogenesis of atrial fibrillation (AF), which represents a global health burden as the most common cardiac arrhythmia encountered in clinical practice.[1] For patients with drug-refractory AF, catheter-ablation may aid in a) prolonged restoration of sinus rhythm, b) decreased in total arrhythmic burden, symptomatic improvement, and c) better quality of life. However, catheter-ablation may not have a durable effect for a significant number of patients despite repeated procedures.[2] A variety of innovative procedural technologies aim to improve patient freedom from AF. Scientific progress in the identification of patient characteristics that suggest a favorable or poor likelihood of procedural success may enhance patient selection for catheter-ablation and optimize time utilization for the cardiac electrophysiologist.

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) has been shown to be a promising, non-invasive tool for the measurement of LA fibrosis, which predicts the recurrence of AF after catheter-ablation.[3,4] While this tissue characterization of the LA represents a promising technology for patients with AF in whom catheter-ablation is being considered, it remains mostly these days at expert centers, has labor-intensive post-processing and necessitates the use of gadolinium contrast, which may exclude patients who have advanced kidney disease or allergic reactions to gadolinium. Functional assessment with intra-atrial dyssynchrony utilizing tissue-tracking represents an elegant technique to characterize LA mechanics that does not require gadolinium contrast or significant post-processing and was recently shown to correlate with the recurrence of AF after catheter-ablation.[4]

In this issue, Ciuffo et al.[5] advance the understanding of adverse LA remodeling and dysfunction in patients with AF. Using CMR to measure intra-atrial dyssynchrony in sinus rhythm, defined as the standard deviation of the time to the peak longitudinal strain [SD-TPS (%)] and pre-atrial contraction strain [SD-TPS$_{preA}$ (%)] corrected by the cycle length. LA fibrosis was quantified using LGE images, which, interestingly, did not differ significantly between paroxysmal and persistent AF types. Notably, SD-TPS was significantly higher in patients with persistent AF than those with paroxysmal AF, although this association did not hold true for SD-TPS$_{preA}$ between the AF types. On multivariable adjustment for age, sex, BMI, AF type, history of heart failure, OSA, hypertension, minimal LA volume and maximum LA longitudinal strain, both SD-TPS and SD-TPS$_{preA}$ remained significantly associated with LA LGE, although the signal was much stronger for SD-TPS. Inter- and intra-reader reproducibility was excellent for both indices, and the data were post-processed in a short amount of time.

These findings highlight the potential for intra-atrial dyssynchrony by CMR to represent a fast and accurate surrogate of LA fibrosis, especially in the prediction of AF recurrence after catheter-ablation.[3,4] The authors have appropriately acknowledged the potential for selection bias in their non-randomized, retrospective cohort, and this technique requires patients to be in sinus rhythm at the time of CMR imaging. Still, Ciuffo et al.[5] have added valuable insights into the understanding of LA remodeling in AF and must be praised for their work, which studied a real-world population and considered the important concern of work-flow for CMR post-processing. Their findings should stimulate more research into the use of intra-atrial dyssynchrony as non-invasive risk stratification for patients with AF, which does not require gadolinium contrast to enhance patient selection for invasive therapies such as catheter-ablation.

Keywords

Atrial Fibrillation; Remodeling Atrial; Atrial Dyssynchrony Diagnostic Imaging; Magnetic Resonance Imaging.

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Review Article

PCSK9 Inhibitors: Clinical Relevance, Molecular Mechanisms, and Safety in Clinical Practice

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Abstract

Coronary artery disease (CAD) is one of the leading causes of mortality. High circulating levels of low-density lipoprotein (LDL) in the blood are associated with cardiovascular mortality, whether through an etiological role or through its association with the progression of CAD per se. Randomized clinical trials have shown that, when LDL levels are reduced, cardiovascular risk is also reduced, which reinforces this association. The first major trial involving a hypolipidemic agent of the statin family, the Scandinavian Simvastatin Survival Study (4S), was published in 1994 and found a significant reduction in mortality in patients at high cardiovascular risk. However, even in subsequent studies with different statins, a residual risk persisted, and this seems not to have changed over time; it is speculated that this risk may be due to statin intolerance. In this scenario, the potential exists for novel hypolipidemic agents to drive a true revolution in the therapy of dyslipidemia. The recent discovery of PCSK9 inhibitors (PCSK9i), a class of hypolipidemic monoclonal antibodies, is extremely promising. PCSK9 inhibition is capable of promoting a mean LDL reduction of up to 60%, with potential for very significant clinical repercussions, as every 38 mg/dL reduction in LDL appears to be associated with a 22% reduction in cardiovascular risk. This review addresses a brief history of PCSK9i, major trials of these drugs, cardiovascular outcomes, and aspects related to their efficacy and safety. Finally, the molecular mechanisms and possible pleiotropic effects of PCSK9i are also discussed.

Introduction

Worldwide, cardiovascular diseases account for almost half of all deaths in people under 70. In Brazil, they were responsible for almost 30% of deaths in 2013.[1] In recent decades, mounting evidence has shown a close link between low-density lipoprotein (LDL) levels and incidence of coronary artery disease (CAD).[2,3] Inadequate hepatic uptake of LDL results in increased levels of circulating LDL, and consequent incidence of premature CAD.[4]

The treatment of dyslipidemias involves a number of factors, and lifestyle changes should be part of all medical prescriptions for this purpose. Non-pharmacological interventions, such as starting a regular exercise program, not smoking or quitting smoking, and adopting a healthy diet can have a significant impact on lipid profile. However, a substantial number of patients need to add hypolipidemic drugs (e.g., statins, ezetimibe, fibrates) to the aforementioned measures to achieve recommended LDL goals.[5]

Substantial advances in lipid-lowering drugs have been achieved in recent years.[6] When used appropriately, these agents play a preponderant role in preventing adverse cardiovascular (CV) outcomes.[7] Hypolipidemic therapy with statins has been shown to have an impact both for primary prevention of atherosclerosis in patients at high CV risk[8] and for secondary prevention. However, some patients do not reach desired LDL levels even at maximal doses of statins (whether as monotherapy or up to triple therapy) or even when ezetimibe is added to statin therapy; this results in an important residual risk of CV events.[9,10] Thus, the search for therapeutic alternatives that can reduce LDL more aggressively, aiming to achieve better outcomes, continues.

Among recent developments, perhaps the most outstanding class of novel lipid-lowering agents are the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i).[11] PCSK9 is a protein that ultimately promotes the degradation of hepatic LDL receptors, leading to hypercholesterolemia.[6,7] The PCSK9i are monoclonal antibodies that increase the availability of LDL receptors. When PCSK9 is inhibited, there is greater uptake of LDL by their respective receptors present in hepatocytes, with reduction of serum and plasma levels of LDL (Figure 1).[12,13]

An important point about the causal relationship between LDL levels and CV outcomes is the dose-response behavior observed. To the extent that high LDL levels increase CV risk, when LDL levels are reduced, so is the rate of adverse CV outcomes. For example, the JUPITER study demonstrated that use of a statin (rosuvastatin) for 2 years was able to protect patients substantially, especially in those with LDL levels were below 45 mg/dL.[14]

Keywords

Cardiovascular Diseases/physiopathology; Coronary Artery Disease/mortality; Proprotein Convertase 9; Cholesterol, LDL; Lipoproteins; Anticholesteromic Agents.

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Clinical relevance

CV risk can be significantly mitigated by aggressive LDL reductions; the higher the risk, the lower the target LDL level. No class of hypolipidemic agents had given rise to such anticipation since the discovery of the statins,[15] as the PCSK9i can promote an additional reduction of up to 60% in LDL levels when compared to statins.[9]

The FOURIER study,[8] a randomized clinical trial (RCT) published in 2017, enrolled more than 27,000 patients with atherosclerotic CV disease and LDL levels ≥ 70 mg/dL. Participants, all of whom were on statin therapy, were randomly allocated to receive add-on evolocumab or placebo for a mean period of 2.2 years. In the evolocumab group, there was a mean reduction in LDL levels of 30 mg/dL from baseline; in absolute terms, when compared to the placebo group, the mean LDL reduction was 56 mg/dL. Most importantly, a 15% reduction was found in the primary endpoint (nonfatal acute myocardial infarction [AMI], stroke, coronary revascularization, hospitalization for unstable angina, and CV mortality), as well as a 20% reduction in the composite secondary hard endpoint of CV death, nonfatal AMI, and nonfatal stroke. At the end of the study, there was an absolute risk reduction of 1.5% for both the primary and secondary endpoints, which translated into a number needed to treat (NNT) of approximately 67.

More recently, the ODYSSEY Outcomes[16] study compared alirocumab plus with statin versus statin alone at maximal tolerated dose in approximately 19,000 patients at very high CV risk for 2.8 years. LDL levels were 53.3 mg/dL in the alirocumab + statin group versus 101.4 mg/dL in the statin group, and an absolute reduction of 54.7% was observed. The primary outcome of major adverse CV events was also significantly lower in the combination therapy group. Furthermore, there was a surprising 15% reduction in deaths from any cause in this group (NNT of approximately 63). In the ODYSSEY Outcomes trial, LDL decreased 47 mg/dL after 1 year of follow-up, which, based on the Cholesterol Treatment Trialists (CTT) model,[17] would represent a 24% reduction in the relative risk of major CV events. However, in practice, only a 15% reduction was observed. This divergence can be explained by the difference in follow-up time between ODYSSEY Outcomes (2.5 years) and the CCT analyses (5 years). In fact, CTT data showed a smaller magnitude of benefit regarding LDL reduction in the first year.[17]

In an analysis of the FOURIER trial,[18] the clinical benefits of evolocumab differed interestingly depending on the severity and extent of CAD. First, evolocumab reduced LDL levels by 61%. Second, patients with a greater risk profile, i.e., those with more recent AMI (< 2 years), multiple anterior AMIs, and multivessel disease, were those who benefited most from the use of PCSK9i: they experienced relative risk reductions for the primary endpoint of 20%, 18%, and 21%, respectively, versus 5%, 8%, and 7% reductions respectively in low-risk comparators subgroups (i.e., participants without these complications). In the high-risk patient subgroups, the absolute risk reductions in 3 years exceeded 3% (3.4%, 3.7%, and 3.6% respectively), versus approximately 1% in the low-risk groups (0.8%, 1.3%, and 1.2% respectively). Thus, the NNT to avoid the primary outcome over a 3-year period was 27 to 30 in each of the high-risk groups versus 54 in all patients with a history of AMI and 79 to 130 in the low-risk subgroups.[18] That is, in those patients who were more difficult to manage and had a higher risk of events, the reduction of CV risk with evolocumab was more substantial. In this context, it would be reasonable, then, to direct this type of therapy preferentially to those patients with more severe dyslipidemia, considering the more substantial reductions of LDL and, consequently, more encouraging benefits and greater cost-effectiveness.

Another aspect to be considered relates to the regression of atheroma volume. Large reductions in LDL levels can promote such an effect, as was suggested by the GLAGOV trial.[19] In this experiment, 968 patients were included in 226 centers across 32 countries. Participants with symptomatic CAD were diagnosed by coronary computed tomography angiography and received monthly evolocumab (420 mg) vs. placebo for 76 weeks, in addition to statins. At the start of the study, the mean LDL level of the participants was 93 mg/dL; by the end, those randomized to evolocumab reached 29 mg/dL, versus 90 mg/dL in controls. In addition, greater regression of atherosclerotic plaque was observed in the evolocumab group (64.3% vs. 47.35%; $p < 0.0001$), making GLAGOV the first study to demonstrate the benefits of PCSK9i on atherosclerotic plaque.[19] These results appear to hold relevance to clinical practice, as well as external validity.

Animal studies play a fundamental role in the development of new drugs. In experiments with mice, administration of alirocumab (3 or 10 mg/kg) for 18 weeks reduced plasma lipid levels, mitigated development of atherosclerosis and improved plaque morphology. When used in combination with atorvastatin (3.6 mg/kg/d), the severity of atherosclerotic lesions was reduced even further, in a dose-dependent manner.[20] However, trials with larger samples – and, preferably, in humans – are lacking.

It is estimated that 24 million patients in the U.S. alone could be eligible for PCSK9i therapy.[21] Although there are no such data for the Brazilian population, the efficacy and safety of these agents have been recognized by regulatory agencies in the country, and two PCSK9i have been approved by the National Health Surveillance Agency (ANVISA) and are commercially available: Praluent® (alirocumab) and Repatha™ (evolocumab).[22] Their approved indications for use in Brazil, as well as dosages and the magnitude of LDL reduction achieved, are summarized in table 1.

General recommendations for the use of PCSK9i in clinical guidelines

Several guidelines, including those cited in subsequent paragraphs, are unanimous in indicating the therapeutic use of PCSK9i only for those patients considered to be at high or very high risk and who were unable to reach LDL targets even after lipid-lowering therapy (such as statins at maximum tolerated dose or statins plus ezetimibe).

The UK National Institute for Health and Care Excellence (NICE) does not recommend the use of PCSK9i for patients with primary non-familial hypercholesterolemia or mixed dyslipidemia without evidence of CV disease, regardless of LDL concentration. In patients at high CV risk, the use of

Table 1 – Indications for PCSK9i use in Brazil, according to the Brazilian Guideline on Dyslipidemia.[24]

Patients at high risk of a CV event	
On treatment with statins at the highest tolerated dose	
Statin or statin + ezetimibe therapy	
Statin-intolerant or has not met recommended LDL or non-HDL goals	
↓	
Evolocumab (Repatha™)	**Alirocumab (Praluent®)**
140 mg by subcutaneous injection every 2 weeks or 420 mg once a month Both doses reduce LDL by approximately 60%.[25]	75 mg or 150 mg by subcutaneous injection every 2 weeks The 75-mg and 150-mg doses are associated with average LDL reductions of 45% and 60%, respectively.[25]

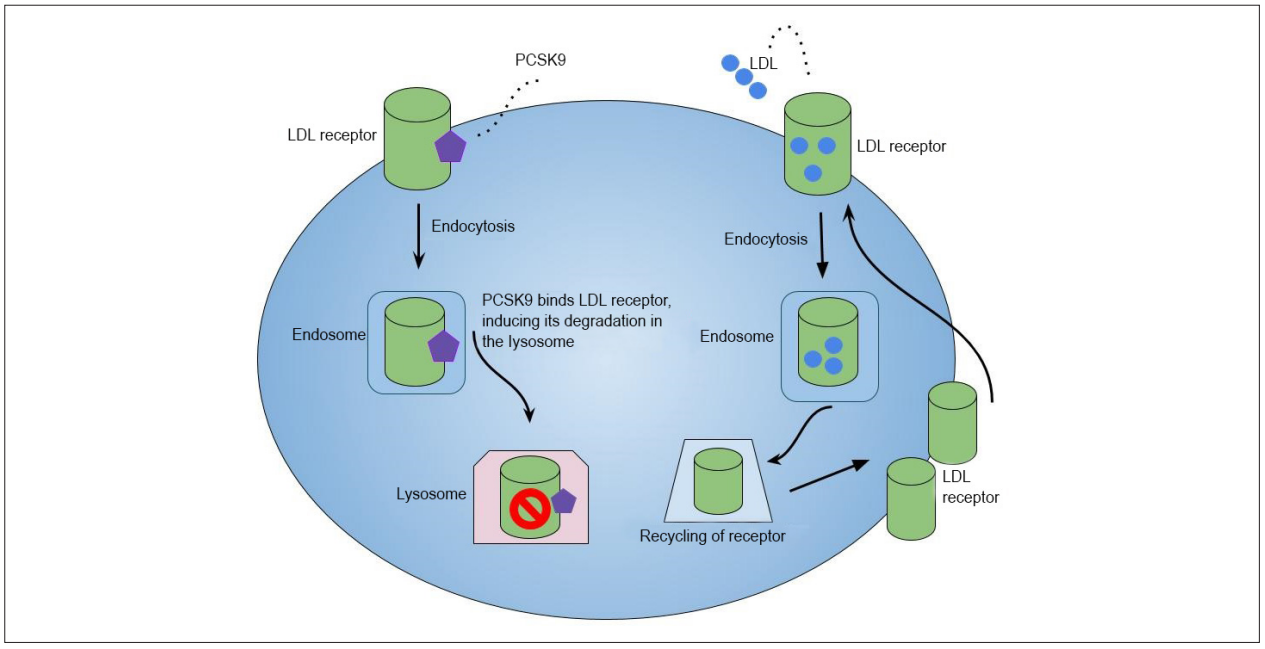

Figure 1 – *Mechanisms of PCSK9 involvement in LDL metabolism.*

PCSK9i is recommended only if the LDL concentration is persistently above 4.0 mmol/L (approximately 154 mg/dL). If the patient is considered to be at very high CV risk, PCSK9i therapy is recommended only if the LDL concentration is persistently above 3.5 mmol/L (approximately 135 mg/dL).[23]

In contrast, the updated Brazilian Guidelines for Dyslipidemias and Prevention of Atherosclerosis[24] adopted a much less conservative addendum. In those patients at high risk for CV disease, the therapeutic goal of LDL should be below 70 mg/dL, while in those considered at very high risk CV, the goal is to reach LDL levels below 50 mg/dL. Accordingly, the 2017 consensus of the American College of Cardiology states that, for patients at higher risk (such as those with acute coronary syndrome or with multivessel CAD), a target LDL level of < 50 mg/dL can be considered.[25] The *American Association of Clinical Endocrinologists*/American College of Endocrinology statement recommends a target LDL level < 55 mg/dL for: a) patients with progressive atherosclerotic CV disease; b) patients with atherosclerotic CV disease in association with diabetes and/or stage 3 or 4 chronic kidney disease; c) patients with heterozygous familial hypercholesterolemia (HF); and d) those with premature atherosclerotic CV disease.

In turn, the *European Society of Cardiology*/*European Atherosclerosis Society* Task *Force* recommends PCSK9i therapy when LDL is ≥ 140 mg/dL and the patient is already on combined statin and ezetimibe therapy; or when LDL is ≥ 100 mg/dL in cases of rapid progression of atherosclerotic CV disease.[26] In these individuals, PCSK9i therapy is recommended with a target LDL level < 70 mg/DL.[27]

Patients with and without diabetes mellitus

Preclinical and clinical epidemiological studies have revealed an association of PCSK9 levels with insulin resistance and the risk of developing type 2 diabetes mellitus (DM2).[28,29] Although genetic study findings have been contradictory, there seems to be a positive association between levels of PCSK9 and the incidence of DM2.[28] The Dallas Heart Study found that PCSK9 levels were significantly higher in patients with DM2.[29] Regular use of statins and fibrates may increase

plasma levels of PCSK9,[30,31] with the latter potentially raising levels by up to 25%.[31] This fact should be taken into account.

Statins themselves may also increase the incidence of DM2. A meta-analysis including more than 91,000 patients followed up for 4 years found a 9% increase in the risk of DM2 with the use of statins.[32] In fact, data show that the gain in function in the LDL receptor gene is capable of impairing the insulin-secreting capacity of the pancreatic beta-cells.[33] Thus, it is only natural that upregulation of LDL receptors with the use of PCSK9i might induce a decline in insulin release, thus facilitating development of new-onset DM2. Following this reasoning, a meta-analysis that evaluated short-term therapy with PCSK9i (1.5 years) found a small, but significant increase in plasma glucose and glycated hemoglobin levels. Moreover, this increase was proportional to the reduction in LDL, but was not enough to cause an impact on the emergence of new cases of DM2.[34]

The safety of PCSK9i therapy has also been assessed. In a pre-specified meta-analysis of the FOURIER trial, the efficacy and safety of evolocumab was investigated in patients with and without DM2, in addition to the effect of evolocumab on blood glucose and on the risk of developing DM2.[35] Of those individuals already living with DM2, 8,000 had available data and 25% were on insulin. Among patients without the disease, 38% had prediabetes and 22% were normoglycemic. Both groups were homogeneous in terms of statin therapy, with 70% on maximal doses.[35] Evolocumab therapy significantly reduced CV risk in both groups, and did not increase the risk of recent-onset DM2; there was no worsening in blood glucose levels. These data suggest that evolocumab therapy is safe and effective in patients with atherosclerotic disease. Furthermore, the number needed to prevent a primary CV event over a 3-year period among DM2 patients was only 37. Therefore, the use of PCSK9i in patients with atherosclerotic CV disease and DM2 can be particularly attractive from the point of view of cost-benefit.[35]

Possible anti-inflammatory mechanisms and pleiotropic effects

The potential for anti-inflammatory action by PCSK9i is unclear. Unlike therapy with statins, there is no evidence of a potential role of PCSK9i in reducing C-reactive protein (CRP) levels, especially when measured by high-sensitivity methods (hsCRP). Two recent meta-analyses that evaluated approximately 7,000 patients[36,37] did not confirm this hypothesis.

Although the relationship between PCSK9 and carotid intima-media thickness in healthy patients is controversial, it may play a direct role in the inflammatory process, contributing to atherosclerotic disease through LDL-independent mechanisms.[38] Whether these monoclonal antibodies interact with other pathways to induce an anti-inflammatory response is still unclear, and warrants further investigation.

The relationship between serum levels of PCSK9 and atherosclerotic plaque characteristics has also been studied. *Virtual-histology intravascular ultrasound* (VH-*IVUS*) was used to analyze 581 patients with CAD,[39] and higher levels of PCSK9 were found to be associated with a greater fraction and amount of central necrotic tissue in coronary atherosclerosis, independent of LDL levels and statin therapy.[39] Therefore, PCSK9 seems to play a role that goes far beyond regulation of LDL.

In another sub-analysis of the FOURIER trial,[40] evolocumab acted effectively against initial inflammatory risk in 27,564 patients at high CV risk. It bears stressing that the relative benefit of therapy with this drug for the prevention of CV events was independent of baseline CRP levels. Although those patients with higher hsCRP levels exhibited greater susceptibility to CV events, they were also those who tended to derive the greatest absolute benefit from evolocumab therapy.[40]

Evidence suggests that vascular smooth muscle cells produce higher amounts of PCSK9 compared to endothelial cells, especially in an inflammatory microenvironment. In those regions where there is lower shear stress (i.e., force of blood friction against the arterial intima), PCSK9 expression is increased in smooth-muscle cells. Moreover, oxidized LDL appears to be implicated in the regulation of PCSK9 expression by modulating the secretion of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α).[41] Corroborating these findings, Ricci et al.[42] tested the hypothesis of a relationship between PCSK9 and pro-inflammatory effects in macrophages. The authors initially performed a series of experiments with macrophages derived from the human monocytes cell line THP-1, incubated with increasing concentrations of recombinant human PCSK9. A positive correlation was observed between levels of PCSK9 and inflammatory response in macrophages, inducing expression of TNF-α, IL-1, IL-6, as well as chemokines such as *monocyte chemoattractant protein-1* (MCP-1). In addition, an inflammatory response was observed when THP-1 macrophages were co-cultured with HepG2 cells overexpressing PCSK9.[42] This provides additional evidence of a pro-inflammatory effect of PCSK9.

Recently, Bernelot Moens et al.[43] evaluated the responses to PCSK9i in monocytes (key mediators of the inflammatory process) of patients with FH who were not on statins due to muscle pain. Several pro-inflammatory and migratory alterations were observed in these monocytes. After 6 months of treatment with PCSK9i, the migratory capacity of monocytes, their lipid content, and their inflammatory responsiveness decreased to levels observed in FH patients on stable statin therapy. The reduction in lipid content with the use of PCSK9i attenuated the pro-inflammatory phenotype of monocytes.[43] These findings are important, because they emphasize that other mediators beyond CRP are involved in inflammation.

Finally, it should be emphasized that the PCSK9i agents have pleiotropic effects, and that their use may have other therapeutic actions, in addition to their already-established hypolipidemic activity.

Safety

In 2012, the U.S. Food and Drug Administration (FDA) issued an alert on the potential adverse effects of statin treatment.[44] Two years later, the FDA asked PCSK9i developers to assess possible adverse events of these drugs in different studies, with special attention to the emergence of new cases of cognitive deficit.[45] This recommendation was based on

some reports that warned of a possible increase in the risk of neurocognitive events with the use of PCSK9i. Indeed, there is some biological plausibility to support the argument that a very sharp reduction in lipids can negatively impact cognitive function, regardless of the ability of the drug to cross the blood-brain barrier.[46,47]

To date, the leading assessment of the risk of cognitive deficits with the use of a PCSK9i (evolocumab) plus statin as compared to placebo plus statin is the EBBINGHAUS trial,[48] which randomized 1,974 patients. The subjects had a mean age of 63 years and were followed up for approximately 19 months. All completed the Cambridge Neuropsychological Test Automated Battery at 6, 12, and 24 months. No difference was observed between the groups in terms of cognitive function, scores on the cognitive function battery, or in subjective self-assessment of daily cognitive ability.[48]

In a pre-specified secondary analysis of the FOURIER study, Giugliano et al.[49] analyzed approximately 26,000 patients, with special attention to the relationship between the LDL concentration reached at 4 weeks and subsequent CV outcomes. There was no reduction in safety with very low LDL concentrations over an average of 2 years.

In the MENDEL-2[50] study, a large trial of evolocumab monotherapy, there was a rapid and marked decrease in levels of LDL and apolipoprotein B over 12 weeks in comparison with the placebo or ezetimibe group. LDL reductions in excess of 50% were reported in 72% of patients who received evolocumab. Severe adverse effects occurred at comparable rates across groups. In addition, injection-site reactions were infrequent with evolocumab and did not differ between groups. Biweekly and monthly evolocumab administration yielded comparable reductions in LDL levels, with good tolerability and safety.[50]

The LAPLACE-2[51] study compared evolocumab versus ezetimibe versus placebo in patients with hypercholesterolemia who were receiving stable doses of statins. Adverse events were similar in the three groups (36% of patients treated with statin plus evolocumab, 40% of those who received statin plus ezetimibe, and 39% of those who received statin plus placebo); musculoskeletal symptoms and headache were the most common. Intolerable adverse events that resulted in discontinuation of treatment occurred in only 1.9%, 1.8%, and 2.2% of participants in the evolocumab, ezetimibe, and placebo groups, respectively. Severe adverse events were reported in 2.1% of the patients treated with evolocumab, 0.9% of those treated with ezetimibe, and 2.3% of those in the control group. Neurocognitive events were reported in only 1 patient treated with evolocumab, compared with 3 patients treated with ezetimibe and no patients in the control groups. It bears stressing that the study was conducted for a short period (3 months) and, despite some adverse events, the benefits seemed to outweigh the risk of PCSK9i therapy.[51]

The GAUSS-2[52] study evaluated evolocumab versus ezetimibe in statin-intolerant dyslipidemic patients over 3 months. The rate of adverse events leading to treatment discontinuation was 8% in the evolocumab group – lower than in the ezetimibe arm (13%). Muscle pain occurred in only 8% of patients treated with evolocumab, versus 18% of those treated with ezetimibe. Discontinuation due to musculoskeletal side effects occurred in 5% of patients the evolocumab group, again a rate numerically lower than in the ezetimibe group (6%).[52] In the GAUSS-3 study,[53] patients who were intolerant to statins were treated with evolocumab 420 mg (with placebo ezetimibe) or ezetimibe 10 mg per day (with placebo evolocumab). Myalgia was reported by approximately 29% of patients treated with ezetimibe and 21% of those treated with evolocumab. However, muscular symptoms leading to discontinuation were very infrequent in the evolocumab group, occurring in only 1 out of 145 treated patients.[53] This seems very relevant, as it suggests that PCSK9i therapy can be used successfully in people with statin intolerance.

Interestingly, subjects with null mutation of the PCSK9 gene have been described. A U.S. woman inherited a mutation from her father and another from her mother which effectively eliminated PCSK9 function.[54] Her lifetime average LDL levels were only 14 mg/dL and, more importantly, she seems to lead a healthy life. In other words, even in a setting of marked reduction of LDL to extraordinarily low levels due to a genetic mutation, there is no evidence of any relevant harm to the overall health of the individual.

Another factor that is worthy of note is measurement of vitamin E levels. It is known that lipoproteins are involved in vitamin E transport,[55] and are necessary for steroidogenesis. Therefore, when levels of LDL are extremely low, vitamin E measurement – and, possibly, supplementation – seems necessary.[56] In fact, data from the DESCARTES[57] study showed that the substantial reduction in LDL in patients treated with evolocumab also reduced their levels of vitamin E. Nevertheless, there was no alteration in tissue levels of vitamin E, and the reduction was not clinically significant. Furthermore, there is no evidence of compromised synthesis of steroid, adrenal, or gonadal hormones, even in patients with extremely low LDL.[57] Overall, these data support that even very low concentrations of LDL by inhibition of PCSK9 do not translate into increased risk. In addition to these results, preliminary data from an analysis of nearly 3,000 patients enrolled in the DESCARTES and OSLER-1 studies showed no increase in adverse events and no cases of hemorrhagic stroke among patients with LDL levels below 40 or 25 mg/dL.[50]

Two open-label extensions of the FOURIER study, designed to evaluate the long-term safety of evolocumab in approximately 6,600 patients, are underway.[49] These results will certainly provide clearer evidence on the safety profile of PCSK9i.

Cost-effectiveness

Despite current evidence supporting the superiority of PCSK9i in the reduction of LDL concentrations in comparison to statins and ezetimibe, the cost-effectiveness ratio cannot be ignored. Estimates suggest that use of these agents is associated with significant expenditures for patients in different scenarios: a) €78,485.00 for those with a family history of hypercholesterolemia alone; b) €176,735.00 for those with

10-year CV risk >30%; and c) €295,543.00 for patients with established CV disease and DM2, all per quality-adjusted life-year (QALY) gained.[58] Additionally, the estimated annual cost of treatment is US$14,000.00.[59] This becomes particularly important when considering the (implicit and estimated) willingness-to-pay threshold in Brazilian, which seems to fluctuate between R$25,000.00 and R$185,000.00 per QALY.[60] Cost-effectiveness ratio and cost-utility ratio estimates indicate values much higher than the Brazilian thresholds, and, at least for the prospect of third-party payers, these drugs will have to spend some time on the market before their prices decline enough for consideration. According to Moore's curve, when a new technology is incorporated, there is a non-negligible gap in time for a reduction in estimated price (e.g., 60% to 70% of the current value).[61-63] Therefore, it is important to evaluate the cost-effectiveness and cost-utility of PCSK9i and their market prices before they can be recommended as a therapeutic option – at this time, still from the patient perspective alone.

Final considerations

Since the discovery of their effect on LDL levels, PCSK9i have been an object of great research interest. The clear association between CV risk factors and the significant reduction in LDL obtained with their use are guiding the development of novel algorithms for the treatment of dyslipidemias and CV diseases as a whole.

Major advances in the treatment of CAD have been achieved in recent decades. Among them, the greater understanding of the importance of LDL as a causal factor was particularly relevant. The results of the RCTs described in this paper have provided the evidence base for the use of PCSK9i and indications for the use of these drugs, as well as the LDL targets to be achieved. Each patient should have their risk adequately assessed, taking into account the cost-effectiveness of treatment and the most appropriate medications for their clinical condition. The inhibition of PCSK9 represents a novel approach to reducing LDL levels and preventing adverse CV outcomes in high-risk patients who have not achieved recommended levels of LDL despite the use of a maximally optimized therapeutic arsenal.

Finally, it is important to stress that the use of PCSK9i should not be indiscriminate, and that it is up to physicians to determine which patients will actually benefit from their use. On the other hand, high-risk patients and those who are intolerant to statins – and who can afford this therapy – certainly have in PCSK9i a treatment option that has so far proven to be safe and attractive.

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Author contributions

Conception and design of the research: Ferrari F, Moriguchi EH; acquisition of data, analysis and interpretation of the data and writing of the manuscript: Ferrari F, Stein R, Motta MT, Moriguchi EH; critical revision of the manuscript for intellectual content: Stein R, Moriguchi EH.

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Window to the Future or Door to Chaos?

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The remarkable advance in technology has caused a new social revolution impacting all areas of knowledge, modifying traditions and practices that were consecrated centuries ago. Advances in informatics and telecommunications with practical application in various sciences are eloquent examples of such transformation.[1]

In medicine, this progress has brought up extraordinary advances in diagnosis and therapy, since the combination of new medical technologies and efficient communication media has bequeathed us telemedicine, which has been practiced for more than two decades with great success, opening the doors for solutions such as a telematic transmission of a simple electrocardiogram to remotely performing robotic surgeries.[2]

In this scenario, the need for regulation of telemedicine in Brazil arose. The Brazilian federal legislation handed over such attribution to the Federal Medical Council (*Conselho Federal de Medicina*, CFM), which performed it by issuing CFM Resolution 2.227/2018,[3] already published in the Union Official Gazette (*Diário Oficial da União*).

In the aforementioned resolution, CFM defined in Article 1 telemedicine as "the practice of medicine mediated by technologies for assistance, education, research, prevention of diseases and injuries, and health promotion." The Council is fully aware of possible benefits that can result of an ethical application of this practice, which can broaden access to public health and maximize the effects of already established public policies. That was why the Council issued the regulations, but it must be aware of the disruptive power of this technology, which confronts, in theory, millennial postulates of professional practice. Medicine, as conceived, does not dispense with physician-patient interaction. Therefore, telemedicine cannot dispense the doctor or replace him with another professional in the practice of those acts that, under the terms of Law 12.842/2013,[4] are exclusively to physicians.

The CFM uses the term teleconsultation as a shelter of telemedicine. The word sounds like a situation where a name comes to have a life of its own as something justifiable, routine, as if it had always existed and dispensed a critical analysis of its origins. However, novelty should not be understood in this way. There are challenges of a technical, ethical, legal, regulatory, and cultural nature regarding teleconsultation, which is exclusive of the physician and requires access to medical records, or in other words, to the set of standardized and ordered documents that the patient might have from a previous care. It is important to emphasize that access to medical record is among the exclusive acts of the physician and the patient has the right to demand that the data recorded are kept secret.[5]

Classically, a consultation includes the triad anamnesis, physical examination, and complementary tests in an integrated and "carousel" dynamic. Thus, physical examination findings, for example, may motivate a return to anamnesis; the image reports, in turn, can determine the making of another physical examination, etc. Who decides this dynamic is traditionally the doctor, who assumes responsibility for his decisions. Now, the teleconsultation can make the physical examination unfeasible, since the doctor will be away from the patient. In this case, who will take responsibility? Will the doctor sitting in front of a computer have a duty to raise an objection of conscience not to proceed? Nowadays, even in well-known cases, prudence – a cornerstone of ethics – suggests that a face-to-face interaction is needed in most cases.[5]

Would the patient be well informed that the teleconsultation and any other methods of telemedicine may represent an incomplete methodology, especially if they involve the waiver or substitution of an actual physician by another type of professional? Would the patient take responsibility for any failures resulting from this new form of assistance and still give consent? Would the lack of a detailed anamnesis, such as those commonly done in traditional consultations, or the shortage of documentary records, not weaken the acts of telemedicine? Incidentally, by documentary evidence, the role of the medical record as a memory, or thread leading to an efficient diagnosis, has the potential to be impaired in the inadequate practice of telemedicine procedures, which can be damaging.

CFM regulation should therefore represent a step forward, not a setback. Broadening access in public health is a common desire of all physicians. In this nuance, telemedicine brings indisputable progress, which justifies its regulation. However, CFM should be vigilant so that everything is done properly, with technical quality discretion, anticipating the regulatory impact of the standard. Regulation should preserve, for example, the millenary postulates of the practice of medicine and promote equality. The major challenge of CFM Resolution 2.227/2018[3] is to be effective and applicable in the advance of social justice and deliberative ethics.

Keywords

Medicine/trends; National Science, Technology and Innovation Policy; Technological Development/ethic; Telemedicine/legislation & jurisprudence; Delivery Health Care/legislation & jurisprudence; Precision Medicine/trends.

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The medical consultation materializes the doctor-patient interaction. Interaction that gains strength because it is based on the confidence of the patient and the conscience of the doctor. These are the bases of respectability of medicine over time.

The CFM, through CFM Resolution 1958/2010,[6] announced that the consultation includes acts such as "anamnesis, physical examination, and elaboration of hypotheses or diagnostic conclusions, request for complementary tests, when necessary, and therapeutic prescription as a complete medical act that can be finished or not in a single moment."

The Code of Medical Ethics,[7] in turn, prohibits the prescription of treatment without prior examination of the patient. Here is the precept:

"Art. 37. To prescribe treatment or other procedures without direct examination of the patient, except in cases of urgency or emergency and a proven impossibility to perform it, and in this case, to do so immediately after cessation of the disability."

The rules can be harmonized because the sole paragraph of this deontological norm speaks of "remote medical care, in the form of telemedicine or other method," determining to do so with respect to the regulations of the CFM.

In establishing the conditions for the practice of telemedicine by doctors in Brazil, the CFM presented a new ethical framework for the practice of medicine in the country. The changes, inserted in the Resolution, update the Code of Medical Ethics, making the old regulation seem like a fossil, in view of the potential for interference of the new digital ethics in medical practice.

The Code of Medical Ethics[7] is a rule that has the same hierarchy as CFM Resolution 2.227/2018.[3] Thus, although considered as the major ethical guide, it is not possible to say that the telemedicine Resolution confronts the Code of Medical Ethics in some of its devices, especially in relation to the need for a direct examination of the patient before the prescription, as established in Article 37 of the Code of Ethics.

The major problem of the rule in question would be in the teleconsultation, regulated in Article 4, because it dispensed the face-to-face examination of the patient prior to the prescription. Although the need for a previous physical examination has not been completely abolished, since Paragraph 1 "implies as a mandatory premise" that the first visit is compulsory, and a new on-site visit is recommended every 120 days. However, the new rule allows for virtual consultation when practicing healthcare coverage to remote sites, where, in theory, there would be a shortage of human resources. It should be noted that, to a certain extent, the same argument was used in the *Mais Médicos* Program, when the revalidation of the diploma of doctors graduated abroad was dispensed in order for them to work in the Unified Health System (*Sistema Único de Saúde,* SUS). Teleconsultation is regulated as follows, *in verbis*:

"Art. 4 Teleconsultation is the remote medical consultation, mediated by technologies, with doctor and patient located in different geographic spaces.

§1 Teleconsultation implies as a mandatory premise the prior establishment of a face-to-face relationship between doctor and patient.

§ 2 In long-term visits or chronic diseases, it is recommended to consult face-to-face at intervals not exceeding 120 days.

§ 3 The establishment of a physician-patient relationship in a virtual way is permitted for healthcare coverage in geographically remote areas, provided there are the recommended physical and technical conditions and health professional.

§ 4 Telemedicine must be duly consented by the patient or his legal representative and performed by free decision and under the professional responsibility of the physician.

§ 5 In case of participation of other health professionals, they must receive adequate training, under the responsibility of the physician, individual, or technical director of the intermediary company."

Resolution 2.227/2018[3] has found strong resistance among physicians, mainly due to its transformative potential. Healthcare providers, large hospitals, and telemedicine solutions companies are euphoric. At the other end, doctors claim that medicine suffered a severe blow for those who had an ethical duty in their practice, turning doctors into true telemarketers.

The detailed and impartial analysis of the Resolution in question points, as already mentioned, to an apparent confrontation with the rules of the Code of Medical Ethics.[7] But by far the greatest problem would arise from the existence of possible offenses to the legal system, as verified in Paragraph 5 of Article 4. There, we can see a delegation of medical powers to other health professionals, such as nurses. At this point, the defect of the norm is not only in the possible offense to Article 2 of the Code of Medical Ethics. It goes further, challenging fences imposed by the law.

The Federal Constitution of 1988[8] ensures in Item XIII of Article 5 the freedom of professional practice, provided that it is practiced "according to the professional qualifications established by law." However, as the law defines what acts are exclusive to doctors, it arises the illegality of the norm contained in the CFM Resolution, which confers additional competence to other health professionals – nurses for example – to practice acts that are exclusive to the physician.

It is known that the Law No. 7.498, from June 25, 1986,[9] which provides for the practice of nursing in Brazil, defines, in Article 1, the practice of that profession throughout the national territory, within the limits of the law. It is not ignored that Article 11 of the aforementioned law attributes to the nurse, as a member of the health team, the competence to prescribe drugs established in public health programs and routinely approved by the health institution. What is said is that the legislation does not attribute to nurses the assignment to participate in teleconsultation, as did CFM in Paragraph 5 of Article 4 of the Resolution discussed.

In other words, Paragraph 5 of Article 4 of the Resolution[3] considered provides for the participation of other health professionals, including nurses, in acts exclusive to doctors, in the case of medical consultation, even in its remote version. Neither would the distinguished CFM have the legal competence to assign to the doctor or technical director of "intermediary company" the prerogative to train other health professionals, whose professions are regulated and governed by their own legal system.

Paragraph 3 of the same Article 4 of the aforementioned resolution allows the "establishment of a virtual doctor-patient relationship" only for health care coverage in geographically remote areas, provided that there are the recommended physical and technical conditions, as well as healthcare professionals.

The argument that teleconsulting fulfills the difficulty of healthcare assistance due to geographic distance requires clarification of the meaning of distance, so that it does not fit something that can be face-to-face, but that presents difficulties of access, for being far, for having complicated transit, for demanding assistance at times incompatible with the availability of the physician, etc. In short, comfort should not serve as justification for the acceptance of an incomplete care from the point of view of identification of signs and symptoms.

It is clear that the new rule has yet to define the meaning of geographically remote areas, leaving room for broader interpretations of the possibilities of the teleconsultation, which cannot lose its merely complementary character, to meet the needs of the assistance of a country of continental dimensions, transforming itself into powerful tool for curtailing patients' rights. That is, teleconsulting, assuming its legality, is only justified to expand access to unserved beneficiaries of the SUS.

On the other hand, in the scope of Supplementary Health, Law 9.656, dated June 3, 1998,[10] which provides for private healthcare plans and insurance, establishes a specific regulatory framework, provided for in the contractual sphere, distinct from the commitment to universal access, provided for in Article 196 of the Federal Constitution. Therefore, the coverage limits of the beneficiaries of the health plan operators are clearly defined by law.

The National Agency of Supplementary Health (*Agência Nacional de Saúde Suplementar*, ANS), which is responsible for regulating the sector and elaborating the Role of Procedures and Events in Health, or Role of Procedures, has already decided that medical consultation is one of the compulsory coverage procedures. Also, teleconsultation could not be used to replace the essential face-to-face consultation, which the beneficiary is totally burdened with, to be used to restrict access to the clear legal right.

Still resorting to Law 7.498/1986,[9] it is clear that the nurse only has legal competence to prescribe "medications established in public health programs and routinely approved by the health institution." Thus, even if it is alleged that the responsibility for the eventual prescription in teleconsultation is of the doctor who is at a distance, the other health professional who also attends the medical act, also participates, in full exercise of his profession, therefore, must behave within the legal limits of the law.

It seems that, in the scope of supplementary health, there is no legal support, for example, for nurses, even under supervision, to prescribe medications or request tests, and the realization of a teleconsultation, with the participation of other health professionals, would be a practice without support in the legislation.[10]

The publication of Resolution 2.227/2018[3] caused uneasiness, since it is necessary to start from a premise: teleconsultation can only be done when the doctor already knows the patient. Necessary, therefore, a prior consultation in which there was a previous face-to-face relation between doctor and patient. However, the presence of this requirement will be difficult to control and oversight, because knowing the patient does not mean knowing the case of the moment. Thus, first-time consultations of the clinical situation are likely to be "confused" with a follow-up consultation, where one could accept the non-presence for information about progression, therapeutic adjustments, and evaluation of the requested tests.

Law 12.871, of October 22, 2013,[11] which established the *Mais Médicos* Program, allowed the revalidation of the medical diploma not to be compulsory in the strict context of this program. That is, Resolution 2.227/2018[3] should make it clear that only in the context of public programs, once the absence of doctors is verified, it would be possible to teleconsult without another doctor with the patient.

It is believed that Hippocrates removed medicine from the gods exactly to allow interaction between humans. We now run the risk of the "deification" of technology to extrapolate its undeniable utility of data transmission within ethical standards. Thus, from the transdisciplinary point of view, about its three foundations – rigor, openness, and tolerance – there is a high risk of compromising technoscientific rigor.[5]

The CFM, when editing the Resolution, embraces the unknown, the unexpected, disregarding the tolerance of opposing opinions, which may arise in the complex process of decision making, in the face of the patient's right to the active voice, when he dialogues directly with the doctor.

Concerning the two important pillars of medical ethics, it is a matter of concern to deal with prudence – caution during the decision-making process – and with zeal – quality of application and observance of the evolution of consensual conduct. Concerning three of the principles of bioethics, it concerns the management of beneficence as well as non-maleficence – that today, because any method is liable to cause harm, has become synonymous with security, in addition to bringing new aspects about autonomy.[5] Finally, does the teleconsultation pass through the sieve of the ten steps[12] essential for a qualified clinical diagnosis in the context of anamnesis-physical examination integration?

It is worth remembering the decalogue that must be observed in order to prepare a good diagnosis: (1) an overall view of the patient made possible by physical proximity; (2) patient's free issue of his complaints and impressions; (3) physician-patient dialogue stimulated to clarify obscure points and hypotheses raised by the physician based on what the patient said; (4) construction of diagnostic hypotheses supported by anamnesis; (5) performing the physical examination and identifying, or not, signs aligned with the hypotheses, or expanding to new hypotheses; (6) return to anamnesis when indicated by physical examination findings that compose new clinical reasoning; (7) evaluation of the need and selection of complementary examination based on anamnesis-physical examination integration; (8) integration of the reports of complementary tests with the clinical reasoning sustaining the request of the tests; (9) formulation of the probable diagnosis; and (10) use as a basis for therapeutic conduct, always remembering to clarify the patient well so

that he can give or not give consent, which should not be obtained at the outset as a *carte blanche*.[12]

Essential questions need to be well defined: (1) level of biological safety for the patient; (2) level of ethical and legal safety for the physician; (3) impact on physician training; (4) impact on society's habits.[5]

Another point worth mentioning is telesurgery, provided for in Article 8 and defined as "performing a remote surgical procedure, mediated by safe interactive technologies, with medical executor and robotic equipment in distinct physical spaces."[3] Telesurgery is only possible due to robotic surgery, whose clinical application in Brazil is still restricted, being that most parts of the techniques lack assessment by the CFM.

In order to be effective, it is imperative that the medical team be composed, at least, of the robotic equipment (remote surgeon) and physician responsible for the instrumental manipulation (local surgeon), both of whom must be specialists with Specialist Qualification Registry (*Registro de Qualificação de Especialista*, RQE) in the area corresponding to the main surgical act, registered with the Regional Council of Medicine (CRM) of its jurisdiction, excluding, at least in theory, the performance of telesurgery by physicians not enrolled in the CRM in other countries.[3]

The legal competence to define the experimental nature or not of medical procedures is of the CFM, with a focus on Law 12.842/2013,[4] embodied in Article 7, authorizing or prohibiting its practice by doctors in Brazil. In this way, it would be appropriate to insert a device in the resolution restricting the practice of robotic telesurgery to techniques already approved by CFM and in current use in the country, since it would be unreasonable to offer something with restricted availability frustrating the fair expectations of the medical profession and Brazilian society.

It is worth mentioning that none of the techniques of robotic surgery is part of Brazil's public policy roll, nor are they included in the ANS Health Procedures and Events Role. In other words, the expansion of the robotic surgery care network, without even being predicted coverage in the country, can inaugurate the "tele-judicialization" of health, a new way of reversing priorities in the country's health system.

Finally, it is opportune to discuss Article 9, which regulates the diagnosis: "Telediagnosis must be carried out according to scientific guidelines proposed by the Association of Specialty linked to the method, recognized by the Joint Commission of Specialties, constituted according to Decree No. 8.516, of September 10, 2015."[13] In this sense, it is important to note that Law 12.401, dated April 28, 2011,[14] defines that the competence to elaborate clinical protocols and therapeutic guidelines[a] within the scope of the SUS is of the National Commission for the Incorporation of Technologies in the SUS (*Comissão Nacional de Incorporação de Tecnologias*, Conitec).

Conitec, based on the discussed legislation, has legal attribution for the elaboration of clinical protocols and therapeutic guidelines. The CFM could not, based on a normative resolution, exclude those who have legal competence to elaborate guidelines within the Brazilian health system, delegating exclusively this attribution to private entity, even if conditioned to its approval. The improvement of the standard in this regard is becoming more pressing.

Moreover, it would not be too much to say that Resolution 2.227/2018[3] does not have the power to legitimize, broadly speaking, the incorporation of telemedicine in Brazil, but only regulates the participation of physicians in its practice. The entry of any technology according to current legislation, this includes telemedicine, will necessarily consider:

I. the scientific evidence on the efficacy, accuracy, effectiveness, and safety of the medication, product, or procedure that is the subject of the proceedings, which is complied with by the entity responsible for registration or authorization for use;

II. the comparative economic evaluation of the benefits and costs in relation to technologies already incorporated, including with regard to home, outpatient or hospital care, when appropriate."

Resolution 2.227/2018,[3] although necessary, as it is drafted, unless it is better judged, confronts the domestic legislation that regulates the other health professions, as discussed, and should be modified, at least as far as the wording of Articles 4, 8, and 9 are concerned. In our understanding, the wording below would be more appropriate for the opportunity and species. The adequation below would be reasonable as a way of making compatible the already published norm and the set of theses defended in this article:

Art. 4 Teleconsultation is the remote medical consultation, mediated by technologies, with doctor and patient located in different geographic spaces.

§ 1 In teleconsultation, the prior establishment of a face-to-face relationship between doctor and patient is a mandatory premise.

§ 2 In long-term care or chronic diseases, it is recommended to consult face-to-face at intervals not exceeding 120 days.

§ 3 The establishment of a doctor-patient relationship in a virtual way is permitted exclusively for health care coverage in geographically remote areas, provided that there are the recommended physical and technical conditions and legally qualified health profissional.

§ 4 For the purposes defined in this article, it is the responsibility of the Regional Councils of Medicine within their jurisdictions to define, in their own act, which are the geographically remote areas.

§ 5 The teleconsultation must be duly consented by the patient or his legal representative and performed by free decision and under the professional responsibility of the physician.

§ 6 In case of participation and training of other health professionals, the requirements of the legislation that regulates their respective professions must be met.

§ 7 Teleconsultation is prohibited in the scope of supplementary health.

Article 8

(...)

§ 10 Surgical procedures not evaluated or considered experimental by the Federal Council of Medicine should be carried out in research protocols according to the rules of the CEP/CONEP System.

[a] II – Clinical protocol and therapeutic guideline: document that establishes criteria for the diagnosis of the disease or health problem; the recommended treatment, with the medications and other appropriate products, when applicable; the recommended dosages; the mechanisms of clinical control; and the monitoring and verification of the therapeutic results, to be followed by administrators at the SUS.

Art. 9 Telediagnosis must be carried out according to scientific guidelines approved by the National Commission for the Incorporation of Technologies in the SUS (Conitec) or proposed by the Specialty Association linked to the method, recognized by the Joint Commission of Specialties, constituted according to Decree N°. 8.516, of 10 September2015.[13]

Prior to the publication of this article, CFM, for the reasons discussed here, revoked the Resolution 2.227/2018[3] to allow its goal to materialize in practice, and the appropriate regulation of extraordinary telemedicine be no longer a promise, becoming an instrument of equity and social justice,[15,16] under risk of telemedicine becoming, instead of a window into the future, a door to chaos.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: MACQ Lopes, Oliveira GMM, Amaral Júnior A, Pereira ESB

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Case 2/2019 – Man with Arrhythmogenic Cardiopathy Followed by Rapidly Progressive Heart Failure

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A 36-year-old man was referred to the medical service for surgical treatment of heart failure refractory to drug treatment.

At the age of 26, 1st-degree atrioventricular block and episodes of non-sustained ventricular tachycardia were detected on the electrocardiogram (ECG). After 4 years, he started to have episodes of pre-syncope.

The magnetic resonance performed at that time (09/29/2010) disclosed diastolic diameter of 59 mm; systolic diameter of 49 mm; 10-mm septum; posterior wall of 11 mm; 48% left ventricular ejection fraction and 53% right ventricular ejection fraction, with no contraction abnormalities. The late enhancement imaging showed an infero-septal, medium-basal subepicardial focus, compatible with fibrosis, suggestive of myocarditis or idiopathic dilated cardiomyopathy.

An electrophysiological study was indicated. After extra-stimuli, sustained ventricular tachycardia with hemodynamic instability was triggered and an implantable-cardioverter defibrillator (ICD) was implanted and the patient received a beta-blocker. However, several episodes of ventricular tachycardia were recorded by the ICD and the use of amiodarone was initiated.

He remained asymptomatic for approximately 3 years until he developed heart failure, which rapidly evolved into functional class IV, which resulted in hospitalization for compensation and with acute pulmonary edema at 34 years of age, followed by a new hospitalization a few months later for new heart failure compensation. At that time, hypothyroidism (TSH of 88 um / L) was diagnosed, which was attributed to amiodarone use. The echocardiogram disclosed severe left ventricular systolic dysfunction, with EF = 21%.

Myocardial resynchronization was indicated, with pacemaker implantation with electrodes implanted at two points in the left ventricle in March 2015, but he was readmitted due to arterial hypotension, atrial fibrillation and heart failure decompensation in September 2015. Amiodarone, dobutamine, spironolactone, furosemide and rivaroxaban were administered.

Keywords

Heart Failure; Stroke Volume; Cardiomyopathy, Dilated; Myocarditis; Heart Transplantation.

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The patient was transferred to the Heart Institute (InCor) for possible surgical treatment of heart failure (heart transplantation) on October 20, 2015. The patient reported a 20 kg loss over a 4-year period. He denied arterial hypertension and diabetes mellitus.

Physical examination showed cachexia, jugular swelling+, hepatojugular reflux, no distension alteration at the Valsalva maneuver or exhalation, vesicular murmurs present in the lungs, slightly reduced on the left pulmonary basis, palpable thrill in the mitral, tricuspid, accessory aortic foci; arrhythmic heart sounds with a more audible holosystolic murmur in the mitral focus, radiating into the posterior axillary line. The abdomen was flat, with a 6-cm hepatomegaly from the right costal border, palpable caudate lobe nearby, without ascites. Lower limbs without edema, with no signs of deep venous thrombosis. He was receiving intravenous dobutamine.

The patient was evaluated by the heart transplant team due to the persistent need of high-dose inotropic and vasodilator drugs during ICU observation. The patient was prioritized for cardiac transplantation due to use of vasoactive drug and joined the list on 11/09/15.

The ECG showed a pacemaker rhythm operating in VAT mode and chest X-ray showed cardiomegaly with signs of pulmonary congestion.

Laboratory tests (10/21/2015) showed hemoglobin 11.1 g/dL, hematocrit 34%, leukocytes 7290 (neutrophils 82%, eosinophils 3%, lymphocytes 7%, monocytes 6%), platelets 259,000/mm^3, urea 28 mg/dL, creatinine 0.92 mg/dL, CRP of 69.34 mg/L, sodium 137 mEq/L, potassium 3.4 mEq/L, PAT (INR) of 2.4; APTT (rel. Times) of 1.31; Urinalysis with proteinuria of 0.67 g/L.

The echocardiogram (10/21/2015) disclosed left ventricle with diffuse hypokinesia, worse in the inferior and inferolateral walls and ejection fraction of 25%; the right ventricle showed moderate diffuse hypokinesia. There was marked mitral regurgitation; the other valves showed no alterations. The pulmonary artery pressure was estimated at 49 mmHg.

He had two bloodstream infections, which were treated with meropenem and vancomycin and tazobactam during the month of November 2015.

Serological tests were positive for toxoplasmosis and mononucleosis in the IgG.

Abdominal, thyroid and carotid artery ultrasonography results were normal.

Right-chamber catheterization disclosed systolic pulmonary artery pressure of 55 mmHg, diastolic pressure of 23 mmHg and a mean pressure of 34 mmHg; the pulmonary occlusion pressure was 24 mmHg, the cardiac output was 5.5 L/min and the transpulmonary gradient was 10 mmHg; pulmonary

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vascular resistance was 1.8 Woods and the systemic vascular resistance was 887 dynes/sec/cm^{-5}.

The transplantation was performed in March 2016 using the bicaval orthotopic heart transplantation technique, without complications; the patient received prophylactic antimicrobial treatment with vancomycin and cefepime.

After the transplantation, the immunosuppressant drugs prednisone, cyclosporine and mycophenolate were introduced. Endomyocardial biopsies performed on March 21 and 31 showed grade I rejection and cytomegalovirus tests were negative.

The echocardiogram performed at hospital discharge on 03/28/2016 showed left atrium of 42 mm, septum and posterior wall of 11 mm, left ventricle of 50x31 with ejection fraction of 68%; normal right ventricle and pulmonary artery pressure of 35 mmHg.

The medication prescribed at the hospital discharge consisted of cyclosporin 100mg + 75mg daily, prednisone 40mg 1x / day, mycophenolate sodium 720mg every 12h.

At the outpatient clinic consultations he remained asymptomatic (April 2017). He currently takes Tacrolimus 4 mg 2x/day; prednisone 5 mg; mycophenolate 720 mg 2x/day; diltiazem 30 mg 3x/day; simvastatin 10 mg 1x/day; vitamin D 900 mg/day; and omeprazole 20mg 1 x/day.

Clinical aspects

The patient developed arrhythmia at 26 years of age. At age 33, in 2013, he developed heart failure, which rapidly progressed to functional class IV, with consecutive hospitalizations due to acute decompensation. In 2015, after the last hospitalization, he was placed on the priority list for heart transplantation due to clinical treatment refractoriness. In March 2016 he underwent the procedure and remained asymptomatic, being followed through outpatient clinic consultations since April 2017.

This is a heart failure case with important aspects that must be investigated: etiology and factors for decompensation.

It is suggested that the probable cause of the index event is myocarditis or idiopathic dilated cardiomyopathy in a 30-year-old man.

The American Heart Association classifies primary cardiomyopathies (predominant heart involvement) into three groups: genetic (hypertrophic cardiomyopathy, right ventricular arrhythmogenic cardiomyopathy, noncompacted left ventricle, glycogen accumulation disease, mitochondrial myopathies and channelopathies); mixed, predominantly non-genetic (dilated cardiomyopathy, restrictive); and acquired (inflammatory (myocarditis), caused by stress (Takotsubo), peripartum, induced by tachycardia, and of the infant, child of an insulin-dependent mother.[1]

The origin of inflammatory heart diseases can be: autoimmune (connective tissue diseases, sarcoidosis, eosinophilic diseases); inflammatory diseases (hypersensitivity myocarditis, endomyocardial fibrosis, hypereosinophilic syndrome); toxic (antineoplastic chemotherapeutic drugs); and infectious (protozoa, fungi, bacteria, viruses and parasites).[2]

Among the infiltrative diseases, which usually occur simultaneously with restrictive syndrome, are: amyloidosis, sarcoidosis and deposition diseases (Fabry, and others).[3]

Amyloidosis could be the etiology of the patient's heart disease, since it is a progressive disease, affects adults from the age of 30 years and its frequent form of extracardiac involvement is kidney disease. In this context, the patient was close to 30 years old and his urinalysis showed the presence of proteinuria. Additionally, the ECG in amyloidosis usually shows atrioventricular block, supraventricular and ventricular arrhythmias, as the patient showed at the beginning of the clinical picture. However, the typical findings at the magnetic resonance and echocardiogram show an enlargement of the septum and posterior wall, which were absent in the present case.

In sarcoidosis, there is a more frequent involvement of individuals between 25 and 60 years, and it is positively associated with lung and lymph node involvement and frequent extracardiac alterations, which were absent in the patient.

Fabry disease, on the other hand, manifests in childhood or adolescence, and shows important dermatological findings, which rule out the possibility of this diagnosis. Regarding the complementary exams, amyloidosis and Fabry's disease show findings that are similar to sarcoidosis on the ECG, magnetic resonance imaging and echocardiogram.[4,5]

However, there are no reports of autoimmune tests, extracardiac investigations, much less the performance of endomyocardial biopsy in the current patient with rapidly progressive heart failure, without a definitive cause, not responsive to clinical treatment and with hemodynamic deterioration.[5]

Recreational drug poisoning, such as alcohol, amphetamines, cocaine and the use of anabolic drugs could be possible causes for myocarditis, considering that the patient is young and a potential user of these drugs. However, the current case does not show a history of drug addiction or drug abuse. Moreover, drug poisoning is expressed by chamber dilatation and not by myocardial thickening.

In South America and Brazil, the Chagasic etiology is a frequent form of myocarditis. However, the patient did not have alterations in the ECG and echocardiogram suggestive of this disease. There was no evidence of right bundle-branch block, anterosuperior divisional block, apical aneurysm, right heart failure manifestations, and the patient did not show positive epidemiology for Chagas disease.[5-7]

Viruses are also frequent infectious myocarditis agents, with the most common agents being adenovirus, enterovirus, parvovirus, herpes simplex, hepatitis C virus, cytomegalovirus and Epstein-Barr virus. However, magnetic resonance imaging shows thickening of the septum and posterior wall, which indicates other causes of myocarditis, since the infectious one is associated with dilated cardiomyopathy.[8]

However, there was not a complete investigation to elucidate a possible infectious cause, either by serology or by endomyocardial biopsy of the right ventricle. The patient is young, viral contaminations are common, he may have circulated in areas of greater risk for Chagas disease contamination and be sexually active, increasing the chances of being infected with HIV and different types of hepatitis.[8]

Regarding the less probable diagnostic hypothesis, one must consider coronary artery disease. Despite presenting segmental dysfunction at the MRI, we have here a young patient with no clinical features or risk factors for this etiology. Additionally, the thickening of the septum and posterior wall have systemic arterial hypertension and hypertrophic cardiomyopathy as important differential diagnoses. However, the patient did not suffer from arterial hypertension and the echocardiography, as well as the magnetic resonance imaging, did not show any characteristic findings of hypertrophic cardiomyopathy: asymmetric septal hypertrophy, left ventricular outflow tract obstruction and septum/wall ratio >1.3. Valvular disease can also be ruled out, since the patient did not show it initially, either at the physical examination or imaging test, and the patient only developed mitral regurgitation after heart failure progression.

Finally, idiopathic dilated cardiomyopathy cannot be ruled out as a diagnostic possibility for this case. It typically affects men between the ages of 18 and 50 and at least 25% of the cases show genetic transmission of the disease. It is believed that genetic factors associated with changes in immune response and infectious factors could act synergistically in the development of structural changes and consequent onset of clinical manifestations. It is estimated that between 10%-20% of cases of idiopathic cardiomyopathy are caused by a previous viral infection sequela.[8,9]

The patient rapidly evolved to functional class IV, showing marked ejection fraction reduction and underwent successive hospital admissions due to the decompensations.

There are many factors that exacerbate heart failure and taking into account the patient's history, one cannot infer a specific precipitating factor for the case described herein. Among the possible hypotheses is the natural evolution of the underlying disease, of which etiology was not clarified, and this fact may have prevented the implementation of specific treatment strategies.

The following are other possible precipitating factors of the acute decompensation observed in the patient:[3,5,10,11] absence of health education performed by the professionals and/or the patient's poor adherence to non-pharmacological measures for heart failure management; inadequate diet and water intake, as well as the abuse of alcohol and other drugs, are frequent factors for decompensation. Moreover, all patients with heart failure should be vaccinated against influenza and pneumococcus, considering that respiratory infections are common etiologies for decompensation; however, in this case, the patient showed no signs of infection leading to hospitalization or leukogram alterations.

As for pharmacological measures, the use of beta-blockers (carvedilol, nebivolol, bisoprolol and metoprolol succinate) in patients with reduced ejection fraction associated with angiotensin-converting enzyme inhibitor is the effective treatment for patients with New York Heart Association functional class I to IV, because they reduce morbimortality by acting on cardiac reverse remodeling. There are contraindications for the use of these classes of drugs; however, there are no records in the clinical case of reasons justifying the absence of introduction of these classes of drugs after the development of systolic heart failure. Furthermore, systolic insufficiency refractory to optimized clinical treatment and ejection fraction ≤35%, also requires the use of aldosterone antagonists, a medication that also has an effect on reverse remodeling, if the patient does not have contraindications to its use. There is information about the introduction of this drug only after the third decompensation event.

Arrhythmia, in turn, is an important decompensatory factor, such as the atrial fibrillation developed by this patient during one of the hospitalizations. Its onset is associated with several adverse hemodynamic effects, such as loss of atrioventricular synchrony and loss of atrial contraction, leading to cardiac output reduction in a heart with an already impaired ventricular function.

Other possible etiologies for decompensation detected in this patient were the concomitant presence of anemia and kidney dysfunction, which are conditions that considerably increase mortality in heart failure.

The patient's hemoglobin level was 11.1 g/dL. Being an important precipitating factor, anemia becomes important due to its deleterious effects on the heart. The erythrocytes, in addition to providing oxygen to myocardial cells, favor the exchange of antioxidants that prevent oxidative stress and programmed cell death, but the impairment of these mechanisms favor myocardial dysfunction. Additionally, in response to hypoxemia resulting from anemia, the sympathetic system is stimulated, leading to tachycardia, increased inotropism and vasoconstriction, further compromising myocyte function and leading to hypervolemia in parallel. Specifically, hypoxemia of anemia and kidney vasoconstriction generate renal ischemia, with the release of inflammatory factors related to myocardial injury and hypervolemia due to the activation of the renin-angiotensin-aldosterone system.

Proteinuria was observed in a urinalysis result, despite normal values of creatinine and urea. Like anemia, nephropathy may be a factor of decompensation, etiology and/or consequence of heart failure. As a precipitating factor, one can point to salt and water retention; alterations in the cardiomyocyte structure and function due to inflammatory activation and calcium and phosphorus metabolism abnormalities; and due to the anemia itself, generated by kidney dysfunction, leading to reduced erythropoietin production. One should consider that nephropathy can also be a consequence of amyloidosis, as it leads to amyloid deposition in the kidneys, impairing their function, and 80% of patients with this disease have proteinuria.

Due to increased pulmonary artery and right ventricular systolic pressure, pulmonary embolism could be a cause for decompensation. However, in this clinical setting, these cardiopulmonary alterations are possibly due to heart failure progression.

Hypothyroidism is a potential cause of heart failure due to bradycardia, systolic and diastolic dysfunction, increased systemic vascular resistance, diastolic hypertension, increased arterial stiffness and endothelial dysfunction.[12] Laboratory examination showed the patient had TSH of 88 um/L and the introduction of levothyroxine was not reported.

The patient may also have decompensated due to marked mitral regurgitation caused by left ventricular

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dilatation and, in this situation, valvulopathy was secondary to the disease progression.

The use of negative inotropic medications, corticosteroids, cardiotoxic chemotherapeutic drugs, non-steroidal anti-inflammatory drugs, antiarrhythmics and glitazone or dipeptidyl phosphatase 4 inhibitors may be decompensation triggers, which can be used through self-medication or by not informing to other physicians about the presence of heart failure. **(Dr. Marcella Abunahman Freitas Pereira, Dr. Wilma Noia Ribeiro)**

Diagnostic hypotheses: Infiltrative cardiomyopathy or idiopathic dilated cardiomyopathy. **(Dr. Marcella Abunahman Freitas Pereira, Dr. Wilma Noia Ribeiro)**

Anatomopathological examination

The explanted heart, devoid of the atria, weighed 598 g (normal = 300 to 350 g). Externally, there was discrete and focal epicardial thickening on the sternocostal and diaphragmatic surfaces of the right and left ventricles. The cross-sectional sections showed a bicuspid aortic valve, with fusion between the left semilunar and non-coronary leaflets, without a median raphe (Figure 1), moderate and diffuse thickening of the semilunar leaflets, with marked retraction and slight calcification at the free border of the semilunar leaflets, macroscopically suggestive of valve regurgitation. The right coronary artery (RCA) ostium was typically located in the right Valsalva sinus. In the left Valsalva sinus, two ostia of coronary arteries originated: the most anterior ostium gave origin to the circumflex (Cx) artery and the posterior ostium, tangentially, originated the anterior descending artery (ADA) (Figure 1). The proximal segments of the ADA and Cx intersected, with the ADA being positioned higher than the Cx (Figure 2). An intramyocardial ("myocardial bridge") trajectory from the fifth to the seventh centimeter of the ADA was also observed (Figure 3). Right predominant coronary artery circulation was observed. There was no significant luminal obstruction in the coronary ostia or epicardial coronary arteries. There was moderate ventricular hypertrophy and dilatation and moderate atrial dilatation. Presence of moderate and diffuse retraction at the free border of the anterior cusp of the mitral valve was observed. The tricuspid and pulmonary valves showed discrete and diffuse retraction at the free border of their leaflets. Emerging from the superior vena cava, there was a cardiac pacemaker cable-lead that was implanted in the endocardium of the anterior wall of the right atrium. Another cardiac pacemaker cable-lead extended from the superior vena cava through the right atrium, tricuspid valve and right ventricle, and was implanted in the ventricular septum endocardium, in its apical portion. There were no thrombi in the heart cavities. The histological study showed moderate hypertrophy in cardiomyocytes and diffuse interstitial myocardial fibrosis, more pronounced in the left ventricle (Figure 4). **(Dr. Léa Maria Macruz Ferreira Demarchi)**

Anatomopathological diagnoses: 1) bicuspid aortic valve; 2) Ventricular hypertrophy and dilatation; 3) Diffuse interstitial myocardial fibrosis, more pronounced in the left ventricle; 4) Congenital anomalies of the origin, course of the anterior and circumflex interventricular epicardial coronary arteries. **(Dr. Léa Maria Macruz Ferreira Demarchi)**

Comment

An association was observed between the bicuspid aortic valve and anatomical alterations in the coronary arteries in the patient's explanted heart, which is a frequent

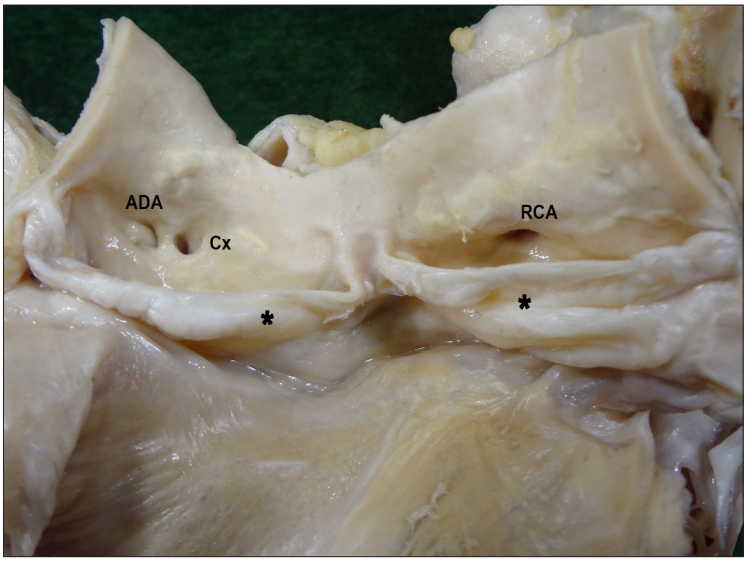

Figure 1 – *Left ventricular outflow tract: bivalve aortic valve, showing thickened semilunar leaflets (*), with moderate retraction at the free border, suggestive of valvular regurgitation. The anterior descending (ADA) and circumflex (Cx) coronary arteries originate from separate ostia, in the left Valsalva sinus; the ADA ostium lies posterior to the Cx ostium and is tangential. The right coronary artery (RCA) ostium is located in the right Valsalva sinus.*

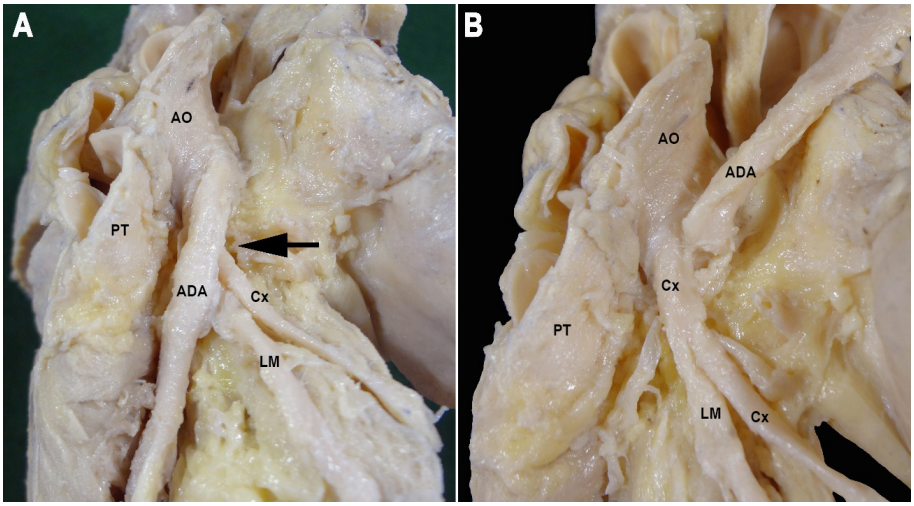

Figure 2 – *Left lateral surface of the base of the heart: A) Crossing (arrow) of the proximal epicardial segments of the anterior descending artery (ADA) and circumflex (Cx) artery; the ADA is in a position above the Cx. B) Cx course from its origin at the aorta (AO). The ADA has been folded superiorly to show the circumflex artery epicardial course. LM: left marginal branch of the Cx. PT: pulmonary trunk.*

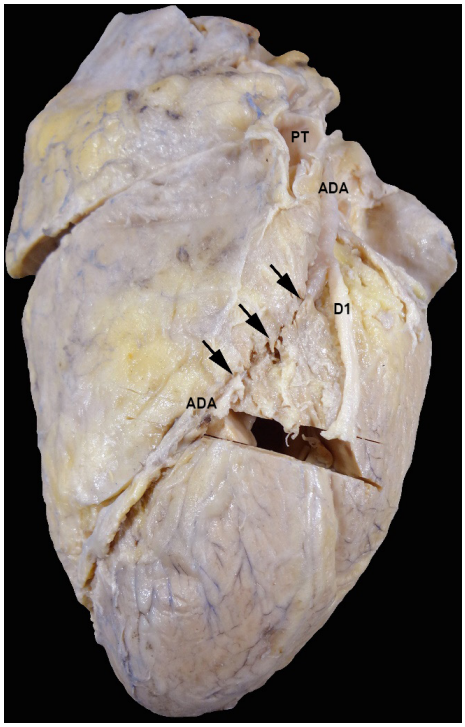

Figure 3 – *Sternocostal surface of the heart: intramyocardial course (arrows) of the anterior descending artery (ADA). D1- First diagonal branch of the ADA. PT: pulmonary trunk.*

finding in the literature.[13] The bicuspid aortic valve is the most prevalent cardiac congenital anomaly and, in autopsy studies, its incidence ranges from 0.9-2.5% in the general population,[14] being more frequent in male individuals, with a men/women ratio ranging from 1.8 to 5.6.[15] The anatomical alterations in coronary arteries may represent variations of the normal anatomy or congenital anomalies, depending on their incidence in the general population.[16] Alterations in the general population are known as variants or anatomical variations of the normal in the general population, whereas those occurring in less than 1% are defined as congenital anomalies. The incidence of coronary anomalies ranges from 0.2% to 1.2% in the different series found in the literature, depending on the analyzed population and the methods

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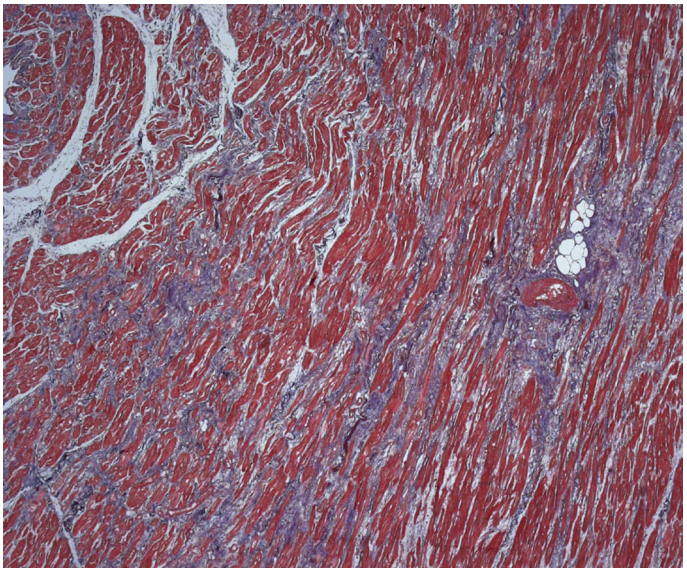

Figure 4 – *Photomicrography of the left ventricular myocardium: Diffuse myocardial fibrosis (in blue). Masson's trichrome, 50x).*

used.[17] Anatomopathological[18] and coronary angiography studies[19] performed in hearts of individuals without other congenital heart malformations divide the coronary anomalies into two groups: those of anomalous arterial origin and course and intrinsic anatomical anomalies of the arteries. In the case of this patient, we observed anomalous origin of the coronary arteries, represented by the absence of the left coronary artery and independent origin in separate ostia and in the same sinus of Valsalva of the ADA and the circumflex artery. The intramyocardial course of the ADA is classified as an anatomical variation, since its occurrence in the middle segment of the ADA ranges from 5% to 80% of patients in different studies.[20] In the other coronary arteries, such an alteration is considered an anomaly, since it occurs is less than 1% of the population. The crossing of epicardial branches is an anomaly of the intrinsic anatomy of the coronary arteries and is quite rare, with few cases having been described in the literature.[20,21] One might question whether there was compression of the arterial segments involved in the epicardial crossing, but in the absence of obstructive coronary alterations and localized ischemic myocardial lesions, anatomopathological examination is limited for such evaluation. Left ventricular hypertrophy and dilatation, as well as diffuse interstitial myocardial fibrosis can be explained by the bicuspid aortic valve dysfunction. **(Dr. Lea Maria Macruz Ferreira Demarchi)**

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Spontaneous Coronary Artery Dissection - Case Report and Literature Review

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Introduction

We report three cases of spontaneous coronary artery dissection (SCAD), with literature review and discussion of the procedures employed. All of them occurred in women, with the diagnosis being made by coronary angiography and, in one case, confirmed by intravascular ultrasound (IVUS).

1st Case

The patient was 25 years old, with no risk factors for cardiovascular disease (CVD), hospitalized with typical chest pain, elevated cardiac enzymes and electrocardiogram (ECG) with diffuse ST-depression and ST-segment elevation in aVR, underwent cardiac catheterization (CC), which disclosed moderate lesion in the left main coronary artery (LMCA), severe lesion in the proximal third of the anterior descending artery (ADA) and parietal irregularities in the circumflex artery (Cx) (Figure 1). Transthoracic echocardiogram (TTE) showed mid-apical hypokinesia of the anterior, inferolateral walls and small apical areas, with preserved biventricular systolic function. The patient was submitted to an IVUS that showed aspect compatible with intramural hematoma from the DA ostium to the first diagonal artery, and spontaneous dissection/hematoma from the proximal third of the Cx to the distal third of the first left marginal artery (image not available). Clinical treatment was chosen with excellent response. During outpatient follow-up, she remained asymptomatic. An angiographic restudy was performed six months after the event, showing significant obstruction improvement (Figure 1).

2nd Case

The patient was 41 years old with hypertension, hypothyroidism and was an ex-smoker, having delivered a child six months before. She sought the emergency service with typical chest pain triggered by emotional stress and ECG showing +/- in the high lateral wall. She was referred to CC, which showed moderate lesion in the middle third of the ADA and moderate/severe lesion in the distal third, suggestive of SCAD. The TTE showed no alterations. Clinical treatment was chosen. Angiographic restudy three months after the event showed persistence of moderate obstruction in the middle third of the ADA, with obstruction resolution in the distal third. At the time, stent implantation was performed in the middle third of the ADA. The procedure showed no complications and was successful (Figure 2).

3rd Case

The patient was 51 years old, with no risk factors for CVD, hospitalized with typical chest pain and elevated cardiac enzymes. The ECG showed no alterations. She was referred to the hemodynamics service, and a severe lesion was disclosed in the distal third of the first left marginal artery, with a pattern suggestive of SCAD. The TTE showed moderate hypokinesia of the left ventricular inferior-lateral, with preserved biventricular systolic function. She received clinical treatment with good response to therapy (Figure 3).

Discussion

In 1931, Pretty first described SCAD during the autopsy of a 42-year-old woman who had sudden death after reporting chest pain.[1] With the onset of the invasive approach to acute coronary syndrome (ACS), the number of diagnosed cases increased. Nevertheless, it is still believed that this diagnosis may be underestimated.[2]

SCAD is a rare cause of ACS, with an incidence of 0.1 to 4.0%.[3] The clinical presentation ranges from unstable angina to sudden death, often being undiagnosed. It mainly affects young women with no classic CVD risk factors.[4] In the reported cases, all of them are young women, two of which did not have CVD risk factors.

The following are described as events that may be related to SCAD: peripartum status, connective tissue diseases, vasculitis, cocaine abuse, heavy isometric exercise and use of oral contraceptives.[5] The most frequently affected artery is the ADA, in 75% of cases, followed by the right coronary artery, in 20% of the patients; the Cx, in 4%, and finally the LCMA, in less than 1% of the cases.[6] Among the three reported cases, two had the ADA as the main affected artery, which corroborates with data found in the literature.

The pathogenesis of SCAD has yet to be fully elucidated. It is known that the main factors responsible for spontaneous dissection are the arterial wall weakening and increased shear forces.[3] It is postulated that the primary rupture of the vasa vasorum occurs, leading to hemorrhage and consequent separation of the coronary artery wall layers, creating a false lumen between the intima and media layers of the vascular wall.[7]

Keywords

Acute Coronary Syndrome; Dissection; Chest Pain; Percutaneous Coronary Intervention; Cardiac Catheterization.

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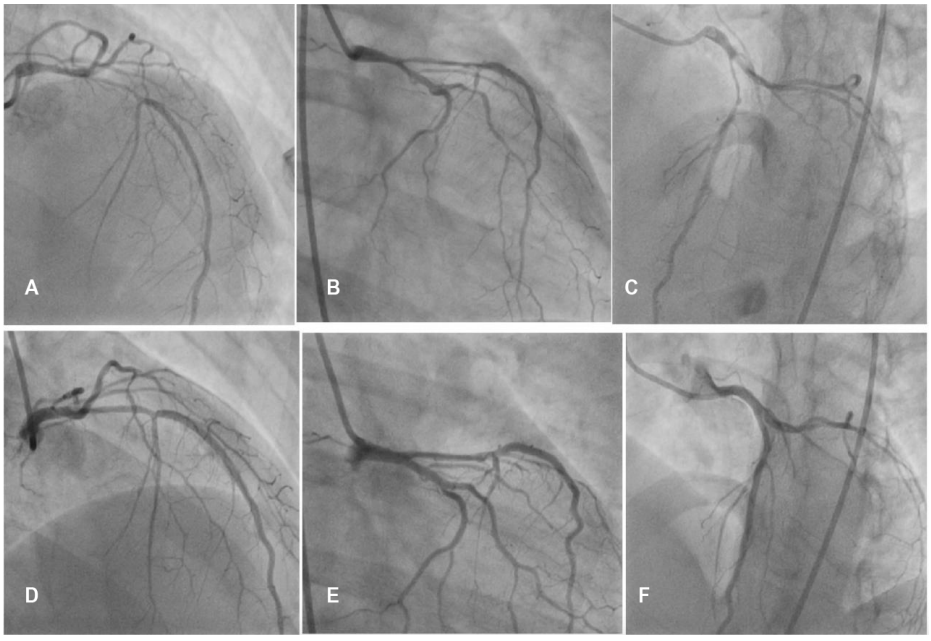

Figure 1 – *Cardiac catheterization showing stenosis in the middle/distal third of the left main coronary artery and severe segmental stenosis in the ostium/ proximal third of the anterior descending artery in the right cranial (A), right caudal (B) and left cranial (C) views. Restudy, after six months, showed a significant improvement of obstructions in the right cranial (D), right caudal (E) and left cranial (F) views.*

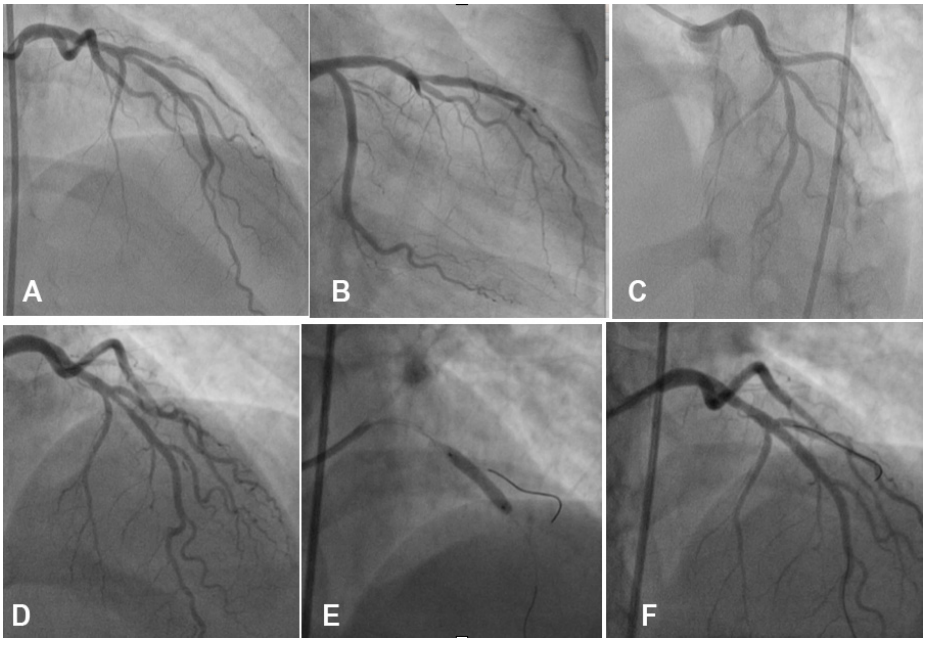

Figure 2 – *Cardiac catheterization showing moderate stenosis in the middle third and moderate/severe segmental stenosis in the distal third of the anterior descending artery (ADA) in the cranial (A), right caudal (B) and left cranial (C) views. Restudy, after 3 months, showed a significant improvement of the obstruction in the distal third of the ADA, with moderate obstruction in the middle third, which was treated with the direct stenting technique (cranial view, images: D, E and F).*

From the angiographic point of view, the diagnosis of CAD should be considered when there is a dissection line, with or without a false lumen, sudden and significant caliber reduction, or obstruction with smooth borders without the aspect of atherosclerotic disease.[6] Because it is a two-dimensional aluminography, the coronary angiography reveals little in relation to the coronary artery wall, where the main SCAD alteration is found.[3]

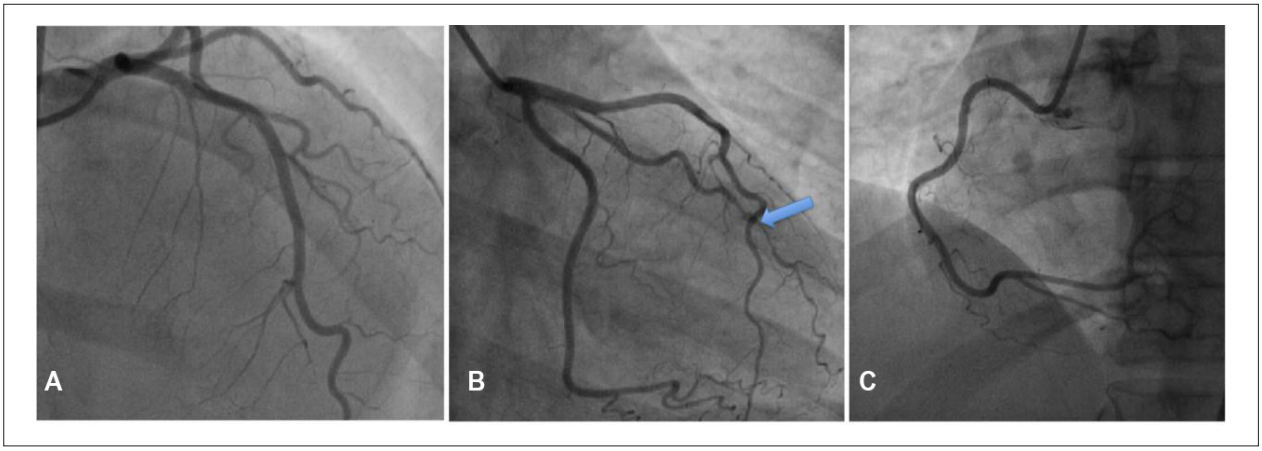

Figure 3 – *Cardiac catheterization showing angiographic aspect compatible with spontaneous dissection of the distal third of the first left marginal branch. The left coronary is observed in the angiographic views: cranial (A) and right caudal (B). The blue arrow (B) identifies the spontaneous dissection segment of the first left marginal branch. The right coronary artery with a normal aspect in the left oblique view (C) is observed.*

The IVUS and optical coherence tomography (OCT) have been shown to be important tools in the diagnosis of SCAD, in cases where there is doubt regarding the angiography, since they allow a more detailed analysis of the lesion. The IVUS may also contribute to guide the percutaneous treatment whenever necessary.[4] In fact, the use of intracoronary images, through IVUS or OCT, allows better visualization of the structure and composition of the coronary wall, allowing the evaluation of the intramural hematoma, as well as the differentiation between the true and the false lumens.[3] The IVUS was performed in one of the reported cases, demonstrating an image compatible with SCAD.

The therapeutic management depends on the clinical severity, hemodynamic status, dissection topography, number of affected arteries, and distal coronary flow.[6] It may range from clinical treatment, stent implantation, or myocardial revascularization surgery.[7]

In the cases described above, due to the clinical and hemodynamic stability with well-defined dissections, clinical treatment with dual antiplatelet therapy (clopidogrel and acetylsalicylic acid), statin and beta-blocker was initially chosen. Since percutaneous coronary intervention for SCAD is associated with a high rate of technical failures, the conservative strategy with clinical treatment and prolonged follow-up is preferable in these cases, with a high incidence of spontaneous resolution and a low incidence of adverse events.[8]

Recent studies have demonstrated the recurrence of cardiovascular events in hypertensive patients in the long-term, and beta-blocker therapy seems to have a protective effect.[9] Therefore, these patients should remain under medical supervision. In one of the cases, during follow-up, persistence of moderate obstruction was demonstrated in the middle third of the ADA, and late stent implantation was performed, aiming at preventing event recurrence.

Finally, we emphasize that the diagnosis of SCAD should be considered in cases of ACS in young patients, especially women of childbearing age and without the classic risk factors for coronary artery disease. The test of choice for the diagnosis consists of coronary angiography, although in some cases it is necessary to perform IVUS or OCT as adjunct methods to corroborate the diagnosis or to determine lesion extent.

Author contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Daniel ECA, Falcão JLAA; Writing of the manuscript: Daniel ECA; Critical revision of the manuscript for intellectual content: Falcão JLAA.

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

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2019: Recommendations for Reducing Tobacco Consumption in Portuguese-Speaking Countries - Positioning of the Federation of Portuguese Language Cardiology Societies

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Introduction

Depending on the epidemiological perspective of the observer and the extent of his concept of causality, tobacco consumption can be considered the second cause in the world of death attributed to classic cardiovascular risk factors, preceded only by hypertension, and the first cause of premature death and disabilities. When understood as an immediate cause without contextualization in the complex that determines and maintains population behavior, smoking was responsible in the world for about 8.10 (7.79-8.41) million deaths and 213.39 (201.16-226.66) million healthy life years lost (*disability-adjusted life-years,* DALYs). Although the number of daily smokers (individuals aged 15 years and older who smoke daily) has decreased, the total number of smokers continues to increase, imposing a major global challenge for healthcare systems.[1]

Physicians, who generally deal directly and individually with the patient, tend to consider health/illness limited to the patient's organic commitment and personal history and are less appreciative of the "causes of the causes" and the psychosocial determinants of the phenomena and behaviors, inseparable from the ecological context and interests. Environmental pollution (which has also a contribution from smoking and is progressively increasing) is currently considered to be the most important cause of morbidity and mortality in the world's population,[2] extending the spectrum beyond the traditionally valued risk factors. This perspective is very important for an understanding of the resistance to smoking control and planning of strategies that are more effective to approach this issue.

In all Portuguese-speaking countries (PSCs), smoking is more frequent among men; the difference in rates between men and women vary among the countries and are greater in the African countries. Table 1 describes the standardized prevalence by sex in 2015 and the annualized difference for men and women from 1990 to 2015 according to the sociodemographic index (SDI).[3] The rates of daily smokers vary from 19.0%, 16.8%, and 7.2%, in African countries, Portugal, and Brazil, respectively.[4]

Available data from the National Health Surveys (NIH) (1987, 1995/96, 1998/99, 2005/06, and 2014) showed that daily consumption of tobacco in Mainland Portugal decreased among men by 35.2% (95% confidence interval [CI] 34.2-36.2%) in 1987 to 26.7% (95% CI 25.2-28.3%) in 2014, and progressively increased in women from 6.0% (95% CI 5.6-6.4%) in 1987 to 14.6% (95% CI 13.6-15.8%) in 2014, with a higher daily consumption in men of more disadvantaged socioeconomic groups and the opposite in women.[5]

The described prevalence of tobacco consumption in Mozambique in 2003 was 39.9% in men and 18.0% in women.[6] In a 2005 sample from the same country, the prevalence of daily smokers (including users of chewing tobacco, snuff, manufactured cigarettes, and hand-rolled cigarettes) reduced to 33.6% in men and 7.4% in women, with different prevalence rates by sex and country regions.[7]

Brazil is the leading country in the control of smoking, with the third largest decline in prevalence of daily smokers since 1990: 57% and 56% for men and women, respectively. This was achieved with a robust public policy, in which advertisements about health damage caused by the tobacco were associated with restrictions on consumption and tax increases for such products, among other measures.[8]

Keywords

Tobacco Use Disorder/epidemiology; Tobacco Use Disorder/mortality; Smoking Prevention; Socioeconomic Factors; Urban Population; Rural Population; Tobacco Smoke Pollution.

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Table 1 – Standardized prevalences by sex in 2015, and annualized difference by sex from 1990 to 2015 according to the sociodemographic index

	SDI Level	Women Standardized Prevalence 2015	Men Standardized Prevalence 2015	Annualized Women Change rate 1990-2015	Annualized Men Change rate 1990-2015
Global		5.4 (5.1-5.7)	25.0 (24.2-25.7)	–1.7 (–2.0/ –1 ·4)	–1.3 (–1.5/ –1.2)
Angola	Low-intermediate	1.6 (0.9-2.6)	14.2 (12.5-16.1)	–0.7 (–3.5/2 ·2)	0.5 (–0.2 /1.3)
Brazil	Intermediate	8.2 (7.5-9.0)	12.6 (11.8-13.5)	–3.3 (–3.9/–2.7)	–3.3 (–3.8/–2.9)
Cape Verde	Low-intermediate	2.5 (1.7-3.6)	9.8 (8.0 -11.7)	–0.9 (–3.1/1.3)	–0.6 (–1.6/0.6)
Equatorial Guinea	Low	1.4 (0.9-2.1)	6.9 (5.6-8 ·4)	–1.0 (–3.5/1.3)	–0.6 (–1.7/-0.5)
Guinea-Bissau	Low	1.0 (0.6-1.5)	11.4 (9.4 -13 ·5)	–0.9 (–3.4 /1.6)	–0.3 (–1.4/-0.8)
Mozambique	Low	3.1 (2.5-3.8)	17.2 (14.5-20.1)	–1.5 (–2.7/–0.2)	–0 ·5 (–1.5/-0.5)
Portugal	High-intermediate	12.7 (11.0 -14.8)	24.9 (22.7-27.2)	1.3 (0.4 /2.1)	–1.0 (–1.4/–0.6)
São Tomé and Principe	Low-intermediate	1.0 (0.7-1.5)	6.2 (5.0 -7 ·3)	–1.0 (–3.2/1.3)	–0.2 (–1.3/0.9)
East Timor	Low-intermediate	12.4 (9.8-15.1)	39.8 (37.2-42.5)	4.5 (2.8-6.3)	–0.1 (–0.5/0.4)

SDI: sociodemographic index. The SDI is the weighted geometric mean of the per capita income, educational level, and total fertility rate.[3]

These measures stemmed from adherence to the recommendations by the World Health Organization's Framework Convention on Tobacco Control (FCTC),[9] such as banning of terms such as ultra-light, light, low tar, and mild or any other terms implying that cigarettes are not so harmful. The PSCs have joined the FCTC at different moments, as discussed below in the section "Legislation."

The percentage of deaths attributed to tobacco use across 195 countries increased from 7.28 (7.01-7.56) million in 2007 to 8.10 (7.79-8.42) million in 2017, an increase of 11.3% (9.1-13.4%), according to the Global Burden of Disease (GBD) study.[1] The same occurred with the DALYs, from 199.80 (188.0-211.72) million in 2007 to 213.39 (201.16-226.67) million in 2017, a 6.8% increase (4.6-9.0%). A similar trend was observed in regard to ischemic heart diseases, from 1.76 (1.68-1.83) million deaths in 2007 to 1.93 (1.83-2.02) million deaths in 2017, a 7.8% increase (4.6-11.1%), whereas the DALYs increased from 44.30 (42.42-46.19) million in 2007 to 47.38 (45.12-49.71) million in 2017, a 5.6% increase (2.4-9.0%). Similar increases were observed in relation to deaths due to ischemic stroke, from 351.19 (326.63-379.84) thousand in 2007 to 399.35 (369.15-433.38) thousand in 2017, a 13.4% (8.6-17.8%) increase, with an increase in DALYs from 8.74 (7.96-9.54) million thousand in 2007 to 10.41 (9.42-11.50) million in 2017, a 19.3% (14.7-23.8%) increase.[1]

It is important to note that approximately 80% of the smokers reside in low- and middle-income countries,[10] which represent most of the population of PSCs, where the reported decline in tobacco consumption seen in high-income countries has not been observed.[4] There is already strong evidence of cost-effectiveness and opportunities to treat smoking in primary care because of its wide coverage and close and continuous physician-patient relationship.[11]

Considering only those risk factors valued in traditional practice, smoking is the only factor that could be completely abolished in the prevention of cardiovascular diseases (CVDs); however, broadening the spectrum and including man-made ecological and behavioral changes, there are many other factors that can be controlled.

In a social environment filled with stressful and frustrating circumstances driven by inequality, with conflicts of interest and fueled by marketing, adherence to the consumption of psychoactive substances like tobacco and alcohol is successful due to the action of these substances in the limbic system (reward circuit), leading to chemical and psychological dependence. This system is part of the evolutionary adaptation process that promoted the preservation of species and is one of the determinants of the repeated relapses observed when the patient intends to quit.[12]

Quitting smoking is known to be the most effective measure in the prevention of tobacco-related diseases. However, smoking does not receive the necessary attention during medical consultations, both at an outpatient and inpatient level, to initiate the process of quitting the most frequent preventable cause of CVD and many cancers.[11] Thus, the objective of this article is to provide an instrument to be used by healthcare professionals in their daily practice in the fight against smoking.

Epidemiology and physiopathologic mechanisms

Table 2 shows the risk attributable to cigarette smoking for some diseases in the PSCs, presented as the percentage of deaths and the percentage of risk attributed to smoking. When smokers and never smokers are compared, the risk of smokers is 2 to 3 times higher for stroke, ischemic heart disease, and peripheral vascular disease; 23 and 13 times higher for malignancy in men and women, respectively; and 12 to 13 times higher for chronic obstructive pulmonary disease. Smokers also have a 2.87 increased risk of death from myocardial infarction compared with nonsmokers.[3]

Smoking is also associated with increased blood pressure and related complications like death and decline in renal function. The same applies to abdominal aortic aneurysms, which have an increased risk attributable to smoking, as well as increased aneurysm growth rate when smokers and nonsmokers are compared. Smoking has been associated with cardiac rhythm disorders such as increased frequency

Table 2 – Percentage of deaths and attributed risk of tobacco consumption in the various Portuguese-speaking countries[3]

Year 2017	Ischemic heart disease	Stroke	Lung, trachea, and bronchial cancer	Chronic obstructive pulmonarydiseases	Alzheimer's disease and other dementias
	DEATH ATTRIBUTED RISK Tobacco Use % (95% CI)	DEATH ATTRIBUTED RISK Tobacco Use % (95% CI)	DEATH ATTRIBUTED RISK Tobacco Use % (95% CI)	DEATH ATTRIBUTED RISK Tobacco Use % (95% CI)	DEATH ATTRIBUTED RISK Tobacco Use % (95% CI)
Angola	4.79 (4.06 -5.60)	3.99 (3.43-4.59)	0.62 (0.50-0.74)	1.24 (1.01-1.67)	0.90 (0.78-1.03)
	22.51 (19.74-25.50)	42.00 (13.13-17.78)	56.32 (51.09 -61.04)	32.93 (26.55-38.62)	13.26 (8.21-18.66)
Brazil	13.03 (12.7-13.27)	9.10 (8.88 -9.29)	2.40 (2.35-2.46)	4.83 (4.71-4.96)	5.44 (5.37-5.50)
	24.41 (22.31-26.56)	16.60 (14.77-18.51)	64.01 (61.19-66.66)	46.63 (41.89-51.37)	13.29 (7.94-19.28)
Cape Verde	15.39 (14.47-16.41)	7.28 (6.43-8.07)	1.65 (1.51-1.79)	2.11 (1.85-2.63)	5.49 (5.16-5.81)
	8.78 (7.34-10.32)	7.35 (5.99-8.71)	32.99 (28.26-37.79)	19.03 (14.88-22.74)	2.93 (1.37-4.84)
Equatorial Guinea	3.80 (3.24-4.40)	2.95 (2.52-3.40)	0.65 (0.46-0.84)	1.30 (0.96-1.89)	1.35 (1.12 -1.60)
	11.38 (9.12-13.65)	7.65 (6.09-9.26)	36.74 (28.63-45.08)	19.91 (15.15-24.66)	6.77 (3.43- 10.67)
Guinea-Bissau	6.22 (5.36-7.04)	5.59 (4.87-6.31)	0.44 (0.33-0.55)	1.30 (1.07-1.53)	0.90 (0.75-1.14)
	11.6 (9.60-13.87)	8.16 (6.45-10.09)	32.58 (26.63-38.67)	19.19 (14.65-23.83)	2.99 (1.43-5.07)
Mozambique	3.77 (3.31-4.26)	5.58 (4.86-6.35)	0.39 (0.33-0.45)	0.91 (0.77-1.08)	0.88 (0.71-1.01)
	18.74 (15.5-22.23)	14.00 (11.2616.60)	48.74 (43.34-54.23)	32.06 (26.60-37.33)	8.56 (4.20-13.38)
Portugal	12.1 (11.53-12.70)	13.91 (13.31-14.53)	3.87 (3.61-4.11)	5.11 (4.81-5.42)	9.49 (9.07-9.86)
	12.69 (11.61-13.74)	7.72 (6.92-8.54)	64.32 (61.42-66.93)	31.71 (27.32-36.26)	7.29 (4.37-10.45)
São Tomé and Príncipe	9.77 (8.63-10.92)	8.61 (7.60-9.93)	1.39 (1.06-1.73)	5.19 (4.23-6.07)	2.28 (2.07-2.48)
	8.59 (6.9-10.34)	5.51 (4.36-6.79)	33.33 (26.09-40.32)	18.26 (14.46-22.25)	3.26 (1.62=5.33)
East Timor	13.00 (10.30-15.20)	15.26 (13.18-17.24)	2.03 (1.65-2.68)	4.34 (3.59-5.08)	2.66 (2.22-3.07)
	24.67 (20.66-28.66)	17.21 (14.23-20.33)	59.83 (53.01-66.64)	47.43 (38.34-54.27)	12.18 (6.20-18.91)

CI: confidence interval

of atrial fibrillation and ventricular tachycardia, and with an increased risk of heart failure and related morbidity and mortality.[13,14]

The main tobacco-related diseases and their relative percentages (in parentheses) include coronary diseases and myocardial infarction (25%); chronic obstructive pulmonary diseases (85%); pulmonary neoplasms (90%); neoplasms of the mouth, pharynx, larynx, esophagus, stomach, pancreas, kidney, bladder, cervix, breast (30%); and cerebrovascular diseases (25%).[1,15]

The risk of ischemic heart disease and related mortality increase with the smoking duration (in years) and the number of cigarettes smoked per day; the risk of disease occurs at all levels of cigarette consumption, even for individuals consuming fewer than five cigarettes per day and passive smokers. In addition, patients who stop smoking after coronary artery bypass surgery have a reduced risk of hospitalization for heart disease. Smoking cessation is the only effective treatment to prevent progression of thromboangiitis obliterans, improving symptoms and reducing the risk of amputation throughout life.[15,16]

Smoking cessation has several benefits that should be mentioned to smokers during consultation (Table 3). Cigarettes contain more than 7,000 toxic substances, which contribute to CVD in different ways, including adverse hemodynamic effects like increased blood pressure and heart rate, imbalance between supply and consumption of oxygen, changes in coronary blood flow, dysfunction and endothelial damage, hypercoagulability and thrombosis, chronic inflammation, and lipid abnormalities, in addition to serving as a substrate for the occurrence of arrhythmias and cardiovascular events. These effects can be observed even in passive smokers.[13,17]

Factors associated with tobacco consumption

Tobacco use must be considered a chronic disease that can begin in childhood and adolescence, since about 80% of the individuals who experiment tobacco do so under the age of 18 years. Also, there is a direct relationship between the onset of smoking and the maintenance of the habit in adult life. Thus, primordial prevention is an essential step in smoking control. Primordial prevention of smoking is understood as the prevention of smoking initiation among children and adolescents. Children who use tobacco for 12 months inhale the same amount of nicotine per cigarette as adults do and experience the symptoms of addiction and withdrawal, which usually develop very quickly at this age. One way to approach primordial prevention is by age groups, by observing five main items **("5 As")** for each group: **ask**, in the sense of inquiring, questioning; **advise** smoking cessation; **assess** the motivation and symptoms of tobacco dependence; **assist** in the attempt to quit smoking; and **arrange** periodic follow-up.[19-21]

Table 3 – Benefits of smoking cessation in the short-, medium-, and long-term

- After 2 minutes: BP and HR return to normal.
- After 3 weeks: easier breathing and circulation improvement.
- After 1 year: the risk of death due to AMI decreases to half, equalizing that of nonsmokers after 15 years.
- In 2-5 years: risk of stroke falls by more than 90%, becoming close to the risk of individuals who never smoked.
- After 10 years of abstinence: cancer risk is about half of a smoker's risk.
- Between 5-10 years: the risk of AMI is equal to that of nonsmokers.
- After 20 years: risk of lung cancer is equal to that of nonsmokers.

AMI: acute myocardial infarction; BP: blood pressure; HR: heart rate. Adapted from reference.[18]

The World Health Organization has launched the **MPOWER** measures, with proven impact on reducing the consumption of tobacco products:[19-21]

Monitoring the epidemic.

Protecting the population against tobacco smoke.

Offering help to quit smoking.

Warning about the dangers of tobacco.

Enforcing the ban on advertising, promotion, and sponsorship.

Raising taxes on tobacco products.

These measures have an impact on smoking cessation at a population level, but most smokers require individualized treatment with healthcare professionals, combining a behavioral approach and often medications to quit smoking altogether.

New forms of tobacco use

New forms of smoking have emerged in the last decade and are advertised as having a reduced or absent risk, like JUUL, popular electronic cigarettes that work as vaporizers of encapsulated nicotine, flavors, and other contents in small replaceable cartridges called "pod mods." These devices, already in their third generation, associate nicotine with other vaporizing or flavoring substances with effects that are still poorly known, but have the potential of inducing health risks.[13,14]

As a result of well-developed marketing campaigns promoting the introduction of new forms of tobacco use, there is currently an intense discussion between the lay society and the scientific community about the inherent risk of electronic cigarettes use as a cause of CVDs and neoplasms. Although the current epidemiological evidence is not extensive and the risk of these new forms of smoking appear to be lower than those of the classic form of smoking, enough evidence is available to claim that their acute consumption causes endothelial dysfunction, DNA damage, oxidative stress, and temporary heart rate increase. As for their chronic use, it seems to increase the risk of myocardial infarction, stroke, and neoplasms of the oral cavity and esophagus.[3,13]

Based on the apparent lower risk of use of the new forms of smoking, electronic cigarettes have been promoted as a method to quit smoking, which lacks proof. In 60% of the cases, smokers use both the classic form of smoking and electronic cigarettes, maintaining the existing high risk. In many cases, these new forms of smoking are adopted for a short time, at which point the smoker resumes his previous habit altogether.[13,14]

Additionally, electronic cigarettes are considered to be a concern by the scientific community, since they lead youths to nicotine addiction and become a gateway to classic smoking.

At the present time, even though we acknowledge that the available scientific evidence is not robust, we recommend any form of smoking to be discontinued or not initiated, including oral tobacco (chewing tobacco, snus, snuff, soluble tobacco, vaping/JUUL), cigarettes, cigars, cigarillos, pipes, or narghile. Secondhand smoke should also be fought, as it exposes to the same risks of smoking, increasing them by 20-30%.[13,14]

Approach to smokers

Most smokers have the perception and recognize that tobacco is harmful to their health. However, this is not enough for them to give up smoking. Similarly, physicians recognize the harmful effects of smoking but in daily practice tend to prioritize disease treatment instead of prevention. The initial approach to a smoker is to encourage him to start treatment regardless of the type of clinical condition and the stage of his illness. Benefits of quitting smoking must be emphasized to all patients at every appointment with a healthcare professional. As many countries have restrictions on smoking in public settings, it is important to ask systematically about tobacco exposure to nonsmokers who live or cohabit with smokers, especially children and youths who may consider the habit of smoking as normal and not harmful to their health and, as in the case of individuals with asthma, may present acute worsening when exposed to tobacco (Table 4, 5, and 6). Table 7 describes common measures to monitor smoking cessation.

Treatment

Most patients require cognitive-behavioral therapy (CBT) (Table 8) backed by pharmacological support to cope with the withdrawal syndrome, which typically lasts between 2 and 4 weeks.

Nicotine withdrawal syndrome

The main signs and symptoms of withdrawal syndrome are shown in Table 9.

Table 4 – Initial assessment in the approach to smoking

ANAMNESIS
• Scales: Fagerström (for nicotine dependence)[22] - Table 5.
• Prochaska and DiClementi (for motivation)[23] - check the counseling techniques per patient - Table 6.
• Clinical and/or psychiatric comorbidities (diabetes, hypertension, depression, alcoholism, stroke, convulsion, cancer).
• Medications for continuous use.
• Risk factors for CVD (dyslipidemia, use of oral contraceptives or estrogen).
• Gestation or breastfeeding.
• Issues related to smoking:
- How long have you been smoking?
- How many cigarettes do you smoke a day?
- Did you try to stop smoking and what was the result?
- Are you interested (or thinking) about quitting smoking?
• Issues related to smoking cessation:
- If planned to set a date to stop smoking and if would like help with that;
- If ever tried to quit smoking, if was successful, if used any medication, and for long did not smoke.
PHYSICAL EXAM
• Monitor BP, especially if using bupropion.
• Monitor body weight: weight gain may be a barrier to starting smoking cessation and a predictor of relapse.
COMPLEMENTARY TESTS
• Cell blood count, liver function tests, and serum glucose, lipids and electrolytes.
• Chest x-ray
• Electrocardiogram.
• Spirometry (not always readily available).
• Measurement of exhaled carbon monoxide (COex), if possible. This measure is directly related to the carboxyhemoglobin and cigarettes smoked per day. The cut-off value is 6 ppm.

CVD: cardiovascular disease.

Inhaled nicotine binds to specific neuronal receptors that lead to the release of excessive dopamine and endorphins, whose effects are perceived by the smoker as stimulating and pleasurable. With the dopamine reuptake, such effects dissipate and the receptors signal the need for a new stimulus (that is, they want more nicotine), which is perceived as an unpleasant sensation (limbic system, reward circuit). Regular smokers live daily with withdrawal; for withdrawal to occur, all is required is smoking to be interrupted for a short time.[15]

Craving is a typical symptom of the physical dependence of nicotine, defined as a strong desire or urge to smoke. Nicotine deprivation produces variable physical effects that last between 7 to 30 days and are more intense in the first 3 days after quitting smoking. However, the craving may persist for many months because the environmental stimuli that have been associated with smoking throughout life continue, and these associations are difficult to erase. In order to face these situations, the former smoker needs to develop skills and strategize to avoid triggering factors leading to lapse and relapse.[15]

Pharmacotherapy should be used to supplement CBT and alleviate withdrawal symptoms. The medications are recommended to be used for 3 months, extending to 6 months in cases with greater difficulty in smoking cessation.[13] With pharmacological therapy, one person is estimated to successfully quit smoking (defined as smoking abstinence for 6 months) for each 6 to 23 people treated.[11]

Table 10 summarizes the criteria for the initiation of pharmacological therapy, which should always take into account the patient's comfort, safety, and preference, as well as the absence of contraindications for the use of a particular drug.

The medications are divided into two basic categories:

1. Nicotine replacement therapies (NRTs);
2. Non-nicotine replacement therapies (NNRTs).

NRTs are considered the first-line treatment approach for smokers and is indicated for patients with moderate to high dependence levels according to the Fagerström test. NRTs should not be combined with tobacco use. The patients should be instructed to stop smoking after initiating an NRT. The numbers needed to treat (NNT) for definitive cessation is 23 and for premature death is 46.[11] Available NRTs are 24-hour release patches, chewing gum (2 mg and 4 mg), and nicotine tablet (2 mg and 4 mg). Table 11 describes the approach with NRTs for smoking cessation.[11-15]

Table 5 – Fagerström test for nicotine dependence[22]

1. How soon after you wake up do you smoke your first cigarette?			
[3] Within 5 minutes	[2] 6 to 30 minutes	[1] 31 to 60 minutes	[0] After 60 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden?			
[1] Yes	[0] No		
3. Which cigarettes would you hate most to give up?			
[1] The first one in the morning	[0] Any other		
4. How many cigarettes per day do you smoke?			
[0] 10 or less	[1] 11 to 20	[2] 21 to 30	[3] 31 or more
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?			
[1] Yes	[0] No		
6. Do you smoke when you are so ill that you are in bed most of the day?			
[1] Yes	[0] No		

→*Total: [0-2] Very low; [3-4] Low; [5] Moderate; [6-7] High; [8-10] Very high.*

Table 6 – Motivation stages and counseling techniques[23]

- **Pre-contemplative:** not yet worried; not ready for behavioral change → inform the risks of continuing smoking and encourage the patient to think ↓
- **Contemplative:** recognizes the need for and wants to change, but still wants to smoke (ambivalence) → ponder about the pros and cons of cessation and keep yourself available to talk ↓
- **Determined:** wants to quit smoking and is ready to take the necessary steps→ choose a date to quit smoking ↓
- **Action:** engaged in attitudes intended to promote changes and quit → follow-up to prevent relapse and relieve withdrawal symptoms ↓
- **Maintenance:** maintains the behavioral change achieved and remains abstinent → reinforce the benefits of quitting smoking and identify risk situations for relapse and coping skills ↓
- **Relapse:** unable to maintain the abstinence achieved and returns to the smoker's behavior → offer support, review, and resume the entire process.

Table 7 – Follow-up of smoking cessation

- Set a date to stop smoking.
- Get to know the social environment of the smoker in such a way that his family, friends, and coworkers are able to help him.
- If other family members smoke, it will be important to encourage them to quit or to smoke outside their home.
- Elaborate the action plan with nonpharmacologic and pharmacologic strategies.
- Follow-up the attempts to stop smoking.
- Inform about possible abstinence syndrome and craving on smoking cessation.
- The patient, along with the physician, should choose the cessation method to be used:
  - Abrupt cessation: is usually the method of choice among smokers, and the abstinence syndrome is the main obstacle.
  - Gradual cessation: the smoker can continue to smoke a small number of cigarettes indefinitely and ends up returning to the previous consumption pattern.

Table 8 – Cognitive-behavioral therapy

- Explain the mechanisms of dependence and ambivalence.
- Discuss the advantages of quitting smoking and the disadvantages of continuing to do so.
- Increase the motivation of the smoker before starting the cessation program, moving from the contemplative posture to a stage of action.
- Structured sessions with booklet support discussing the main aspects of addiction, withdrawal symptoms, and obstacles to overcome.
- Four to six weekly 90-minute sessions (cessation sessions) and three to four biweekly 90-minute sessions (maintenance sessions) in the first 3 months of treatment.
- Guide patients to set a smoking cessation date between the second and third therapy sessions, regardless of the therapeutic protocol chosen.
- The maintenance phase is focused on preventing episodes of lapse or relapse. This phase lasts 12 months, with monthly follow-up (in person or by phone).
- The first 6 months after smoking cessation are considered the most critical period for lapses or relapses.

Table 9 – Symptoms of nicotine withdrawal syndrome

Neurobehavioral symptoms	Physical symptoms
Anxiety	Reduced blood pressure
Headache	Reduced heart rate
Difficult concentration	Sweating
Difficult memorization	Dizziness
Restlessness	Craving (urgency to smoke)
Irritability	Tremors
Feel of frustration or anger	Increased appetite
Depressed mood	Weight gain
Insomnia	Motor incoordination

Table 10 – Determinants of initiation of drug therapy

- Smokes 20 or more cigarettes per day, OR
- Smokes the first cigarette of the day up to 30 minutes after waking up and smokes at least 10 cigarettes per day, OR
- Previous attempt with cognitive-behavioral therapy alone was ineffective due to withdrawal symptoms.

In the pharmacological approach with NNRTs, bupropion and varenicline are available as first-line medications (Table 12).[11-15] Clonidine and nortriptyline are second-line treatment options, due to their side effects. The NNTs for bupropion and varenicline are 18 and 10, respectively, for successful treatment, and 36 and 20, respectively, for avoiding premature death.[11] Table 13 presents a summary of the usual pharmacological treatment for smoking.[11-15]

Legislation

Since smoking is a population phenomenon that also imposes risks for nonsmokers, pregnant women, fetuses, and children, in addition to wasting a large amount of public (financial and organizational) resources and causing dependence (which is equivalent to making individuals vulnerable to addiction to other drugs), medical care and health education are not sufficient. Legislation must contemplate control of tobacco exploitation and use in any form, alongside the control of other addictive drugs.

Economic interests involved in tobacco growing, production, industrialization, commercialization, and advertising are large and transnational, which makes the categorization of tobacco as an issue that is purely medical

Table 11 – Nicotine replacement therapy (NRT)

Rapid nicotine delivery: nicotine gum and lozenge
• Used in the presence of craving (imperative need to smoke) or at intervals of 1-2 hours.
• Promotes faster nicotine delivery. May be combined with nicotine patch or associated with bupropion and varenicline.
• Nicotine is released in approximately 5 minutes with the tablets and 10 minutes with the gum.
• The maximum tolerated dose is around 10 gums/lozenges per day.
• The patient should chew the gum/tablet until it tastes spicy. At this point, he should stop chewing for 2 minutes (time to absorb the nicotine) until the taste disappears; then should chew again by repeating the cycle within 20 minutes for a second nicotine release. A glass of water should be drank before use to neutralize the oral pH, which changes with food consumption, and for removal of food residues, which may decrease absorption by the oral mucosa.
• Side effects: hypersalivation, nausea, hiccups, gingival ulceration leading to teeth softening, and temporomandibular joint (TMJ) pain.
• Contraindication: inability to chew, lesions of the oral mucosa, peptic ulcer, TMJ subluxation, and use of removable dental prostheses.
Slow nicotine delivery: nicotine patch
• The patches are available in packages with seven units each, with dosages ranging from 7 to 25 mg.
• Recommended for maintaining a continuous level of circulating nicotine during 24 hours, in a process of gradual smoking cessation.
• May be recommended as a pre-cessation therapy for 2 to 4 weeks in smokers who find it very difficult to reduce the number of cigarettes or set a date to stop.
• The patches should be applied in the morning, in covered areas, in the upper part of the thorax, and anterior, posterior and superior arm areas, with site rotation and replacement daily at the same time. Avoid sun exposure on the site.
• May be used in combination with bupropion or varenicline.
• Therapeutic schedule:
– **Smokers of 20 cigarettes/day and/or with a Fagerström score of 8-10 points:** Patches with 21 to 25 mg/day between the 1st and 4th week; 14 to 15 mg/day between the 5th to 8th weeks; 7 mg/day between the 9th and 10th weeks. Recommended application in the morning upon awakening. In cases of insomnia, should be removed after 16 hours of use. In special cases of increased dependence, up to two adhesives of 21 mg may be applied, if no contraindication.
– **Smoker 10-20 cigarettes/day and/or Fagerström score of 5-7 points:** Patches with 14 to 15 mg/day for the initial 4 weeks and 7 mg/day from the 5th to the 8th week.
• Side effects: pruritus, rash, erythema, headache, nausea, dyspepsia, myalgia, and tachycardia when the dose is excessive.
• Contraindications: history of recent myocardial infarction (in the previous 15 days), severe cardiac arrhythmia, unstable angina pectoris, peripheral vascular disease, peptic ulcer, cutaneous diseases, pregnancy, and lactation.

Table 12 – Non-nicotine replacement therapy (NNRT)

Bupropion hydrochloride
• Simulates some of the effects of nicotine in the brain, blocking neuronal uptake of dopamine and norepinephrine. May be used in combination with nicotine replacement therapy with patch.
• Excellent choice for subgroups of smokers who are more prone to relapse, those with depression after smoking cessation, for women, and for those with a high degree of addiction. Success cessation rates are 30% to 36%.
• Therapeutic regimen: Start treatment 8 days before smoking cessation. - 150 mg in the morning for 3 days, followed by 150 mg in the morning and afternoon with 8-hour intervals for 3 months; may be increased for up to 6 months. Control blood pressure; if blood pressure increases, the dose may be reduced to 150 mg/day before discontinuation in refractory cases. Reduce doses in renal and hepatic failure to 150 mg/day. Monoamine oxidase inhibitors should be suspended 15 days before starting bupropion. Use with caution or avoid in patients taking antipsychotics, theophylline, and systemic steroids, as it predisposes to the occurrence of seizures.
• Contraindications: – **Absolute:** history of seizure (including febrile seizure), epilepsy, traumatic brain injury, electroencephalographic abnormalities, brain tumor, severe alcoholism, anorexia nervosa and bulimia, pregnancy, and lactation. – **Relative:** Concomitant use of barbiturates, benzodiazepines, cimetidine, pseudoephedrine, phenytoin, oral hypoglycemic agents, or insulin.
Varenicline tartrate
• Partial agonist for the α4β2 nicotinic acetylcholine receptor, mediating the release of dopamine in the brain.
• Double effect: reduces withdrawal symptoms and desire to smoke.
• Therapeutic regimen: start 1 week before the interruption day, with 0.5 mg for 3 days in the morning; 0.5 mg from the 4th to the 7th day in the morning (7 pm) and afternoon (7 pm); and 1 mg a day for 3 months in the morning (7 am) and afternoon (7 pm). May be extended for up to 6 months if full smoking cessation is not achieved, or if there is risk of relapse. Oral administration, no hepatic metabolism, and practically *in natura* renal excretion.
• Adverse effects: nausea (20%), headache, vivid dreams, and weight gain. Rarely, mood changes, agitation, and aggressiveness.
• Because it does not undergo hepatic metabolism, varenicline does not interfere with digoxin, metformin, or warfarin used concomitantly. Cimetidine may cause increased varenicline bioavailability.
• Caution is advised in patients with renal insufficiency.
• Contraindication: gestation, lactation, age below 18 years, bipolar disorder, schizophrenia, or epilepsy.

Table 13 – Usual pharmacological treatment for smoking

Medication	Start of treatment	Therapeutic scheme	Duration (weeks)
Nicotine replacement therapy: patch	On the date chosen to quit smoking	21-25 mg/day - 4 weeks 14-15 mg/day - 4 weeks 7 mg/day - 2 weeks Smokers with increased dependence may require doses greater than 21 mg	8 to 10
Nicotine replacement therapy: gum or lozenge	On the date chosen to quit smoking	2 mg or 4 mg: 1 a 4/day	8 to 10
Non-nicotine replacement therapy: bupropion	One week before the date chosen to quit smoking	First to third day - 150 mg 1 x day Fourth day to the end - 150 mg 2 x daily	12
Non-nicotine replacement therapy: varenicline	One week before the date chosen to quit smoking	First to third day - 0.5 mg 1 x day Fourth to seventh day - 0.5 mg 12/12 hours Eighth day to end - 1 mg 12/12 hours	12

or limited to health services insufficient. Therefore, the World Health Organization has promoted the Framework Convention, ratified by 168 countries in 2003,[9] when the countries committed to observing certain principles that must be progressively incorporated into their laws. It is up to the health sectors of each country to remain vigilant and promote these principles with the population and political class.

The following are the dates of signing of the treaty and the ratifications among PSCs: Angola (June 29, 2004 / September 20, 2007), Brazil (June 16, 2003 / November 03, 2005), Cape Verde (February 17, 2004 / October 4, 2005), Equatorial Guinea (April 1st, 2004 / November 7, 2007), Guinea-Bissau (November 7, 2008), Mozambique (June 18, 2004 / July 14, 2017), Portugal (January 9, 2004 / November 8, 2005), São Tomé and Príncipe (June 18, 2004 / April 12, 2006), and East Timor (May 25, 2004 / December 22, 2004).[24,25]

Organizations specifically focused on monitoring political activities and compliance with the treaty have emerged in many countries. Like the Brazilian ACT (Non-Governmental Tobacco Control Alliance - Health Promotion - http://actbr.org.br/), non-governmental organizations and national associations or committees exist within medical entities or in other healthcare segments interested in social mobilization, coordination, and permanent updating of control actions.[24,25]

Conclusions

Smoking in all forms represents a serious public health problem in the prevention and treatment of chronic noncommunicable diseases. General practitioners and cardiologists must identify patients who smoke, become aware of all available tools, apply these tools to encourage smokers to seek professional help to quit smoking, and avoid missed key opportunities like diagnoses of coronary artery disease, peripheral arterial disease, or cerebral or tobacco-related malignancies among patients, their family members, and key society members. The increasing awareness of the population about the risks of smoking makes the current moment very favorable to approach smokers. Treatment is more accessible (NRT and bupropion are available in PSCs) and can be performed at any healthcare level.

The association of CBT with pharmacological support to cope with abstinence increases the effectiveness of the interventions. Relapses are part of the smoking dependence cycle and should serve as a lesson for a new attempt. Finally, cessation of smoking at any age brings benefits to the individual's health and to the health of those around him, and physicians must always be ready to offer care, whatever the stage in which the individual dependent on nicotine is.

New forms of smoking, especially using electronic systems, are far from proving their innocence or even contributing to the overall reduction of smoking and its harmful effects, and their use should be discouraged.

Smoking must be considered as a problem that transcends the damage caused to the organs affected by the smoke and tobacco products, and related to a set of problems produced by the individual himself involving economic, social, cultural, and ecological aspects compromising our quality of life and our own survival.

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