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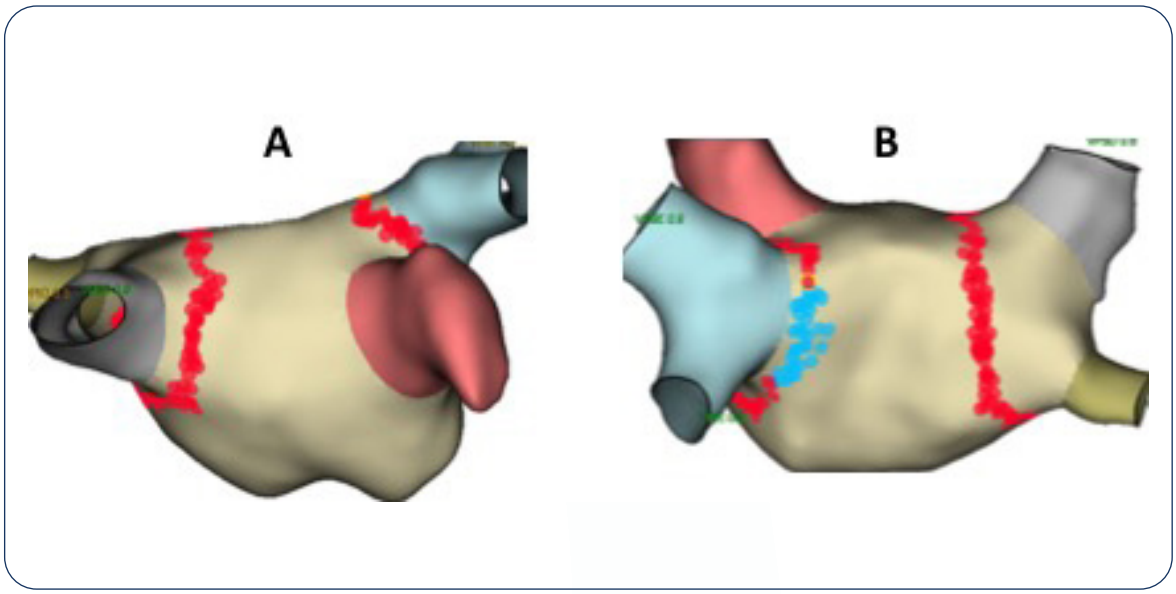

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ABC Cardiol
Journal of Brazilian Society of Cardiology

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Editorial

Interaction among Cardiovascular Scientific Journals in Brazil: A Model that should be Better Explored

Carlos Eduardo Rochitte[1]

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In the environment of intense, and apparently unlimited competition among scientific journals for the best article, and the highest number of citations and impact factor (IF), the *Arquivos Brasileiros de Cardiologia* (ABC Cardiol) has taken actions to foster the growth of other journals with similar scope in the national scientific community. The main objective is to promote dissemination of our best science by journals of increasingly higher quality, so that it can attract deserving attention and make a stronger contribution to the world scientific community.

With the current IF of nearly 1.7 according to the Journal of Citation Reports (JCR), the ABC Cardiol has attracted more and more submissions from national and international authors.[1,2] Our acceptance rate is no more than 15% and tends to decrease even more. In this scenario, many papers of significant quality cannot be accepted for publication in the ABC Cardiol, including articles from studies developed in our successful postgraduate programs. This has an undesirable effect – the reduced exposure of our best science in indexation sources such as PubMED, Scielo, among others.

With this in mind, the editorial board of the ABC Cardiol has suggested to the authors of manuscripts not accepted for publication, either the possibility of recommendation of these papers for publication, or the transfer of these papers to other potential national journals that would be adequate for dissemination of that specific scientific information. It is important to point out that the decision to transfer or submit the manuscript to one of the journals recommended by the ABC Cardiol is solely and exclusively made by the authors. This is a "win-win situation" where both authors and journals win, the first for having their manuscript rapidly published by high quality journals, and the second for increasing the likelihood of citations and indexation in international scientific databases.

One example of such collaboration is the up-close relationship between the ABC Cardiol and the International Journal of Cardiovascular Sciences (IJCS), both held by the SBC and indexed in Scielo. This allows that articles are submitted through the same unique system, the ScholarOne, and can be directly transferred, including the revisions, once authorized by the authors. While the ABC Cardiol focuses more on cardiovascular disease, the IJCS focuses more on multidisciplinarity, including other areas such as Nutrition and Physiotherapy, which makes the relationship between these journals synergistic rather than competitive. Thus, the partnership with the Editor-in-Chief of the IJCS, Dr. Claudio Tinoco Mesquita, has effectively boosted the recognition and the impact of both journals.

In an intermediate level of collaboration, the *ABC Imagem Cardiovascular* and the Journal of Transcatheter Interventions (JOTCI), together with the ABC Cardiol, constitute a large family of scientific journals in the cardiovascular field. However, these journals are not members of Scielo, and hence cannot be integrated to the ScholarOne system without additional cost. For this reason, when a manuscript is rejected for publication by the ABC Cardio, an e-mail is sent to the authors, containing a link to journals that, according to the ABC Cardiol's editorial board, may be adequate to publish that scientific material. This model facilitates and speeds up the (re)submission of the manuscript.

At this point, I would like to thank the Editor-in-Chief of the JOTCI, Dr. Pedro Beraldo de Andrade, for reporting about this collaboration in an editorial published in the JOTCI, and commenting about the first publication of an article resulting from this model in an international journal.[3] I would also like to thank the Editor-in-Chief Dr. Silvio Henrique Barberato of the *ABC Imagem Cardiovascular* for the close relationship with the ABC Cardiol.

Also, we find it important to implement a collaboration to other societies that support other journals relevant to the national science, such as the *Jornal Brasileiro de Pneumologia* and the Brazilian Journal of Cardiovascular Surgery. This is my suggestion for consideration by the respective Editors-in-Chief Dr. Bruno Guedes Baldi and Dr. Domingos M. Braile.

The proximity of the journals in a "family" model allows a greater success of each journal individually. This has been a tendency of the world science, particularly in Cardiology, as exampled by the impressive growth of the American College of Cardiology (JACC)'s family of journals, associated with the USA American of Cardiology, and the European Heart Journal's (EHJ) family, associated with the European Society of Cardiology (ESC) in Europe. As example, in the period from 2011 and 2018 (short seven editorial years), the IF of the EHJ increased from 10.4 to 24.8, the European Journal of Heart Failure had its IF increase from 4.8 to 13.9, the European Journal of Preventive Cardiology from 2.6 to 5.6, the EHJ Cardiovascular Imaging from 2.3 to 5.2, and the Europace from 1.9 to 6.1. These increases in IF, in such a short period of time, are impressive. Therefore, this model seems very effective in improving the dissemination of science while enabling the increase of the IF of each member of the family.

Keywords

Bibliometrics; Journal Impact Factor; Periodicals as Topic/trends; Database.

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Either as a family or as "friends", I believe that an effective collaboration between national renowned journals allows the growth of a group of journals that would not be seen by the journals alone. Hopefully, this initial and preliminary collaboration will lead to a broader discussion and closer interaction between journals with similar aims and scope. I invite everyone to think together about models that would increase the visibility of our scientific papers in the world science. Although the high quality of our scientific production is already recognized, we still need to minimize the barriers to effectively disseminate our science. This must be a joint effort of the Brazilian scientific journals.

Among the actions of ABC Cardiol in this direction are the reshaping of the journal's digital portal and the use of modern digital tools. Among them are tools that suggest similar articles in other journals when a search is carried out on its digital portal, focusing on national journals in the cardiovascular family. The opportunities are many and we have to work to take full advantage of them.

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Safety of Catheter Ablation of Atrial Fibrillation Under Uninterrupted Rivaroxaban Use

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Abstract

Background: Atrial fibrillation (AF) ablation under uninterrupted warfarin use is safe and recommended by experts. However, there is some controversy regarding direct-acting oral anticoagulants for the same purpose.

Objective: To evaluate the safety of AF ablation under uninterrupted anticoagulation with rivaroxaban.

Methods: A series of 130 patients underwent AF radiofrequency ablation under uninterrupted rivaroxaban use (RIV group) and was compared to a control group of 110 patients under uninterrupted warfarin use (WFR group) and therapeutic International Normalized Ratio (INR). We analyzed death, rates of thromboembolic events, major and minor bleedings, activated clotting time (ACT) levels, and heparin dose in the procedure. The ablation protocol basically consisted of circumferential isolation of the pulmonary veins guided by electroanatomic mapping. It was adopted a statistical significance of 5%.

Results: The clinical characteristics of the groups were similar, and the paroxysmal AF was the most frequent type (63% and 59%, RIV and WFR groups). A thromboembolic event occurred in the RIV group. There were 3 patients with major bleeding (RIV = 1 and WFR = 2; p = 0.5); no deaths. Basal INR was higher in the WFR group (2.5 vs. 1.2 ± 0.02; p < 0.0001), with similar basal ACT levels (123.7 ± 3 vs. 118 ± 4; p= 0, 34). A higher dose of venous heparin was used in the RIV group (9,414 ± 199 vs. 6,019 ± 185 IU; p < 0.0001) to maintain similar mean ACT levels during the procedure (350 ± 3 vs. 348.9 ± 4; p = 0.79).

Conclusion: In the study population, AF ablation under uninterrupted rivaroxaban showed a safety profile that was equivalent to uninterrupted warfarin use with therapeutic INR. (Arq Bras Cardiol. 2020; 114(3):435-442)

Keywords: Catheter Ablation/methods; Atrial Fibrillation; Rivaroxaban /therapeitic use; Anticoagulants/therapeutic use; Anticoagulants/adverse effects.

Introduction

Catheter ablation is a well-established therapy for patients with atrial fibrillation (AF), particularly in symptomatic cases where antiarrhythmic drug control has failed. Its main technique consists in the electrical isolation of the pulmonary veins (PVs) through radiofrequency (RF) applications or cryoenergy in the atrial portion of the PV ostia.[1,2] Thromboembolic events (TE), especially cerebrovascular accident (CVA), or stroke, are among the most feared complications and, to avoid them, intraoperative intravenous systemic anticoagulation is recommended, with heparin and the use of oral anticoagulants (OAC) during the periprocedural period.[1,2] However, the management of these drugs becomes challenging during this period, as hemorrhagic complications can occur, especially hemopericardium (cardiac tamponade), a potentially fatal event if not diagnosed and addressed in time.

Multicenter clinical studies have shown that continued use of warfarin during such procedures, while maintaining International Standardized Ratio (INR) at therapeutic levels, significantly reduces rates of bleeding complications and TE events when compared to the previous strategy, which consisted in its withdrawal and the "bridge" with unfractionated heparin.[3,4] With the advent of direct-acting OACs (DOACs), non-vitamin K-dependent, the use of warfarin has become increasingly restricted. Large-impact clinical studies have shown a safer profile of these drugs in relation to warfarin in the prevention of TE phenomena of patients with nonvalvular AF.[5]

In recent years, DOACs have been tested against the scenario of AF ablation. Although evidence suggests the uninterrupted use of these drugs is safe, there is some controversy regarding their applicability due to fears of hemorrhagic complications in the presence of drugs that previously, did not have a direct reversing agent. Rivaroxaban, a factor Xa inhibitor, was one of the (DOAC) drugs that was most often tested in an uninterruptedly manner and the first to show satisfactory results in a randomized clinical trial.[6]

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In our service, we started performing ablation under uninterrupted RIV use in mid-2016, after a long experience with uninterrupted warfarin (therapeutic INR ablation). This study aimed to evaluate the safety of performing AF ablation with RF under uninterrupted rivaroxaban use.

Methods

Study design

This is a retrospective study in which a consecutive series of 130 patients was submitted to the first session of ablation with RF (January 2016 to October 2018) for AF treatment under uninterrupted rivaroxaban use (RIV group) and compared to a control group, consisting of 110 patients submitted to similar procedures (October 2010 to March 2017) under continuous warfarin use (WFR group) and who had INR between 2 and 3.5 on the eve of the procedure. Patients who had an INR outside the specified therapeutic range in the WFR group, and patients who used other anticoagulants or had ablation with OAC interruption were excluded from this study (Figure 1). The analyzed primary outcomes were: thromboembolic event rate (stroke/transient ischemic attack (TIA) and procedure-related major bleeding (up to 30 days). Based on the International Society on Thrombosis and Haemostasis (ISTH) criteria, major bleeding was considered: fatal bleeding; symptomatic bleeding that has affected critical areas or organs; which caused a decrease > 2 g/dL or required replacement of blood products.[7] Secondary outcomes were minor bleeding rates and parameters related to intraoperative anticoagulation, such as mean levels of activated clotting time (ACT) in the procedure and heparin doses required to maintain them at the established goal (between 300 and 400 seconds). All data were collected at hospital admission and stored in the service's own database. All patients underwent preanesthetic consultation and signed a consent form for the procedure.

Anticoagulation Protocols (Pre and Postoperative)

In the RIV group, patients received single-dose rivaroxaban after dinner, 20 mg or 15 mg, according to creatinine clearance, greater than 50 mL/min/m^2 or less, respectively, for 3 or more weeks before the procedure. The last dose was given on the night before the procedure and the next dose on the same day of the procedure, at least 4 hours after sheath removal and medical evaluation.

In the control group, patients received oral warfarin under fasting condition to maintain the INR between 2 and 3.5 for at least 3 weeks before the procedure. The INR was checked the day before the procedure. The first dose after ablation was given on the same day or on the following day, depending on the new INR measurement and medical evaluation.

All patients were submitted to transesophageal echocardiography (TEE) the day before the procedure to exclude intracavitary thrombi. The immediate postoperative (PO) (first 12 hours) was performed in a cardiological intensive care unit.

Procedure

The procedures were performed under general anesthesia after 8 hours of fasting. Suspension of antiarrhythmic drugs was decided individually, based on the clinical picture. Routine electrocardiogram, noninvasive blood pressure and esophageal temperature were monitored.

The procedures consisted of ipsilateral and antral circumferential isolation of the PVs guided by electroanatomic mapping (Ensite/NAVX System, versions 4.1 and 5.0 – St. Jude Medical/Abbott) and portable fluoroscopy in both groups. Additional ablation techniques, such as linear ablation and complex fractional atrial electrograms (CFAE), were performed in some cases according to the operator's preference, usually in cases of persistent and long-standing persistent AF. Cavo-tricuspid isthmus (CTI) ablation was

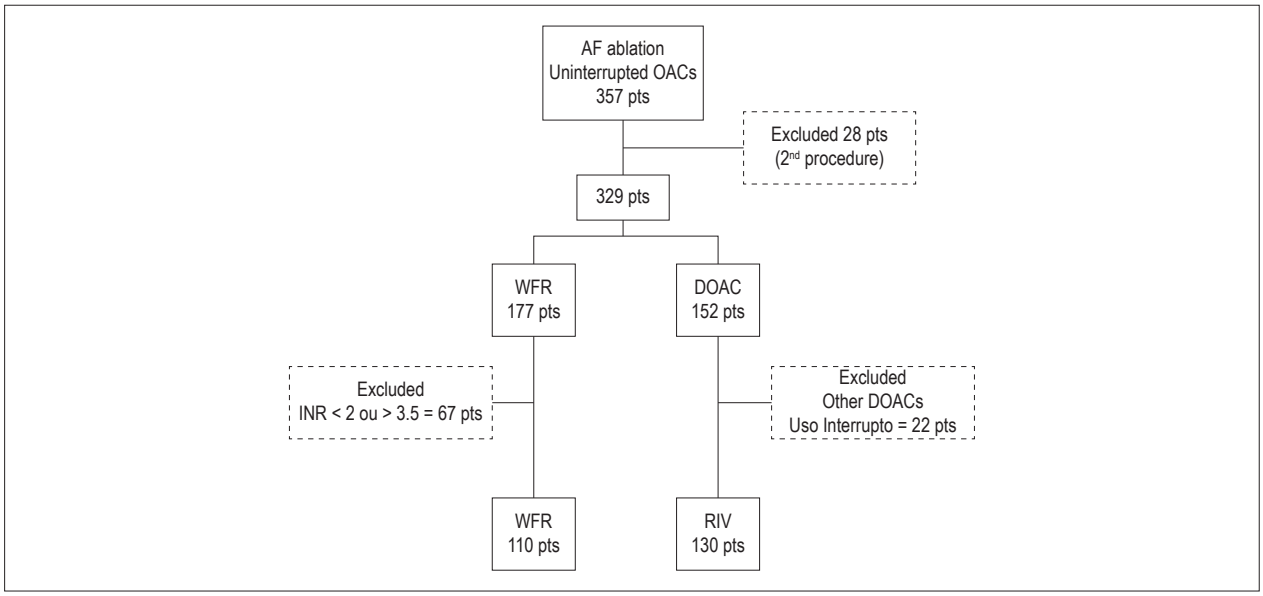

Figure 1 – *Study flowchart. OAC = oral anticoagulant; WFR: warfarin; DOAC: direct acting oral anticoagulants; RIV: rivaroxaban; INR: International Normalized Ratio.*

performed whenever there was a typical atrial flutter electrocardiographic record or if it occurred (spontaneously or not) during the procedure. The standard protocol consisted of three right femoral punctures, not guided by ultrasound; deflectable decapolar catheter placed in the coronary sinus using a 7F introducer sheath and two transseptal punctures, performed only with the aid of fluoroscopy. Decapolar or duodecapolar circular catheters were used in a conventional SL1 sheath (SwartzTM; St. Jude Medical/Abbott) for mapping of LA/PVs and irrigated catheter for ablation (without or with contact sensor) in an SL1 or deflectable sheath (AgilisTM; St Jude Medical/Abbott). RF applications were limited to the power of 20 to 25 W in the posterior wall and 30 to 35 W in the other walls and monitored by the impedance curve, esophageal temperature and contact force (when available). The criteria for interrupting an RF application were: sudden increase in impedance, esophageal temperature reaching 37.5ºC and contact force greater than 40 g. RF applications were performed continuously to fill the entire circumference of the PV antra (Figure 2). We considered as full isolation of the PVs the complete disappearance of the electrograms in the circular catheter placed at its most proximal portion (inlet block) and also the demonstration of electrical dissociation between the PVs and the LA through programmed stimulation of the same circular catheter (outlet block). The adenosine test (12 mg) was performed 20 minutes after the completion of PV isolation and additional applications were performed if PV-LA reconnection was observed.

Anticoagulation in the procedure

Prior to transseptal punctures, the sheaths and transseptal needle were washed with saline solution containing 50 IU/mL of heparin, and basal ACT was measured. The first dose of heparin (loading dose) was administered immediately after the first transseptal puncture (directly in the sheath), with 100 IU/kg in the RIV group and 50 IU/kg in the WFR group (maximum dose of 10,000 IU); the reduced dose in the control group was based on prior group experience and literature data.[8-10] After that, the ACT was systematically measured every 30 minutes, aiming to maintaining it between 300 and 400 seconds. Additional doses of intravenous heparin were given whenever the ACT was below 300 seconds, calculated according to the formula created and tested by the group.[11]

$$\text{RIV group:} \rightarrow \text{Hep Dose (IU)} = \frac{\text{Weight (Kg)} \times \text{CI}^*}{2}$$

$$\text{VRF group:} \rightarrow \text{Hep Dose (IU)} = \frac{\text{Weight (Kg)} \times \text{CI}^*}{3}$$

*CI= Correction Index

ACT (sec)	CI*
150 – 200	75
201 – 250	50
251 – 300	25
> 301	0

The removal of the sheaths was performed still in the operating room after protamine sulfate infusion (5,000 IU).

Statistical analysis

Data for all variables were evaluated for normality through Histogram and D`Agostino & Pearson's Test. Continuous variables were described as mean and standard deviation and compared using unpaired Student's *t* test, except for the variable "baseline INR" (data evaluated as "non-normal"), which was compared using the Mann-Whitney test. Categorical variables were described as absolute numbers and percentages in relation to the sample and compared using Fischer's exact test. The level of statistical significance was set at 5%. GraphPad Prism 7.0e software was used for statistical analysis.

Results

The clinical characteristics of the groups were similar, including the CHA_2DS_2-VASC score, presence of structural heart disease and predominance of paroxysmal AF. At the end of the procedure, 100% isolation of the PVs in both groups was demonstrated. The percentage of patients who received linear ablation of the LA and the cavo-tricuspid isthmus was similar, but the ablation of fragmented CFAEs was more frequent in the WFR group, probably due to the progressive abandonment of this technique in recent years. There was no statistically significant difference regarding the total procedure time (Table 1).

According to the described protocol, no patient had intracavitary thrombus at the TEE on the day before the procedure. It is noteworthy that no patient was excluded from this study due to LA thrombus.

There were no deaths.

Primary outcomes: One patient had procedure-related ischemic stroke in the RIV group, evolving with mild dysarthria in the immediate postoperative period, with spontaneous resolution within 48 hours without further sequelae (Figure 3). This patient had paroxysmal AF without structural heart disease or risk factors for TE events (CHA_2DS_2-VASC = 0).

No thromboembolic events occurred in the WFR group. Major bleeding occurred in 2 patients in the WFR group: 1 hemopericardium with cardiac tamponade and 1 large hematoma at the femoral puncture site. The first case was controlled by pericardiocentesis, volume replacement and administration of protamine sulfate. The second case required blood transfusion and longer hospital stay. Both were discharged without further complications. Major bleeding – retroperitoneal hematoma – occurred in the RIV group and required surgical intervention (drainage) due to uncontrollable pain, and the patient was discharged without sequelae.

Secondary outcomes: Only one puncture site hematoma, clinically not relevant, was observed in the WFR group; none was observed in the RIV group. As expected, the baseline INR was higher in the WFR group (2.5 ± 0.03 *vs.* 1.2 ± 0.02; $p < 0.0001$), but there was no difference in baseline ACT between the WFR and RIV groups (123.7 ± 3 *vs.* 118 ± 4.2; $p = 0.34$).

The mean ACT level during the procedure was adequate in both groups, within the recommended range and similar in

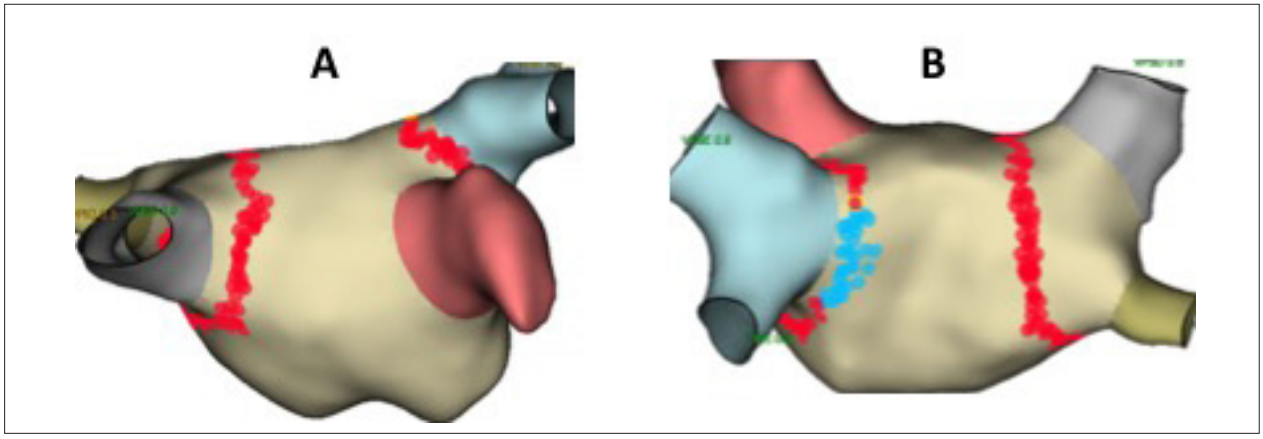

Figure 2 – *Radio Frequency Applications. Images generated by left atrial geometric reconstruction using an electroanatomical mapping system (Ensite/NAVX – St. Jude Medical/Abbott). A – Previous view. Dots in red show the radiofrequency applications. B – Posterior view. Blue dots show locations of radiofrequency applications where esophageal temperature increases.*

Table 1 – Characteristics of the groups

	Rivaroxaban	Warfarin	p
N	130	110	-
Age (years)	57.8 ± 1	60.6 ± 1	0.055
Male	96 (73.8%)	86 (78%)	0.45
BMI	28.3 ± 0.3	28.6 ± 0.4	0.51
Heart disease	28 (21%)	21 (19%)	0.74
CHA_2DS_2-VASC	1.32 ± 0.1	1.23 ± 0.1	0.38
Paroxysmal AF	82 (63%)	65 (59%)	0.59
LVEF (%)	62.26 ± 0.6	65.5 ± 0.6	0.16
LADD (mm)	42 ± 0.6	41.7 ± 0.7	0.81
Isolated PVs (%)	100	100	1
Linear Ablation	14 (10.8%)	26 (23%)	0.009
CFAE	4 (3%)	21 (19%)	< 0.0001
CT isthmus	35 (26.9%)	37 (33.6%)	0.26

BMI: body mass index; LVEF: left ventricular ejection fraction; LADD: left atrial diastolic diameter; PVs: pulmonary veins; CFAE: complex fractional atrial electrograms; CT: Cavo-tricuspid.

the RIV and WFR groups (350.1 ± 3 vs 348.9 ± 4; p = 0.79). However, a higher dose of heparin was used in the RIV group (9,414 ± 199 *vs*. 6,019 ± 185 IU; p < 0.0001) to maintain these optimal levels of ACT (Figure 4).

Discussion

AF ablation under uninterrupted warfarin use (therapeutic INR) has long been the most recommended periprocedural anticoagulation strategy for the prevention of TE events, especially stroke.[12] Most observational studies have reported low rates of stroke and hemorrhagic complications with this strategy. However, in practice, as well as in the clinical use of warfarin, it is difficult to keep INR within the therapeutic range stable in the periprocedural period, causing patients to have thromboembolic risks[13] or have their procedures suspended.

The favorable clinical outcomes of DOACs[5] have encouraged their use in the scenario of AF ablation worldwide, even before the publication of further scientific evidence. Unlike clinical use, the anticoagulant effect of these drugs had not yet been tested in a distinct thrombogenic situation related to the presence of sheaths and catheters in the LA and endocardial lesions caused by RF. The initial results of dabigatran as an anticoagulant drug during AF ablation were unfavorable, with higher rates of hemorrhagic and embolic complications.[14] However, it was suspected that discontinuation of the drug for 24 to 48 hours before the procedure (discontinued use) may have influenced

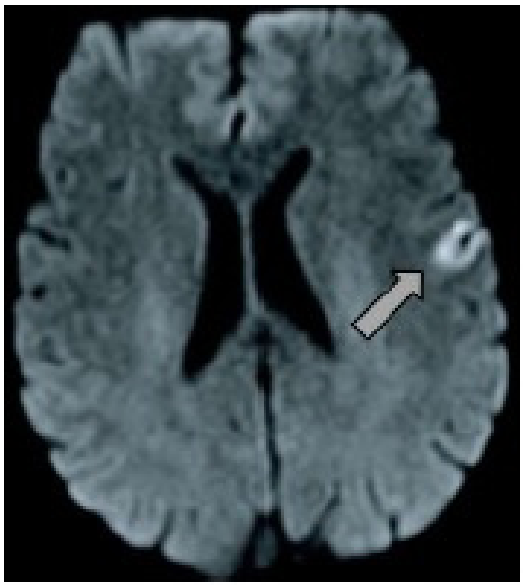

Figure 3 – *Cerebrovascular accident (CVA) - Magnetic Resonance Imaging of a Patient with CVA – Hyperintense lesion on Flair sequence in the left central gyrus topography, compatible with acute ischemia.*

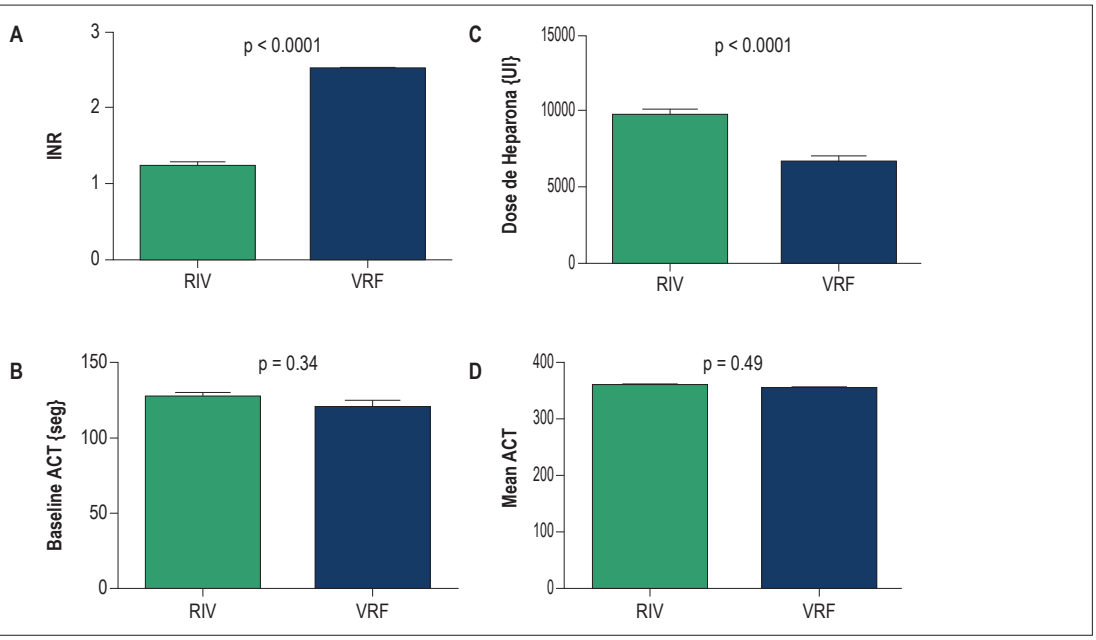

Figure 4 – *Results: Secondary outcomes related to anticoagulation level monitoring. A - Preoperative International Normalized Ratio (INR); B - Baseline ACT (activated clotting time), measured after the first venipuncture; C – Mean dose of intravenous heparin used throughout the procedure; D – Mean ACT during the procedure.*

the results of this study.

Rivaroxaban was compared to warfarin, this time without interruption of DOAC, in a prospective, multicenter study involving 642 patients. Patients (CHA_2DS_2-VASC = 2/paroxysmal AF = 50%) were given the last dose of rivaroxaban the night before the procedure, ensuring that it was performed within the therapeutic window of the drug, and there was no significant difference regarding embolic and hemorrhagic complications.[15]

DOAC in AF ablation were tested in multicenter and randomized studies.[6,16-18] In the Venture-AF Trial, the first randomized trial comparing uninterrupted DOAC (rivaroxaban) to warfarin in AF ablation, the rate of TE or hemorrhagic events was low, similar between the groups;[6] in the RE-CIRCUIT Trial, dabigatran use resulted in fewer bleeding complications than warfarin (1.6% *vs.* 6.9%; $p < 0.001$).[16] In the AXAFA-AFNET 5, 674 patients were randomized to ablation under continuous use

of apixaban or warfarin. The combined outcome of death, stroke or bleeding was similar (22/318 pts *vs.* 23/315 pts; p = 0.0002 for noninferiority). Brain magnetic resonance imaging, after the procedure, showed similar rates of "silent" cerebral ischemic lesions.[17] In the AEIOU trial, Reynolds MR et al. described similar bleeding rates and no stroke in 3 groups – uninterrupted edoxaban, interrupted (interruption of one dose) edoxaban and warfarin.[18]

A meta-analysis that included 7400 pts from 15 observational and 1 randomized studies reported a trend toward lower rate of TE events in patients receiving rivaroxaban compared to warfarin (p = 0.052), with similar bleeding complications (1.15% vs. 1.66%; p = 0.23).[19] Sawhney V et al. compared DOAC (64% rivaroxaban) to warfarin, uninterrupted in 1884 AF ablation procedures, and found no difference between the groups in relation to the primary outcome consisting of death, TE or major bleedings (2.2% vs. 1.4% p = 0.2).[20] With these now more consistent results, catheter ablation of AF under uninterrupted use of warfarin, dabigatran or rivaroxaban is now class I recommendation in the latest expert consensus (HRS, EHRA, ECAS, APHRS, SOLAECE), published in 2017.[1]

In our service, which has 14 years of experience in AF ablation, with current 50 to 100 procedures/year, after a long period using uninterrupted warfarin (therapeutic INR) for AF ablation, we chose rivaroxaban as an alternative based on the presented results, in a major adaptation to our routine, to the preoperative group protocol and drug pharmacokinetics. The dose taken on the previous night allowed the procedure to be performed on the following day, with the patient within the drug therapeutic window and, at the same time, outside its peak of action. Moreover, the next dose, to be taken on the day of the ablation, would be administered a few hours after the end of the procedure, an adequate period to observe complications. The low overall rates of adverse events reported in both groups was in agreement with the abovementioned literature results. The low rate of hemorrhagic events in the RIV group was noteworthy, even those related to venous access, performed by conventional puncture without the aid of ultrasound (US). This tool has been used to guide venipuncture in patients using anticoagulants. Data from a meta-analysis (4 observational studies) showed a 60% and 66% reduction in major and minor vascular complication rates, respectively, with the use of US.[21] However, randomized trials have not yet confirmed these data. Yamada et al. randomized 320 patients for punctures guided or not by US (Ultra-Fast Trial); they reported shorter time to puncture, less fluoroscopy use, fewer inadvertent arterial punctures and less local postoperative pain when using US, but without significant difference regarding major (vascular) complications.[22] In the present series, one should consider that the approach of our group regarding the accesses – only 3 femoral punctures, without jugular punctures or intracardiac echocardiography (larger sheaths) – may have contributed to low rates of vascular complications. Moreover, one cannot rule out that the US, if used to guide the punctures, would have prevented such complications. On the other hand, ischemic stroke occurred in one patient in this group, a fact that had not been observed with warfarin throughout the group's experience. We considered the event as occasional, as it statistically corresponds to the rates reported in the literature. The main fear of using rivaroxaban is the lack of a direct "antidote" in case of bleeding complications, especially cardiac tamponade, a potentially lethal event, if not treated quickly. This study did not allow us to assess this risk situation because no cardiac tamponade occurred. In studies with available DOAC so far, although some have reported greater drainage in cases of cardiac tamponade, there were no significant differences in the management of these complications or mortality compared to warfarin. In the J-CARAF (Japanese AF ablation registry), in contrast, there was a lower rate of pericardial effusions that required drainage with DOAC than with warfarin ($p < 0.05$).[23]

In general, in situations of major bleedings with warfarin or DOAC, supportive measures (saline replacement and vasoactive drugs), reversal of heparin (protamine sulfate), eventual use of prothrombin complex or Factor VII, and immediate drainage by pericardiocentesis are recommended, and the service should be prepared for the immediate approach of such complications. Certainly, the availability of a direct reversing agent would bring a greater sense of safety to the procedure, but the potential risk of thromboembolic complications should be considered when reversing anticoagulation completely after extensive RF applications to the left atrial endocardium. In the RE-CIRCUIT trial, bleeding complications with dabigatran were treated without the use of the specific direct reversing agent, idarucizumab, despite its availability in the centers involved in the study.[16] It is generally agreed that regardless of the elected periprocedural anticoagulation strategy, intravenous heparin should be administered before or immediately after the first transseptal puncture at doses that maintain the ACT levels between 300 and 400 seconds.[1,12] Previous studies have shown that patients on continuous warfarin use reach the ACT target levels faster and with lower heparin doses compared to those who transitioned to unfractionated heparin for ablation.[8-10] In case of uninterrupted DOAC use for ablation, more recent studies report that higher doses of heparin are required.[9] Due to these data, we used a loading dose and additional doses (formula described above) of heparin in patients in the WFR group. Our findings showed that, as with enoxaparin, rivaroxaban patients received higher doses of heparin to achieve adequate levels of ACT compared to those using uninterrupted warfarin. Well-controlled heparin replacement in these patients, using the formula previously tested in the group, also prevented large extrapolations in ACT levels (over 400 seconds), which may have influenced the low incidence of hemorrhagic events.

Study limitations

Potential limitations include: (1) retrospective, nonrandomized study; (2) unlike the WFR group, the baseline INR in the RIV group was not necessarily collected on the day before the procedure, but randomly in the weeks or days preceding it; however, this consideration may have no impact due to the low influence of DOACs on INR; (3) the fact that there was no cardiac tamponade in the RIV group made it impossible for us to conclude on the severity of this hemorrhagic complication in this group of patients or to compare their approach to the control group; (4) regarding cerebral ischemic events, the study was limited to clinical data, and no routine imaging study was performed to investigate the so-called silent ischemic lesions, previously described

in these procedures.

Conclusions

Radiofrequency ablation of atrial fibrillation under uninterrupted rivaroxaban use was safe, with low rates of thromboembolic or hemorrhagic complications when compared with the conventional strategy of uninterrupted warfarin anticoagulation.

Author contributions

Conception and design of the research: Silva MA, Elias Neto J, Kuniyoshi R; Acquisition of data: Silva MA, Futuro GMC, Merçon ES, Vasconcelos D, Agrizzi RS, Elias Neto J, Kuniyoshi R; Analysis and interpretation of the data and Statistical analysis: Silva MA; Writing of the manuscript: Silva MA, Elias Neto J; Critical revision of the manuscript for intellectual content: Futuro GMC, Merçon ES, Elias Neto J.

Potential Conflict of Interest

Márcio Augusto Silva - Participation in courses and congresses by Bayer and lectures paid by Bayer and Daiichi Sankyo. Jorge Elias Neto - Participation in courses and congresses by Bayer. Ricardo Kuniyoshi - Participation in courses and congresses by Bayer

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

Ethics approval and consent to participate

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

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Uninterrupted Direct Oral Anticoagulants in Atrial Fibrillation Catheter Ablation: Ready for Prime Time

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Short Editorial related to the article: Safety of Catheter Ablation of Atrial Fibrillation Under Uninterrupted Rivaroxaban Use

Catheter ablation is a well-established, safe, and effective strategy to achieve rhythm control in patients with symptomatic atrial fibrillation (AF) who are either intolerant or refractory to pharmacologic rhythm control or who wish to avoid long-term use of anti-arrhythmic drugs. Historically, when vitamin-K antagonists (VKAs) were the only option for oral anticoagulation, catheter ablation was performed after interruption of the VKA for several days and a transition (bridge) to subcutaneous or parenteral anticoagulation, typically with low-molecular-weight heparin. This strategy, however, was cumbersome and fraught with bleeding complications. Furthermore, the COMPARE randomized trial and observational studies showed that the thromboembolic risk was 10 to 15-fold higher with VKAs and heparin bridging as compared to uninterrupted VKAs.[1] After these results, uninterrupted VKAs with a therapeutic international normalized ratio (INR) became the standard of care for periprocedural anticoagulation, and patients would routinely undergo catheter ablation with INR ranging between 2 and 3.5.

This option, however, also has two important setbacks. First, ablation becomes contingent on a therapeutic INR on the day of the procedure. A supra-therapeutic INR may entail a decision to postpone the procedure or administer blood products for correction, whereas a sub-therapeutic INR would typically imply deferring ablation to another day or require IV heparin until an ideal INR is reached. Second, the use of uninterrupted VKAs conflicts with the ever growing use of direct oral anticoagulants (DOACs). Electrophysiologists planning catheter ablation for patients on DOACs are faced with the following decision: (1) transition to VKAs for uninterrupted periprocedural anticoagulation or (2) continue periprocedural DOAC.

This important question was addressed by Silva et al.[2] in this issue of the Brazilian Archives of Cardiology. They compared 130 consecutive patients with AF who underwent catheter ablation in a single center while receiving uninterrupted rivaroxaban to 110 patients in a historic control group who had previously undergone catheter ablation on uninterrupted VKA with a pre-procedure INR between 2 and 3.5. Major bleeding occurred in 1 (0.7%) and 2 (1.8%) individuals in the rivaroxaban and VKA groups, respectively. The event in the rivaroxaban group was a retroperitoneal hematoma requiring surgical drainage. In the VKA group, there was a femoral hematoma treated conservatively and a pericardial effusion requiring pericardiocentesis. One patient had an ischemic stroke in the rivaroxaban group (0.7%), while there were no thromboembolic events with VKAs.

Other studies, including randomized trials with all four DOACs (rivaroxaban, apixaban, edoxaban, and dabigatran), have reached similar conclusions. In a meta-analysis including 12 studies and nearly 5,000 patients treated with uninterrupted VKAs or DOACs, the incidence of periprocedural stroke or transient ischemic attack was low, and it was not significantly different between the two groups (DOAC 0.08%, VKA 0.16%).[3] In a sub-cohort of patients who underwent routine post-procedure brain imaging, the incidence of clinically silent embolic events was also not significantly different between both groups (DOAC 8%; VKA 9.6%; OR 0.86; 95% CI 0.42 – 1.76). There was a lower incidence of major bleeding in those who received DOACs (0.9%) than in patients anticoagulated with VKAs (2%) (OR 0.50; 95% CI 0.30 – 0.84; $p < 0.01$). There was no difference between groups in the occurrence of pericardial tamponade (0.7% vs. 0.8% with DOACs and VKAs, respectively).[3]

Altogether, we have learned several lessons from the study by Silva et al.[2] and similar studies in the literature. First, the incidence of periprocedural stroke with uninterrupted DOAC use is exceedingly low, well under 1%, and similar to that of uninterrupted VKAs. This represents a major improvement compared to the historic strategy of interrupting oral anticoagulation with a heparin bridge, where the incidence of thromboembolic events ranged from 1% to 5%.[1] The importance of this finding cannot be overstated. A low incidence of thromboembolic events is paramount when treating AF by catheter ablation, a procedure that is indicated almost exclusively for symptom control and not for life-saving purposes. It is noteworthy that the clinical significance of asymptomatic cerebral embolism in patients who undergo catheter ablation is unclear at this point. Further studies should examine long-term clinical outcomes and cognitive function in those who have clinically silent cerebral embolic events.

Second, the incidence of major hemorrhagic complications with uninterrupted DOACs is also low, and it is comparable to, if not better than, that of uninterrupted VKAs. In the present study, a power calculation, with two-sided alpha of 0.05 and a 2.5% event rate in control group, would yield an estimated power of only 3% to detect a 1% difference in major bleeding events between groups with the sample size

Keywords

Atrial Fibrillation; Anticoagulants; Catheter Ablation; Rivaroxaban/therapeutic use.

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of 240 patients. This, however, should not be viewed as a limitation to the study, but rather as a testament to the safety of the procedure with both VKAs and DOACs. Similarly, two large randomized trials, VENTURE-AF (rivaroxaban) and RE-CIRCUIT (dabigatran), including 248 and 704 patients, respectively, acknowledged being underpowered for their primary endpoint of major bleeding.[4,5]

Previously, apprehension regarding the lack of reversibility of DOACs limited widespread acceptance of this strategy. This concern has largely abated with the development of idarucizumab and andexanet alpha, reversal agents for dabigatran and factor Xa inhibitors, respectively. More importantly, perhaps, is that the overall strategy of uninterrupted DOACs has proven to be very safe with a low incidence of major bleeding events. In RE-CIRCUIT idarucizumab, although it was available, was not required in any of the 317 patients who underwent catheter ablation while on uninterrupted dabigatran, which included a dose administered on the morning of ablation.[5] In a pooled analysis of 14 patients with cardiac tamponade from 3 randomized trials of uninterrupted DOACs vs. VKAs, all underwent pericardiocentesis; 12 received protamine; and 2 (in the VKA group) received prothrombin complex concentrate. None received a direct DOAC reversal agent.[6]

Bleeding events can also be prevented by meticulous attention to hemostasis. The use of a figure-of-eight suture for venous closure in patients who are fully anticoagulated at the end of the procedure also has the potential to decrease hematoma formation and shorten bedrest duration after catheter ablation.[7] This hemostatic suture may obviate the need for protamine reversal, extending therapeutic anticoagulation during the hours following the procedure. Whether this technique further reduces the (already low) thromboembolic risk with an acceptable incidence of bleeding events warrants further investigation.

Finally, it is important to highlight the distinction between a truly uninterrupted strategy, where the DOAC is given pre-procedurally at the usual time and dose and an alternative minimally interrupted strategy, where 1 or 2 doses of the DOAC are held prior to catheter ablation. In both strategies, the DOAC is typically resumed at a minimum of 4 hours after femoral venous sheath removal. This is a particular dilemma with twice-daily agents, where a decision has to be made about the morning DOAC dose on the day of ablation; it is less of a concern with once-daily options, such as rivaroxaban, where the drug can be administered uninterruptedly in the evening prior to catheter ablation, without requiring a morning dose. In the ABRIDGE-J trial, 504 patients scheduled for AF catheter ablation were randomized to minimally interrupted dabigatran (holding 1 to 2 pre-procedure doses) or uninterrupted VKAs. There were no thromboembolic events in the 220 patients who underwent ablation in the dabigatran group. Minimally interrupted dabigatran was associated with a lower incidence of major bleeding (1.4%) as compared to uninterrupted VKAs (5%).[8] It should be emphasized, however, that while there is robust and consistent data supporting a strategy of uninterrupted DOACs for anticoagulation in patients undergoing AF catheter ablation, the use of a minimally interrupted strategy has neither been extensively studied nor directly compared to uninterrupted DOAC use in large randomized studies.

In conclusion, studies have demonstrated that uninterrupted anticoagulation with DOACs for patients undergoing AF catheter ablation is effective in the prevention of periprocedural thromboembolic events (< 1%). This strategy also has a low risk of major bleeding events, comparable to or lower than bleeding events with uninterrupted VKAs. Prospective studies in the field will hopefully investigate mechanical approaches to minimize bleeding events and evaluate the efficacy and safety of a minimally interrupted DOAC strategy. Until then, the use of uninterrupted DOACs should be strongly favored as the preferred anticoagulation option for patients undergoing AF catheter ablation. The authors should be congratulated for their initiative and well-conducted study.

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Short Editorial

Creation and Implementation of a Prospective and Multicentric Database of Patients with Acute Myocardial Infarction: RIAM

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Abstract

Background: Multicenter registries representing the real world can be a significant source of information, but few studies exist describing the methodology to implement these tools.

Objective: To describe the process of implementing a database of ST-segment elevation acute myocardial infarction (STEMI) at a reference hospital, and the application of this process to other centers by means of an online platform.

Methods: In 2009, our institution implemented an Registry of Acute Myocardial Infarction (RIAM), with the prospective and consecutive inclusion of every patient admitted to the institution who received a diagnosis of STEMI. From March 2014 to April 2016, the registries were uploaded to a web-based system using the REDCap software and the registry was expanded to other centers. Upon subscription, the REDCap platform is a noncommercial software made available by Vanderbilt University to institutions interested in research.

Results: The following steps were taken to improve and expand the registry: 1. Standardization of variables; 2. Implementation of institutional REDCap (Research Electronic Data Capture); 3. Development of data collection forms (Case Report Form - CRF); 4. Expansion of registry to other reference centers using the REDCap software; 5. Training of teams and participating centers following an SOP (Standard Operating Procedure).

Conclusion: The description of the methodology used to implement and expand the RIAM may help other centers and researchers to conduct similar studies, share information between institutions, develop new health technologies, and assist public policies regarding cardiovascular diseases. (Arq Bras Cardiol. 2020; 114(3):446-455)

Keywords: Myocardial Ischemia/physiopathology; Cardiovascular Diseases/mortality; Myocardial Infarction/physiopathology; Multicenter Study; Database; Public Health Policy.

Introduction

Ischemic cardiomyopathy (IC) is one of the leading causes of death in the world.[1] According to DATASUS (Brazilian Basic Health Indicators and Data), acute myocardial infarction (AMI) is the leading cause of death from heart disease in Brazil, but information on clinical characteristics and treatment received by most patients with AMI in the country are poorly known.[2] Many international registries of acute coronary syndromes have been published, which include the collaboration of some Brazilian centers:[3,4] however, only a few nationwide studies reporting AMI treatment outcomes have been published so far.[5,6]

The management of registry data demands technological support for their storage in computerized databases, with software that provides safe, reliable and easy access to data. Research Electronic Data Capture (REDCap) is a software for clinical data capture and storage which is widely used for clinical research. It is a fast and secure web application currently used by 3,175 institutions in 128 countries.[7] Few studies have reported in detail the methodology of recording clinical data in cardiology, and references describing the steps for the implementation of a clinical registry and for the use of REDCap as an online platform are scarce.[8-11]

The Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia (IC/FUC) started the Registry of Acute Myocardial Infarction (RIAM) in 2009, with consecutive, prospective and uninterrupted data collection since it was implemented.[12] A national ST-segment elevation myocardial infarction (STEMI) registry derived from the expansion of a registry such as RIAM could be a source of representative data for this pathology in Brazil. The aim of this study is to describe the implementation of a STEMI database in a reference hospital as well as the use of an online platform to apply it to other centers across the national territory.

Methods

This section describes the steps taken to migrate the RIAM database from Microsoft Access into the online system and

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to expand the registry to reference hospitals treating STEMI across the national territory. This took place from March 2014 to April 2016 and included the standardization of variables; the implementation of dedicated software (REDCap); the development of data collection forms; and the inclusion of new centers with staff training.

RIAM and the expansion to other centers

RIAM is a prospective and consecutive clinical registry of STEMI patients treated at IC/FUC, in Porto Alegre/RS, Brazil. The registry was started in 2009 and currently has more than 3,500 patients. This initiative contributed to new studies with ideas for scientific and technological research in the institution.[12] IC/FUC will coordinate the expansion to seven other national centers, initially.

Eligibility and workflow

The inclusion criteria were patients aged at least 18 years old and STEMI with less than 12 hours of symptoms. Patients with more than 12 hours of symptoms and reporting chest pain at admission are also included. The registry was approved by the Ethics Committee of IC/FUC number 5025/14, with registration in Plataforma Brasil (CAAE: 38352714.0.0000.5333), and each participating center will also submit it for approval in their local institutional ethics committees. All patients are required to sign an informed consent form and their data will be collected in accordance with the principles of the current revision of the Declaration of Helsinki and the latest version of the Good Clinical Practice Guidelines (ICH-GCP), as well as Resolution 466/12 of the Brazilian National Health Council.[13-15] The study was expanded according to Brazilian legal and regulatory requirements.

Results

Registry design

The following steps were taken to migrate the system to the online database and expand the registry, as shown in Figure 1: Step 1. Standardization of variables; Step 2. Implementation of institutional REDCap software; Step 3. Development of data collection forms (Case *Report Form* - CRF); Step 4. Expansion of registry to other reference centers using the REDCap software; Step 5. Creation of SOPs (Standard Operating Procedures) for training teams and participating centers.

Standardization of variables

The nomenclature assigned to the variables already used in the Microsoft Access™ database were compared with internationally standardized variables to ensure the information in the registry is compatible with other national and international databases.

Variables were standardized based on the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) clinical data standards for acute coronary syndromes and coronary artery diseases, published in 2013. They were also based on data element forms from the National Cardiovascular Data Registry (NCDR), the ACTION Registry®-GWTG™ (NCDR® ACTION Registry®-GWTG™ v2.4 Coder's Data Dictionary, replaced by the NCDR® Chest Pain - MI Registry™ v3.0 Coder's Data Dictionary as of June 2018), an ACCF-coordinated quality care program for patients with MI.[16,17] For national data regarding ethnicity the classification recommended by the Brazilian Institute of Geography and Statistics (IBGE)[18] was used. In addition, a review of the standardized data used by the Brazilian Society of Cardiology was carried out to facilitate international and national interoperability.[9] Table 1 shows some of the variables selected for the registry according to the NCDR ACTION Registry®.[17]

Among the selected variables, the RIAM and ACTION Registry® – GWTG™ databases were found to have a similar profile across variables, suggesting that the RIAM (Table 2) already had a pattern comparable to the main MI registries in the world today (Table 3).

Subsequently another spreadsheet was generated containing the sessions of registry with the number of fields to be included in REDCap CRF (Table 4).

A codebook in English was included for each variable to enable smoother integration with other national and international databases, and an interface in portuguese was added for data collection in Brazil.

Deployment of REDCap software

REDCap was the software used by means of an online platform. It is internationally acknowledged for its security and applicability for clinical data capture and storage. The system is based on the international model by the Duke Clinical Research Institute, complying with international security requirements as well as with the Brazilian National Health Surveillance Agency (ANVISA).[19,20]

Some of the features of REDCap are: (1) an intuitive interface for validated data entry, with automated data type and range checks; (2) audit trails for tracking data manipulation and export procedures, (3) automated data export procedures for common statistical packages and (4) procedures for importing data from external sources.[21] Data collection is performed on any device with internet access such as a computer, tablet or smartphone, or even offline via the REDCap application, which synchronizes the data once there is internet access.[22]

REDCap is a noncommercial secure web-based database management solution offered by the Center for Research Informatics (CRI). It is used for the collection and management of research data and was developed following guidelines from the Health Insurance Portability and Accountability Act (HIPAA).[23] After obtaining a license from Vanderbilt University, the software was hosted on a local server protected by the IC/FUC system firewall.

Access requires an individual username and password requested and approved by the local software manager at the institution. REDCap allowed the creation of a CRF, which contained the standardized variables of the study.

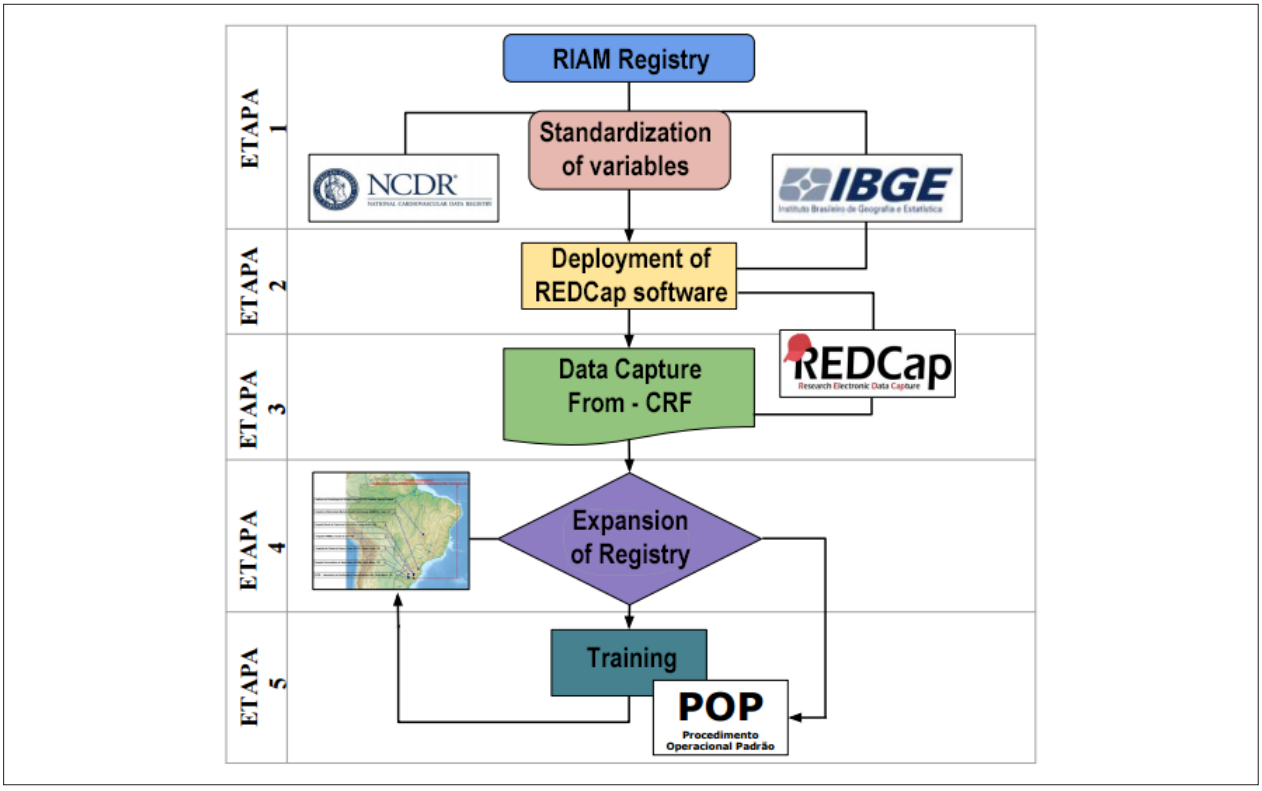

Figure 1 – *Improvement and expansion flowchart for the multicenter Registry of Acute Myocardial Infarction. Source: Lucidchart. Available in: https://www.lucidchart.com*

Development of a data collection form (Case report form - CRF)

The electronic data form – *Case Report Form* (CRF) was developed using REDCap. Figure 2 shows the necessary steps to set up the CRF.

The steps for the creation of a CRF followed the guidelines of the software. Within the third step, a pilot test was run with patients randomly chosen from the Microsoft Access™ RIAM database for the purpose of CRF validation. Automated export procedures for data download for programs such as Microsoft Excel and common statistical packages such as SPSS, SAS and R were performed to ensure software security and reliability.

Registry Expansion to other reference centers using the institutional REDCap

Invited centers were selected because of the existence of interventional cardiology sectors with STEMI treatment 24 hours a day, 7 days a week. Initially, a meeting was held with local coordinators of other centers (called Principal Investigator - PI) to present the proposed expansion. Afterwards, the invited centers were informed of the participation processes via e-mail.

The institutions that agreed to participate in the multicenter phase of the RIAM Registry are located in many regions in Brazil (Figure 4):

1. Instituto de Cardiologia - Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, Rio Grande do Sul, Brazil – Coordinating Center;
2. Instituto de Cardiologia do Distrito Federal (IC-DF), Brasília, Distrito Federal, Brazil.
3. Hospital e Maternidade Marieta Konder Bornhausen (HMMKB), Itajaí, Santa Catarina, Brazil;
4. Hospital Geral de Caxias do Sul (HGCS), Caxias do Sul, Rio Grande do Sul, Brazil;
5. Hospital UNIMED, Caxias do Sul, Rio Grande do Sul, Brazil;
6. Hospital da Cidade de Passo Fundo (HCPF), Passo Fundo, Rio Grande do Sul, Brazil;
7. Hospital Universitário de Santa Maria (HUSM), Santa Maria, Rio Grande do Sul, Brazil;
8. ICOR - Instituto do Coração de Santa Maria (ICOR), Santa Maria, Rio Grande do Sul, Brazil;

RIAM registry protocols were created to include participating centers to then start multicenter expansion. These protocols were sent by email in PDF (Portable Document Format) for later printing, completion and signature. Once signed, the protocols were sent back to the coordinating center via scanner, email, mail or personally delivered to the RIAM registry coordinators.

Training - SOP (Standard Operating Procedure)

Before data collection, the principal investigator and their researchers received an email with a link to access REDCap and an individual username and password, which upon receipt may request the creation of a new password, ensuring the confidentiality of the researcher in institutional REDCap.

Table 1 – Pre-selected variables in ACTION Registry®–GWTG

A. Demographic Data	Variable in English	Legend	Selection
Last name	Last_name	Indicates the patient's last name	
First name	first_name	Indicates the patient's first name	
Patient's identification number	Patient_ID	Indicates the number entered automatically by the software that uniquely identifies this patient	
Date of birth	Birth_date	Indicates the date of birth of the patient	
Sex	Sex	Indicates the patient's sex at birth	Male; Female
B. Admission Data	**Variable in English**	**Legend**	**Selection**
Patient's ZIP code	patient_zip_code	Indicates the zip code of the patient's primary home	
Date of admission	admission_date	Indicates the date the patient was admitted to the institution for the treatment of the current episode	
Private health plan	insurance_payor_private	Indicates whether the patient's insurance payor includes a private health plan	No; Yes
C. Clinical Data	**Variable in English**	**Legend**	**Selection**
Date of symptom onset	symptom_onset_date	Indicates the date the patient first reported ischemic symptoms for 10 minutes or more.	
Date of first ECG	first_ECG_date	Indicates date of first 12-lead electrocardiogram	
Heart failure	heart_failure	Indicates the existence of heart failure on first medical contact	No, Yes
Cardiogenic shock	cardiogenic_shock	Indicates whether the patient was in cardiogenic shock on first medical contact	No, Yes
Heart rate	heart_rate	Indicates the first heart rate record (in beats per minute)	
Systolic blood pressure	systolic_blood_pressure	Indicates first record of systolic blood pressure in mmHg	
Cardiac arrest	cardiac_arrest	Indicates whether the patient was in cardiac arrest on first medical contact	No, Yes

ID: Identification; ECG: Electrocardiogram; mmHg - Millimeters of mercury. Source: ACTION Registry®–GWTG™. Previously available at: www.ncdr.com/webncdr/action/home/datacollection (replaced by NCDR® Chest Pain - MI Registry™ as of June 2018, available at: https://cvquality.acc.org/NCDR-Home/registries/hospital-registries/chest-pain-mi-registry)

Table 2 – Variables RIAM - ACCESS

Demographics	Database
Patient ID	RIAM of ACCESS
Birth Date	RIAM of ACCESS
Sex	RIAM of ACCESS
Race	RIAM of ACCESS
Admission	Database
Prior MI	RIAM of ACCESS
Prior angina	RIAM of ACCESS
Systemic Systolic Blood Pressure	RIAM of ACCESS
Systemic Diastolic Blood Pressure	RIAM of ACCESS
Risk factors	Database
Diabetes	RIAM of ACCESS
Dyslipidemia	RIAM of ACCESS
Prior CVA	RIAM of ACCESS
Prior CABG	RIAM of ACCESS
Hypertension	RIAM of ACCESS
Tobacco use	RIAM of ACCESS

Table 3 – Variables ACTION Registry

Demographics	Database
Patient ID	ACTION Registry®
Birth Date	ACTION Registry®
Sex	ACTION Registry®
Race	ACTION Registry®
Admission	Data Base
Prior MI	ACTION Registry®
Prior angina	ACTION Registry®
Systemic Systolic Blood Pressure	ACTION Registry®
Systemic Diastolic Blood Pressure	ACTION Registry®
Risk factors	Data Base
Diabetes	ACTION Registry®
Dyslipidemia	ACTION Registry®
Prior CVA	ACTION Registry®
Prior CABG	ACTION Registry®
Hypertension	ACTION Registry®
Tobacco use	ACTION Registry®

Source: Table 2 - Institutional RIAM Registry, Microsoft ACCESS™; Table 3 - ACTION Registry®–GWTG™. Previously available at: www.ncdr.com/webncdr/action/home/datacollection (replaced by NCDR® Chest Pain - MI Registry™ as of June 2018, available at: https://cvquality.acc.org/NCDR-Home/registries/hospital-registries/chest-pain-mi-registry). Access: Database management system from Microsoft; ACTION Registry: MI patient database from the American College of Cardiology Foundation; CVA: Cerebrovascular Accident; CABG: Coronary Artery Bypass Graft; MRS: Myocardial revascularization surgery; Acute MI: Acute Myocardial Infarction; ID: Identification; MI: Myocardial Infarction; RIAM: Registry of Acute Myocardial Infarction.

Table 4 – Session of standardized variables

Name of Instrument	Fields	Session of Registries
Demographic data	6	Patient identification; date of birth; age; health insurance payor; education; race; sex.
Contacts	4	Main phone number; second phone number; family member's phone number; patient's e-mail address.
Clinical data 24h	18	Symptoms and initial care; Onset of ischemic discomfort; origin; ECG data; MI wall; Vital Signs and Physical Examination; Reperfusion Strategy.
Medication 24h	23	Medication given for 24h.
Clinical History	22	Height; Weight; BMI; DM; Tobacco user; HAS; Dyslipidemia; Angina; AMI; ACTP; CRM; Cardiac insufficiency; Family history; CVA; Chronic Kidney Failure; cancer; antidepressant; Peripheral arterial disease; FA and Flutter; Previous cardiac device.
Catheterization and Intervention	34	Cardiac Catheterization and ACTP Data; Angiography findings; Angioplasty data; Angiographic aspects;
Laboratory data - admission	20	Laboratory tests performed on admission; Positive myocardial injury markers within first the 24 hours.
Procedures and complications - hospitalization	26	Infarction Type; Procedures until discharge; Complications until discharge.
Data from hospital discharge form	9	Death before hospital discharge; Date of hospital discharge; Length of hospital stay; Medication prescribed at hospital discharge; MACE during hospitalization.
Outcome and follow-up	24	Records/Patient/Family information; Date of contact; death; Cause of death; Hospitalization since last contact; MI since last contact; Angina; CA since last contact; CVA since last contact: ICP since last contact; CRM since last contact; Intra-stent restenosis; MACE; Review contact information.

ACTP: percutaneous transluminal coronary angioplasty; CVA: cerebrovascular accident; MRS: myocardial revascularization surgery; DM: diabetes mellitus; ECG: electrocardiogram; AF: atrial fibrillation; SAH: systemic arterial hypertension; MI; acute myocardial infarction; PCI: percutaneous coronary intervention; BMI: body mass index; MACE: major adverse cardiac events; CA: cardiac arrest.

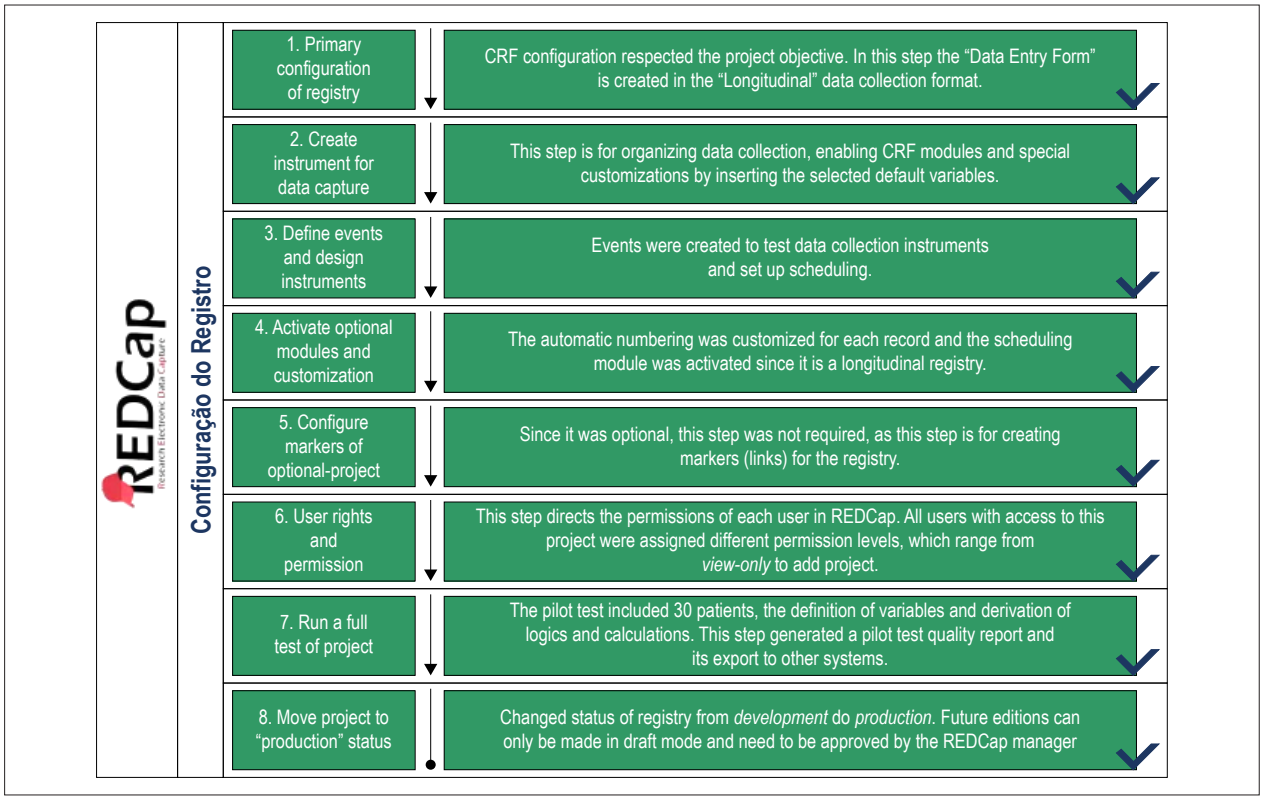

Figure 2 – *Options Diagram for the creation of the Case Report Form. Source: REDCap IC/FUC http://redcap.cardiologia.org.br/redcap/redcap_v6.1.0/ProjectSetup/index.php?pid=23*

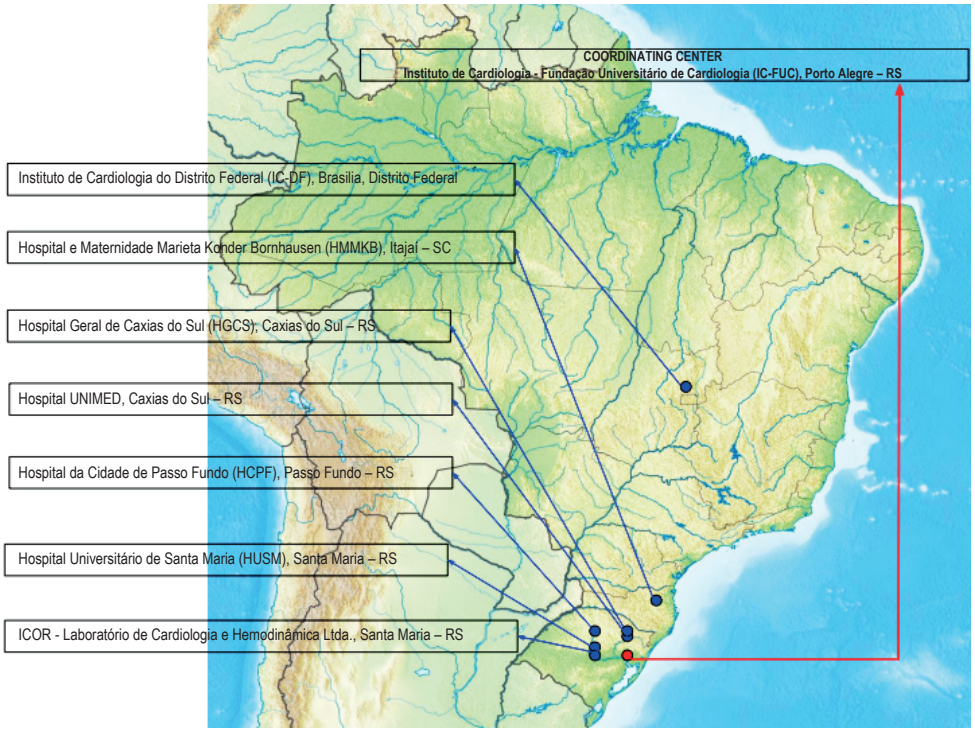

Figure 3 – *National Distribution - Centers of the multicenter Registry of Acute Myocardial Infarction. Via Google Drawings - https://docs.google.com/drawings*

The training focused on the goal of the registry, clarifying the process of collecting and entering data into REDCap. The SOP for data collection ensures standardized and consistent data collection and contains a description of all data elements, including their definitions and procedures to be used while entering data (Figure 4). In addition, online and face-to-face training was provided to researchers to clarify possible questions about the data collection process. Data entry activities were monitored online.

Data quality reports by REDCap software

For the generation of automated quality control reports and to prevent incomplete data, the main variables were included as required data, and the limits were defined as minimum and maximum ranges for numerical variables (*ranges*). Missing data reports (*missing*) were sporadically generated for internal checking of the required variable (*records*). Field validation reports for checking incorrect data were also generated, as well as numeric field reports for checking non-standard, invalid, or unfilled variables. (Figure 5).

Discussion

In this study, we described the process of implementing a STEMI database in a reference hospital and its application to other centers across the national territory through the use of a web-based platform. We also detailed the processes for standardization of variables, implementation of institutional REDCap software, development of case report forms (CRF), expansion of the registry to other reference centers using the REDCap software, and training of staff and participating centers using an SOP (Standard Operating Procedure).

Randomized controlled trials (RCTs) are the gold standard for demonstrating the effectiveness of a given intervention and form the theoretical basis for formulating guidelines. Observational data such as those obtained from clinical records complement scientific evidence of RCTs by demonstrating effectiveness in clinical practice.[24] The assessment of clinical practice in Brazil requires access to national records representing the STEMI patient population to provide the analysis of clinical and therapeutic characteristics in addition to its outcomes. Besides that, it allows to measure compliance to guidelines, develop risk stratification tools and inform public policies to improve the treatment of this pathology in our country.[4,25,26] The evaluation of outcomes requires the standardization of variables using standard terminology, thus allowing comparison with results from other studies such as international registries and RCTs. It also promotes collaboration from information exchange across STEMI patient care centers. During the process of improvement and standardization of variables in our registry, the NCDR STEMI registry coordinated by the ACCF was used as a reference, and the same variable profile was found both in RIAM and NCDR databases.[16,17]

Any registry seeking national representativeness and coverage should include the largest number of consecutive patients and an association of quality and efficiency in data collection. In addition to that, it is important to keep minimal interference in clinical practice.[11] REDCap, developed by Vanderbilt University, has the necessary features to serve as a tool for data collection and storage. Software features include

Figure 4 – *Standard Operating Procedure for entering data in REDCap. Source: REDCap IC/FUC - http://redcap.cardiologia.org.br*

an intuitive interface for editing data collection forms (CRF), easy data entry with double-typing, real-time data validation, data auditability, security in storage and information exchange, and an export function for statistical packages.[21]

The decision to focus this article on the methodology of implementing a database using REDCap aims to serve as a benchmark in the development of quality clinical registries, as well as to make integration of RIAM research centers friendly.

Limitations

One limitation in the implementation and expansion of this observational, registry-based study is the absence of integration between electronic medical records and database, which causes increased workload and, eventually, the need for dedicated research staff during patient care. The evaluation of clinical registry data should also consider the need for informed consent in data collection, which jeopardizes the inclusion of all eligible patients in the event of one single negative participation. It should also consider the possibility of a change of behavior because of the patient's awareness of their participation in a study, even if observational (Hawthorne effect).[27]

Conclusion

In this study, we described the logistics and systematics of developing a clinical registry of STEMI patients in the digital platform REDCap, adapted from an existing clinical registry. This data may be useful for institutions planning to elaborate new registries or improve existing ones. The standardization of registry operation and the use of dedicated databases allow to optimize this tool in terms of quality and speed of implementation. The use of similar systems can also make sharing information across institutions easier as well as assist the development of new health technologies and in the decision making of public policies regarding cardiovascular disease.

Author contributions

Conception and design of the research: Vaz J, Gottschall CAM; Acquisition of data: Abelin AP, Oliveira PP; Analysis and interpretation of the data: Vaz J, Oliveira PP, Gottschall CAM, Quadros A; Statistical analysis: Vaz J, Schmidt MM, Quadros A; Writing of the manuscript: Vaz J, Abelin AP, Gottschall CAM, Rodrigues CG, Quadros A; Critical revision of the manuscript for intellectual content: Schmidt MM, Quadros A.

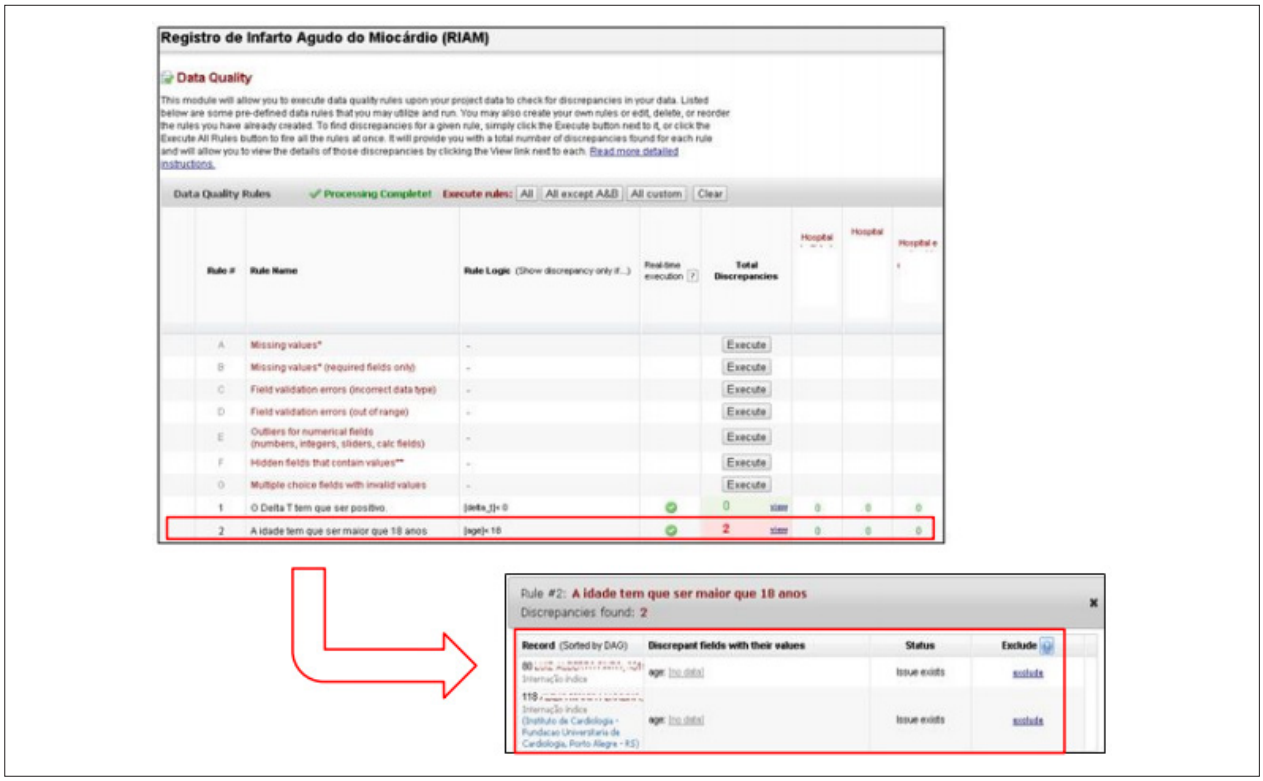

Figure 5 – *Data Quality Report. Source: REDCap IC/FUC - http://redcap.cardiologia.org.br*

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 under the protocol number 5025/14. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Original Article

Short Editorial: "Creation and Implementation of a Prospective Multicenter Registry of Acute Myocardial Infarction: RIAM"

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Cardiovascular diseases, including acute myocardial infarction (AMI), represent a major public health issue in Brazil and worldwide, with elevated incidence and mortality rates.[1] The rates of Brazilian mortality for this group of causes (183.3/100,000)[1,2] are amongst the highest in the world and is similar to that of countries such as China and areas such as the east of Europe.[1,3]

The implementation of health promotion policies, early diagnosis and effective treatment are some of the most important prevention and treatment strategies for these diseases, which remain the leading cause of mortality among adult patients globally. However, the recognition of these diseases, as well as their real and effective measurements, are among the strategies that must be optimized in our field.

Thus, it is necessary to effectively identify and quantify patients with a diagnosis of AMI so that effective and assertive measures can be taken in an attempt to reduce their morbidity and mortality. One of the best-known measurement techniques is the creation of a representative database that can be easily accessed and interpreted. But here we run into yet another problem: how to create and implement it. Much of these questions were elegantly answered by Vaz J. et al.,[4] in their article entitled: "Criação e Implementação de um Banco de Dados Prospectivo e Multicêntrico de Paciente com Infarto Agudo do Miocárdio: RIAM" ("Creation and Implementation of a Prospective Multicenter Registry of Acute Myocardial Infarction: RIAM").[4] The clear and objective description of the steps required to create, implement and expand these databases provides a unique and unmissable literature for all involved in the approach of these pathologies.

The possibility of having access to information generated by well-designed and reliable databases provides a framework closer to Brazilian reality, increasing decision-making efficacy and improving financial management, which is of paramount importance for public health policies.

Keywords

Cardiovascular Diseases/mortality; Epidemiology; Myocardial Infarction/prevention and control; Public Health Policy; Database; Decision Making.

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Anticoagulation Therapy in Patients with Non-valvular Atrial Fibrillation in a Private Setting in Brazil: A Real-World Study

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Abstract

Background: **The safety and effectiveness of warfarin depend on anticoagulation control quality. Observational studies associate poor control with increased morbidity, mortality and healthcare costs.**

Objectives: **To develop a profile of non-valvular atrial fibrillation (NVAF) patients treated with warfarin in a Brazilian private ambulatory and hospital setting, evaluate the quality of anticoagulation control, and its association with clinical and economic outcomes.**

Methods: **This retrospective study, through a private health insurance dataset in Brazil, identified NVAF patients treated with warfarin between 01 MAY 2014 to 30 APRIL 2016, described their anticoagulation management, and quantified disease-related costs. Data on demographics, clinical history, concomitant medication and time in therapeutic range (TTR) of international normalized ratio (INR) values were retrieved. Patients were grouped into TTR quartiles, with good control defined as TTR ≥ 65% (Rosendaal method). Major bleeds and all-cause direct medical costs were calculated and compared between good and poor control subgroups. P-values < 0.05 were considered statistically significant.**

Results: **The analysis included 1220 patients (median follow-up: 1.5 years; IQR: 0.5–2.0). On average, each patient received 0.95 monthly INR measurements (mean INR: 2.60 ± 0.88, with 26.1% of values < 2 and 24.8% > 3), (median TTR: 58%; IQR: 47–68%), (mean TTR: 56.6% ± 18.9%). Only 31% of patients were well-controlled (mean TTR: 78% ± 10%), with 1.6% having major bleeds within median follow-up, and direct medical costs per member per year (PMPY) of R$25,352(± R$ 37,762). Poorly controlled patients (69%) were associated with 3.3 times more major bleeds (5.3% vs. 1.6%; p < 0.01) and 40% higher costs (R$35,384 vs. R$25,352; p < 0.01).**

Conclusions: **More than 60% of the patients were below the desired target and the associated costs were higher. (Arq Bras Cardiol. 2020; 114(3):457-466)**

Keywords: **Warfarine/therapeutic use; Anticoagulants/adverse effects; Atrial Fibrillation/comlications; Hospitals, Private/economics; Health Care Quality, Access and Evaluation.**

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia that affects more than 33 million people worldwide. Most cases are non-valvular AF (NVAF) patients.[1-3] Epidemiology data for AF in Latin America is limited and a significant proportion of patients has poor control of key risk factors and does not receive appropriate anticoagulation treatment (18.3% – 24.6%).[4,5]

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Clinical guidelines recommend the use of an oral anticoagulant (OAC) in NVAF to reduce the risk of stroke.[2,3] For decades, vitamin K antagonists (VKAs), the most commonly used of which is warfarin, have been the cornerstone of OAC therapy for NVAF. However, the safety and efficacy of warfarin have limitations and depend on the tight quality of anticoagulation control.[2] This is achieved using a standardized measure of clotting time known as the international normalized ratio (INR), which is desired to be between 2 and 3.[6] Frequent INR monitoring and dose adjustment are needed to maintain target INR levels.[2,3] However, monitoring can increase the medical and economic burden.[7]

Time in therapeutic range (TTR) is the standard means of assessing the long-term quality of anticoagulation control and the risk–benefit profile of warfarin.[6] TTR represents the proportion of time that a patient's INR values are between 2 and 3, having the maximum benefit when the TTR is 60% to 70% or higher.[2] In Latin America, the median TTR was at the lower

end of the recommended levels of anticoagulation (near 60%).[4,8] In Brazil, some observational studies in the public setting showed that most patients had good anticoagulation control, though TTR levels were in the lower end of the threshold.[9-11] Managing OAC use, including INR monitoring, are costly and inaccessible for many patients in Latin America.[4] To date, few studies have been conducted in private settings in the region. Associations of TTR levels with clinical or economic outcomes were generally not reported. The objective of this study was to develop a profile of patients receiving warfarin for NVAF in a private setting in Brazil, and to evaluate the quality of anticoagulation control and clinical/economic outcomes.

Methods

Data Sources

Data from May 1, 2014 to April 30, 2016 were pulled from a large private health insurance dataset in Brazil – AMIL. AMIL is one of the largest health insurance companies in Brazil, with over 4 million beneficiaries and clinical care programs with integrated and structured information of prevalent diseases. The AMIL dataset combines electronic medical records containing information on patient demographics, enrolment and clinical history, with medical claims from outpatient and inpatient hospital admissions, ambulatory care facilities and emergency departments.

For warfarin-treated patients, AMIL runs a private anticoagulation phone monitoring program named VIVA AMIL.[12] Within this program, trained nurses and nursing technicians make monthly phone calls to patients to collect patient data, self-reported results of the last INR test, occurrence of thromboembolic and bleeding events, medication regularity and adverse effects.

An existing template, created to capture data from the monitored patients, was used to ensure the test results, experienced events and patterns were reported consistently to meet the program needs. An initial call was made to collect clinical and demographic data (if otherwise not available), including the presence of chronic conditions and medications under use. Each patient then received monthly outbound calls, but patients also had the option to call as needed.

In case the patient did not have a current or recent INR test result, a nurse would support them by requesting the test and reminding them to call back and report the results. In the situation in which the INR results reported by the patient were out of the target range (INR 2-3), the nurse would discuss dose adjustments with the patient and advise them to seek medical advice in person.

Patient Selection

Patients aged 18 or older were included if they had an AF diagnosis (ICD-10-CM code I48) or were assessed for AF in a specific system form in the electronic medical record, if they received at least one prescription for VKA during the study period, had continuous health plan coverage and if they were followed by the phone-monitoring program for at least 4 months with a record of the calls in at least 50% of the months during the study period. Patients with evidence of moderate/severe mitral stenosis, VTE or a mechanical prosthetic valve were excluded. The research protocol was approved by the local Institutional Review Board.

Variables and Outcome Measures

Key characteristics of patients receiving warfarin were analyzed from claims, electronic medical records and self-reports: demographics and clinical history (CHA_2DS_2-VASc score, comorbidities, prior stroke or bleeds, INR and TTR). Specifically, patients were classified as having chronic renal failure when there was at least one of the selected ICD-10 codes (Appendix A) linked to them in the dataset during the entire study period, or if chronic renal failure was present in the data collection form managed by the nurse. Concomitant medication utilization and INR frequency patterns were also assessed.

Consistent with guidelines and prior studies,[2,6] the quality of INR control was based on the percentage of time during which a patient receiving warfarin was within therapeutic range (2.0-3.0) over the entire follow-up period. Good control was defined as TTR ≥ 65%. The number of INR tests for each patient was obtained through the claims dataset, which did not record the INR values. During the phone monitoring calls, the trained nurse would ask the patient to report the values of the INR tests undertaken since the last call. The INR test frequency was used to calculate the total and mean INR tests per patient. Since the INR is a low-complexity and low-cost procedure, the test could have been paid out-of-pocket by the patient and therefore not reported in claims. In order to reduce the impact of unstated INR tests, during the phone monitoring calls the nurse would ask the patient to also report the date of the INR test, along with the INR values. For those cases in which a corresponding claim was absent, the nurse would manually add the test frequency information in the electronic medical record. TTR was calculated using the Rosendaal method, computed using the INR values that were recorded in the electronic medical records.[13]

The clinical outcomes assessed were major and minor bleeding events, identified using the ICD-10 codes of inpatient claims listed in Appendix A.[14] Self-reported situations were also considered. The diagnosis codes used for major bleeds were based on a validated administrative claim-based algorithm, as well as the International Society on Thrombosis and Hemostasis definition of major bleeding.[15,16] Bleeding rates were calculated as the number of patients with at least one self-reported bleeding episode during the monitoring period, divided by the total number of patients. To assess the outcomes, patients were followed until April 30, 2016, unless health plan disenrollment or death occurred first.

All-cause direct medical costs were assessed from the claims of each patient for office elective visits, emergency department visits, outpatient tests/procedures, inpatient admissions, and home health/care transition admissions. The costs represented the actual costs borne by the insurance provider (AMIL). Out-of-pocket costs were not included. The costs were available in the data source over the study period and were annualized by dividing them by the months of the study period and multiplying them by 12. After this calculation, costs were expressed

per member per year (PMPY), in Brazilian Reals (R$) and converted to US dollars. A conversion factor of 0.33 USD/BRL was obtained by averaging the daily exchange rates within each year of the study period (May 1, 2014 to April 30, 2016). The daily exchange rates were obtained from historical records of a public currency exchange calculator.[17]

Out-of-pocket costs were not included. Finally, key characteristics, clinical and economic outcomes were observed and compared amongst TTR quartiles.

Statistical methods

Due to the exploratory nature of the study, key characteristics and outcomes were descriptively analyzed.

Descriptive statistics were reported as counts, percentages, means, medians, standard deviations and quartiles. Continuous variables were described as mean and standard deviation or median and respective interquartile range, depending on whether or not a normal distribution was found. Categorical variables were described as frequencies and percentages. Comparisons were made between continuous variables using an independent unpaired two-sample *t*-test and between categorical variables using the chi-square test. P-values < 0.05 in two-tailed tests were considered statistically significant. All analyses were carried out using SAS 9.4.

Subgroup analysis

The key characteristics, clinical and economic outcomes were analyzed for the overall population and for patients with poor (TTR $< 65\%$) and good (TTR $\geq 65\%$) control.

Sensitivity analysis

To check for main analysis consistency, some patient characteristics, INR, TTR levels and PMPY costs were observed for a group of patients followed for at least 6 months with records of the calls in at least 50% of the months during the study period.

Results

Patient characteristics

A total of 1,220 patients with NVAF were included for the main analysis (Figure 1). Overall, median follow-up was 1.5 years (interquartile range [IQR]: 0.5–2.0 years). Key patient characteristics are listed in Table 1. The mean age was 63.9 ± 14.7 years and 50.7% were females. The mean CHA_2DS_2-VASc score was 2.45 ± 0.88. Most patients (85.7%) were from the Southeast region of Brazil. Approximately 10% of patients were on concomitant statin therapy and a minority of patients (~4%) were receiving concomitant antiplatelet therapy with aspirin and/or Clopidogrel. Hypertension was the most prevalent comorbidity (38.5%), followed by heart failure (19.8%), prior stroke (13.7%) and diabetes (13.6%).

Anticoagulation control

Each patient had a mean of 15.63 (±9.13) INR tests over a median of 18 months of follow-up, equivalent to approximately 0.95 tests per month. The mean INR value was 2.60 ± 0.88, the median INR value was 2.44 (IQR: 1.99 – 3.00). Among all measured INR values, 49.1% were within the therapeutic range (2.0–3.0), whereas 26.1% of all INR values were < 2.0, and 24.8% were > 3.0 (Figure 2A). The median and mean patient-level TTRs were 58% (IQR 47%–68%) and 56.6% (±18.9%), respectively. The TTR distribution is reported in Figure 2B. Only 377 patients (31%) exhibited good control (TTR $\geq 65\%$) and 843 patients (69%) had poor control (TTR $< 65\%$).

Clinical outcomes

Among all patients, the major and minor bleeding rates of patients in the program were 4.2% and 10.3%, respectively (Figure 3). The major bleeding rate among well-controlled patients (TTR ≥ 65) was 1.6%, whereas it was 5.3% for poorly controlled patients (TTR $< 65\%$). Therefore, the major bleeding rate was 3.3 times higher in poorly-controlled patients when compared with well-controlled patients ($p < 0.01$). While the trend was not as strong with minor bleedings, fewer minor bleeds were observed in subgroups with highest TTR.

An exploratory analysis was conducted to observe the closest INR value prior to the event on a sample of patients admitted for a stroke. Out of 15 patients, 12 (80%) experienced a hemorrhagic or unspecified stroke event, despite having an INR within the therapeutic range 2-3 (Supplementary information).

Economic outcomes

The PMPY cost across the entire cohort was R$32,284 (USD$10,679). Inpatient costs represented ~64% of all costs (R$20,710 or USD$6,851); outpatient costs represented ~36% (R$11,573 or USD$3,828). The mean INR monitoring cost PMPY was R$362 (USD$120), ranging from R$296 (USD$98) to R$417 (USD$138) and representing < 1% of the total direct costs (Table 2).

The PMPY cost was R$25,352 (± R$37,762) or USD$8,386 (± USD$12,492) per well-controlled patient (TTR $\geq 65\%$) and R$35,384 (± R$50,900) or USD$11,705 (± USD$16,838) per poorly-controlled patient (TTR $< 65\%$). Thus, patients with suboptimal warfarin control were associated with 40% higher costs, on average ($p < 0.01$).

PMPY costs with and without major bleeds were R$62,145 (USD$20,558) and R$30,981 (USD$10,249), respectively. In all cases, inpatient costs were greater than outpatient costs (Table 2).

Metrics per TTR quartile

Some key characteristics and outcomes were observed across TTR quartiles to see which, if any, were more prevalent in patients with lower TTR compared with the overall population and patients with higher TTR. As shown in Table 1, patients with lower TTR were more often females, had more comorbidities (diabetes, renal disease, heart failure), fewer INR tests and a lower overall monitoring period.

Sensitivity analyses

A total of 934 patients were included in the sensitivity analyses. An identical mean INR value of 2.60 ± 0.96 and a similar median INR (2.43; IQR: 2.00-3.00) were observed

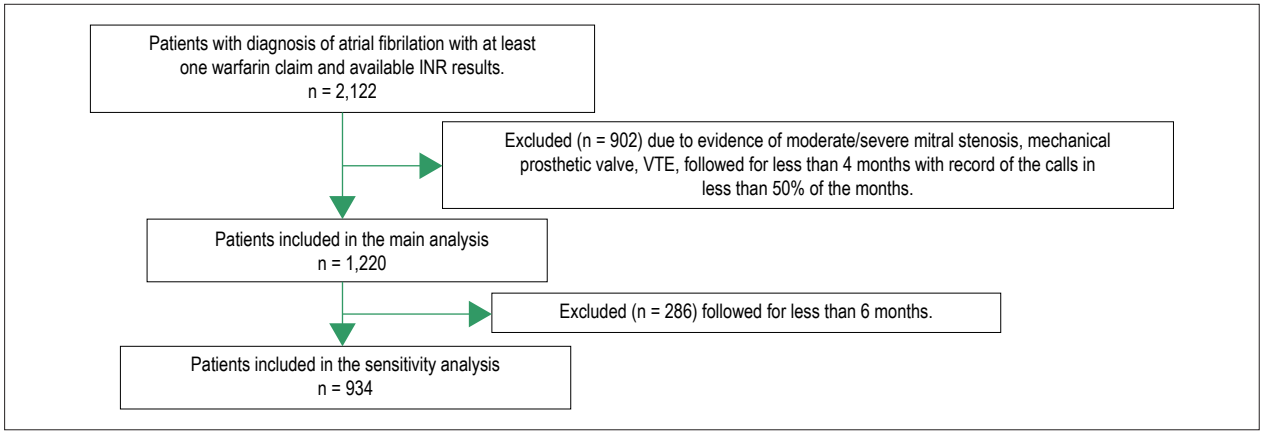

Figure 1 – *Flow chart describing inclusion and exclusion criteria.*

in this patient group. The median and mean patient-level TTRs were almost the same, 57% (IQR 45%–68%) and 58% ± 16.2%, respectively. In this group of patients, PMPY costs, including inpatient and outpatient, were also quite similar, R$31,229 (USD$10,331), versus R$32,284 (USD$10,680) for the main analysis.

Discussion

Overall, it was observed that the quality of anticoagulation management was suboptimal: only half of all INR values drawn were in the therapeutic range (INR: 2-3) and patients spent a bit more than half of the time within the therapeutic range. TTR varied across the population and up to two thirds of patients were not adequately controlled (TTR < 65%). These patients were associated with more unfavorable clinical and economic outcomes i.e. more major bleeds and higher costs.

Epidemiological data suggest that there were over 700,000 strokes in Brazil in 2010, accounting for over 141,000 deaths.[18] While there are several underlying causes of stroke, it is estimated that approximately 20% of ischemic strokes are attributable to atrial fibrillation,[19] and strokes associated with atrial fibrillation tend to be larger and associated with worse outcomes.[20]

Anticoagulation therapy has the potential to greatly reduce the risk of stroke in patients with atrial fibrillation. Warfarin has been shown to reduce the risk of ischemic stroke by 64% and mortality by 26% but the usefulness of warfarin is variable due to the narrow therapeutic range, with the risk of ischemic events increasing when the INR is below 2, and the risk of hemorrhagic events increasing above 3.5.[21]

Costs associated with strokes are significant and sustained. It was estimated that the 2008 cost of ischemic strokes in Brazil was $329 million USD, the per-patient cost of hospitalization was $1902 USD, and the mean length of stay was over 13 days.[20] Hemorrhagic events also represent a substantial cost as part of the overall management of stroke risk for atrial fibrillation patients receiving oral anticoagulation treatment.[22] A US study has shown that non-adherence and underuse of warfarin by insured patients with AF has a negative impact on health and costs. It has also been demonstrated that the degree of anticoagulation control is directly correlated to improved outcomes for patients with atrial fibrillation receiving warfarin treatment.[23-25]

Few studies have assessed the extent of anticoagulation control with warfarin in Latin American countries. Past research reported close to acceptable levels of anticoagulation control in Brazil, with TTR levels close to 60% in controlled settings[26-28] and between 60 and 65% in the real world.[9-11] However, these studies were conducted mostly in one or two public hospitals or anticoagulation clinics, in populations with limited sample size and broad use of warfarin.

The TTR is the accepted measure of anticoagulation control for warfarin patients and is correlated with clinical outcomes. While often reported by center or even country in clinical trials, there is substantial heterogeneity in individual patient TTR.[29,30] The results from this current study are consistent with this concept in that even though the overall patient population had a fair TTR, in fact most of the patients had a TTR which was below the threshold considered optimal.[23]

The present study furthers the understanding of the anticoagulation care model in routine clinical practice. It is representative of a relatively young AF population presenting with a lower prevalence of comorbidities than what has been reported in other observational studies and controlled settings.[26-28,31] In addition, the study is representative of real-world data in a specific private setting of AMIL, including a structured program and phone calls, and it is not generalizable to other settings like the public sector. The approach to managing and regularly monitoring the patients through the care program was found to be quite unique. Studies that addressed a similar research question[9-11] did not report the existence of such a dedicated program for warfarin patients. INR monitoring was performed approximately once a month, more frequently than in other observational studies[32] but less than in controlled settings.[26] Despite the regular follow-up, only about half (49.1%) of all INR values drawn were in the therapeutic range and a limited portion of the population had good TTR control. The TTR results were consistent with past research within the care practice, indicating that warfarin patients spend only a

Table 1 – Patient characteristics and metrics per TTR quartile

Values	Period (months)					
	4 – 24					6 – 24 (Sensitivity analysis)
	Q1 N = 303	Q2 N = 306	Q3 N = 305	Q4 N = 306	Total N = 1220	N = 934
Demographics						
Age (mean/±SD)	62.02 (±15.92)	64.58 (±13.83)	64.49 (±14.48)	64.30 (±14.63)	63.85 (±14.75)	64.75 (±14.03)
Female (%)	50.8	55.2	52.5	44.1	50.7	51.5
Anticoagulation						
INR (mean/±SD)	2.56 (± 1.25)	2.67 (± 1.10)	2.61 (± 0,89)	2.54 (± 0,62)	2.60 (±0.88)	2.60 (±0.96)
INR (median/IQR)	2.22 (1.70-3.16)	2.50 (1.97-3.20)	2.48 (2.06-2.98)	2.44 (2.13-2,78)	2.44 (1.99-3.00)	2.43 (2.00-3.00)
TTR (mean/±SD)	32.6% (±11.5%)	51.2% (±3.3%)	62.0% (±3.2%)	80.2% (±9.8%)	56.6% (±18.9%)	58.0% (±16.2%)
TTR (median/IQR)	36% (28-42%)	52% (48-54%)	62% (59-65%)	78% (72-86%)	58% (47-68%)	57.0% (45-68%)
INR tests per patient (mean/±SD)	12.79 (±8.09)	17.49 (±9.65)	18.00 (±9.27)	14.20 (±8.40)	15.63 (±9.13)	18.44 (±8.60)
Risk factors and baseline conditions						
CHA_2DS_2-VASc (mean/±SD)	2.38 (±1.72)	2.46 (±1.69)	2.55 (±1.69)	2.44 (±1.74)	2.45 (±1.71)	2.58 (±1.72)
Stroke (%)	13.9	12.1	11.5	17.3	13.7	14.6
Hypertension (%)	33.3	39.2	43.6	37.9	38.5	41.3
Diabetes (%)	13.2	14.4	15.4	11.4	13.6	14.5
Chronic kidney failure (%)	4.6	2.0	4.3	2.6	3.4	3.0
Congestive heart failure (%)	20.5	18.3	21.3	19.0	19.8	21.1
Region						
Southeast	86.8	85.9	85.6	84.3	85.7	85.9
Central	6.9	8.2	8.5	9.8	8.4	8.6
South and Northeast	6.3	6.0	5.9	5.9	6.0	5.5
Concomitant medications						
Phenprocoumon	11	6	5	11	33	26
Aspirin	10	6	15	0	31	25
Clopidogrel	7	5	2	2	16	9
Aspirin + clopidogrel	3	0	1	0	4	2
Statins	27	29	33	29	118	99
Nitrate	2	3	5	6	16	14
Amiodarone	1	3	3	3	10	7
Follow-up						
Months of monitoring (mean/±SD)	13.87 (± 7.37)	16.04 (± 7.29)	18.02 (± 7.02)	17.24 (± 7.11)	16.30 (± 7.36)	18.13 (± 6.45)
Months of monitoring (median/IQR)	14.00 (7.0-20.0)	17.00 (9.0-23.0)	21.00 (12.0-24.0)	19.00 (11.0-23.0)	18.00 (10.0-23.0)	20.00 (13.0-23.0)

CHA_2DS_2-VASc: congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category; IQR: interquartile range; SD: standard deviation; TTR: time in therapeutic range.

bit more than half of the time within the therapeutic range.[32] The reported TTR levels for the overall population treated with warfarin in this study were slightly below the lower limit of the recommended threshold interval.[9,11,25] An interesting finding is that the TTR distribution in Figure 2B was skewed to the right, meaning that there was a niche of patients with very high TTR control. Around 22% of patients had TTR > 70%.

International data that assessed the association between warfarin control and outcomes indicate that poor warfarin control patients experience more unfavorable clinical and economic outcomes than well controlled patients.[21,33] The results of the present study are quite aligned with prior work and further contribute to the understanding of how warfarin control could impact on both clinical events

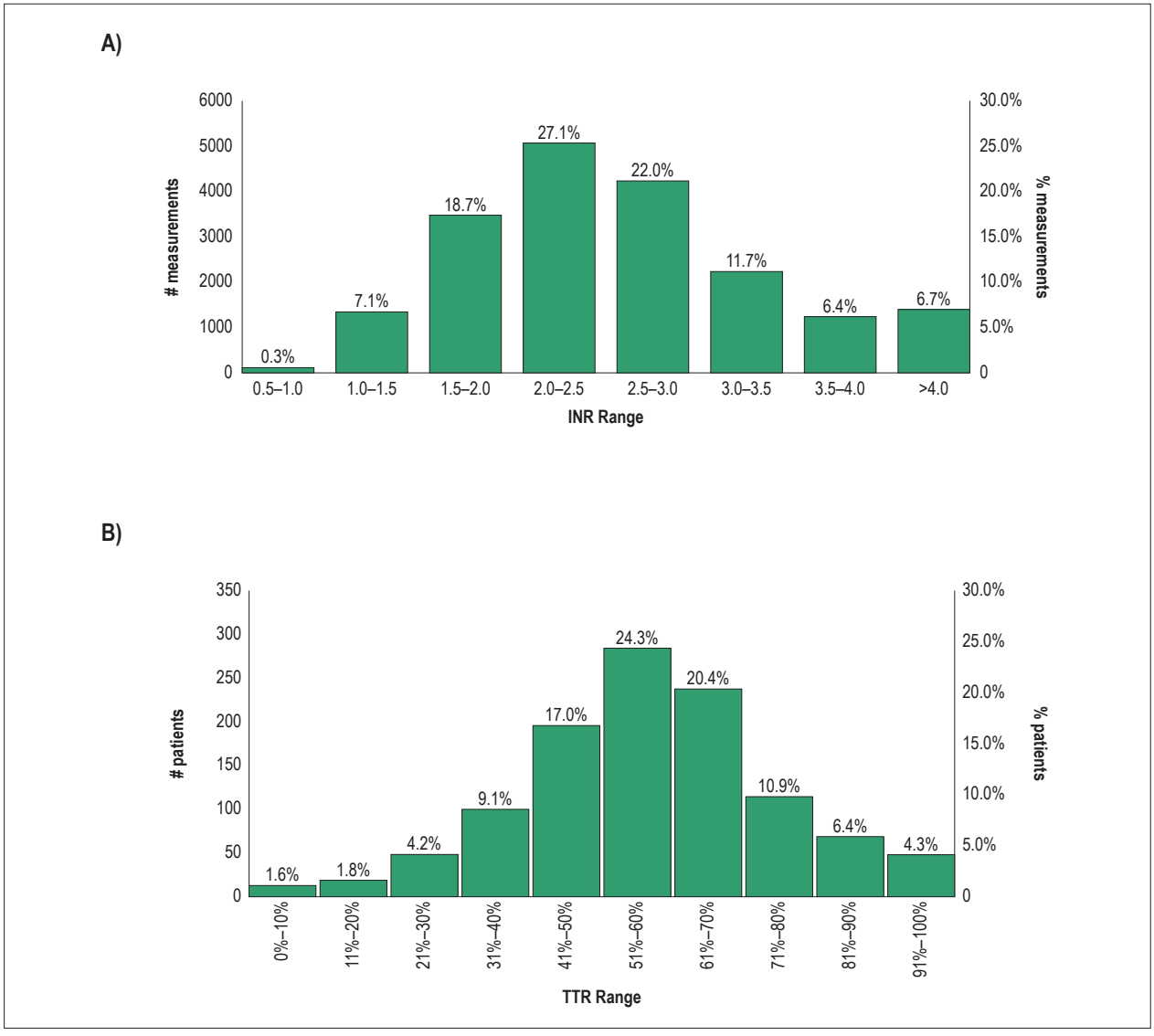

Figure 2 – *INR and TTR results. A. Measurement distribution per INR range. B. Patient distribution per TTR range.*

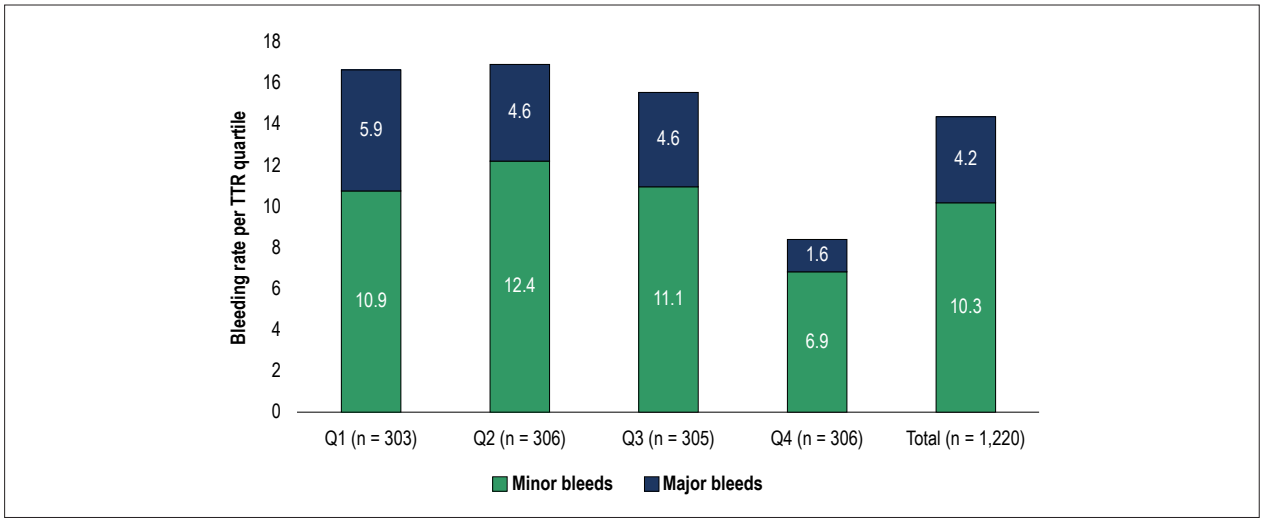

Figure 3 – *Bleeding rate per TTR quartile.*

Table 2 – PMPY costs with and without major bleeds (R$)

Values. *Costs are expressed as (mean/±SD)*	Q1	Q2	Q3	Q4	Total
All patients					
Number of patients	303	306	305	306	1220
Cost per patient (total)	39,171 (± 59,728)	33,996 (± 48,637)	31,797 (± 42,030)	24,236 (± 35,158)	32,284 (± 47,480)
Cost per outpatient	14,417 (± 31,295)	11,425 (± 18,544)	11,760 (± 17,866)	8,719 (± 12,084)	11,573 (± 21,218)
Cost per inpatient	24,754 (± 45,652)	22,570 (± 43,267)	20,037 (± 40,199)	15,517 (± 35,849)	20,710 (± 41,725)
INR cost per patient	296 (± 187)	405 (± 223)	417 (± 214)	329 (± 194)	362 (± 211)
Without major bleedings					
Number of patients	285	292	291	301	1169
Cost per patient (total)	36,704 (± 58,663)	33,217 (± 49,138)	30,244 (± 40,852)	24,106 (± 35,376)	30,981 (± 46,858)
Cost per outpatient	13,957 (± 31,658)	11,381 (± 18,955)	11,771 (± 18,261)	8,672 (± 12,181)	11,409 (± 21,419)
Cost per inpatient	22,747 (± 44,912)	21,835 (± 44,213)	18,473 (± 38,417)	15,434 (± 36,298)	19,572 (± 41,328)
INR cost per patient	291 (± 182)	400 (± 220)	416 (± 216)	329 (± 195)	359 (± 210)
With major bleedings					
Number of patients	18	14	14	5	51
Cost per patient (total)	78,236 (± 64,550)	50,248 (± 33,950)	64,092 (± 53,895)	32,072 (± 17,703)	62,145 (± 52,163)
Cost per outpatient	21,698 (± 25,175)	12,343 (± 6,755)	11,540 (± 6,290)	11,565 (± 3,997)	15,348 (± 16,170)
Cost per inpatient	56,538 (± 49,698)	37,905 (± 30,108)	52,552 (± 50,731)	20,507 (± 15,797)	46,796 (± 44,386)
INR cost per patient	382 (± 247)	523 (± 259)	432 (± 190)	357 (± 164)	432 (± 231)

Conversion factor: 0.33 USD/BRL.

and costs in the Brazilian routine practice. High quality of anticoagulation control was associated with a lower incidence of major and minor bleeds and substantial direct medical cost savings from both reduced inpatient and outpatient costs. Poorly-controlled patients had 3.3 times more major bleeds and 40% higher PMPY costs than well-controlled patients.

Despite anticoagulation treatment, strokes will still occur, as observed in this study, both ischemic and hemorrhagic ones. Of note, out of 10 confirmed hemorrhagic strokes that were identified in this study, the preceding INR value for 7 of the 10 was within the therapeutic range of 2 to 3, with the other 3 being 3.66, 3.87, and 5.13. This is consistent with the findings from a sub-analysis of the ARISTOTLE trial which showed that for about 80% of the intracranial hemorrhages that occurred in warfarin-treated patients, the preceding INR was between 2 and 3.[34]

Past research explored predictors of poor TTR[6,26,32] suggesting that patients with lower TTR were more often females, had less schooling and more comorbidities, specifically diabetes, chronic kidney disease, heart failure and prior stroke. Quite consistently, female patients and patients with more comorbidities such as chronic kidney disease and ischemic heart disease tended to have lower TTR values in this study, too. Moreover, patients with lower TTR had fewer INR tests and a shorter overall monitoring period. The results suggest that there is a need to identify patients with labile INRs and further assess opportunities to improve their TTR, such as education or closer follow-up. Failing that, other forms of anticoagulation such as the more recently approved non-vitamin K anticoagulant class should be considered. This class does not require routine monitoring, has fewer drug-drug and drug-food interactions than warfarin, and has been shown to be at least as safe and efficacious as well-controlled warfarin, and to have a lower rate of intracranial haemorrhage.[35]

Limitations

Our study has several strengths and limitations. The patient cohort of the study was one of the largest thus far among real-world studies in Brazil. The combined use of claims and the care program added significant value to the study, especially by allowing the analysis of INR values, commonly not available in claims. However, given its retrospective observational nature, only associations could be concluded. This study observed TTR variations over time and as such was vulnerable to the effects of repeated measurements as an intervention. No advanced statistical techniques were used to balance characteristics of the TTR patient subgroups and therefore no inferential conclusions about cofactors could be drawn. We could not calculate the mean HAS-BLED risk score, as not all the data points of the score components were captured in the dataset (i.e. alcohol use). The incidence of other outcomes such as stroke, mortality, discontinuation and adherence was not analyzed. Sensitivity analyses at other specific TTR thresholds (e.g. 60% or 70%) were not conducted. The stability of INR over time was not assessed. Only direct medical costs were available; these referred to

all-cause costs incurred by each patient, disregarding the reason for the utilization, consequently, they could have been overestimated. Healthcare resource utilization and patient subgroups were not evaluated.

According to Brazilian standards for procedure codes (Appendix A), INR has no individual code, but it is included within the "Coagulation test" code. As it was not possible to segregate, the INR measurement was considered as the entire coagulation test, and not as a percentage of it, for all patients.

It was found that a significant portion of patients taking warfarin (11%) had CHA_2DS_2-VAS_C scores of zero, which is greater than the proportion reported in other studies (6.1%).[36] CHA_2DS_2-VAS_C assessment is subject to the clinical documentation of patients' clinical history, and details of pre-existing conditions might have been underreported.

The phone monitoring program was offered to patients of a specific health insurance company and when a patient's contract terminated, follow-up was not possible.

Finally, some of the study limitations were inherent to a retrospective observational study design. These include potential coding errors and missing data which may have introduced biases into the study and affected the number of excluded patients, and the fact that the data assessed was not originally collected for clinical research purposes.

Conclusions

This study examined patient profiles, quality of anticoagulation and clinical/economic outcomes among NVAF warfarin patients in a private health insurance company in Brazil. It is representative of a large and relatively young cohort of warfarin patients. The overall quality of anticoagulation management was suboptimal. Warfarin patients were within the therapeutic range slightly more than half of the time. Up to two thirds had poor control (TTR < 65%) and were associated with more bleeding events and costs. This analysis highlights the importance, in terms of outcomes and costs, of tight anticoagulation control for NVAF patients treated with warfarin, and the difficulty in maintaining an adequate TTR even with a well-designed and run program. Additional research is needed, as more real-world data becomes available, to further assess the use of warfarin as well as the adoption of NOACs *versus* warfarin.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Silva PGMB, Sznejder H, Vasconcellos R, Charles GM, Mendonca-Filho HTF, Mardekian J, Nascimento R, Dukacz S, Di Fusco M; Acquisition of data: Sznejder H; Statistical analysis: Mardekian J, Di Fusco M; Obtaining financing: Silva PGMB, Sznejder H, Vasconcellos R, Charles GM, Mendonca-Filho HTF, Di Fusco M; Writing of the manuscript: Silva PGMB, Sznejder H, Vasconcellos R, Charles GM, Dukacz S; Critical revision of the manuscript for intellectual content: Silva PGMB, Sznejder H, Vasconcellos R, Charles GM, Mendonca-Filho HTF, Mardekian J, Nascimento R, Dukacz S, Di Fusco M.

Potential Conflict of Interest

Silva PGMB reports to have received fees and research grants from Pfizer; Mardekian J, Nascimento R and Di Fusco M report being Pfizer employees.

Sources of Funding

This study was funded by Pfizer.

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 Pró-Cardíaco under the protocol number 1.835.148. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Are DOACs a Good Bang for Your Buck in Atrial Fibrillation Prevention in Real-Life?

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Short Editorial related to the article: Anticoagulation Therapy in Patients with Non-valvular Atrial Fibrillation in a Private Setting in Brazil: A Real-World Study

Mr. D., a 75-year-old retired university professor with a prior stroke, wakes up in the morning, drives to the hospital to have blood drawn to adjust his warfarin dosage and then goes to work. A couple of hours later, he gets a call from the nursing team telling him how to adjust the dose: "starting today you should take 7.5 mg of warfarin on Mondays, Wednesdays and Fridays. On the other days of the week you can keep up with the 5 mg pill you are used to. If you do not have a 7.5 mg pill you can cut the 5 mg in half and take one and a half pills on those days. It is not too complicated, is it? By the way, remember to go slow on that kale and spinach I know you like!". Were it not for the fact the Mr. D. also takes enalapril and atenolol for his blood pressure and to control the heart rate of his atrial fibrillation (AF), a statin for secondary prevention since the stroke, and metformin for his diabetes; cutting pills in half and remembering on what day he should take which dosage should be too complicated.

Unfortunately, Mr. D. is about the average non-valvular AF patient seen in clinics in private practices in Brazil and places around the world, though patients from the Brazilian Unified Health System (*Sistema Unico de Saúde*, SUS) usually spend substantially more time at the hospital waiting for the results in person or coming back the next day to check them, due to more limited resources to contact patients over the phone.

Since most patients using warfarin face such complexities, it should come as no surprise that its real life adequate use is far from ideal.[1] Patients on average spend at least a third of their time above or below target international normalized ratio (INR) values.[2] Interestingly, only about one in every four patients has a stable therapeutic INR during 6 consecutive months. And even among those, only a third remains with a stable therapeutic INR over the following year, according to data from the United States (U.S.).[1] Unfortunately, in Brazil, Latin America and other countries with lower socioeconomic status, the time within the therapeutic range (TTR) for INR is shorter than those reported for the U.S. or Europe even in randomized trials.[3] In such countries, other real-life challenges to attain adequate anticoagulation has led to its underuse, including limited access to INR measurements in rural areas, and other constraints in resources.[4] Moreover, recent data suggests that approximately one quarter of the entire cost related to warfarin use is related to the travel time and costs associated with INR measurements in Finland, and such costs are usually not covered by any health insurance company.[5]

Within the context of such constraints in warfarin use, the development of direct oral anticoagulants (DOAC), where no monitoring is needed, and a fixed dose can be used is highly expected by the medical community. Not only did these drugs have shown to be more effective and safer than warfarin in a randomized trial of non-valvular AF patients,[6] but comparable results were seen in a large U.S. registry.[7] Moreover, DOACs are likely to be cost effective in the United Kingdom.[8] However, the real-life practice patterns, as well as cost implications, are highly variable and might not be easily reproduced in other countries. For example, DOACs are not currently covered by the SUS in Brazil. Thus, data on outcomes and cost-effectiveness studies focusing on the reproduction of such studies in other scenarios, such as in Brazil, are needed.

The manuscript by Barros e Silva, et al.,[9] published in the current issue, provides Brazilian data from patients with non-valvular AF receiving oral anticoagulation and covered by a private insurance provider.[9] Their results suggest that, at least for those covered by a large private healthcare insurance plan, the patterns and implications of warfarin vs. DOAC use in Brazil resembles the patterns in other countries. First, only about half of the INR were within the therapeutic range, and on average patients spent almost half of their time outside the target, as reported previously. More importantly, spending less than 65% of the time within the therapeutic range was associated with a three-fold increase in the risk of major bleeding, from 1.6% to 5.3%. Finally, the direct costs associated with such devastating events was substantial, more than R$25,000 per member per year. Although no formal cost-effectiveness analysis was performed in the present study, the findings seem to be in line with the recent UK study, and DOAC are likely to be more cost effective if adverse bleeding events are lower, as such events are costly. Additionally, with the burden associated with INR monitoring, the use of DOACs is even more likely to be cost-efficient from a societal perspective. Collectively, the present study supports the overall idea that DOAC should be the preferred choice with private insurance coverage in Brazil. However, due to the significant differences in cost and practice patterns between private and public healthcare systems in Brazil, more robust SUS data is needed prior to the translation of current findings into routine practice in the public health care system, even if the expectations are that patients like Mr. D. would be better off without their the need to come for their monthly INR assessment.

Keywords

Stroke/prevention and control; Atrial Fibrillation; Anticoagulants/administration and dosage; Varfarin/economy; Cost-Benefit Analysis.

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Original Article

Discordance of Low-Density Lipoprotein Cholestrol and Non-High-Density Lipoprotein Cholestrol and Coronary Artery Disease Severity

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Abstract

Background: **A sizeable proportion of patients have discordant low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C).**

Objectives: **We assessed the relationship between discordance of LDL-C and non-HDL-C and coronary artery disease (CAD) severity.**

Methods: **We retrospectively evaluated the data of 574 consecutive patients who underwent coronary angiography. Fasting serum lipid profiles were recorded, SYNTAX and Gensini scores were calculated to establish CAD complexity and severity. We determined the medians for LDL-C and non-HDL-C to examine the discordance between LDL-C and non-HDL-C. Discordance was defined as LDL-C greater than or equal to the median and non-HDL-C less than median; or LDL-C less than median and non-HDL-C greater than or equal to median. A p value < 0.05 was accepted as statistically significant.**

Results: **LDL-C levels were strongly and positively correlated with non-HDL-C levels ($r = 0.865$, $p < 0.001$) but 15% of patients had discordance between LDL-C and non-HDL-C. The percentage of patients with a Gensini score of zero or SYNTAX score of zero did not differ between discordant or concordant groups ($p = 0.837$, $p = 0.821$, respectively). Mean Gensini and SYNTAX scores, percentage of patients with Gensini score ≥20 and SYNTAX score >22 were not different from group to group ($p = 0.635$, $p = 0.733$, $p = 0.799$, $p = 0.891$, respectively). Also, there was no statistically significant correlation between LDL-C and Gensini or SYNTAX scores in any of the discordant or concordant groups. Additionally, no correlation was found between non-HDL-C and Gensini or SYNTAX score.**

Conclusions: **While there was discordance between LDL-C and non-HDL-C (15% of patients), there is no difference regarding CAD severity and complexity between discordant and concordant groups. (Arq Bras Cardiol. 2020; 114(3):469-475)**

Keywords: **Coronary Artery Disease/physiopathology; Atherosclerosis; Lipoproteins, LDL; Lipoproteins, HDL; Discordance.**

Introduction

Low-density lipoprotein-cholestrol (LDL-C) is a risk factor for both new-onset coronary heart disease and recurrent coronary events.[1] The main target of lipid-lowering therapy is to prevent atherosclerotic events.[1,2] However, despite the achivement of low levels of LDL-C with treatment or having basal low levels of LDL without treatment, some patients still experience adverse events.[3]

Non-high-density lipoprotein cholestrol (non-HDL-C) contains cholestrol in all potential atherogenic lipid particles including LDL, intermediate-density lipoprotein and very-low-density lipoprotein (VLDL). Some studies suggest that non-HDL-C is a better predictor of cardiovascular disease mortality than LDL-C.[4-6] The recommendation is to reduce non-HDL-C as a secondary lipid-lowering target.[1,2] But not all patients have concordant LDL-C and non-HDL-C levels. Studies have shown that a sizeable proportion of patients presents low LDL-C and high non-HDL-C or high LDL-C and low non-HDL-C.[7,8]

It is not yet clear whether the discordance between LDL-C and non-HDL-C predicts severity and prognosis of coronary artery disease (CAD). Therefore, we detected the discordance of LDL-C and non-HDL-C, and assessed the relationship between this discordance and CAD severity in patients who had undergone coronary angiography.

Methods

Study Population

This retrospective study assessed the data of 892 patients who had undergone coronary angiography between January 2017 and June 2018 in our angiography laboratory because of suspected stable coronary artery disease. Among these, 318 patients were excluded; 3 had incomplete data, 8 had

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missing values for any lipid measurements, 6 had systemic inflammatory disease, renal or hepatic failure, hypo/hyperthyrodism or malignancy, and 301 had previous history of coronary revascularization. Finally, we included the data of 574 patients in our analysis. The clinical parameters assessed were age, gender and coronary risk factors. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current medication with antihypertensive drugs. Patients were defined as diabetic if they had been informed of this diagnosis prior to the study and had been using oral antidiabetic drugs or insulin treatment upon study admission. Body mass index (BMI) was calculated as body weight in kilograms divided by the squared height in meters (kg/m^2).

Angiographic Evaluation

Baseline diagnostic angiograms of the patients were assessed independently by two experienced interventional cardiologists who were blinded to patients' lipid paremeters. SYNTAX score for each patient was calculated by scoring all coronary lesions producing ≥ 50% diameter stenosis in vessels ≥ 1.5 mm using the SYNTAX score algorithm, which was available on the SYNTAX website. Gensini score was calculated by assigning a severity score to each coronary narrowing on the basis of the degree of luminal stenosis and its location.[9] Decreases in luminal diameter of 25%, 50%, 75%, 90%, 99%, and total occlusion were given scores of 1, 2, 4, 8, 16 and 32, respectively. The score was then multiplied by a factor symbolizing the functional significance of the myocardial area supplied by that segment, that is, 5 for the left main artery, 2.5 for the proximal left anterior descending artery or proximal circumflex artery, 1.5 for the mid left anterior descending artery, 1 for the distal left anterior descending artery, right coronary artery and obtuse marginal artery, and 0.5 for all other areas. In cases of disagreement regarding SYNTAX or Gensini scores, an additional observer was consulted and the final decision was made by consensus. A low SYNTAX score was defined as ≤ 22, while intermediate and high SYNTAX scores were set as > 22.[10] Patients with Gensini score of ≥20 were defined as severe CAD, which was approximately equal to having a 70% or more stenosis in the proximal left anterior descending artery.[11]

Laboratory Measurements

Lipid measurements were performed on fasting blood samples taken before the angiography. Plasma concentrations of total cholestrol, LDL-C, HDL-C and triglycerides were measured with a Clinical Biochemistry Analyzer (Abbott Architect c 8000). The enzymatic colorimetric method was used for quantitative determination of total cholestrol. The endpoint colorimetric method was used for quantitative determination of HDL-C. LDL-C was measured by quantitative colorimetric method. The glycerol phosphate oxidase method was used for quantitative determination of triglycerides level. Non-HDL-C was calculated as total cholestrol minus HDL-C.

Statistical analysis

Categorical variables were defined as numbers and percentages. The distribution of continuous variables was considered as normal or not based on the Kolmogorov-Smirnov test. Unless specified otherwise, continuous data were described as mean ± standard deviation for normal distributions, and median (interquartile range) for skewed distributions. First, we determined the medians for LDL-C and non-HDL-C to examine the discordance between them. We categorized patients into groups according to less than, greater than or equal to median levels of LDL-C and non-HDL-C. As there is no standard cutoff point for discordance, we chose the median to define discordance and to make it easier to apply to our study population. Discordance was defined as LDL-C greater than or equal to the median, and non-HDL-C as less than median; or LDL-C less than median and non-HDL-C greater than or equal to median. Concordant groups were defined as both LDL-C and non-HDL-C greater than or equal to median, or both LDL-C and non-HDL-C less than median. Differences between baseline characteristics of patients across these categories were analyzed with the chi-square test for comparing categorical variables and the One-way ANOVA for comparing means of continuous measures. The LSD test was used for binary comparisons. Pearson's correlation analysis was used to examine the correlation between continuous variables, including LDL-C, non-HDL-C, Gensini and SYNTAX scores in the sample. Spearman's correlation was used to examine correlations between these parameters in concordant and discordant groups. Data analyses were performed on SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). A p value < 0.05 was accepted as statistically significant.

Results

The mean age of the study population was 61.1 ± 11.4 years, and 57.5% of the 574 patients were males. Baseline characteristics are presented in Table 1. Nearly 50% of the patients had hypertension, 30% had diabetes mellitus, 32% had past smoking history, and one third of the patients were on statin treatment. Mean LDL-C was 117.4 ± 38.3 mg/dl and non-HDL-C was 156.7 ± 46.8 mg/dl. Mean difference between non-HDL-C and LDL-C was 39.2±23.6 mg/dl. Patients with high difference between non-HDL-C and LDL-C were more commonly females, receiving less statin therapy and having more diabetes mellitus and high triglycerides levels. Mean Gensini score was 25.3 ± 39.6, and the median was 12 (0-191); mean SYNTAX score was 7.1 ± 11.2, and the median was 4 (0-53).

LDL-C levels were strongly and positively correlated with non-HDL-C levels ($r = 0.865$, $p < 0.001$), but there was discordance between them. Discordance of LDL and non-HDL-C was found in 15% of patients. The magnitude of discordance and distribution of LDL-C and non-HDL-C levels according to medians are shown in Figure 1. Non-HDL-C was correlated with triglyceride (TG) ($r = 0.431$, $p < 0.001$). Gensini score was highly correlated with SYNTAX score ($r = 0.927$, $p < 0.001$). Neither Gensini nor SYNTAX were correlated with LDL-C ($p = 0.9$ and $p = 0.9$, respectively). Also, both scores were not correlated with non-HDL-C ($p = 0.4$ and $p = 0.4$, respectively).

To further evaluate the characteristics of patients with discordance and concordance of LDL-C and non-HDL-C, we classified patients into 4 subgroups. Group 1: LDL-C < median and

Table 1 – Baseline characteristics of the study population

Characteristics	
Clinical characteristics	
Male gender (%)	57.5
Age in years (mean ± standart deviation)	61.1 ± 11.4
Smoking (%)	32.1
Hypertension (%)	49.6
Diabetes (%)	30.1
BMI (kg/m^2) (mean ± standart deviation)	28.8 ± 4.1
Statin usage at admission (%)	33.3
Biochemical analysis (mean ± standart deviation)	
Total cholesterol (mg/dl)	198.5 ± 49.1
LDL-C (mg/dl)	117.4 ± 38.2
HDL-C (mg/dl)	41.8 ± 11.3
Triglyceride (mg/dl)	163.2 ± 84.2
Non-HDL-C (mg/dl)	156.7 ± 46.8
Fasting glucose (mg/dl)	114.6 ± 40.9
Creatinine (mg/dl)	0.95 ± 0.48
CAD severity	
Mean Gensini score	25.3 ± 39.6
Median Gensini score (interquartile range)	12 (31.1)
Mean SYNTAX score	7.1±10.2
Median SYNTAX score (interquartile range)	4 (11.0)

CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; BMI: body mass index.

non-HDL-C <median, group 2: LDL-C <median and non-HDL-C ≥ median, group 3: LDL-C ≥median and non-HDL-C < median, group 4: LDL-C ≥ median and non-HDL-C ≥ median. Groups 2 and 3 were discordant groups (Table 2).

The variables age, BMI, smoking history, and percentage of patients with hypertension were not different between groups. The percentages of patients with diabetes mellitus and of patients receiving statin treatment were significantly different between groups ($p = 0.004$ and $p < 0.001$, respectively). Patients in Group 2 (LDL-C < median and non-HDL-C ≥ median) had the highest prevalence of diabetes mellitus and the lowest percentage of current statin treatment. The percentage of patients on statin treatment was the highest in Group 1 (LDL-C < median and non-HDL-C < median). Gender was significantly different from group to group ($p = 0.036$). Group 1 had the lowest percentage of females (LDL-C < median and non-HDL-C < median), while Group 4 had the highest (LDL-C ≥median and non-HDL-C ≥ median). Total cholesterol and LDL-C were present in high proportions in the groups with LDL-C ≥median and non-HDL-C ≥ median, but triglycerides was the highest in the group with LDL-C < median and non-HDL-C ≥ median ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively).

The percentage of patients with Gensini or SYNTAX score of zero did not differ between groups ($p = 0.837$ and $p = 0.821$, respectively). Mean Gensini and SYNTAX scores, percentage of patients with Gensini score ≥ 20 and SYNTAX score > 22 were also not different between groups ($p = 0.635$, $p = 0.733$, $p = 0.799$ and $p = 0.891$, respectively). There was also no statistically significant correlation between LDL-C and Gensini or SYNTAX scores in any of the 4 subgroups. Additionally, no correlation was found between non-HDL-C and Gensini or SYNTAX scores in subgroups (Table 3).

Discussion

In the present study, we assessed the cross-sectional association between CAD severity/complexity and discordance between LDL-C and non-HDL-C numbers. While discordance was present between LDL-C and non-HDL-C in patients submitted to coronary angiography (15% of the sample), there was no difference regarding CAD severity and complexity between discordant and concordant groups.

Non-HDL-C represents the cholesterol content of all circulating atherogenic lipoproteins and it is not influenced by fasting conditions. Several studies have indicated that non-HDL-C is a better predictor of cardiovascular risk and mortality than LDL-C.[4,5,12,13] It has been also reported that non-HDL-C was more closely associated with cardiovascular events than LDL-C in patients receiving statin therapy.[3,14] There are some explanations for these states. Firstly, non-HDL-C includes VLDL and LDL cholestrols, and VLDL is also atherogenic.[15,16] Secondly, non-HDL-C is an indirect measure of LDL-particles (LDL-p), and LDL-related atherosclerotic risk is better determined by the LDL-p number.[17-19] Finally, non-HDL-C is correlated with the Apolipoprotein B (ApoB).[20] ApoB carrying lipoproteins initiate and maintain the atherosclerotic process by entering and trapping within the arterial wall, so the total number of ApoB particles is a critical determinant of cardiovascular risk.[5,21-23] To calculate non-HDL-C, no additional measurement beyond the routine lipid parameters is required, so no additional expense is made, which is an advantage for non-HDL-C over apoB.

LDL-p may be cholesterol-depleted or enriched. This variation causes discordance between LDL-C and non-HDL-C. The discordance rate in our study is similar to that of previous studies. In a study with 27,533 participants, prevalance of discordance was 11,6% and, in another study with 1,757 patients, it was 14.6 %.[7,8] Also in a study conducted with aproximately 1.3 million adults, a similar discordance rate (15%) was found, especially at lower LDL levels.[24] Discordance is high among subjects with high triglycerides level, lower HDL-C, dysglycemia and obesity.[7,25,26]

Coronary risk was found to be either underestimated or overestimated by LDL-C in individuals presenting discordance.[7] Both LDL-C, non-HDL-C and discordance in relation to future cardiovascular events were evaluated in several studies. However, data about lipid parameters or discordance accurately predicting the severity or complexity of coronary atherosclerosis are limited and also contraversial.

In a study by Budde et al.,[27] there was no relation between LDL-C and number, severity, and lenght of coronary lesions.[27] Also, there was no relationship between LDL-C and coronary plaque volume, 3-vessel or left main coronary disease and

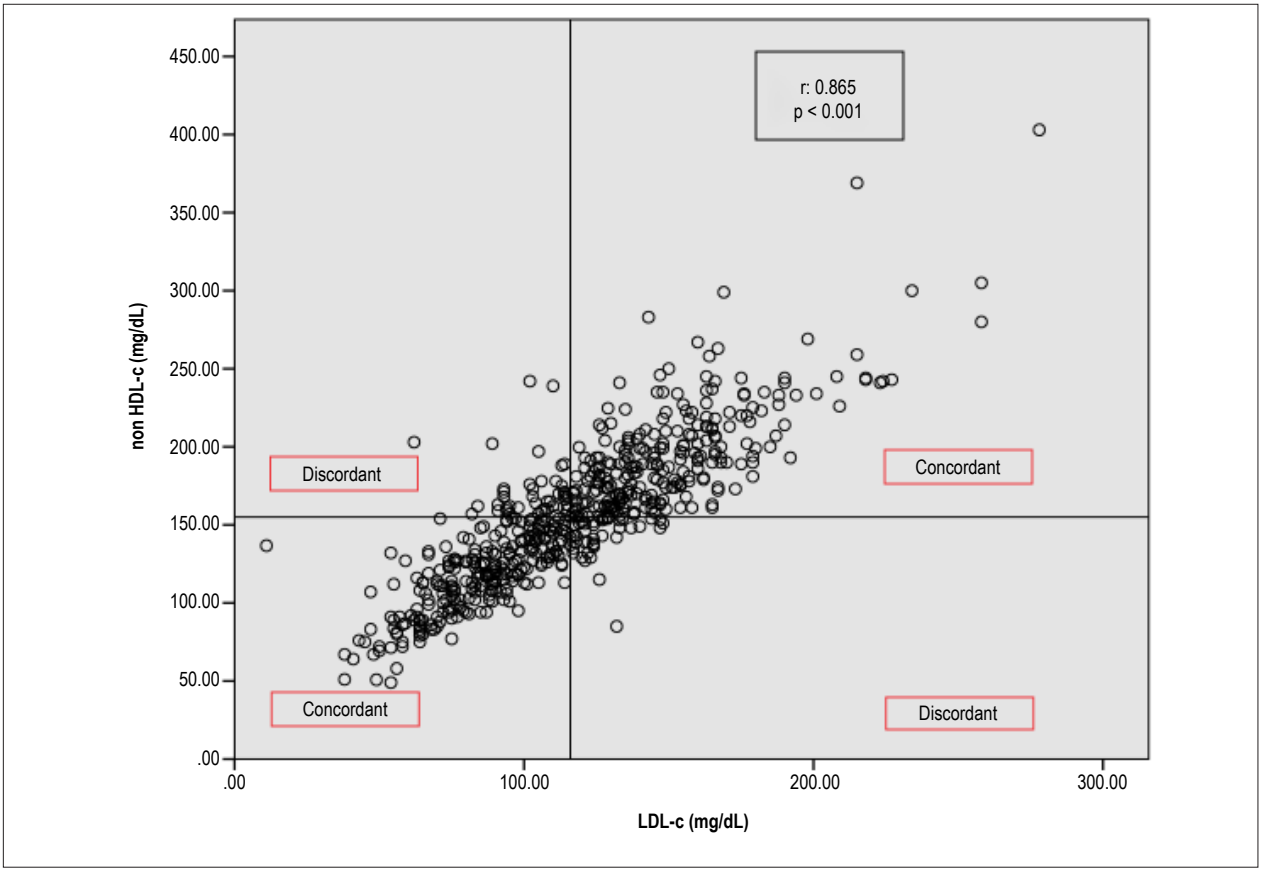

Figure 1 – *Scatterplots and prevalence of discordance and concordance defined according to median values of LDL-C and non-HDL-C. LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol.*

severe coronary stenosis.[28] In a study by Onat et al.,[29] LDL-C was not a predictor of new-onset coronary heart disease.[29] In two studies evaluating Gensini score and LDL-C relationship, LDL-C showed no significant difference when compared to high and low Gensini scores.[30,31] In our study, LDL-C was not correlated to Gensini or SYNTAX scores. Non-HDL-C was found to be higher in patients with a Gensini score of 50 or greater than patients with a Gensini score of less than 50.[30] There was a weak correlation ($r = 0.113$, $p < 0.001$) between non-HDL-C and Gensini score in a study by Zhang et al.[8] In our study, the proportion of patients with high SYNTAX scores and high Gensini scores was low. Lack of association between CAD severity and non-HDL-C may have resulted from the relatively limited number of patients with severe CAD in our population.

There is a limited number of studies that evaluate the effect of discordance of LDL-C and non-HDL-C on coronary atherosclerosis severity. It was found that Gensini score was overestimated among patients with LDL-C greater than or equal to the median and non-HDL-C below the median.[8] Shiiba et al.[32] assessed the relationship between discordance and the mid-term outcome of coronary stent implantation. It was found that 3-vessel disease or left main tract disease did not differ among discordant and concordant groups, and discordance between LDL-C and non-HDL-C levels did not predict major adverse cardiovascular events after stent implantation.[32] We assessed CAD severity by Gensini score and complexity by SYNTAX score, and these did not differ between discordant and concordant groups in our study.

Study limitations

This study has several limitations. It has, for example, a retrospective design, which paves the way for the possibility of bias from unmeasured cofounders. One third of patients were using statins and the lack of association between discordance and CAD severity may have stemed from it. In addition, information about doses, species and duration of statin treatment were lacking. There is no absolute definition and standard cut-off values for the discordance of LDL-C and non-HDL-C. We used median values for our study population. Therefore, further large-scale prospective studies would be required to validate our results.

Conclusion

While discordance was present between LDL-C and non-HDL-C (15% of patients), there is no difference regarding CAD severity and complexity between discordant and concordant groups. But the patients with LDL-C < median and non-HDL-C ≥ median present some high-risk features such as diabetes mellitus and higher triglyceride levels, and they may need further evaluation and close follow-up.

Table 2 – Characteristics of patients with concordant and discordant LDL-C and non-HDL-C

	LDL-C < median non-HDL-C < median n = 245 (group 1)	LDL-C < median non-HDL-C ≥ median n = 43 (group 2)	LDL-C ≥ median Non-HDL-C < median n = 43 (group 3)	LDL-C ≥ median Non-HDL-C ≥ median n = 243 (group 4)	p-value
Age (years)	62.0 ± 12.5	58.6 ± 11.7	61.4 ± 10.8	60.7 ± 10.2	0.266
Female gender (%)	35.9	41.9	44.2	49.0	0.036
Smoking (%)	34.3	30.2	30.2	30.6	0.818
Hypertension (%)	50.6	53.5	41.9	49.2	0.704
Diabetes (%)	34.7	46.5	20.9	24.3	0.004
Receiving statin (%)	45.3	18.6	30.2	24.4	0.001
BMI (kg/m^2)	28.5 ± 4.0	29.1 ± 4.9	29.1 ± 3.0	29.0 ± 4.2	0.501
Total cholesterol (mg/dl)	156.4 ± 27.2	208.2 ± 20.4	190.1 ± 16.8	240.7 ± 35.3	< 0.001[a,b,c,d,e,f]
LDL-C (mg/dl)	84.2 ± 18.9	103.0 ± 11.3	126.6 ± 8.5	151.8 ± 26.8	< 0.001[a,b,c,d,e,f]
HDL-C (mg/dl)	40.1 ± 11.7	36.1 ± 9.5	46.6 ± 13.4	43.7 ± 10.1	< 0.001[a,b,c,d,e, f]
Non-HDL-C (mg/dl)	116.4 ± 23.4	172.1 ± 19.2	143.4 ± 13.1	197.0 ± 34.6	< 0.001[a,b,c,d,e,f]
Triglyceride (mg/dl)	132.0 ± 81.6	256.1 ± 118.3	127.8 ± 60.4	184.5 ± 96.5	< 0.001[a,c,d,e,f]
Fasting glucose (mg/dl)	121.1 ± 50.4	119.4 ± 40.4	107.4 ± 20.9	108.5 ± 30.9	0.003[b,c]
Mean Gensini score	24.7 ± 38.1	28.2 ± 36.4	18.7 ± 28.1	26.5 ± 40.1	0.635
Mean SYNTAX score	7.1 ± 11.2	6.7 ± 11.3	5.4 ± 9.3	7.4 ± 11.6	0.733
Gensini score = 0 (%)	24.9	30.2	23.3	23.9	0.837
SYNTAX score = 0 (%)	55.1	60.5	58.1	54.3	0.821
Gensini score ≥ 20 (%)	34.7	27.9	30.2	34.2	0.799
SYNTAX score > 22 (%)	13.5	9.3	11.6	12.8	0.891

Data are expressed as percentage for categorical variables; chi-square test was used. Data are expressed as mean±standard deviation for continuous variables; one-way ANOVA was used; Statistically significant p-values are in bold. LSD test was performed for binary comparisons between groups and the p-value was set at 0.05. Significant differences were found between a) group I vs group II, b) group I vs group III, c) group I vs group IV, d) group II vs group III, e) group II vs group IV, f) group III vs group IV. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; BMI: Body Mass Index.

Table 3 – Correlation of LDL-C, non-HDL-C, Gensini and SYNTAX scores with Spearman's rho and p-value

	LDL-C < median Non-HDL-C < median n = 245 (group 1)		LDL-C < median Non-HDL-C ≥ median n = 43 (group 2)		LDL-C ≥ median Non-HDL-C < median n = 43 (group 3)		LDL-C ≥ median Non-HDL-C ≥ median n = 243 (group 4)	
	Gensini score	SYNTAX score	Gensini score	SYNTAX score	Gensini score	SYNTAX score	Gensini score	SYNTAX score
LDL-C	r = 0.118	r = 0.101	r = 0.088	r = 0.18	r = 0.127	r = 0.029	r = 0.031	r = 0.002
	p = 0.064	p = 0.115	p = 0.577	p = 0.910	p = 0.418	p = 0.853	p = 0.635	p = 0.972
Non-HDL-C	r = 0.046	r = 0.031	r = 0.190	r = 0.165	r = 0.104	r = 0.183	r = 0.025	r = 0.034
	p = 0.469	p = 0.624	p = 0.221	p = 0.290	p = 0.506	p = 0.240	p = 0.694	p = 0.596

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Kurmus O, Erkan AF, Ekici B, Eren M; Acquisition of data, Statistical analysis and Writing of the manuscript: Kurmus O, Aslan T, Eren M; Analysis and interpretation of the data: Kurmus O, Erkan AF, Ekici B, Aslan T, Eren M.

Potential Conflict of Interest

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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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Discordance of Low-Density Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol with Severity of Coronary Artery Disease

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Short Editorial related to the article: Discordance of Low-Density Lipoprotein Cholestrol and Non-High-Density Lipoprotein Cholestrol and Coronary Artery Disease Severity

Cardiovascular diseases (CVDs) are the leading cause of mortality world.[1] Dyslipidemia is a risk and causal factor and is the focus of the therapy for primary and secondary prevention of CVDs.

There is consensus and broad understanding of the causal mechanisms of low-density lipoproteins (LDL) in CVDs, and the benefit of the hypolipidemic therapy, with a magnitude of effect proportional to the reduction in serum levels.[2] However, despite intensive use of lipid lowering agents, there remains a residual risk, a constant target of research and therapy.

Recent evidence confirms that the initial event of atherogenesis is the retention of LDL and other particles in the vessel wall.[3] High non-HDL cholesterol levels help identify patients who despite having low serum LDL levels remain at high risk for cardiovascular events.[4]

Keywords

Cardiovascular Diseases/mortality; Lipoproteins,LDL; lipoproteins,HDL; Coronary Artery Disease; Hyydroxymethylglutaryl-CoA Reductase Inhibitors; Proprotein Convertase 9.

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The present study[5] retrospectively evaluated the anatomical characteristics of 574 patients diagnosed with acute coronary syndrome and correlated the findings with LDL and non-HDL serum levels. There was 15% disagreement between LDL and non-HDL, which was similar to previous studies.[6] However, no significant anatomical differences were identified in the assessment of the severity of atherosclerotic disease. Prior use of statins may have a more significant effect on LDL reduction than non-HDL, which may explain the lack of association.

In addition, the sensitivity of LDL levels in identifying cardiovascular risk is reduced in diabetes.[7] In fact, the present study reported discrepancies in the association between diabetes mellitus and LDL levels. Perhaps the sample size was not adequate enough to evidence anatomical differences between the groups. The follow-up of patients with discrepant associations could identify a subgroup at higher risk of new events.

The Brazilian guideline already includes both LDL and non-HDL targets, seeking to identify individuals with high residual risk of cardiovascular events despite adequate LDL levels. Prospective studies will help better identify the subgroup of patients who require more intense treatment approach, who would probably benefit from more expensive and effective therapies such as PCSK9 inhibitor and Lomitapide.[8] These drugs have already been shown to be effective in reducing cardiovascular events and apolipoprotein(a) in some groups of patients.

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Factors Associated with Recurrence in Takotsubo Syndrome: A Systematic Review

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Abstract

Background: Takotsubo syndrome (TTS) is characterized by a temporary systolic dysfunction of the left ventricle (LV) related to a stressful event. However, the factors associated with its recurrence are still not well established.

Objective: To analyze the main factors associated with TTS recurrence.

Methods: A systematic review was performed using the PRISMA model. Observational studies, published between January 2008 and October 2017, which presented a recurrence rate of at least 3% and/or 5 or more patients with recurrence, and who met at least 80% of the STROBE criteria were included.

Results: six articles reached the criteria to compose this systematic review. The recurrence rate ranged from 1 to 3.5% per year (global recurrence rate 3.8%). One study associated higher recurrence rate with the female gender, four reported the time between the first and second episodes, one study associated body mass index (BMI) and hypercontractility of the LV middle anterior wall to a higher recurrence rate. No association between recurrence and electrocardiographic changes were determined. Beta-blockers use was not associated with recurrence rates.

Conclusions: Female gender, time from the first episode of the syndrome, low BMI and midventricular obstruction were reported as potential predictors of TTS recurrence. (Arq Bras Cardiol. 2020; 114(3):477-483)

Keywords: Takotsubo Syndrome; Takotsubo cardiomyopathy; Recurrence.

Preamble and case report

A 62-year-old female patient was admitted for elective rhytidoplasty and blepharoplasty surgeries. She weighed 61 kg and was 1.65 m tall, with a history of glaucoma and hypothyroidism. She was considered at low cardiovascular risk for the procedure, with no personal or family history of cardiovascular disease. During surgery, under general anesthesia, she presented idioventricular rhythm followed by circulatory shock and cardiorespiratory arrest. She was successfully resuscitated and her electrocardiography (ECG) showed an ST elevation pattern in lateral leads. She was promptly submitted to cardiac catheterization that showed no coronary lesion but akinesia in apical and medial ventricular walls and hyperkinesia of the basal parts, a pattern that resembles the Takotsubo Syndrome (TTS). This pattern was confirmed in an ECG which showed an ejection fraction of 40%. After adjustments for heart failure therapy, she was discharged from the hospital in 10 days, clinically stable. In six months, she had already recovered her global and segmental functions. After 1 year, she was planning to undergo another plastic surgery and asked about her recurrence risk. This question was the main drive for this systematic review.

Introduction

TTS, also called Takotsubo cardiomyopathy or broken heart syndrome,[1,2] is characterized by a temporary left ventricle systolic and diastolic dysfunction, usually associated with an event of great emotional or physical stress. It presents clinically with acute chest pain, dyspnea, electrocardiographic changes, and the presence of elevated cardiac injury biomarkers, being very similar to an acute coronary syndrome despite the absence of significant coronary stenosis related to the affected area.[3] It is estimated that about 2% of patients with suspected acute coronary syndrome actually have TTS.[4]

Postmenopausal women are the group most affected by this condition, probably due to hormonal issues, although men and young people can also have TTS. It is suggested that the pathophysiology of the disease is related to a large and abrupt discharge of catecholamines.[2] Therefore, the use of beta-blockers (BB) has been proposed as a prevention strategy.[3]

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The prognosis is usually good and characterized as benign by many authors, even though there is a 1-2% risk of ventricular arrhythmias and approximately 2% of in-hospital mortality associated with TTS.[5] Patients with a history of TTS have an annual recurrence rate of 1.5%, though it may be as high as 11% in 4 years.[3,5,6]

In recent years, there has been an increase in the number of published TTS-related studies, especially in the USA, Europe, and Japan. Much of the data on this pathology comes from the International Takotsubo Registry (InterTAK Registry), an international collaborative network with data from 35 cardiovascular centers in 15 different countries.[2,7] However, predictors of TTS recurrence are still not well established.

Objective

The present study aimed to analyze the main factors associated with TTS recurrence.

Methods

A systematic review of the literature was proposed, using the PRISMA model. The main databases of international literature – PubMed, Scielo, Lilacs, and Cochrane – were searched.

As a search strategy, the following descriptors were used: Takotsubo Syndrome; Left Ventricular Apical Ballooning Syndrome; Takotsubo Cardiomyopathy; Stress Cardiomyopathy; Broken Heart Syndrome. The PubMed MeSH tool was used adding Recurrence as a complementary descriptor.

Strategy for articles selection: the selection was carried out in October 2017. All articles published between January 2008 and October 2017 were initially included for further appreciation. First, the titles were evaluated, followed by the abstract, and finally, a careful analysis of the complete article was conducted in order to identify its quality and relevance to the proposed objective. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria[8] for assessing the methodological quality of observational studies were used, with a minimum of 80% compliance of the 22 items in the STROBE checklist to be included in this study. This whole process was carried out by two researchers. Articles were also searched based on the references of the selected articles.

Only articles characterized as prospective cohort study, retrospective cohort study, case control or case series study were selected. Articles in which the text was not in English were excluded. Only studies reporting at least 3% recurrence rate and/or five or more patients with recurrence were included, so that there could be a significant analysis of the recurrence predictors.

Results

Initially, a total of 164 articles were identified. Four other studies were identified and selected from the references of the initially identified articles. At the end of the analysis of the studies, six were selected to compose this systematic review (Figure 1 and Table 1).

Globally, the recurrence rate, before excluding the four articles that did not meet the criteria of at least 3% recurrence rate and/or five or more patients with recurrence, ranged from 0.2 to 5% per year. The global recurrence rate, considering the selected studies, was 3.8% in a follow up that ranged from 5 to 17 years.

Table 2 shows the main information for each selected article. Looi et al.[9] studied a prospective cohort study of 100 patients diagnosed with TTS by the Mayo criteria. From these, seven patients (7%) had a recurrence and one presented with four recurrent episodes. Recurrences occurred between 99 and 679 days after the first episode. All recurrences occurred within two years after the first episode, being more frequent in the first year. In four of the seven patients who presented with recurrences (57%), the initial and subsequent events were triggered by emotional stress. Four of the seven patients who had recurrences were already using a BB in the second episode.

Templin et al.[3] presented a case-control study with 1,750 TTS patients, according to the Mayo criteria. From these, 455 patients were matched, by age and gender, with patients diagnosed with acute coronary syndrome (ACS) and who had their data obtained through the Zurich Acute Coronary Syndrome Registry. During a 17-year follow-up period, 57 patients with TTS had recurrences, representing a rate of 1.8% recurrence per patient-year. The second episode occurred from 25 days to 9.2 years after the first one. A total of 29 of 57 patients with recurrences (50.8%) were on BB therapy at the time of their recurrent episode.

In the retrospective cohort study by Patel et al.,[10] 224 patients diagnosed with TTS had their data obtained through the Mayo Clinic database over a 10-year period. Only 7 recurrent episodes were documented. None of the men had TTS recurrence. During a mean follow-up of 3.5 years, 2 women under 50 years of age (16%) and 5 women aged 50 years old or older (3%) developed TTS recurrence ($p = 0.017$).

Elesber et al.[11] studied a retrospective cohort and analyzed data from 100 patients diagnosed with TTS over a period of 16 years and 11 months. Recurrence rate was 11.4% at a mean follow-up time of 4.4 ± 4.6 years, being higher in the first 4 years (2.9% per year), and decreasing to about 1.3% per year in subsequent segment time. There was no difference between patients with or without recurrences in relation to the use of: aspirin (60 *versus* 67%; $p = 0.67$); angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) (60 *versus* 51%; $p = 0.59$); BB (80 *versus* 52%; $p = 0.10$); or statins (40 *versus* 33%; $p = 0.67$).

In another prospective cohort study,[12] 23 patients who underwent coronary angiography were diagnosed with TTS according to the Mayo criteria, over a period of 7 years and 11 months. Five patients (21.7%) developed recurrent TTS and one patient presented with 2 recurrent episodes. The mean time to a recurrent episode was 105.4 ± 83 days, and the recurrence rate was higher in the first 3 months. Compared with patients with no recurrences, those with a recurrent episode were older (71.4 *versus* 65.7 years), had lower ejection fraction (36.5 *versus* 44.2%), higher systolic blood pressure (139 *versus* 128.4 mmHg) and higher peak troponin levels (8.1 *versus* 2.5 μg/ml). Three of the five patients who presented with a recurrence were on BB.

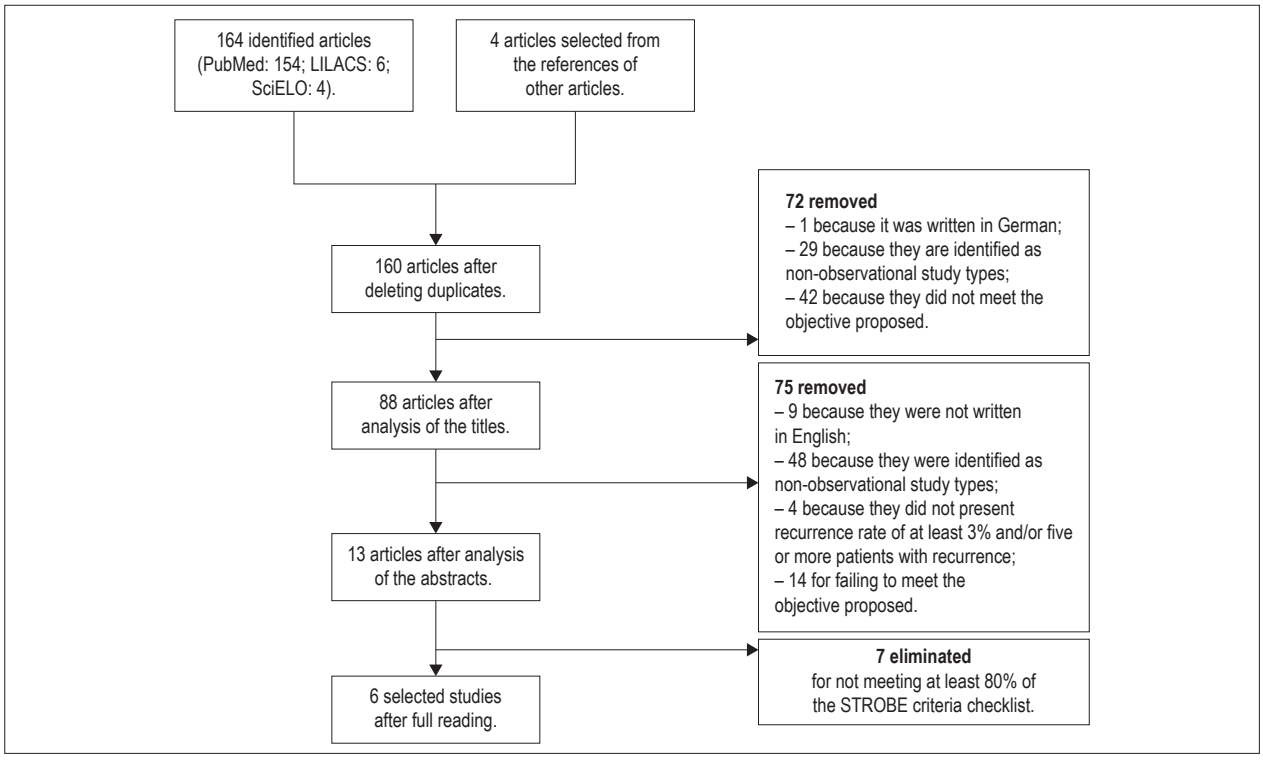

Figure 1 – *Prisma Flowchart of the studies selection for the composition of the systematic review.*

Table 1 – Score and percentage of articles quality based on STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria

Reference	Study design	Publishing journal	Points on STROBE	%
Looi et al.,[9]	Prospective cohort.	Journal of Heart, Lung and Circulation.	18	81.8
Templin et al.,[3]	Case-control.	The New England Journal of Medicine.	19	86.3
Patel et al.,[10]	Retrospective cohort.	Journal of Cardiac Failure.	19	86.3
Elesber et al.,[11]	Retrospective cohort.	Journal of the American College of Cardiology.	19	86.3
Vriz et al.,[12]	Prospective cohort.	Journal of Cardiovascular Medicine.	18	81.8
Nishida et al.,[13]	Case-control.	Heart and Vessels.	20	90.9

Nishida et al.[13] presented a case-control study. Data from 251 patients who composed the BOREAS Registry (with 15 participating countries) from June 1999 to March 2012, were analyzed. Patients were divided into two groups, those with apical ballooning (type A), classic TTS presentation, and those with non-apical ballooning (non-A type), which included all other presentation forms of the syndrome. During a follow-up of 2.6 ± 2.8 years, the recurrence rate was 2.8% (7/251), with no significant difference between A and non-A groups (2.8 and 2.9 %, respectively). In the univariate analysis, low Body Mass Index (BMI) ($p = 0.048$), midventricular ($p = 0.01$), and concomitant right ventricular involvement ($p = 0.06$) were associated with TTS recurrence. Only BMI (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.54–0.99; $p = 0.048$) and midventricular obstruction (HR 14.71; 95% CI 1.87–304.66; $p = 0.01$) remained significantly associated with TTS recurrence.

Discussion

TTS recurrence rate is variable in the literature and the factors associated with it were not clearly defined as well. This statement was clear when, recently, that 62-year-old female patient who had a history of being resuscitated for cardiac arrest a year before during an elective surgery and had a diagnosis of TTS, and who recovered to normal left ventricular (LV) function, now 1 year after the index episode, came to the office of one of the authors asking for a cardiovascular risk evaluation for another elective plastic surgery.

After careful selection, data from the six studies were analyzed, in which factors with possible association with TTS recurrence were considered. The female gender was more prone to recurrence. Proximity to the first episode of the syndrome was a factor described by some authors as predisposing to a greater chance of recurrence. Low BMI and

Table 2 – Selected studies characteristics

Reference	Studied population	Level of Significance adopted	Recurrence rate (recurrence N/total N)	Analyzed data with possible recurrence association
Looi et al.,[9]	Patients admitted to Middlemore Hospital, Auckland City Hospital and North Shore Hospital, Auckland, New Zealand.	p < 0.05	7% (7/100)	– Time between manifestations: recurrences occurred from 99 to 679 days after the first episode, being more frequent in the first year. – Triggering factor: 57% of patients with recurrence presented emotional stress as a trigger. – Clinical characteristics: recurrence in patients presenting ST elevation was not higher when compared to patients who did not present ST elevation (7.4 and 6.3%, respectively); p = 1.00. – Medications in use: 4 (57%) of the patients used BB on recurrence.
Templin et al., [3]	Patients obtained through the Mayo Clinic database. Patients with ACS from Zurich Acute Coronary Syndrome Registry.	p < 0.05	3.26% (57/1750)	– Time between manifestations: recurrence occurred from 25 days to 9.2 years after the first episode. – Medications in use: 29 patients (50.8%) used BB during the second episode.
Patel et al., [10]	Patients obtained through the Mayo Clinic database.	p < 0.05 for men versus women p < 0.25 for comparison with women ≥ 50 years of age (due to multiple comparisons)	3.13% (7/224)	– Gender: there were no recurrences in men and all 7 recurrences were in women (14.8%) – Age: recurrence in women aged < 50 years was more prevalent in relation to recurrence in women aged ≥ 50 years (16 and 3%, respectively; p = 0.017).
Elesber et al., [11]	Patients diagnosed with TTS submitted to the Mayo Clinic catheterization center database.	p < 0.05	11.4% (10/100)	– Time between manifestations: 4.4±4.6 mean years between episodes, with a higher recurrence rate in the first 4 years compared to subsequent years (2.9 and 1.3% a year, respectively). – Medications in use: recurrence in patients in use X without use of: aspirin (60x67%), p = 0.67; ACEI/ARB (60x51%), p = 0.59; BB (80x52%), p = 0.10; Statins (40x33%), p = 0.67.
Vriz et al.,[12]	Patients at San Antonio Community Hospital (San Daniele del Friuli, Udine, Italy).	p < 0.05	21.7% (5/23)	– Age: more frequent in older patients. – Time between manifestations: recurrence occurred on an average of 105.4 ± 82.92 days after the first episode, being more frequent in the first 3 months. – Clinical characteristics: more frequent recurrence in patients with lower LVEF, lower SBP and higher troponin peak. – Medications in use: therapy with BB did not prevent recurrence.
Nishida et al.,[13]	Patients from the BOREAS Registry database.	p < 0.05	2.8% (7/251)	-Clinical characteristics: low BMI, medium-ventricular hypercontractility and right ventricular involvement were both associated with a higher rate of recurrence of TTS (p = 0.048, 0.01, and 0.06, respectively). HRs of recurrence for BMI (per increase by 1 kg/cm^2) and MVO were 0.75 (95% CI 0.54–0.99) and 14.71 (95% CI 1.87–304.66), respectively.

BB: beta-blocker; ACS: acute coronary syndrome; TTS: Takotsubo syndrome; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LVEF: left ventricle ejection fraction; SBP: systolic blood pressure; BMI: Body Mass Index; HRs: hazard ratios; CI: confidence interval; MVO: microvascular obstruction.

medium-ventricular hypercontractility were also reported as predisposing to TTS recurrence. Use of BB or other heart failure (HF) medications was not proven to reduce the chance of recurrence.

Some authors may understand that new episodes of TTS are not recurrence, but instead a clinical spectrum of the disease. In accordance with international consensus and statements, the term recurrence was used here as after the first episode patients recover their global and segmental ventricular function recurring the disfunction in the subsequent episode.

Only one study of this systematic review[10] analyzed gender as a recurrence variable, with no recurrence in men and a recurrence rate in women of 14.8%. In all other studies selected, as in the rest of the literature,[6] if not all, most patients who had recurrence were women. Although there are reports of recurrence in men,[14] they are extremely rare. These data strongly suggest that female gender is a predisposing factor to TTS recurrence.

In relation to age, Patel et al.[10] found a higher rate of recurrence among women aged less than 50 years, when

compared to women aged 50 years old or older (16 *versus* 3%, respectively; p = 0.017). This suggests that younger women tend to have recurrence of the syndrome more often. However, in this study, women younger than 50 years of age had higher rate of psychiatric disorders, leaving in doubt whether the higher rate of TTS recurrence was due to lower age or to association with psychiatric disorders. Vriz et al.[12] reported higher recurrence rate in older patients – patients who had recurrence had a mean age of 71.4 years, while those with only one episode had a mean age of 65.7 years. A systematic review with meta-analysis, composed of 31 studies,[6] found an average age of 65.5 years among patients who presented recurrence, most of them women. These data show the divergence between different studies in relation to the age group that would be more predisposed to an episode of TTS recurrence. Cohorts with greater samples, covering larger age groups, are necessary to better clarify this association.

Four studies of this systematic review reported the time between the first and second episodes. Episodes of recurrence have been reported for about 22 days[12] until slightly more than nine years after the first episode.[3] Although there is a recurrence report up to ten years after the initial episode,[15] cases like this are extremely rare. Looi et al.[9] found that recurrence was more frequent in the first year after the initial episode. Elesber et al.[11] showed higher annual recurrence rate in the first four years compared to subsequent years (2.9 *versus* 1.3% per year, respectively). Vriz et al.[12] reported in their study a higher recurrence of the syndrome in the first three months after the first episode. Another study, published in 2017,[16] reported TTS recurrence in five patients, with the second episode occurring in an average of 2.1 years. All these data corroborate the idea that a person's likelihood of TTS recurrence decreases over time, being more likely in the first few months following the first episode, and there is a gradual decrease in the chances of a second episode over the years, reducing significantly after four years.

To date, the only study identified in this review that conducted an association between TTS recurrence and BMI was the one by Nishida et al.[13] In this study, low BMI was a risk factor for TTS recurrence. The higher the BMI of the individual the lower his chances of recurrence, with a HR of 0.75 (for each 1kg/m^2 increase). A clear explanation for this association was not possible, but recent studies[17,18] have suggested that the hemodynamic response to mental stress is more intense in people with lower BMI, while the basal activity of the sympathetic nervous system of these individuals is lower than in individuals with higher BMI. Thus, one may suggest that the greater sensitivity of the sympathetic nervous system in people with lower BMI would reduce their threshold to emotional stress, triggering potential TTS.

Regarding the clinical presentation of the patients who presented TTS, Looi et al.[9] described an absolute higher rate of recurrence in patients presenting ST elevation in their ECG when compared to patients who did not present it, with a recurrence rate of 7.4 *versus* 6.3%, respectively; there was no statistical significance, p = 1.00. Another study by Dib et al.[19] reported that there was no difference in the 5-year recurrence rate related to ECG presentation, 13% in those who presented ST segment elevation, 5% in those who presented with T wave inversion, and 17% in those whit non-specific changes in the ST segment and T wave (p = 0.25). Such data do not suggest that a specific electrocardiographic alteration changes the prognosis of those affected by TTS with respect to its recurrence.

The study by Nishida et al.[13] initially showed an association between biventricular involvement and recurrence, but no statistical significance was reached in this analysis, p = 0.06. Another study, by Kagiyama et al.,[20] also analyzed this relationship with the morphological pattern of the syndrome manifested by the patients, being the recurrence rate in patients with biventricular involvement greater when compared to those with classic morphology, that is, 4.8 and 0%, respectively. Nishida et al.[13] found higher recurrence rate in patients with medium ventricular obstruction, which corresponds to hypercontractility of the middle third of the left ventricle, which occurred in patients with apical ballooning, probably as a compensatory mechanism. No further studies were found to evaluate this relationship.

Four studies of this systematic review analyzed the use of BB as a possible method of preventing TTS recurrence. In the Looi et al.[9] study, four (57%) of the patients were in use of BB on recurrence; Templin et al.[3] reported that 29 patients (50.8%) were in use of BB during the second episode; in the study by Vriz et al.,[12] BB therapy did not prevent recurrence; Elesber et al.[11] showed a recurrence rate of 80% among patients on BB and 52% in patients who did not use this medication, without statistical significance (p = 0.10). Together, these data suggest that BB therapy is not associated to prevention of episodes of TTS recurrence. Elesber et al.[11] also compared recurrence among patients in and without use of aspirin, ACEI/ARB, and statins. In their study, patients taking aspirin had a recurrence rate of 60%, whereas those who did not use this medication had a 67% recurrence rate, with no statistical significance (p = 0.67). The recurrence rate between patients who did and those who did not use ACEI/ARB was 60 and 51%, respectively (p = 0.59). From the patients who presented recurrence, 40% used statins and 33% did not, nor was there any statistical significance (p = 0.67). Given the above, none of the studies of this systematic review suggested specific drug therapy to prevent TTS recurrence. In several studies, the use of BB showed no efficacy in TTS prevention. This medication was also not useful for this purpose in a systematic review with a meta-analysis of 31 studies[6]. However, this same study[6] showed a negative association between the use of ACE inhibitors or ARB and the recurrence rate, that is, the use of these medications decreased recurrence rates, different from those found by Elesber et al.[11] Long-term segmental cohorts with a greater number of patients who presented TTS and made use of ACEI/ARB are necessary to better clarify this association.

The largest study in this review was the one by Templin et al.[3] This was a case-control study with 1,750 TTS patients according to the Mayo criteria and 57 recurrences cases were found in the long term follow up. The authors aimed to evaluate clinical features, prognostic predictors, clinical course, and outcomes of TTS in a wide population. However, as they did not focus specifically on recurrence predictors, the article does not bring specific insights about this subgroup apart from the use of BB.

This article updates and complements the systematic review by Singh et al.[6] Some data could be confirmed in

this opportunity, such as the association between female gender and higher recurrence rate, and the non-efficacy of BB in the prevention of a second episode. Other variables, not yet addressed by Singh et al.,[5] could be associated with a higher rate of recurrence by this systematic review, such as the shorter time after the first episode, low BMI and LV middle third hypercontractility. In this study, the STROBE[8] was used in order to evaluate and select the studies found, while Singh et al. used the "Quality of Reporting of Observational Longitudinal Research",[21] and special focus was given to TTS recurrence rate, selecting articles that reported a minimum of 3% of recurrence rate, which may have turned this systematic review into more task-specific.

Given the local experience of the authors, a TTS prevalence of 3.2% was observed in patients initially suspected of ST elevation acute myocardial infarction and there were no recurrences in the 1-year ambulatory median follow up.

No data about the risk of recurrence when submitted to the same stress factor again were found. Whether a second exposure to the same stressor should be avoided may be a matter of interest for future studies.

Among the limitations of this review, as those of the selected studies, are: the fact that some studies were performed in a single population without external validation; the lack of more clinical details of the patients who presented recurrence (most articles do not bring data from the patients that recurred in an individual basis, thus it was not possible to analyze the combining data from individual patients together); in addition to the scarcity of studies related to the topic, although this factor did not prevent this systematic review realization to be carried out. A strong methodology, with a high cut-off point in STROBE and the use of the PRISMA model, provided a solid basis for consistently constructing this systematic review.

Conclusion

Considering the above, female gender, lower BMI, LV middle third hypercontractility, and shorter time after the first episode were associated to a greater recurrence chance. Patient's age and electrocardiographic presentation, related to the manifestation of a second TTS episode, deserve to be better investigated by studies with larger populations.

Author contributions

Conception and design of the research and Acquisition of data: Campos FAD, Ritt LEF; Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Campos FAD, Ritt LEF, Costa JPS, Cruz CM, Feitosa Filho GS, Borges QO, Darze ES.

Potential Conflict of Interest

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Ethics approval and consent to participate

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

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Takotsubo Syndrome: A Recurrent Disease?

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Short editorial related to the article: Factors Associated with Recurrence in Takotsubo Syndrome: A Systematic Review

Several terms (such as happy heart syndrome, broken heart syndrome, and takotsubo cardiomyopathy) have been used to refer to the recently defined Takotsubo Syndrome (TTS). The first case of TTS was described in Japan (Hiroshima City Hospital) in 1983 and a report of five cases was published in a Japanese medical textbook in 1990.[1]

However, in contrast to other cardiomyopathies that are usually not transient in nature, TTS is characterized by a temporary wall motion abnormality of the LV in the absence of pheochromocytoma, myocarditis and shares common features with acute coronary syndrome (ACS) similar symptoms at presentation, ECG abnormalities, elevated cardiac biomarkers, as well as a comparable in-hospital mortality with ST-segment elevation myocardial infarction (STEMI) and non-STEMI, specifically in terms of a microvascular ACS form.[2] The European Society of Cardiology (ESC) has also established the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria), which implement a diagnostic algorithm and assign a score to TTS.[3]

As the typical Takotsubo symptoms are sudden onset of chest pain, breathlessness or collapse, these patients have an initial belief that they are experiencing acute coronary syndrome. Approximately 1%–3% of all patients who present with symptoms consistent with ACS and undergo coronary angiography, are identified to have TTS.[4]

The high level of catecholamine seems to be due to hyperactivation of the hypothalamus-pituitary gland-adrenal system in response to an exogenous trigger, which is not always easily recognized. These findings suggested a potential heart-brain interaction in the pathophysiology of TTS, the role of the link between the heart and brain and that of triggering factors and gender, and the reasons why this syndrome displays different phenotypes and sometimes recurs.[5]

At the beginning of the studies, a fundamental characteristic of Takotsubo is the spontaneous recovery of the LV ejection fraction, which returns to normal or near normal in all patients over a variable period of time (days to weeks).[6]

Keywords

Takotsubo Cardiomyopathy/diagnosis; Takotsubo Cardiomyopathy/etiology; Biomarkers/blood; Catecholamines/blood; Estrogens/blood.

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However, TTS may recur, with a recurrence rate estimated to be 1.8% per-patient year.[7] Because recurrence is not frequent, it precluded further analyses of predictors and outcomes. TTS recurrence is defined as new wall motion abnormalities in the absence of obstructive coronary disease after recovery of the index TTS events.[8]

In this study published in the Arquivos Brasileiros de Cardiologia aims to analyze the main factors associated with Takotsubo syndrome recurrence. The global recurrence rate, considering the selected studies, was 3.8% in a follow up that ranged from 5 to 17 years. Female gender, time from the first episode of the syndrome, low BMI and midventricular obstruction were reported as potential predictors of TTS recurrence.[9]

There is increasing recognition of gender differences in the presentation, triggers, severity, and complications of TTS. The current literature shows a female preponderance in the number of patients with TTS (female to male ratio 9:1).[7] Various explanations have been offered, including factors such as estrogen deficiency, underlying triggers, and a heightened autonomic nervous system response.[6,7]

In a systematic review and meta-regression of long-term prognosis and outcome predictors in Takotsubo Syndrome, of 54 studies that included a total of 4,679 patients, during a median follow-up of 28 months (interquartile range: 23 to 34 months), the annual rate of total mortality was 3.5% with an annual rate of recurrence of 1.0%. A meta-regression analysis showed that long-term total mortality in each study was significantly associated with older age ($p = 0.05$), physical stressor ($p = 0.0001$), and the atypical ballooning form of TTS ($p = 0.009$). Neurological disorders (hazard ratio: 1.76; $p = 0.048$) and psychiatric disorders (hazard ratio: 1.77; $p = 0.033$) emerged as independent predictors of recurrence. These findings suggest that TTS needs a strict follow-up, due to the possibility of severe adverse events over the long term.[10,11]

Takotsubo cardiomyopathy has 4 main anatomic variants and a category of other rare variants: Apical, typical, or classic variant, Midventricular variant, Basal, reverse, or inverted variant and the Focal variant. The classic and most frequent variant of Takotsubo cardiomyopathy usually affects the left ventricular apex. However, several cases have described an atypical variant.[12] Relative distributions of the beta-2 adrenoceptors are believed to determine the different anatomic variants. A variable TTS pattern at recurrence is common in up to 20% of recurrence cases.[8] Mid-left ventricular hypokinesia with basal and apical hypercontractility is reported for 14.6% of patients in the International Takotsubo Registry.

Recently, the multicenter GEIST (German Italian Stress Cardiomyopathy) Registry included 749 consecutive patients with TTS, enrolled from 9 centers. Overall, TTS recurrence was

documented in 30 patients (4%) at a median follow-up of 830 days. Cardiovascular risk factors, such as arterial hypertension were significantly higher in the recurrence group. Interestingly, in 14 patients (46%), TTS was triggered by a new stressor compared with the first TTS event (9 patients experienced an emotional trigger, and 5 patients experienced a physical trigger) and up to 2 TTS recurrences were documented in 6% of cases.[10]

There remain many unanswered questions regarding this complex syndrome. Interestingly, in this review the use of betablockers or other heart failure medications was not proved to reduce the chance of recurrence. Kato et al.,[11] showed that 59.6% of patients were on regular betablocker therapy on admission related to TTS recurrence, most of which were beta 1-selective compounds in 84.6%, suggesting that beta 1-selective antagonists might not prevent TTS recurrence and an optimal treatment still needs to be determined.[11]

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Exercise Intensity during 6-Minute Walk Test in Patients with Peripheral Artery Disease

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Abstract

Background: Non-supervised ground walking has been recommended for patients with symptomatic peripheral artery disease (PAD). However, the magnitude of the effort required by this activity and the characteristics of patients whose ground walking is more intense are unclear.

Objectives: To determine whether ground walking exceeds the ventilatory threshold (VT), a recognized marker of exercise intensity, in patients with symptomatic PAD.

Methods: Seventy patients (61.4% male and aged 40 to 85 years old) with symptomatic PAD were recruited. Patients performed a graded treadmill test for VT determination. Then, they were submitted to a 6-minute walk test so the achievement of VT during ground ambulation could be identified. Multiple logistic regression was conducted to identify predictors of VT achievement during the 6-minute walk test. The significance level was set at $p < 0.05$ for all analyses.

Results: Sixty percent of patients achieved VT during the 6-minute walk test. Women (OR = 0.18 and 95%CI = 0.05 to 0.64) and patients with higher cardiorespiratory fitness (OR = 0.56 and 95%CI = 0.40 to 0.77) were less likely to achieve VT during ground walking compared to men and patients with lower cardiorespiratory fitness, respectively.

Conclusion: More than half of patients with symptomatic PAD achieved VT during the 6-minute walk test. Women and patients with higher cardiorespiratory fitness are less likely to achieve VT during the 6-minute walk test, which indicates that ground walking may be more intense for this group. This should be considered when prescribing ground walking exercise for these patients. (Arq Bras Cardiol. 2020; 114(3):486-492)

Keywords: Walk Test/methods; Peripheral Arterial Disease/complications; Physical Exertion; Exercise; Intermittent Claudication; Vital Capacity/physiology.

Introduction

Peripheral artery disease (PAD) affects approximately 12% of older adults in the United States[1] and 21.6% of the elderly population in Brazil.[2] Patients with symptomatic PAD (intermittent claudication) have impaired walking capacity,[3] lower muscular strength,[4,5] and several comorbid conditions.[6] In addition, patients with symptomatic PAD present poor cardiorespiratory fitness evidenced by lower peak oxygen consumption (VO_2) and worse walking economy than age-matched controls.[7] Therefore, in these patients, walking performed during everyday activities are done at relatively higher intensities than in age-matched controls.

Ventilatory threshold (VT) is an important marker of exercise intensity. Higher VT indicates that patients can sustain an increase in anaerobic metabolism during exercise.[8] In symptomatic PAD patients, lower VT is associated with lower walking tolerance and greater disease severit.[9,10] In addition, VT is most likely to be achieved before the onset of claudication pain.[11,12]

Ground walking have been widely used to assess walking impairment in PAD patients through a 6-minute walk test, as this is a main clinical outcome in this group.[13] Recently, it has also been used in home-based exercise programs. However, the intensity in which ground walking is performed by patients with PAD is unknown. From a practical point of view, understanding the magnitude of effort in the 6-minute walk test might support the use of over-ground as an exercise modality in PAD patients. Thus, the purpose of this study was to describe the intensity of the 6-minute walk test according to VT in patients with symptomatic PAD. We also analyzed the predictors of the achievement of VT during the 6-minute test.

Methods

The procedures of this study were approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center (protocol #2337). A written informed consent was obtained from each patient prior to their participation.

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Recruitment and Patients

PAD patients classified as Rutherford Grade I and Category 1 to 3 were evaluated at the Clinical Research Center at the University of Oklahoma Health Sciences Center. Patients arrived fasted, but were permitted to take their usual medications. Patients were recruited by referrals from the Health Sciences Center vascular clinics, as well as by newspaper advertisements for possible enrollment into an exercise study.[14,15] However, patients were included in the study if they fully met the following criteria: (a) graded treadmill test limited by intermittent claudication symptoms and (b) an ankle brachial index (ABI) ≤ 0.90 at rest, or an ABI ≤ 0.73 after exercise.[1]

Patients were excluded if they met any of the following criteria: (a) inability to obtain an ABI measure due to non-compressible vessels (ABI ≥ 1.40), (b) asymptomatic PAD determined from their medical history and verified upon the graded treadmill test, (c) exercise tolerance during progressive treadmill test limited by factors other than claudication symptoms (e.g. clinically significant electrocardiographic changes during exercise indicative of myocardial ischemia, dyspnea, poorly controlled blood pressure), (d) failure to achieve VT during treadmill exercise, (e) inability to complete the 6-minute walk test without stopping, and (f) failure to complete the testing within three weeks.

Study Design

This study was divided into three steps: 1) clinical examination, 2) graded treadmill test, and, 3) 6-minute walk test. Step 1 included evaluations for medical history, anthropometry, and ankle-brachial index. During step 2, patients performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain, in order to obtain the VT. In step 3, the 6-minute walk test was applied aiming to identify the patients who did not and those who did achieve VT (Figure 1). The details of all evaluations are described below.

Medical History and Anthropometry

Demographic information, height, weight, body mass index, waist circumference, claudication history, physical examination and comorbid conditions (osteoarthritis, obesity, hypertension, diabetes, dyslipidemia, metabolic syndrome and heart disease) were assessed at the beginning of the study by a physician. Obesity was defined as body mass index > 30 kg/m^2.[16] Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or use of anti-hypertensive medication.[16] Diabetes was defined as fasting blood glucose ≥ 126 mg/dl, or use of hypoglycemic medication.[17] Dyslipidemia was defined as triglycerides ≥ 150 mg/dl, LDL-C ≥ 130 mg/dl, total cholesterol ≥ 200 mg/dl or HDL-C ≤ 40 mg/dl (men) and ≤ 50 mg/dl (women), or use of lipid-lowering medication.[18] Metabolic syndrome was defined as three or more of the following components: (1) abdominal obesity (waist circumference >102 cm in men and > 88 cm in women), (2) elevated triglycerides (>150 mg/dl), (3) reduced HDL-C (< 40 mg/dl in men and < 50 mg/dl in women), (4) elevated blood pressure (> 130/85 mmHg), and (5) elevated fasting glucose (> 110 mg/dl), as well as diagnosis of diabetes.[19]

Ankle Brachial Index

ABI was obtained after 10 minutes of supine rest by measuring the ankle and brachial systolic blood pressure using Doppler technique in the brachial artery and both posterior tibial and dorsalis pedis arteries. The highest value between the two measurements of arterial pressure from each leg was recorded, and the leg yielding the lowest ABI was used in the analyses, as previously described.[20]

Graded Treadmill Test

A graded treadmill test was used to obtain the VT and to assess walking capacity. Patients performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain, as previously described.[21] The test started at 2 mph with 0% grade and the workload was increased 2% every 2 minutes. All patients were informed of the test protocol before being submitted to it. Oxygen consumption (VO_2) was continuously measured by a metabolic cart (Medical Graphics Corp., St Paul, MN), and averages of 30s were applied for analysis. The VT was visually detected by two experienced evaluators and defined as a nonlinear increase in respiratory quotient, carbon dioxide production and ventilation, as well as the increase in end-tidal oxygen pressure. The following variables were analyzed: oxygen uptake (VO_2), carbon dioxide output (VCO_2), ventilatory equivalent (VE), ventilatory equivalent for O_2 (VE/VO_2), ventilatory equivalent for CO_2 (VE/VO_2), end-tidal oxygen ($PETO_2$) and carbon dioxide partial pressures ($PETCO_2$), and respiratory exchange ratio, as previously described.[22] A third researcher compared the results to check possible discrepancies in the determination of VT between evaluators. In this case, the determination of VT was repeated by both evaluators and the third evaluator made the final determination. Patients not presenting any of these respiratory parameters during the progressive graded cardiopulmonary treadmill test were considered to not have achieved the VT and were therefore excluded from the sample.

Claudication Measurements and Peak Oxygen Uptake

The claudication onset time was defined as the walking time at which the patient first experienced leg pain during the treadmill test, and the peak walking time was defined as the walking time at which the patients could not continue walking due the leg pain. VO_2 peak was defined as the 30-second window with the highest VO_2 achieved during the treadmill test. Using these procedures, the test-retest intra-class reliability coefficients are r = 0.89 for claudication onset time and r = 0.93 for peak walking time.[24]

6-minute Walk Test

A trained technician administered the 6-minute walk test which was conducted in a 30-meter long corridor. Subjects were instructed to walk as many laps around the cones as possible while bearing a light weight (0.8 kg), portable oxygen uptake unit (COSMED K4 b^2, COSMED USA, Inc, Chicago, IL) which continuously measured oxygen uptake via indirect calorimetry. The technician was blinded to the VT results, and the test was performed following the standardized instructions, as previously described.[23] VO_2 was obtained breath-by-breath and then

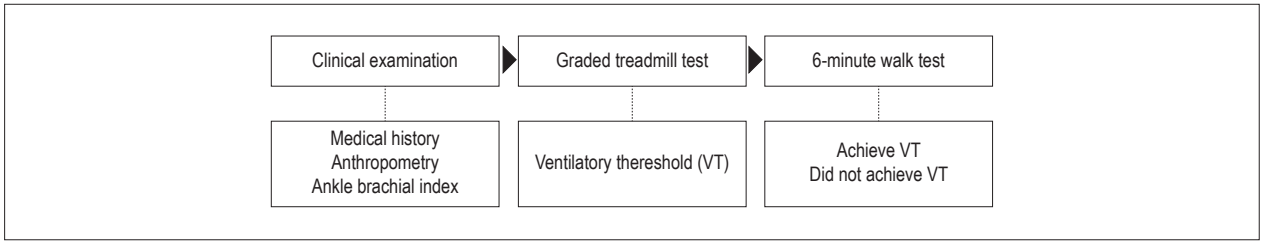

Figure 1 – *Study design.*

averaged per each minute during the test, which allowed for the identification of patients who achieved VT. For this, patients were supposed to have completed the test without stopping after intermittent claudication symptoms. Thus, patients were divided into two groups: those who did not achieve VT and those who did achieve VT during ground walking.

Statistical Analysis

All statistical analyses were made in the Statistical Package for the Social Sciences software – SPSS/PASW version 20 (IBM Corp, New York, USA). Normality of data was checked by the Shapiro-Wilk test. Continuous variables were summarized as mean and standard deviation, whereas categorical variables were expressed as relative frequency. Patients were grouped according to whether or not they achieved VT, and the clinical characteristics between groups were compared by the independent t-test for continuous variables and the chi-square test for categorical variables.

Multiple logistic regression was conducted to identify whether demographic data, cardiovascular risk factors, comorbid conditions, ABI and walking capacity are predictors of achieving VT during the 6-minute walk test. To this end, stepwise backward techniques were used to enter covariates into the model using only variables with $p < 0.30$ in the bivariate analyses. In the multiple regression, only variables with $p < 0.05$ remained in the final model. The Hosmer-Lemeshow test was used to assess the model's goodness-of-fit. The significance level was set at $p < 0.05$ for all analyses.

Results

One hundred and thirty-three patients performed the 6-minute walk test. Among them, 63 stopped during the test due to claudication symptoms and were excluded from the analysis. Among the 70 patients who did not stop during the test, the VT was achieved during the 6-minute walk test by 42 patients (60%) and was not achieved by 28 patients (40%). Table 1 shows the comparison of clinical characteristics of patients who achieved and who did not achieve the VT during 6-minute walk test. VO_2 at VT obtained during the treadmill test was higher in patients who did not achieve VT during the 6-minute walk test in comparison with patients who achieved it ($p < 0.05$). Moreover, the ankle brachial index was higher in patients who did not achieve VT in comparison with patients who did ($p < 0.05$).

Table 2 shows the predictors to achieve the VT during the 6-minute walk test. Women were less likely to achieve VT during 6-minute walk test than men ($p < 0.05$). Moreover, patients with higher VO_2 at VT were less likely to achieve the VT during 6-minute walk test ($p < 0.05$).

Table 3 shows the comparisons by sex. In women, the prevalence of obesity was higher and cardiorespiratory fitness was lower as compared to men ($p < 0.05$). VO_2 peak in both the 6-minute walk test and the treadmill test was higher in men than in women ($p < 0.05$).

Discussion

The main findings of the study were: a) 60% of symptomatic PAD patients did achieve the VT during 6 minute-walk test, and b) women and patients with higher VO_2 at VT obtained during the treadmill test were less likely to achieve VT in the 6-minute-walk test.

VT is defined as the exercise intensity above which metabolic predominance changes from aerobic to anaerobic,[8] providing information about aerobic capacity during exercise. In patients with symptomatic PAD, VT have been associated with walking tolerance and disease severity.[9,10] In this study, 60% of patients achieved VT in the 6-minute walk test, indicating that for most patients with symptomatic PAD this ground walking is a relatively high-intensity exercise. This could partially explain the lower daily physical activity levels and higher time spent in sedentary behavior in these patients.[25,26] Therefore, the intensity in which ground walking is performed by most patients with PAD demands a fairly high effort, which suggests that this exercise has potential to improve functional capacity of patients with PAD and, therefore, endorses the use of home-based programs to improve cardiorespiratory fitness.

On the other hand, almost 40% of the patients did not achieve VT in the 6-minute walk test. The most plausible hypothesis for part of PAD patients not achieving VT was that the ground walking was not intense enough to elicit VT achievement. This hypothesis is corroborated by the fact that patients with higher cardiorespiratory fitness were less likely to achieve the VT during ground walking.

Women were less likely to exceed VT during the 6-minute walk test than men, indicating that ground walking is performed at a lower relative intensity by women than by men. This is surprising given previous studies[27,28] have shown that women with symptomatic PAD have lower walking capacity,[29,30] are less physically active[29,30] and report more barriers to practicing physical activity compared to men.[31] In addition, women present more adverse calf muscle characteristics and lower VO_2 peak than men.[32]

Table 1 – Characteristics of patients with intermittent claudication included in the study

Variables	Did not achieve VT (n = 28)	Achieved VT (n = 42)	p
Age, years	66.1 ± 9.9	66.9 ± 10.2	0.745
Body mass index, $kg^{-1}m^2$	29.9 ± 6.0	29.0 ± 5.6	0.486
Ankle brachial index	0.85 ± .21	0.71 ± .21	0.013
Claudication onset time, seconds	297 ± 192	271 ± 191	0.572
Peak walking time, seconds	576 ± 266	541 ± 219	0.542
Six-minute pain-free distance, meters	189 ± 144	214 ± 96	0.417
Six-minute walk test, meters	382 ± 73	399 ± 67	0.332
VO_2 at VT, $mL.kg^{-1}.min^{-1}$	12.0 ± 2.4	10.1 ± 1.9	< 0.001
VO_2 peak, $mL.kg^{-1}.min^{-1}$	13.9 ± 3.7	13.5 ± 3.4	0.627
Sex, % women	52	48	0.109
Diabetes mellitus, % yes	46	54	0.419
Hypertension, % yes	41	59	0.789
Dyslipidemia, % yes	38	62	0.436
Coronary artery disease, % yes	13	88	0.093
COPD, % yes	53	47	0.211

VT: ventilatory threshold; VO_2: oxygen uptake; COPD: chronic obstructive pulmonary disease.

Table 2 – Multiple logistic regression model predicting achieved ventilatory threshold during the 6-minute walk test in patients with intermittent claudication

Dependent variable	Independent variables	β (EP)	OR	95%CI	p
Achieved VT	Sex, men = reference	-1.72 (0.65)	0.18	0.05 – 0.64	0.008
	Oxygen uptake at VT, $mL.kg^{-1}.min^{-1}$	- 0.58 (0.17)	0.56	0.40 – 0.77	< 0.001

VT: ventilatory threshold; β (EP): Regression coefficient (error-standard); OR: odds-ratio. 95% CI: 95% confidence interval. Hosmer-Lemeshow test: $\chi^2 = 9.607$, $p = 0.298$.

Table 3 – Comparison of clinical parameters of intermittent claudication between men and women included in the study

Variables	Women (n = 28)	Men (n = 43)	p
Age, years	64.9 ± 9.5	67.6 ± 10.3	0.265
Body mass index, $kg^{-1}m^2$	31.1 ± 6.6	28.3 ± 5.0	0.044
Ankle brachial index	0.80 ± .23	0.75 ± .22	0.258
Claudication onset time, seconds	241 ± 164	306 ± 203	0.330
Peak walking time, seconds	507 ± 196	585 ± 256	0.180
VO_2 at VT, $mL.kg^{-1}.min^{-1}$	10.3 ± 2.3	11.3 ± 2.2	0.035
VO_2 peak in treadmill test, $mL.kg^{-1}.min^{-1}$	12.0 ± 2.9	14.7 ± 3.4	0.001
VO_2 peak in 6-MWT, $mL.kg^{-1}.min^{-1}$	11.1 ± 3.0	12.5 ± 2.1	0.034

6-MWT: 6-minute walk test.

Some practical messages can be draw from this study. The 6-minute walk test is harder for men and patients with low cardiorespiratory fitness. Is recommended that exercise training intensity should be performed above VT in order to improve cardiovascular function in cardiac patients and the elderly.[33,34] Considering that the 6-minute walk test simulates an over-ground walk, the current results support its use as an exercise mode to increase both daily physical activity and cardiorespiratory fitness in men and in patients with low cardiorespiratory fitness. However, in women and in patients with higher cardiorespiratory fitness, over-ground walking may not be enough to improve activity and fitness levels.

The cross-sectional design of this study is a limitation, as no causality can be inferred. Patients with severe cardiac disease and asymptomatic PAD or PAD more severe than claudication were excluded in the screening; therefore, the results can be extended only to our current sample of patients with claudication. Given we were not able to precisely identify VT in patients who stopped during the 6-minute walk test, generalization is also

restricted to these patients. In addition, to accurately detect the VT in the 6-minute walk test, we only included patients that did not stop while performing it. These findings are also limited by the relatively small sample size, particularly when it comes to patients who did not achieve the VT.

Conclusion

More than half of patients with symptomatic PAD achieved VT during the 6-minute walk test. Men and patients with lower cardiorespiratory fitness are more likely to achieve VT during the 6-minute walk test.

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Author contributions

Conception and design of the research: Farah BQ, Dias RR, Cucato G, Gardner A; Acquisition of data: Montgorery P, Gardner A; Analysis and interpretation of the data: Farah BQ, Dias RR, Gardner A; Statistical analysis: Farah BQ; Obtaining financing: Gardner A; Writing of the manuscript: Farah BQ, Dias RR, Cucato G; Critical revision of the manuscript for intellectual content: Montgorery P, Gardner A.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Oklahoma Health Sciences Center under the protocol number 2337. 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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Exercise and Six-Minute Walk Test in Lower Extremity Occlusive Peripheral Arterial Disease

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Short Editorial related to the article: Exercise Intensity during 6-Minute Walk Test in Patients with Peripheral Artery Disease

The article "Exercise Intensity During 6-min Test in Patients with Peripheral Artery Disease"[1] provides original, practically useful information to be considered in the diagnosis, prognosis and mainly in the functional assessment that allows a better prescription of physical exercise in the medical treatment of the disease. The study was conducted with the aim of determining whether overground walking would allows the detection of the first ventilatory threshold, also known as anaerobic threshold (AT), in symptomatic patients with lower extremity occlusive peripheral arterial disease (LE-OPAD). AT is a marker of exercise intensity, useful for the determination of the optimal zone for physical training focused on improvement in cardiorespiratory fitness.[2]

LE-OPAD is an important public health problem. According to global epidemiology report, the disease affected 202 million individuals in 2010, and 237 million in 2015, with a 22% increase during this period.[3] The association of OPAD with major cardiovascular events (MACE) has been well documented; in the severe stage of the disease, with presence of critical ischemia, there is a high risk of cardiovascular events, lower limb amputation and death,[4] with association with elevated levels of cardiac troponin and N terminal pro-brain natriuretic peptide (NT-proBNP).[5]

LE-OPAD is highly suspected in the presence of pain in lower limbs when walking, without apparent orthopedic problem, and an ankle brachial index (ABI) lower than 0.90 at rest. Walking tests should be performed to help in the diagnosis, particularly when the ABI is greater than 0.91, and in the functional classification and exercise prescription.[6] Field walking tests allow the identification of intermittent claudication, with determination of the distance walked to symptom onset (initial claudication) and to maximum functional limitation (absolute claudication). In treadmill tests, the measurement of the ABI has been proposed, both at rest and after exercise. The presence of the disease is strongly suspected when ABI is reduced by at least 20% and 30mmHg after exercise compared with rest.[7] However, resting ABI, which has been widely used in clinical practice, can produce false negative results, which is of particular importance in patients with poorly compressible arteries. In the study by Tóth-Vajna et al.,[8] almost one fourth of the individuals with a diagnosis had poorly compressible arteries or was considered symptomatic with a negative ABI. Therefore, in case of suspicion of LE-OPAD, a deeper investigation is recommended despite normal ABI values.

In symptomatic patients, exercise can affect morbidity and mortality, with improvement of symptoms and quality of life and increase of maximum walking distance, and thus must be part of the optimized treatment.[6,7] Therefore, all patients with intermittent claudication should receive optimized medical treatment, i.e., a combination of lifestyle changes with pharmacological therapy, considering the body of evidence showing a reduction in cardiovascular events and improvement of the outcomes related to the lower limbs.[9]

Physical training has been shown to be safe, and the walking tests with claudication symptom induction considered the best option.[6,7] However, when walking tests cannot be performed, other exercises such as cycling, resistance exercise and exercises using an upper extremity ergometer have been shown effective.[5,6] It is worth mentioning that patients with critical ischemia cannot perform physical exercises, but should be considered eligible as soon as the interventionist approach is successfully completed.[10,11]

Many clinical trials have consistently shown that supervised treadmill training improves the gait of patients with LE-OPAD. In a meta-analysis, Fakhry et al.[12] evaluated 1,054 patients from 25 studies and concluded this type of exercise training was effective in increasing maximum walking distance (mean increase of 180 meters) and pain-free walking distance (mean increase of 11 meters).[12]

Three randomized clinical trials that evaluated 493 patients with LE-OPAD, showed that home-based exercise programs that included behavior change techniques, improved walking capacity, and higher performance gain on the six-minute walk test compared with supervised treadmill training.[13,14] In other words, while supervised treadmill walking programs are superior in the improvement of treadmill walking performance, the home-based programs are superior in improving overground walking, which is more related to daily life activities.[14]

Although home-based overground walking programs have been recently shown effective in improving the performance in daily life activities, apart from being more convenient and cheaper compared with supervised treadmill exercise,[14] small older studies showed little or no benefit. Therefore, the American College of Cardiology/American Heart Association

Keywords

Peripheral Arterial Disease; Intermittent Claudication; Anaerobic Threshold; Exercise; Walk Test; Physical Activities of Daily Living.

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2006 Practice Guidelines state that there was no evidence to support the recommendation for the patient "to go home to walk". However, since 2011, successful clinical trials with home-based exercise interventions that included much more than recommendations like "go home to walk", such as the instructions for patients to stablish exercise goals and monitor their exercises, thereby promoting a change of focus. Even adding behavior change techniques, home-based exercises require fewer resources and less cost compared with supervised treadmill exercise, and thus are more accessible and probably more acceptable by many patients, which may ultimately lead to higher treatment compliance.[13]

In functional assessment of patients with LE-OPAD, six-minute walk test has gained popularity as a validated measure and better related to physical activity levels compared with the treadmill test, with no association with the learning effect of repeated tests.[13] In patients with LE-OPAD, compared with treadmill tests, changes in the performance on six-minute walk test have been more associated with outcomes as mortality and loss of mobility.[14]

In the paper "Exercise Intensity During 6-min Test in Patients with Peripheral Artery Disease",[1] AT was reached in 60% of patients, and peak oxygen consumption and ABI during treadmill test were higher in the other 40% patients. The six-minute walk test was more difficult for women and patients with low cardiorespiratory fitness, indicating a higher relative intensity of exercise effort for these patients. This is relevant in practice, since it is recommended that exercise training be performed above the AT aiming at improving cardiovascular function.[15] Therefore, the study corroborates the use of overground walking as the exercise mode of choice for women and patients with low cardiorespiratory fitness. More intense exercise training should be considered for men and patients with better cardiovascular fitness including cycle and elliptical ergometers, and even treadmills, to reach the AT and consequently improve physical fitness.

Finally, it is worth pointing out that the article "Exercise Intensity During 6-min Test in Patients with Peripheral Artery Disease" provides original and interesting results, but since it is an observational, monocentric study, it has limitations that prevent firm conclusions being drawn. Therefore, the study provides important information that are applicable to clinical practice and should be considered as the subject of future research.

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Short Editorial

Software for Post-Processing Analysis of Strain Curves: The D-Station

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Abstract

Background: **The use of speckle-tracking echocardiography for evaluation of cardiac function has great applicability in different scenarios. The broad use of this method requires tools that allow the extraction of relevant data from strain curves and inclusion of these data in traditionally used parameters.**

Objectives: **The present study aimed to present and validate a free software, called D-station, for analysis of strain curves.**

Methods: **From raw data files, the D-Station determines the phases of the cardiac cycle, and simultaneously exhibits the strain and strain rate curves of different cardiac chambers. Validation of the software was done by global longitudinal strain (GLS), and the analyses were performed: 1) graphical comparison of EchoPAC and D-Station paired measurements in relation to equality line; 2) by coefficient of correlation of these measurements; 3) test of hypothesis ($p > 0.05$); and 4) Bland-Altman analysis.**

Results: **The Spearman's rho correlation coefficient indicated a strong correlation between the measurements. Results of the test of hypothesis showed a p-value = 0.6798 >> 0.05, thus also indicating an equivalence between the softwares. The Bland-Altman analysis revealed a bias ≤ 1% and dispersion ≤ 2% between the measurements. The tests showed that, for GLS values lower than 10%, there was a trend for higher percentage difference between the values, although the absolute values remained low.**

Conclusion: **The D-Station software was validated as an additional tool to the EchoPAC, which uses the raw data from the strain and strain rate curves exported from a proprietary software. (Arq Bras Cardiol. 2020; 114(3):496-506)**

Keywords: **Cardiovascular Diseases/diagnostic imaging; Prognosis; Echocardiography/methods; Ventricular Dysfunction, Left/physiopathology; Speckle Tracking.**

Introduction

Analysis of cardiac strain by speckle tracking echocardiography has great applicability in different scenarios, including clinical cardiology practice[1] and research,[2] providing information about local and global mechanics of cardiac chambers.

Although left ventricular global longitudinal strain (GLS) is a robust parameter of cardiac function,[1-3] it assesses cardiac strain between the onset of isovolumetric contraction and the end of ventricular ejection. Therefore, valuable information of other phases, like isovolumetric relaxation, is not measured by the GLS.

Therefore, other tools are needed to obtain relevant data from the strain curve that can be used as additional methods to currently used ones.

Most of offline softwares supplied by different manufacturers (proprietary softwares) has preset analysis modes and parameters of cardiac strain. If on the one hand, this can make the software simpler and user-friendlier in daily clinical practice, on the other, makes it difficult to use this technology in research. In addition, the access to these tools may be limited and expensive.

International reference centers for study on cardiac strain usually have customized softwares that allow offline processing, without exclusive rights established by the manufacturers, and adjustments to their needs.[4]

The present study aims demonstrate the use of a new, free software called D-station, as an additional tool for the analysis of strain curves provided by any proprietary software. Besides, the study aims to validate this new software by comparison of its GLS values with GLS values obtained by the EchoPAC (GE) software.

Methods

D-Station: post-processing software for strain curve analysis

D-Station is a free, customized software written in Python 3, designed to enable an offline post-processing of the strain curves. The steps of execution of D-Station

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program are illustrated in Figure 1. D-Station does not replace pre-existing platforms, but rather expands the possibilities of post-processing.

Separation into phases

Each strain curve corresponds to one or more cardiac cycles in certain region of the cardiac chamber and can be divided into the mechanical phases of this cycle. According to previous studies,[4] definition of these phases relies on the times of opening and closing of the aortic and mitral valves, on the time of electrical events, obtained from electrocardiogram (ECG) waves, as well as the time of the onset of the first and the second QRS complex, and onset of P-wave.[5,6] The ECG curves match well with the strain curve and the strain rate (SR) in the files.

Considering the onset of the cardiac cycle at the onset of the QRS complex, six phases were defined, as follow (in order of occurrence): electrical mechanical coupling (EMC), isovolumic contraction (IC), ejection phase (Ejec), isovolumic relaxation, early filling (E), atrial contraction (A). A detailed description of definitions of each phase of the cardiac cycle is provided in the supplementary material.

Algorithm of reading of the signs and parameters calculation

The program entries are: 1) time of opening and closing of aortic and mitral valves; 2) raw data files containing the strain curves or strain rate; 3) identifier of the test; and 4) visualization option selected by the user. Further information can be found in the software manual, presented in the supplementary material of the study.

Six visualization options are available in the current version of the software:

- *Strain - LV* (left ventricular strain), *strain rate - LV* (left ventricular SR) and ECG;
- *Strain - LV*, *strain - LA* (left atrial *strain*) and ECG;
- *Strain - LV*, *strain rate - LA* and ECG;
- *Strain - LV*, *strain - RV* (right ventricular strain) and ECG;
- *Strain - LV*, *strain rate - LV* and ECG, where *SR* is obtained from the strain curves;
- *Test option (CircAdapt interface): strain - LV* and *strain rate - LV*

In all these options, curves are exhibited simultaneously as shown in Figure 2.

From raw data containing information of three-, four-, and two-chamber planes, left ventricular strain curves can be visualized, according to the model of the 18 segments proposed by the American Heart Association (AHA).[7]

Processing of the raw data sheets consists in changing the format to optimize the software functioning. In addition, due to small changes in heart rate on ECG curves, the four-chamber apical view was adopted as standard. After formatting of the sheets, a picture containing strain, SR and ECG curves is exhibited. The user should then define three points in the figure – the onset of QRS complex, the onset of P-wave and the onset of the second QRS complex.

Based on the values obtained form these points and timing of the opening and closing of the valves, it is possible to determine each phase of the cardiac cycle. The D-station terminal exhibits the time points of each of these phases, as well as the values of each calculated parameter. The user can decide between a picture containing the curves of cardiac chambers of interest (Figure 3) or the picture containing the points used in the parameters' calculation.

Event timing and calculated parameters

Each of the longitudinal strain curves presented in Figure 3 has an important event for the calculation of the software's parameters: the peak systolic strain, defined as the peak value during systole, according to the EACVI/ASE.[7]

The peak systolic strain of each segment is used for calculation of GLS, defined as the arithmetic mean of peak systolic strain values of all segments.

All these possibilities of post-processing allow and/or facilitate the analysis of new parameters, including the strain/SR of left and right atrium, right ventricular strain and diastolic recovery (diastolic stunning)[8] for example.

Algorithm for recognition of the peak systolic strain

The D-Station defines the peak systolic strain as the most negative strain value between the onset of the QRS and the AVC. This contrasts with the EchoPAC software, which determines the peak systolic strain according to the criterion presented in Figure 4.

Validation of the D-Station: database and statistical analysis

To validate the D-Station software, files containing strain curves of 48 individuals were obtained from the database of the Division of Echocardiography of *Hospital Beneficiencia Portuguesa de São Paulo*. We did not perform a sample calculation, and hence a convenience sample was selected by retrospective analysis of the database. All tests were performed

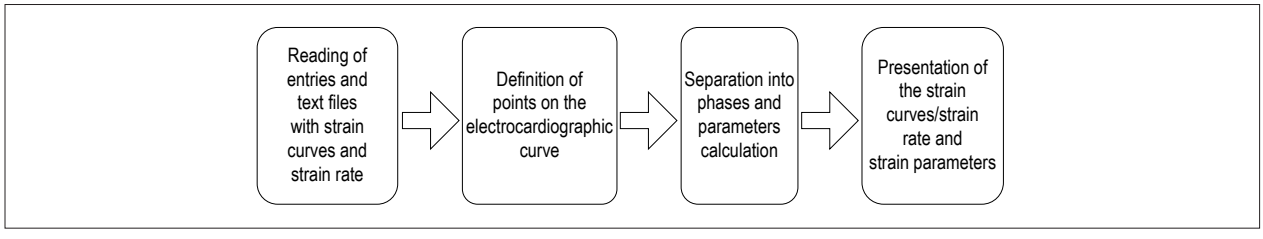


Figure 1 – *D-Station algorithm. ECG: electrocardiogram.*

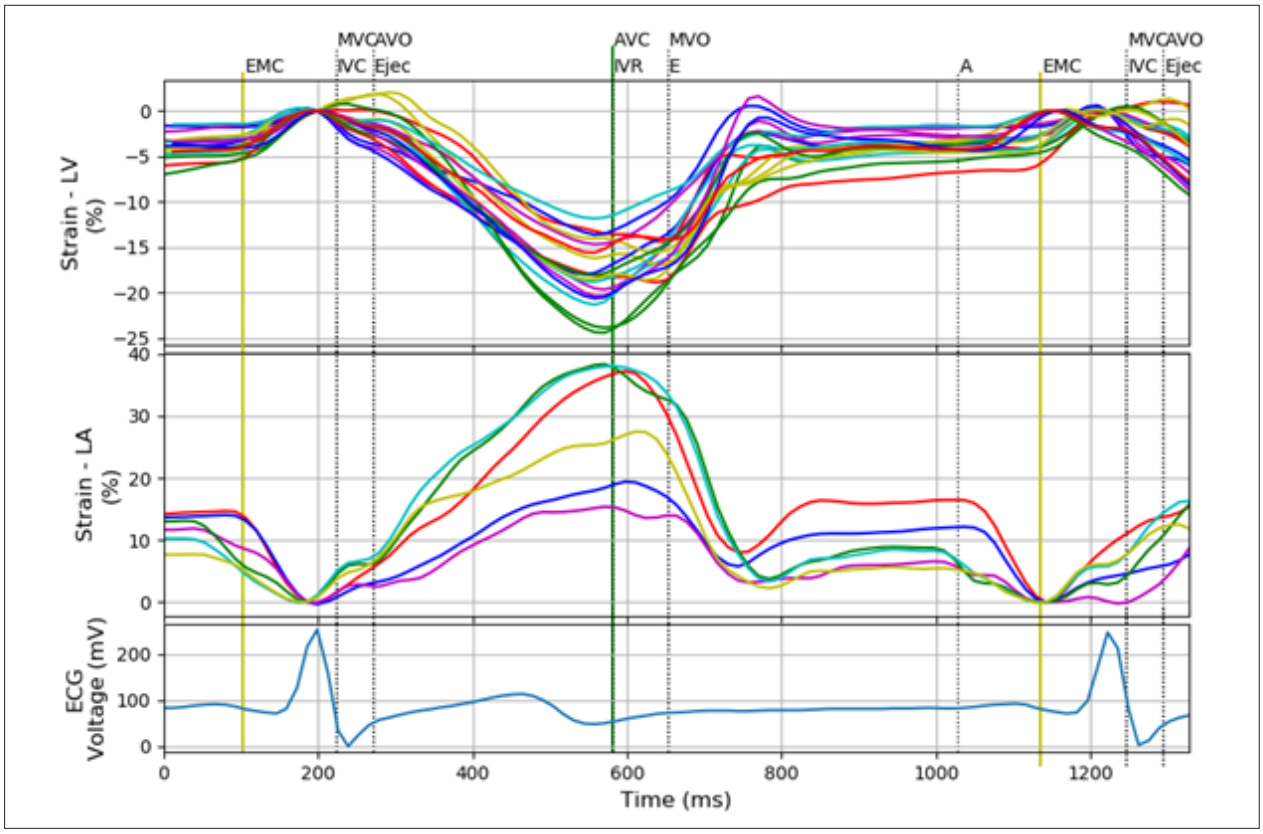


Figure 2 – *Left ventricular strain, left atrial strain, and echocardiographic curves with division into cardiac cycle phases. Eighteen strain curves corresponding to 18 segments of the left ventricle, six left atrial strain curves, and one electrocardiographic signal. Colors of the strain and strain rate curves correspond to those attributed to the segments by the proprietary software; MVC: mitral valve closure; AVO: aortic valve opening; AVC: aortic valve closure; MVO: mitral valve opening.*

after participants signed an informed consent form. The study was approved by the Ethics Committee of the institution (CAEE approval number 91350318.4.0000.5483).

The time of opening and closing of the mitral and aortic valves were registered. Some test results showed more than one event time registered; tests with discrepancies of time higher than 10 ms were excluded.

The cardiac cycle with the best image quality in the apical three- four- and two-chamber view was selected. In case of three cycles with poor-quality image, the last cycle was selected. The endocardial board was defined by delineation of the region of interest using the option *Q-analysis* of the EchoPAC software. A visual inspection of the tracking quality was made, which was confirmed by the "approve" option, and finally the GLS_EchoPAC value was registered. In case of poor-quality tracking (by visual inspection), this process was repeated. Tests with two or more segments with suboptimal quality were excluded.

The raw data of the strain curves were extracted using the "Store Trace" option, which generates .txt files that are used in data processing in D-Station.

The GLS was chosen as a parameter of validation of measurement equivalence in the EchoPAC processing (a well-established technique – gold standard) and the D-station (the proposed technique), showed in Table 1.

Methods used in the analyses:

a) Normality test of GLS obtained by EchoPAC, D-Station and the differences (EchoPAC – D-Station), using a graphical method (Q-Q plot), followed by a statistical method (Shapiro-Wilk test) to confirm normality assumption found by the graphical method;

b) Graphs of GLS by EchoPAC and D-Station in case of equality or coefficient of correlation (Pearson's correlation or Spearman's correlation for normal and non-normal distribution, respectively, of EchoPAC and D-Station data);

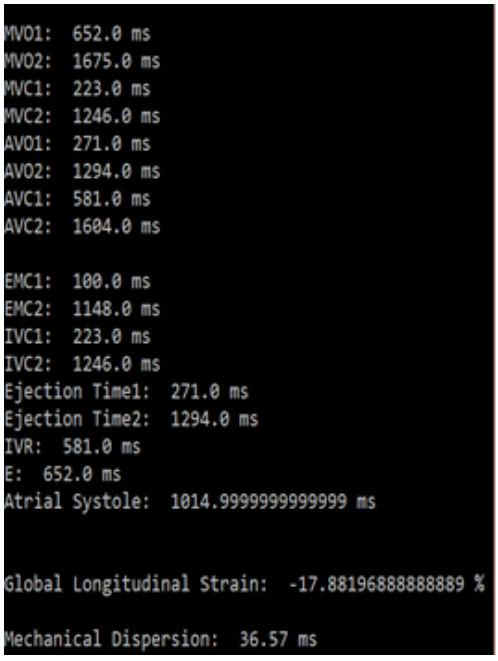
c) Test of the hypothesis of difference between GLS values by EchoPAC and D-Station GLS, paired data, level of significance of 5% by Student's t-test or the non-parametric Wilcoxon test in case of normal and non-normal distribution of data, respectively.

d) Agreement test by Bland-Altman plot[9,10]

The Stats and the BlandAltmanLeh packages of the R software version 3.5.2 (2018-12-20) were used, which has the necessary commands and outputs for p-value calculation and Bland-Altman analysis.

Validation criteria

From the clinical point of view, the criteria used to determine whether D-Station can be used as an alternative method to EchoPAC (equivalence), were the following:



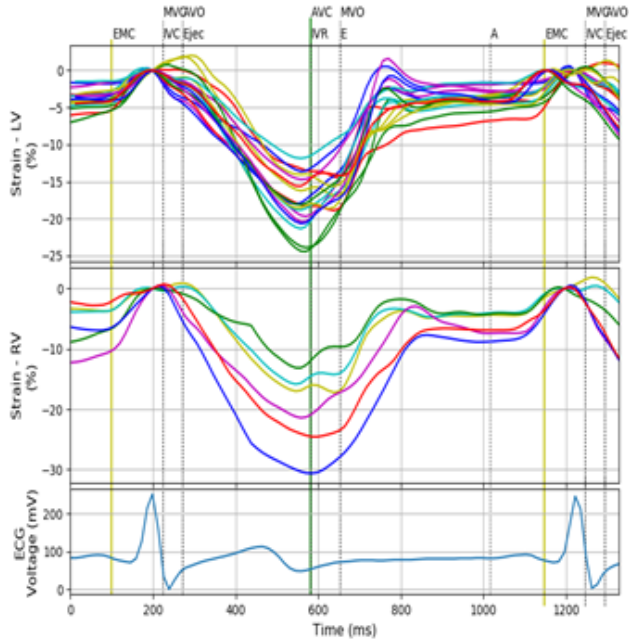


Figure 3 – *Simultaneous visualization of strain longitudinal curves of the left (18 segments) and the right (six segments) on the right. Time of the onset of the phases and parameters calculated in the terminal on the left. Other configurations can be accessed through the options available; MVC: mitral valve closure; AVO: aortic valve opening; AVC: aortic valve closure; MVO: mitral valve opening.*

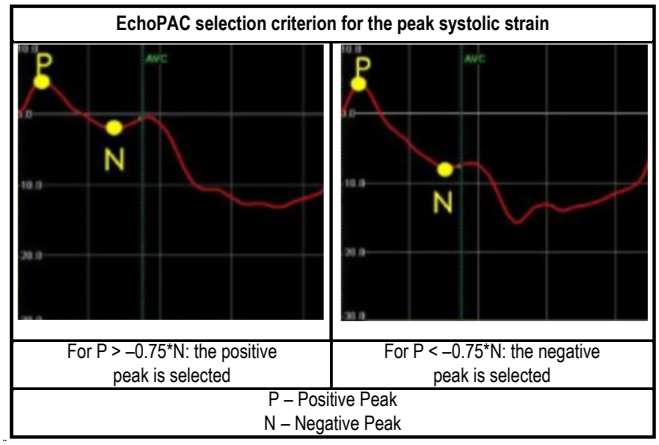


Figure 4 – *EchoPAC selection criterion of the peak systolic strain.*

a) Normality test

The analysis using the Q-Q plot is visual and hence subjective. If data are normally distributed, the points lie on a straight line constructed with data analyzed.

The assumption of normality (Shapiro-Wilk test) was accepted if p-value was > α (level of significance = 5%).

b) Spearman correlation coefficient ≥0.95.

c) Hypothesis testing: p-value>0.05 (equivalence between the measurements)

Ho: mean difference (EchoPAC - D-Station) = 0

Ha: mean difference ≠ 0

d) Bland-Altman

- Systematic error (bias) ≤ 1%
- scattering of the data ≤ 2%

(*) Please note that the unit of measurement of GLS is % and therefore these values refer to absolute variation.

Results

Simultaneous visualization of the curves in different cardiac chambers

The D-Station software provides the simultaneous display of all strain curves and SR of different cardiac chambers, allowing the study of the interaction between them. Additional options

Table 1 – Global Longitudinal Strain (%) obtained by EchoPAC and D-Station

Subject	GLS_Echopac	GLS-D-Station	Subject	GLS_Echopac	GLS-D-Station	Subject	GLS_Echopac	GLS-D-Station
1	–17.90	–17.88	17	–19.00	–19.03	33	–24.40	–24.62
2	–7.90	–9.50	18	–16.90	–16.82	34	–19.10	–19.57
3	–10.50	–11.10	19	–19.500	–16.68	35	–7.40	–6.46
4	–8.50	–8.19	20	–19.80	–19.83	36	–2.70	–3.37
5	–13.30	–13.55	21	–16.70	–17.04	37	–5.70	–5.22
6	–18.40	–18.26	22	–20.50	–20.93	38	–4.50	–4.32
7	–4.60	–4.21	23	–14.90	–14.71	39	–10.50	–9.83
8	–21.60	–21.48	24	–20.20	–19.76	40	–9.40	–10.95
9	–16.20	–16.36	25	–17.80	–18.19	41	–10.60	–10.47
10	–11.90	–11.41	26	–20.10	–20.47	42	–11.10	–11.15
11	–8.80	–7.33	27	–17.30	–17.60	43	–3.20	–3.69
12	–17.30	–17.23	28	–17.50	–16.96	44	–8.20	–8.64
13	–20.40	–20.32	29	–21.20	–20.28	45	–6.60	–6.01
14	–19.80	–19.40	30	– 23.00	–23.06	46	–6.90	–6.85
15	–16.40	–15.27	31	– 20.70	–19.91	47	–10.60	–10.11
16	–19.20	–19.38	32	–21.10	–21.22	48	–8.80	–9.28

including combinations of different displays can be easily added to the program, with consequent extraction of other parameters for the study on cardiac strain in different chambers simultaneously and by cardiac cycle. As example, exhibits the curves of left and right ventricles, which facilitates the analysis of the interactions between them.

CircAdapt Interface: generation of virtual cardiac models

The D-Station "Test" option has been designed to define the strain curve parameters without separation into phases. Consequently, the ECG curve is no longer necessary, and the program becomes compatible with the mathematical model CircAdapt. This model, combined with the MultiPatch Module, proposed by Walmsley et al.,[11] can retrieve the strain curves corresponding to simulations and the times of mechanical events, without ECG signals, as shown in Figure 6. Thus, the D-Station software can work with virtual cardiac models developed according to Walmsley et al.[11-14]

Applicability of machine learning techniques

Machine learning consists of a subset of artificial intelligence, capable of processing complex problems of interaction between variables and making accurate predictions. It has been widely used in different areas of cardiology. The storage format of entries and data obtained by the program allows the implementation of machine learning algorithms and thereby the automatic extraction of parameters, classification of a large number of signals and reading of space-time characteristics of the entire strain curve, as proposed by Tabassian et al.[15]

Validation analysis results

a) Normality testing of measures

Figure 7 shows the Q-Q plot of EchoPAC (Figure 7a), D-Station (Figure 7b) and EchoPAC - D-Station (Figure 7c). As can be seen in Figures 7a and 7b, several points are out of the red reference line, indicating that EchoPAC and D-Station data are not normally distributed. On the other hand, in Figura 7c, most of the points lie on or are very close to the red reference line (except for two points in the right upper corner), indicating that the difference between the measurements tend to be normally distributed.

Since the difference between measurements will be used in the hypothesis test, we sought to confirm the hypothesis of normality in the distribution of these differences obtained by the graphical method by using the Shapiro-Wilk test, which confirmed the hypothesis of normality ($p > 0.05$) (Figure 8).

b) Graphs of EchoPAC and D-Station measurements in relation to equality line and coefficient of correlation

Figure 9 shows the distribution of EchoPAC and D-Station (paired data) in relation to the equality line, evidencing a distribution of points close to and in both sides of the line, suggesting a low bias from the qualitative viewpoint and scattering. Since these measures did not have a normal distribution, we used the Spearman correlation test, which indicated a strong correlation ($r = 0.99$) between results obtained by the two methods.

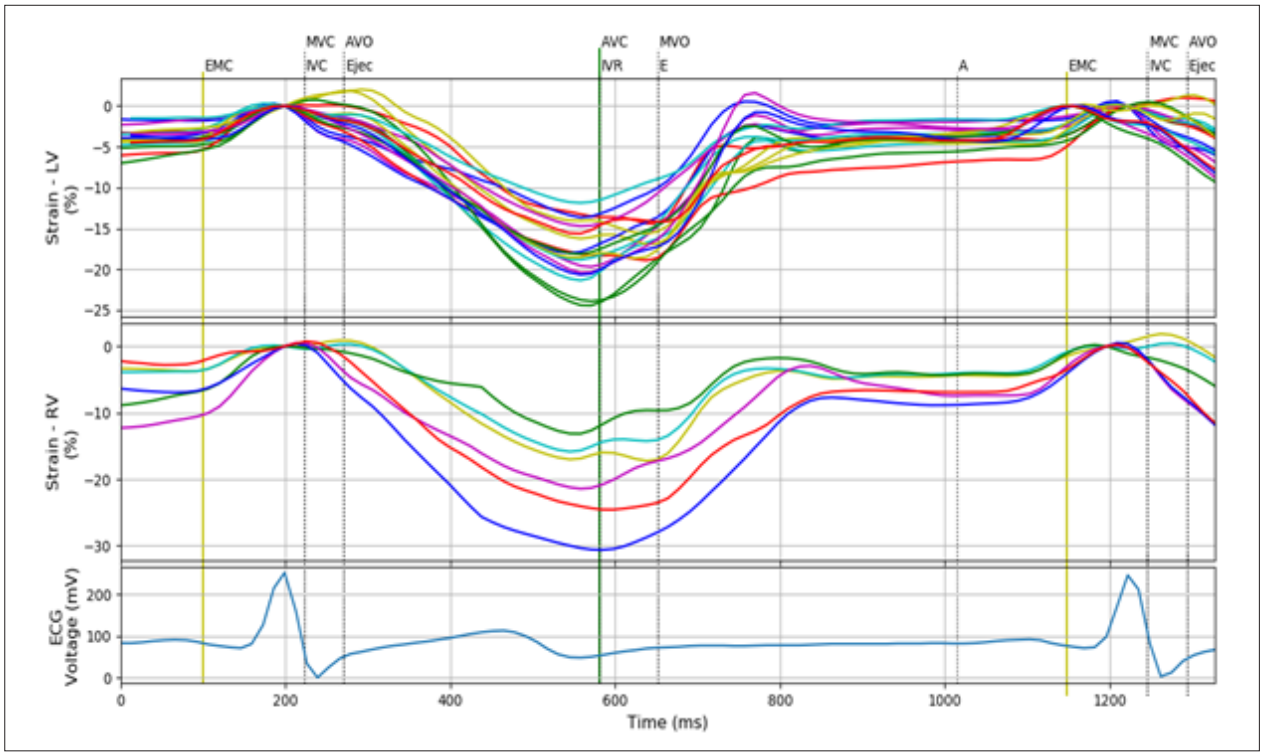


Figure 5 – *Simultaneous display of 18 strain curves of the left ventricle, six strain curves of the right ventricle and electrocardiographic curve; MVC: mitral valve closure; AVO: aortic valve opening; AVC: aortic valve closure; MVO: mitral valve opening.*

c) Hypothesis test of the differences between EchoPAC and D-Station GLS values

Since the differences between the measurements had normal distribution, we used the paired t-test (significance level of 5%). Results are presented in Figure 10, with a p-value of 0.6798, indicating acceptance of null hypothesis, *i.e.*, equivalence between the methods.

d) Bland-Altman agreement analysis[9,10]

Figure 11 despicts the Bland-Altman plot, which indicates agreement between the two methods as they meet the third (c) validation criterion . There is an evidence of large % differences for absolute (module) values of GLS < 10%.

Discussion

Analysis of agreement between the methods

Validation analysis results met the validation criteria, indicating equivalence between GLS values obtained by EchoPAC and D-Station. In a detailed analysis of the data, we can see that, for values lower than 10%, there was a trend of higher percentage difference. Intriguingly, all these subjects had important ventricular dysfunction with intraventricular dyssynchrony of left bundle branch block type. Such discrepancies may be precipitated by some factors, as follow:

1) Low absolute values result in higher percentage differences;
2) Ventricular dyssynchrony with left bundle branch block usually presents a stretching of the basal segment of the inferolateral and/or anterolateral wall at the beginning of systole, as well as erratic, mid- and telesystolic movements of the septum after the typical "septal flash". Both can generate positive peaks. While D-Station defines systolic peak as the most negative value, regardless of the positive (or less positive) peak in case of exclusively positive curves, the EchoPAC assumes, as a rule for systolic peak (peak systolic strain), a positive peak 75% greater than the negative systolic peak mode value, as shown in Figure 4. Also, in EchoPAC, although manual adjustments are common in these cases, we decided not to make these adjustments aiming at greater accuracy of the method.

In summary, discrepancies in the definition of systolic peak reduce the reproducibility of GLS between programs in patients with left bundle branch block. This issue should be addressed in future studies.

However, these discrepancies do not have a negative impact, especially if we consider the intraobserver variability of GLS values reported in the literature (5.2%),[16] and inter-software discrepancies regarding speckle filtering and tracking.[17-19]

Therefore, analysis of the results validates the D-Station as an alternative to EchoPAC.

Potential Applications of the D-Station Software

There are numerous potential applications of the D-Station software: simultaneous analysis of different chambers allows the study on the interaction between left and right ventricles, as well as left ventricle and left atrium, which may be relevant in heart failure with preserved ejection fraction, pericardial disease and interventricular dyssynchrony.

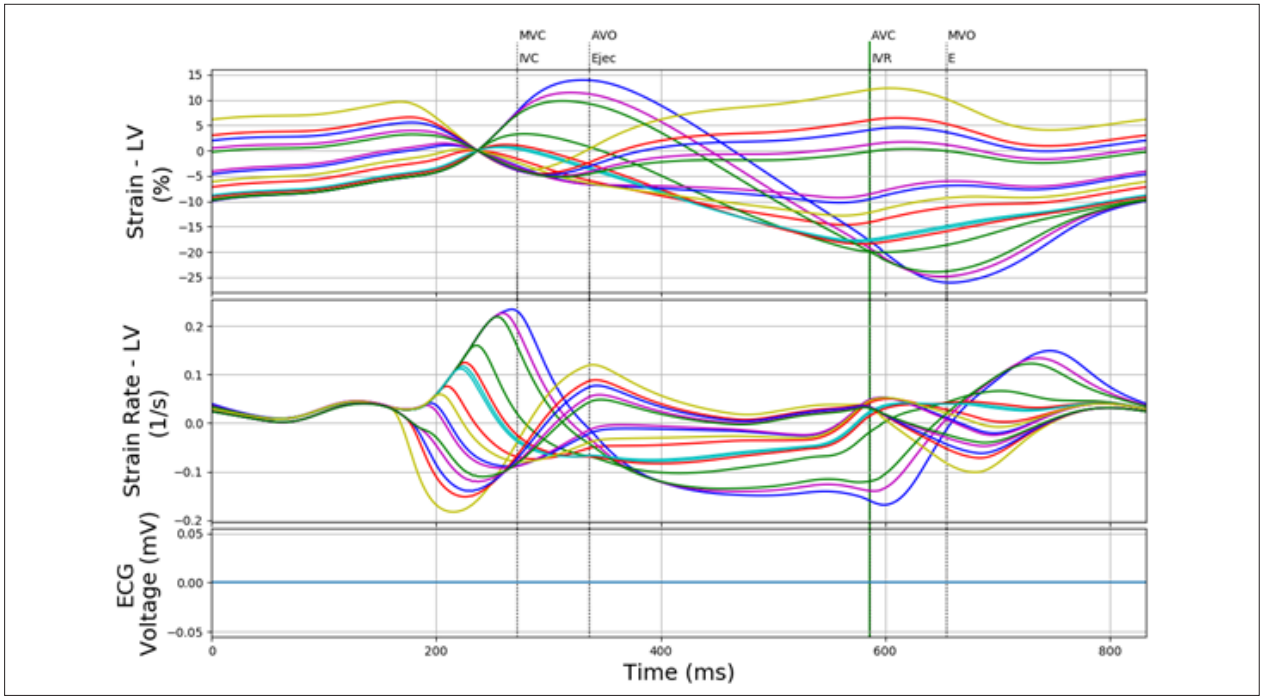


Figure 6 – *Simultaneous display of 18 strain curves of the left ventricle, 18 strain rate curves of the left ventricle obtained by CircAdapt; thus, there is no electrocardiographic signal or separation into phases; MVC: mitral valve closure; AVO: aortic valve opening; AVC: aortic valve closure; MVO: mitral valve opening.*

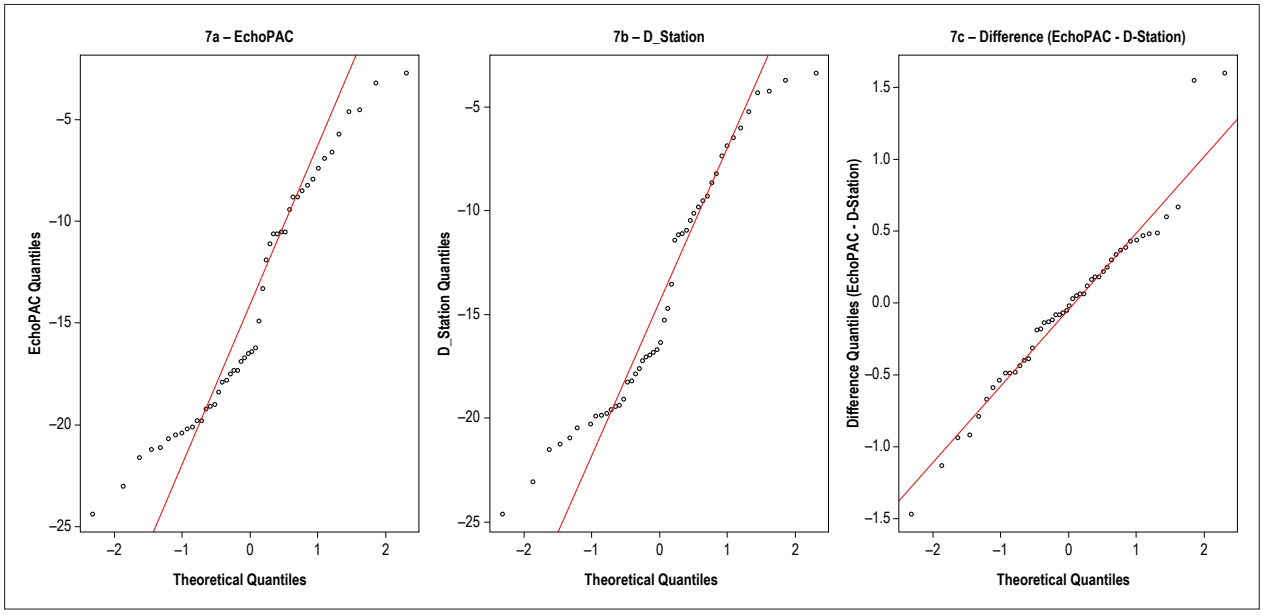


Figure 7 – *Q-Q plots.*

The interface of D-Station with Circadapt model combined with the MultiPatch module allows the formulation of hypotheses and comparison of signals between real patients, as previously performed.[12-14] This contributes with the teaching of the pathophysiology of cardiac strain, in addition to potentially reduces the time to select the variables of interest and spare resources in the development of animal models in some research scenarios.

The machine learning technique may be configured to process a great number of signals, identify variables of interest by data mining, and enable the use of the points of the strain curve/SR as described by Tabassian et al.[15] This can lead to extraction of further relevant data obtained from the study on cardiac strain, potentiated by the machine learning techniques, mainly by the imminent arrival of the high frame rate speckle tracking.[20]

```
Data: cran$Dif
W = 0.96266, p-value = 0.1293
```

Figure 8 – *Shapiro-Wilk normality test.*

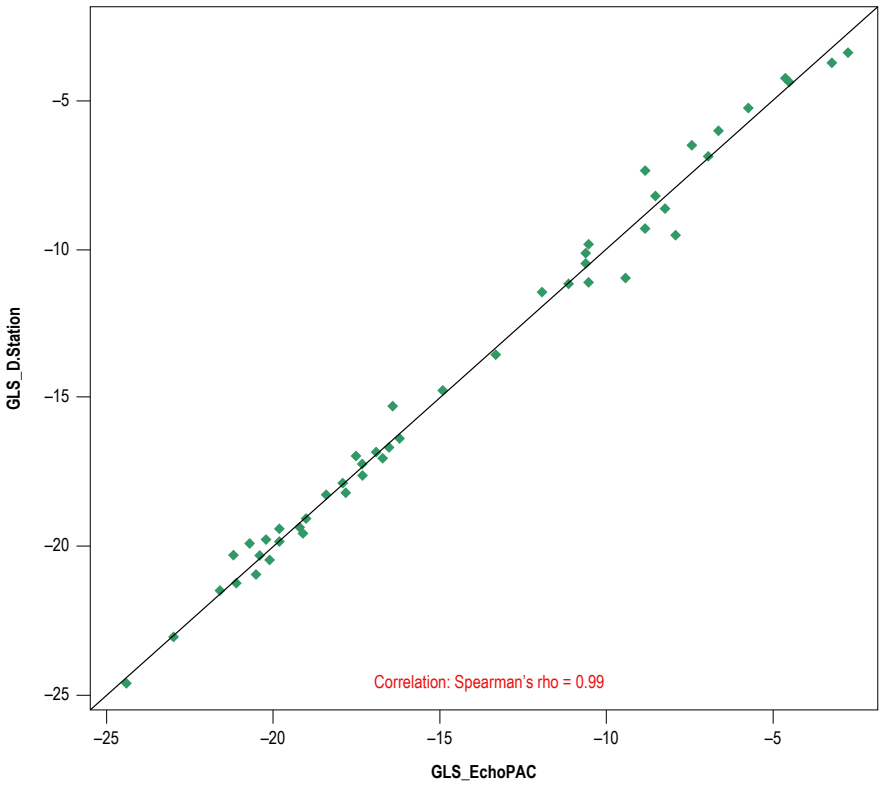


Figure 9 – *Global longitudinal strain values obtained by EchoPAC and D-Station in relation to the equality line.*

```
data: GLS_Echopac and GLS.D.Station
t = –0.41525, df = 47, p-value = 0.6798
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
–0.2033456 0.1337622
sample estimates:
– 0.03479167
```

Figure 10 – *Paired t-test*

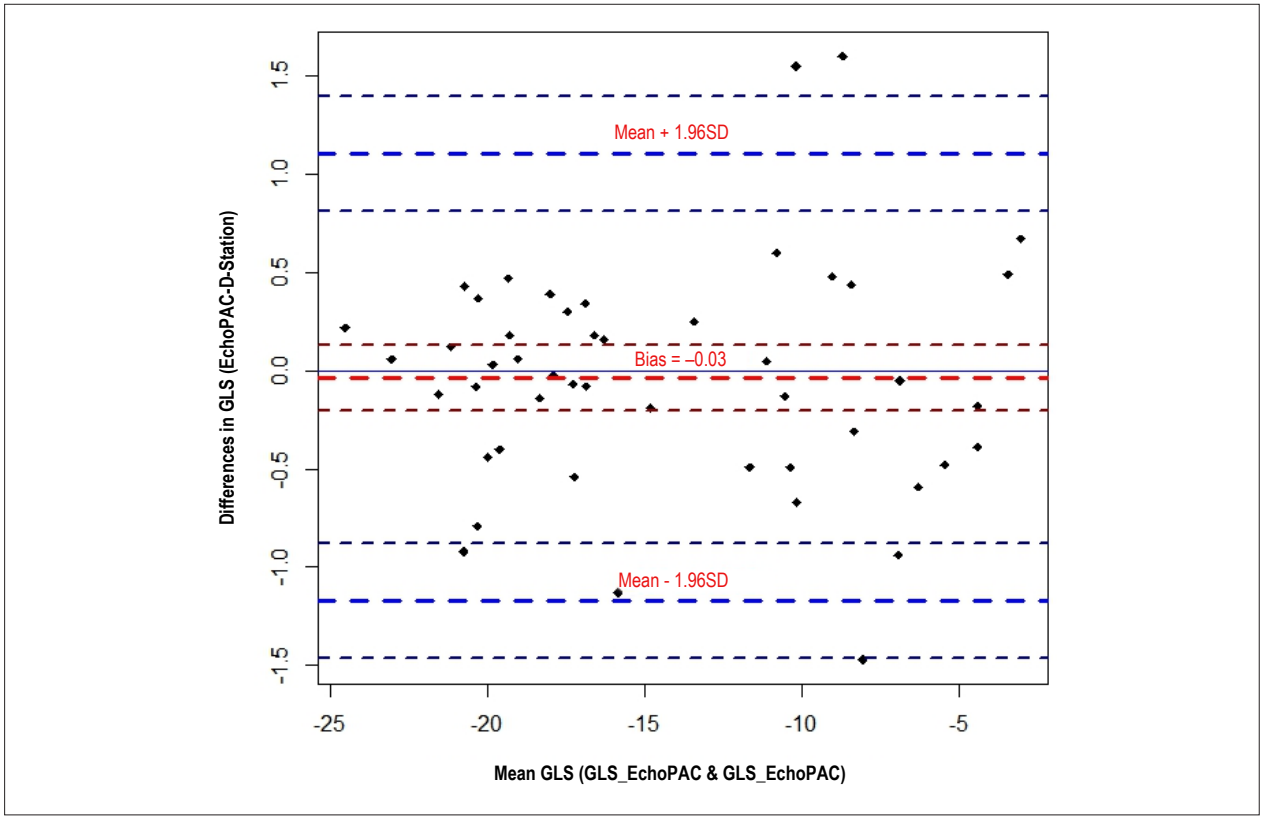


Figure 11 – *Differences and means of global longitudinal strain (GLS) values obtained by EchoPAC and D-station.*

Finally, future updates may expand the possibilities of analysis, including *strain* radial, circumferential and Twist, as well as the optimization of the interface between proprietary softwares, by incorporating strain parameters, Doppler signals, chamber volumes, tissue Doppler, among others. This will allow the automated extraction of many new, pre-established parameters at the user's discretion.

Limitations

The current version of the D-Station software does not allow the update of visualizations. In other words, to alter the chamber selection and its strain/SR curves, the user must restart the program. The same occurs in case of erroneous definition of the points on the ECG curve.

Differences in the measurement of cardiac strain between manufacturers are a critical issue in speckle tracking, as previously discussed by Mirea et al.[18] Further studies are needed to evaluate the impact of this software on discrepancies between manufacturers.

Conclusion

The D-Station software is an additional tool for the assessment of strain curves obtained by raw data exported from another proprietary software, with good correlation in the measurement of GLS as compared with the EchoPAC (GE) software.

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Author contributions

Conception and design of the research and Analysis and interpretation of the data: Hortegal RA; Acquisition of data: Sousa RD, Santos I, Hortegal RA, Abensur H; Statistical analysis: Szewierenko P, Hortegal RA; Obtaining financing: Regis CDM, Abensur H; Writing of the manuscript: Sousa RD, Regis CDM, Santos I, Hortegal RA, Szewierenko P; Critical revision of the manuscript for intellectual content: Regis CDM, Hortegal RA, Abensur 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 Hospital Beneficência Portuguesa de São Paulo under the protocol number CAEE 91350318.4.0000.5483. 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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*Supplemental Materials

For additional information, please click here.

High Serum Netrin-1 and IL-1β in Elderly Females with ACS: Worse Prognosis in 2-years Follow-up

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Abstract

Background: Several markers have been evaluated for a potential impact on clinical decisions or mortality prediction in acute coronary syndrome (ACS), including Netrin-1 and IL-1β that have been associated with cardiovascular disease.

Objective: Our study examined the prognostic value of Netrin-1 and IL-1β in patients with ACS (2-year follow-up).

Methods: We evaluate Netrin-1, IL-1β and other risk factors in the serum sample of 803 patients. Kaplan-Meier curves and Cox regression were used for the analysis of all-cause mortality, cardiovascular mortality, and a combined outcome of fatal myocardial infarction (MI) or new non-fatal MI, considering p-value < 0.05.

Results: There were 115 deaths from all causes, 78 deaths due to cardiovascular causes and 67 events in combined outcomes. Netrin-1 levels above the median (>44.8 pg/mL) were associated with a worse prognosis (all-cause mortality and cardiovascular mortality) in elderly females, even after model adjustment (HR: 2.08, p = 0.038 and HR: 2.68, p = 0.036). IL-1β levels above the median (>13.4 pg/mL) in elderly females were associated with increased risk of all outcomes after adjustment (all-cause mortality - HR: 2.03, p = 0.031; cardiovascular mortality - HR: 3.01, p = 0.013; fatal MI or new non-fatal MI - HR: 3.05, p = 0.029). For males, no associations were observed between Netrin-1 or IL-1β and outcomes.

Conclusion: High serum levels of Netrin-1 and IL-1β showed significant association with worse prognosis in elderly females. They may be useful as prognostic indicators in ACS. (Arq Bras Cardiol. 2020; 114(3):507-514)

Keywords: Acute Coronary Syndrome/physiopathology; Netrin-1; Interleukin-1 beta; Atrial Remodeling; Hypertension; Diabetes Mellitus; Dyslipidemias; Stroke; Aged; Women.

Introduction

Coronary heart disease (CHD) is the leading cause of death and years of life lost.[1] Responsible for the largest number of deaths in Brazil, CHD has high prevalence and a poor prognosis.[2] Despite the reduction in acute coronary syndrome (ACS) mortality observed in recent decades,[1] it is estimated that near 14% of patients who have had a myocardial infarction (MI) will die of it.[3] The risk of illness and death is 1.5 to 15 times higher for patients who survive the acute stage of MI than for the general population.[3] Of those who have a first MI, approximately 17% of males and 21% of females at ≥ 45 years will have a recurrent MI or fatal CHD within five years.[3]

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Inflammation is an important factor in the pathophysiology of ACS as well as in the cardiac remodeling after AMI. Several markers have been evaluated for a potential impact on clinical decisions or mortality prediction.[4] Recently, neuronal guidance molecules, especially Netrin-1, have been identified as important modulators of atherosclerosis, although their specific role (protective or deleterious) is still controversial.[5-7] Netrin-1 is a member of a family of proteins structurally similar to laminins, which are structural components of the basal membrane of tissues.[8] The role of Netrin-1 in cardiovascular disease and inflammation is an emerging area of study.[5]

Interleukin-1 (IL-1) is one of the major mediators of inflammation-induced coagulation.[9] IL-1β is capable of inducing the expression of other molecules that favor the recruitment of inflammatory cells to the lesion and tissue injury.[10] A high level of IL-1 has been described in MI.[11,12] Recently, a randomized clinical trial among people who suffered a MI showed that canakinumab, an agent that block IL-1β reduced the incidence of non-fatal CHD, non-fatal stroke events and cardiovascular death.[13]

Despite the importance of these two molecules in ACS, studies evaluating their prognostic value are scarce. Our objective was to evaluate the role of these molecules as predictors of prognosis in a 2-year follow-up.

Methods

Study design

The patients were participants of the "ERICO" (Strategy of Registry of Acute Coronary Syndrome) study, described in detail in previous reports.[14,15] Briefly, it is a prospective cohort study that included individuals admitted to treatment for ACS at the University of São Paulo Hospital (HU-USP), a teaching community hospital with 260 beds located in the District of Butantan, São Paulo, Brazil, from February 2009 to December 2013. The study protocol was in accordance with the Declaration of Helsinki. This study was approved by the Research Ethics Committee (CEP-HU/USP 866/08), and all patients signed the Informed Consent Form.

Acute myocardial infarction (AMI) was defined by the presence of symptoms consistent with myocardial ischemia within 24 hours of hospital admission and troponin I level above the 99th percentile value with a coefficient of variation <10%. ST-segment elevation myocardial infarction (STEMI) was defined by the criteria for AMI, in addition to (a) the presence of persistent ST-segment elevation ≥1 mm in two contiguous electrocardiographic leads (lead ECG) or (b) new (or supposedly new) left bundle branch block (LBBB). Non-ST-segment elevation myocardial infarction (NSTEMI) was defined by the criteria for AMI plus the absence of persistent ST-segment elevation ≥1 mm in two contiguous ECG leads and of new or supposedly new LBBB. Unstable angina (UA) was defined as the presence of symptoms compatible with myocardial ischemia in the last 24 hours, absence of AMI diagnosis and at least one of the following five criteria: (a) history of previous coronary artery disease; (b) positive stratification of invasive or non-invasive ischemic heart disease; (c) dynamic or evolutionary ECG changes; (D) troponin I >0.4 ng/mL (ensuring troponin I levels above the 99th percentile regardless of the utilized kit) or (e) agreement on UA diagnosis between two independent physicians.

Data collection and outcomes

After 6 months and annually for 2 years after the hospital admission, all individuals were contacted by telephone to update vital status information, including fatal and nonfatal cardiovascular outcomes. Whenever a participant reported a potential new MI event, new investigation procedures were initiated to confirm the event.

Study outcomes were all-cause mortality, cardiovascular mortality, and the combined outcome (fatal AMI and new non-fatal AMI). The strategy for collecting and classifying mortality data, including searching for official death records, was detailed in a previous report.[15] In cases where it was not possible to determine the cause of death, the data were censored for all outcomes, except for death from all causes.

During the hospital phase, trained interviewers collected data related to sociodemographic characteristics, cardiovascular risk factors, and medication, as previously described.[15] Blood samples were collected within 24 hours of admission. Analyses of plasma glucose, triglycerides, and total and HDL cholesterol were performed at HU-USP. LDL cholesterol was calculated using the Friedewald equation.[16] Concentrations of Netrin-1 and IL-1β on admission were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA), following the kit instructions (Netrin-1: SEB827HU; USCN Life Science Inc., Wuhan, China and IL-1β: 88-7010-88 eBioscience Inc., San Diego, CA, USA). Patients were classified according to Netrin-1 and IL-1β concentrations in "low" and "high" groups if their concentration were below or above the median.

Statistical analysis

Data were assessed for normality using the Kolmogorov-Smirnov test. The chi-square and Mann-Whitney (all continuous variables presented nonparametric distribution) tests were used to compare groups. Values were expressed as median (interquartile interval) or n (%). Kaplan-Meier curves were used, and the log-rank test was used to evaluate the difference between low and high groups. Risk estimates (hazard ratios with their respective 95% confidence intervals) for the events were calculated using Cox regression. In addition to Netrin-1 and IL-1β, the following variables were used to construct models: age, type of ACS, diabetes, hypertension, and dyslipidemia. A two-tailed p-value < 0.05 was considered significant.

The software programs SPSS (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY: IBM Corp.) and GraphPad Prism (version 5.01 for Windows, San Diego, California: GraphPad Software) were used to carry out the analyses.

Results

A total of 803 patients were included in this study, including 333 women and 470 men. Comparing the main characteristics of male and female groups, we observed that women were older and had higher HDL-c concentration than men. Women were also more frequently affected by hypertension, diabetes, and dyslipidemia (Table 1). The most frequent type of ACS in male and female groups was NSTEMI (about 40% of cases) followed by UA and STEMI that had a similar frequency (about 30% each).

During the 2 years follow up, there were 115 deaths from all causes (65 men and 50 women) including 78 deaths (67.8%) due to cardiovascular causes. We also identified 67 cases of AMI (fatal or non-fatal) in this same follow-up. Since age is an important factor involved in the mortality rate, we analyzed separately in women and men younger and older than 60 years.

To evaluate a possible role of Netrin-1 and IL-1β as prognostic markers, we compared the frequency of ACS in the patients with levels of Netrin-1 and IL-1β levels above and below the respective median. There were no associations between levels of Netrin-1 and IL-1β and all-cause mortality, cardiovascular mortality and fatal or new non-fatal MI outcomes for males independently of their age (data not shown). For this reason, we focused our investigation on the female group (333 patients). The main characteristics of the female group (younger and older than 60 years) are shown in Table 2.

At admission, women presented similar values of BMI, serum concentrations of glucose, triacylglycerol, and HDL cholesterol regardless in both age groups. The frequency of important risk factors such as hypertension, dyslipidemia and diabetes were higher in older women. However, levels of LDL cholesterol were lower in older ones. Current smokers

Table 1 – General characteristics in the hospital phase in males and females

Parameter	Male (n = 470)	Female (n = 333)	p
Age	60 (52 – 71)	65 (56 – 76)	< 0.0001
BMI	26.8 (23.8 – 29.6)	26.8 (24.0 – 30.9)	0.128
ACS type			**0.027**
NSTEMI	191 (40.6)	142 (42.6)	
STEMI	147 (31.3)	77 (23.1)	
UA	132 (28.1)	114 (34.2)	
Smoking habits			
Current	141 (31.3)	85 (27.2)	< 0.0001
Former	198 (43.9)	82 (26.3)	
Never	112 (24.8)	145 (46.5)	
Hypertension	339 (73.7)	267 (80.9)	0.018
Diabetes	156 (34.7)	148 (45.0)	0.004
Dyslipidemia	197 (48.0)	181 (60.7)	0.001
Glucose	125.0 (101.0 – 157.0)	124.0 (103.0 – 175.0)	0.652
Triacylglycerol	132.0 (94.0 – 190.3)	126.0 (97.0 – 183.0)	0.685
Total Cholesterol	171.5 (141.0 – 205.0)	170.0 (139.0 – 204.0)	0.720
HDL - Cholesterol	35.0 (30.0 – 44.0)	39.0 (32.0 – 46.5)	< 0.0001
LDL - Cholesterol	102.5 (77.0 – 134.3)	99.0 (77.0 – 124.3)	0.386
Netrin-1	44.8 (34.2 – 65.8)	44.8 (34.8 – 62.8)	0.813
IL-1β	15.1 (7.4 - 28.8)	13.8 (7.1 – 29.7)	0.536

Values are median (interquartile interval) or n (%). ACS: acute coronary syndrome. BMI: body mass index in kg/m². HDL: high-density lipoprotein. LDL: low-density lipoprotein. NSTEMI: non-STsegment elevation Myocardial Infarction. STEMI: ST-segment elevation Myocardial Infarction. UA: unstable angina. Data of plasma glucose, triglyceridemia, total cholesterol, HDL and LDL are presented as mg/dL. Netrin-1 and IL-1β are presented as pg/mL. Mann-Whitney test or chi-square test. p-value comparing male and female groups.

were more frequent in younger women while more than 50% of the older women never smoked (Table 2). We did not find differences in the median of Netrin-1 between age groups. However, the median of IL-1β was higher in the younger group.

Associations between low and high Netrin-1 or IL1- β and the outcomes, according to the age range were presented in Table 3 and Table 4, respectively. The number of death of all-cause was very low (3 death) in the women younger than 60 years and only 6 cases of the combined outcome, avoiding reliable analyzes in this group. However, in the older (>60 years) group, we found associations between the highest level of Netrin-1 and deaths from all causes and cardiovascular causes. An association between high IL-1β and death for CVD as also found among older women (p = 0.034).

These data showing a worse prognostic in older females with high levels of Netrin-1 and IL-1β at admission were confirmed by Kaplan-Meier curves. High levels of Netrin-1 showed a lower rate of survival when considering all-cause mortality (p = 0.011, Figure 1A) and also considering only cardiovascular deaths (p = 0.024, Figure 1B). The marker only tended to be associated with fatal MI or new non-fatal MI (p = 0.067, Figure 1C). High levels of IL-1β also showed a lower rate of survival when considering cardiovascular deaths (p = 0.031, Figure 1E) and tended to be associated with fatal MI or new non-fatal MI (p = 0.064, Figure 1F).

The analysis of the hazard ratios (Table 5) showed an increased risk of death from all causes for the high Netrin-1 group that remained significant in the adjusted model. The same results were seen for risk of death from cardiovascular causes.

Considering the high levels of IL-1β, we did not find significant HR in the crude model for all-cause mortality and fatal or new non-fatal MI (Table 5). However, significant HR for all-cause mortality and fatal or new non-fatal MI were observed in the adjusted model. We also observed an increased risk of death from cardiovascular causes for the high IL-1β group even after model adjustment.

Discussion

This work is the pioneer in evaluating the prognostic value of Netrin-1 in ACS and presents new information about the prognostic value of IL-1β in this condition.

In our study, we observed an association between the highest levels of Netrin-1 and worse prognosis when all-cause mortality and cardiovascular mortality were analyzed, in elderly females.

Table 2 – General characteristics in the hospital phase in younger (<60 y) and older (>60 years) females

Parameter	Total (n = 333)	Younger (<60 years) (n = 111)	Older (>60 years) (n = 222)	p
BMI	26.8 (24.0 – 30.9)	26.8 (24.5 - 31.1)	26.7 (23.8 – 30.8)	0.532
ACS type				**0.031**
NSTEMI	142 (42.6)	40 (36.0)	102 (45.9)	
STEMI	77 (23.1)	35 (31.5)	42 (18.9)	
UA	114 (34.2)	36 (32.4)	78 (35.1)	
Smoking habits				**< 0.0001**
Current	85 (27.2)	47 (44.3)	38 (18.4)	
Former	82 (26.3)	28 (26.4)	54 (26.2)	
Never	145 (46.5)	31 (29.2)	114 (55.3)	
Hypertension	267 (80.9)	79 (72.5)	188 (85.1)	0.006
Diabetes	148 (45.0)	39 (35.8)	109 (49.5)	0.018
Dyslipidemia	181 (60.7)	48 (48.5)	133 (66.8)	0.002
Glucose	124.0 (103.0 – 175.0)	121.0 (103.0 – 163.0)	128.0 (104.0 – 180.0)	0.381
Triacylglycerol	126.0 (97.0 – 183.0)	151.0 (97.0 – 201.0)	122.0 (93.5 – 174.0)	0.080
Total Cholesterol	170.0 (139.0 – 204.0)	185.0 (157.5 – 215.3)	161.0 (134.0 – 196.0)	0.002
HDL- Cholesterol	39.0 (32.0 – 46.5)	36.0 (32.0 – 45.0)	41.0 (33.0 – 47.2)	0.065
LDL- Cholesterol	99.0 (77.0 – 124.3)	114.0 (89.0 – 134.0)	93.0 (72.0 – 118.0)	0.0004
Netrin-1	44.8 (34.8 – 62.8)	44.8 (33.8 – 65.8)	44.8 (34.7 – 65.0)	0.861
IL-1β	13.8 (7.1 – 29.7)	15.5 (7.9 – 49.7)	13.4 (7.1 – 24.1)	0.037

Values are median (interquartile interval) or n (%). ACS: acute coronary syndrome. BMI: body mass index in kg/m^2. HDL: high-density lipoprotein. IL-1β: Interleukin - 1beta. LDL: low-density lipoprotein. NSTEMI: non-STsegment elevation Myocardial Infarction. STEMI: ST-segment elevation Myocardial Infarction. UA: unstable angina. Data of plasma glucose, triacylglycerol, total cholesterol, HDL and LDL are presented as mg/dL. Netrin-1 and IL-1β are presented as pg/mL. Mann-Whitney test or chi-square test.

Table 3 – Outcomes according to the Netrin-1 in females

	Female - Total			< 60 years			> 60 years		
2 years follow-up	Low Netrin-1	High Netrin-1	p	Low Netrin-1	High Netrin-1	p	Low Netrin-1	High Netrin-1	p
All-cause mortality	18 (36.0)	32 (64.0)	0.021	2 (66.7)	1 (33.3)	0.612	16 (34.0)	31 (66.0)	0.011
Cardiovascular mortality	12 (35.3)	22 (64.7)	0.052	2 (66.7)	1 (33.3)	0.612	10 (32.3)	21 (67.7)	0.029
Fatal or new non-fatal MI	11 (39.3)	17 (60.7)	0.193	4 (66.7)	2 (33.3)	0.467	7 (31.8)	15 (68.2)	0.066

Values are n (%). MI: myocardial infarction. Chi-square test.

Plasma Netrin-1 is a diagnostic biomarker of many cancer types.[17-19] It was verified that the higher gene expression or concentration of Netrin-1 in these tissues was associated with a worse prognosis, probably related to the anti-apoptotic and angiogenic effects of Netrin-1. However, the role of Netrin-1 in atherosclerosis and cardiac remodeling after MI is still controversial. It has been described that netrin-1 could promote or protect against atherosclerosis, in the dependency of environmental conditions.[20] Reduced endogenous levels of Netrin-1 can also lead to deleterious effects since pro-atherogenic factors can reduce the expression of this molecule.[20] In models of MI, netrin-1 administration reduced the severity of myocardium lesion when compared to the non-supplemented controls.[21,22]

In our study, it is possible that the "High Netrin-1" group is composed of patients who had a more severe ACS event. Our hypothesis is that the level of Netrin-1 increases in more severe cases of ACS. This hypothesis is based on studies that indicate that the expression of Netrin-1 is induced after cellular injury and can be used as a biomarker for organ damage or disease[23] as seen in the cardiac surgery.[24] Moreover, hypoxia, a condition closely linked to atherosclerosis and ACS is also an inducer of Netrin-1 expression.[25] Moreover, Van Gils et al.[6] observed increased expression of the molecule in cholesterol-loaded macrophages promoting the retention of these cells *in vitro*, which could contribute to a more rapid evolution of the atherosclerotic plaque and consequently increase the chance of thrombus formation and occurrence of infarction.

Table 4 – Outcomes according to the IL-1β in females

	Female - Total			< 60 years			> 60 years		
2 years follow-up	Low IL-1β	High IL-1β	p	Low IL-1β	High IL-1β	p	Low IL-1β	High IL-1β	p
All-cause mortality	21 (42.0)	29 (58.0)	0.221	0 (0.0)	3 (100.0)	0.118	19 (40.4)	28 (59.6)	0.140
Cardiovascular mortality	12 (35.3)	22 (64.7)	0.071	0 (0.0)	3 (100.0)	0.118	10 (32.3)	21 (67.7)	0.034
Fatal or new non-fatal MI	10 (35.7)	18 (64.3)	0.117	2 (33.3)	4 (66.7)	0.438	7 (31.8)	15 (68.2)	0.075

Values are n (%). IL-1β: Interleukin - 1beta. MI: myocardial infarction. Chi-square test.

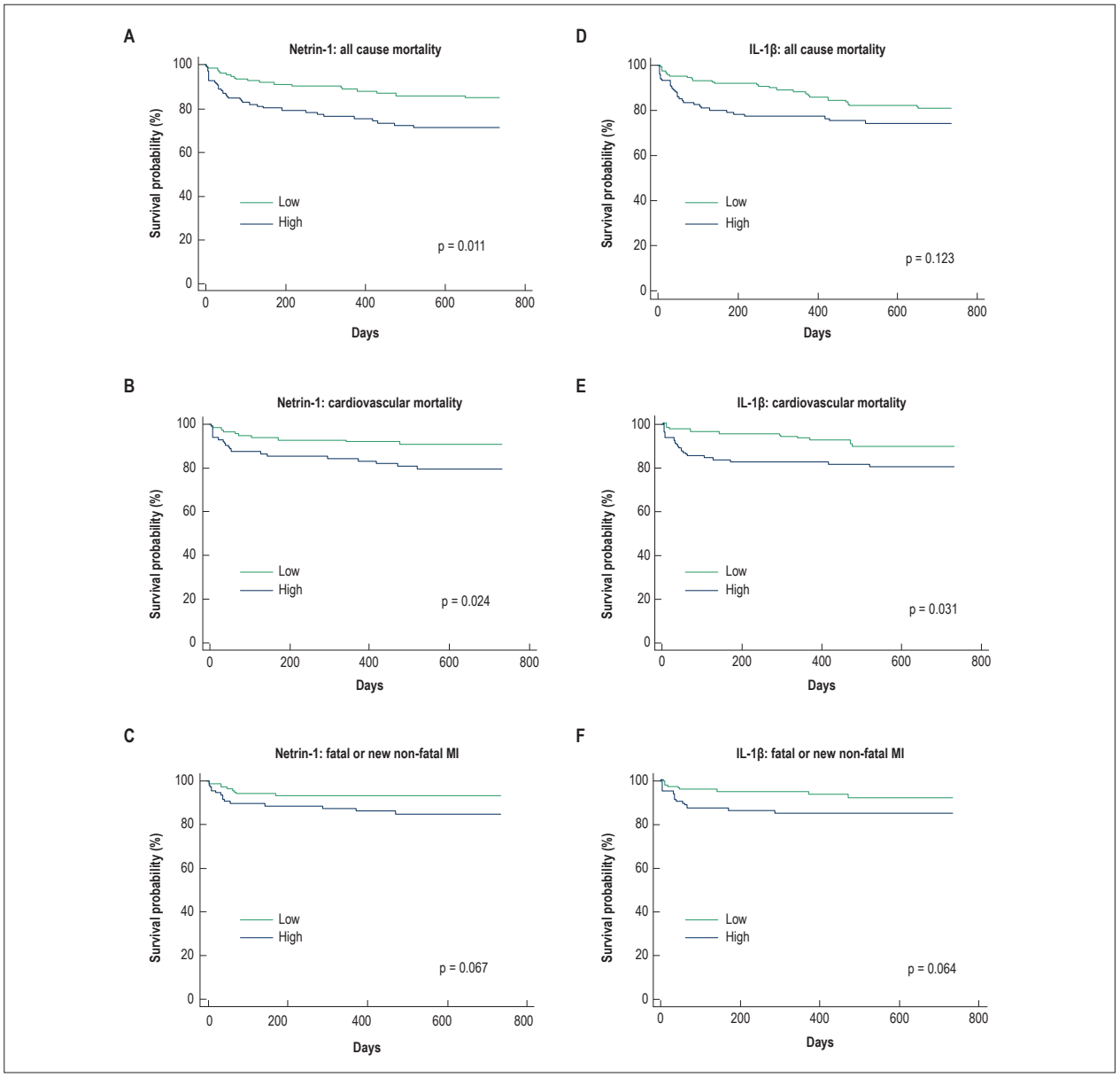

Figure 1 – *Kaplan-Meier curves for Netrin-1 (A – C) and IL-1B (D – F) in older (>60 years) females considering a 2-year follow-up. IL-1β: Interleukin - 1beta. MI: myocardial infarction.*

Table 5 – Hazard Ratios for high Netrin-1 and IL-1β and all-cause mortality, cardiovascular mortality and fatal or new non-fatal MI in older (>60 years) females

	All-cause mortality		Cardiovascular mortality		Fatal or new non-fatal MI	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
			Netrin-1			
Crude	2.15 (1.17 – 3.93)	0.013	2.31 (1.09 – 4.92)	0.029	2.25 (0.92 – 5.54)	0.075
Adjusted *	2.08 (1.04 – 4.16)	0.038	2.68 (1.06 – 6.74)	0.036	1.82 (0.65 – 5.07)	0.247
			IL-1β			
Crude	1.57 (0.87 – 2.81)	0.127	2.23 (1.05 – 4.75)	0.036	2.27 (0.92 – 5.58)	0.073
Adjusted *	2.03 (1.06 – 3.89)	0.031	3.01 (1.26 – 7.17)	0.013	3.05 (1.12 – 8.32)	0.029

*CI: confidence interval. HR: hazard ratio. IL-1β: Interleukin - 1beta. MI: myocardial infarction. * Adjusted for age, type of Acute Coronary Syndrome, diabetes, hypertension and dyslipidemia.*

These factors lead us to believe that the highest number of unfavorable outcomes, as well as the higher risk of death from all causes and from cardiovascular causes observed in women over 60 years of age with higher Netrin-1 levels are associated with the severity of event and the higher degree of inflammation (as suggested by the high levels of IL-1β) which may have contributed to a worse prognosis.

Regarding IL-1β, high levels of this one and other pro-inflammatory cytokines have already been identified in patients with ACS.[26] Nonetheless, few studies were addressed to the prognostic value of this cytokine.[27,28] In agreement with our results, these studies suggest that higher levels of IL-1β were seen in patients with ACS who underwent new events during follow-up.

IL-1β is capable of increasing the expression of molecules that contribute to plaque rupture and thrombus formation, culminating in the occurrence of ACS.[10,29] Thus, higher levels of serum IL-1β could reflect exacerbated inflammation, favoring the occurrence of cardiovascular complications.

Higher IL-1β levels suggest an exacerbated inflammation that could impair cardiac remodeling. Adverse remodeling after MI is the structural basis for ischemic heart failure. Although adequate amounts of IL-1β and other inflammatory cytokines are essential in the initial phase of remodeling, the decrease of cytokine levels is needed to promote effective healing.[30] It has been described that elevated levels of IL-1β up to two months after infarction in patients with STEMI were strongly associated with a worsening of cardiac function after one year of follow-up.[31] Furthermore, cytokine was a strong predictor of left ventricular hypertrophy, which is important in predicting cardiovascular morbidity and mortality.[31]

Several factors may help to understand the absence of association with worse prognosis found among men and younger women. Cardiac and vascular tissues are influenced by hormones such as estrogen and testosterone, varying according to sex and age.[32,33] Older women have a larger left ventricle mass than men, due to factors that indicate lower arterial capacity, such as reduced carotid wall thickness.[33]

The relationship between inflammatory cytokines and gender has not yet been elucidated, although differences between concentrations are observed in the literature.[32] Studies indicate that IL-β concentration is higher in males.[33,34] Furthermore, cytokine levels are inversely related to age, as seen in our work and literature.[35] The literature does not provide data on sex differences for Netrin-1. Since we did not observe statistical gender differences in the levels of the markers, our hypothesis is that in our female group the levels of these were higher than the normal. This possible increase may be related to the higher frequency of cardiovascular risk factors in this group in the present study, factors that may lead to an increase in levels of inflammatory markers.[36] However, even after adjusting for these factors, high levels of Netrin-1 and IL-1β remained associated with worse prognosis, demonstrating that these inflammatory markers are independently associated with worse prognosis, and may be related to the reduction of arterial capacity already observed in older women when compared to men.

We point out as limitations of the study its unicentric characteristic and the absence of a control group. Furthermore, we did not collect data from the pre-event period, which would allow us to determine the variation in marker concentration after ACS.

Conclusions

Higher levels of Netrin-1 and IL-1β are associated with worse prognosis in elderly females with ACS. The mechanism for such association can be related to maintenance of inflammation and adverse cardiac remodeling, propitiating further cardiovascular events.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Leocádio P, Goulart A, Santos I, Lotufo P, Bensenor I, Alvarez-Leite, J; Acquisition of data: Leocádio P, Menta P, Dias M, Fraga J, Goulart A, Santos I, Lotufo P, Bensenor I; Statistical analysis: Leocádio P, Goulart A, Santos I; Obtaining financing: Lotufo P, Bensenor I; Writing of the manuscript: Leocádio P, Menta P, Dias M, Fraga J; Critical revision of the manuscript for intellectual content: Goulart A, Santos I, Lotufo P, Bensenor I, Alvarez-Leite, J.

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 Universitário - USP under the protocol number CEP-HU/USP 866/08. 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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Acute Coronary Syndrome in Elderly Women: Inflammation Strikes Again

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Short Editorial related tothe article: High Serum Netrin-1 and IL-1β in Elderly Females with ACS: Worse Prognosis in 2-years Follow-up

Atherosclerosis is the most common pathological mechanism underlying coronary artery disease (CAD), encompassing both acute coronary syndromes (ACS) and chronic coronary syndromes (CCS). Traditionally, the plaque formation process has been perceived as a consequence of cholesterol accumulation (particularly scavenger receptor-mediated uptake of modified low-density lipoprotein), leading to continuous plaque growth. Subendothelial intimal layer build-up further leads to progressive stenosis, reduced blood flow, and, eventually, tissue hypoxia. In addition, spontaneous thrombotic vessel occlusion and embolic events may constitute the common pathophysiological pathway for acute major cardiovascular events, namely myocardial infarction (MI) and stroke.[1]

Although John Hunter first pioneered the inflammatory theory in 1794, it was not until 1994 that worse outcomes in patients with ACS were linked to higher C-reactive protein (CRP) levels, and it was proposed that plaque inflammation could be responsible for plaque fissuring. Hence, inflammation was finally linked to atherosclerosis and thrombosis. Moreover, it was later demonstrated that interleukin (IL) 1β, a pro-inflammatory cytokine, facilitates hematopoietic progenitor cell proliferation through glucose and cholesterol metabolism, thus promoting neutrophil extracellular trap formation in the growing plaque. Indeed, MI is accompanied by neutrophil infiltration, which is paramount to inflammation regulation.[2]

Nowadays, it is commonly accepted that atheroma is the result of a dynamic biological process. This modernizes the old view, where plaque was seen as an inanimate mass of accumulated lipids, to the understanding of it as a turbulent, lively core of inflammatory reactions.

Despite initially disappointing experimental investigations and randomized controlled trials with corticosteroids and antioxidants drugs, recent landmark trials have convincingly proven the so-called inflammatory hypothesis. In the CANTOS trial,[3] 10,061 patients with MI and elevated high-sensitivity (hs) CRP were randomized to 50, 150, or 300 mg of canakinumab (a human monoclonal antibody targeting IL-1β) or placebo. The primary outcome (cardiovascular death, MI, or stroke) was significantly reduced in the canakinumab 150 mg group in comparison to placebo (3.86/100 vs. 4.50/100 person-years; p = 0.02), in parallel with a reduction in hsCRP. In fact, patients who had greater reductions in hsCRP derived a greater benefit.[4] The COLCOT trial[5] enrolled 4,745 patients with a recent (< 30 days) MI and complete revascularization, who were randomized to low-dose colchicine (0.5 mg daily) or placebo. The primary composite outcome (cardiovascular death, MI, stroke, resuscitated cardiac arrest, or urgent hospitalization for unstable angina leading to revascularization) was significantly reduced by colchicine compared to placebo (5.5% vs. 7.1%; p = 0.02), in parallel with a reduction in inflammatory markers (namely hsCRP).

It is indisputable that inflammation plays a role in ischemic heart disease, including both ACS and CCS. However, there are multiple intriguing questions that have yet to be elucidated, including the following:

(1) How do we detect residual inflammation? There are several inflammatory markers available, including hsCRP, IL-1, IL-2, IL-6, IL-8, tumor necrosis factor α, and monocyte chemoattractant protein-1,[6] just to name a few. In addition to plasma biomarkers, imaging may also offer measurements of inflammation (e.g., perivascular fat attenuation index determined by coronary computed tomography angiography, which has been shown to enhance cardiac mortality prediction over and above current assessment).[7] Nonetheless, the optimal parameter for detecting residual inflammation (easily measured and cost-effective) has yet to be clearly defined;

(2) Which patients might benefit from anti-inflammatory treatment? In the CANTOS trial, patients whose hsCRP decreased to < 2 mg/dL had a 25% reduction in major adverse cardiovascular events; however, we lack a decisive marker to adequately select patients who may benefit the most from "anti-inflammatory" therapies, and it should be noted that these are not without risk (for instance, canakinumab was associated with cellulitis, pseudomembranous colitis and fatal infection or sepsis). Hence, we may need to be able not only to refine residual inflammation detection but also to discover new effective and safe drugs (or rediscover new indications for existing drugs) to further improve outcomes in patients with CAD;

(3) Is the residual risk driven solely by inflammation? There is evidence that residual risk may be due to plaque erosion and rupture unrelated to systemic inflammation. Plaque vulnerability has been shown to correlate with higher hsCRP and greater local macrophage infiltration (as measured by intracoronary optical tomographic coherence imaging),[8] yet it has also been shown that alteration of hyaluronan metabolism is associated with plaque erosion that may not be detected by usual markers of inflammation.[9]

In this issue,[10] Leocádio et al.[10] have investigated the prognostic role of netrin-1 and IL-1β in a prospective single-

Keywords

Atherosclerosis; Inflammation; Netrins; Coronary Artery Disease; Syndrome Coronary Acute; Myocardial Infarction; Stroke

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center study enrolling 803 patients with ACS (333 women, with a mean age of 65 years). The authors have found that increased levels of netrin-1 and IL-1β were independently correlated with all-cause death and/or major cardiovascular events in elderly (> 60 years) women (but not in men) at 2-years of follow-up. Interestingly, compared to their counterparts, elderly women had a higher prevalence of traditional cardiovascular risk factors, hence suggesting that inflammation may have had an add-on decisive role for progressive atherosclerosis, increasing meaningful events in this subgroup. However, this hypothesis needs to be further corroborated, as previous studies have consistently found a prognostic role of IL-1β regardless of sex,[6] and netrin-1 has not been widely investigated in CAD. In addition, events were scarce in young women (i.e., 3 all-cause deaths and 6 MI), hindering any definite conclusion. Nonetheless, whether these biomarkers may lead to tailored interventions in carefully selected patients (e.g., postmenopausal women) is an interesting concept worth further assessment.

Netrin-1 is one of five types of netrins, similar in structure to laminins. They are thought to act as a regulator of neurons and cell migration during development. They may also be involved in angiogenesis (including pathways in cancer development), anti-ischemia reperfusion injury and atherosclerosis. Indeed, a study enrolling 180 patients with CAD and 79 controls without CAD demonstrated that netrin-1 (amongst other inflammatory markers) was more effective than classical biomarkers in the diagnosis (number and severity of lesions) and risk assessment of patients with CAD.[11] IL-1β is among the first described cytokines, resulting from the purification of proteins responsible for inducing fever. Notable effects of IL-1β on different cell types include inflammatory activation of endothelial cells participating in the atherogenic process. Furthermore, IL-1β activity has been shown to be an independent predictor of all-cause mortality, ACS, lower left ventricular ejection fraction, and higher hsCRP levels in the AtheroGene study[12] (prospective registry of 1,337 CAD patients with ACS or stable angina). Leocádio and associates have found a potential prognostic value of increased netrin-1 and IL-1β in their cohort of patients with ACS, particularly in elderly women, indicating a higher risk of major cardiovascular events even after adjustment for age, type of ACS, diabetes mellitus, hypertension, and dyslipidemia.[10]

Future studies will focus on adequately selecting patients with CAD who may benefit most from "anti-inflammatory" drugs in an effective and safe manner. Hence, the role of the cardiologist caring for these patients may eventually include using adequate tools (e.g., plasma biomarkers) to identify "residual" risk in clinical practice and further reduce major cardiovascular events by tackling inflammation. The presented study[7] suggests that netrin-1 and IL-1β may be of value in stratifying cardiovascular risk in elderly women.

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Short Editorial

Analysis of Risk Scores to Predict Mortality in Patients Undergoing Cardiac Surgery for Endocarditis

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Abstract

Background: **Risk scores are available for use in daily clinical practice, but knowing which one to choose is still fraught with uncertainty.**

Objectives: **To assess the logistic EuroSCORE, EuroSCORE II, and the infective endocarditis (IE)-specific scores STS-IE, PALSUSE, AEPEI, EndoSCORE and RISK-E, as predictors of hospital mortality in patients undergoing cardiac surgery for active IE at a tertiary teaching hospital in Southern Brazil.**

Methods: **Retrospective cohort study including all patients aged ≥ 18 years who underwent cardiac surgery for active IE at the study facility from 2007-2016. The scores were assessed by calibration evaluation (observed/expected [O/E] mortality ratio) and discrimination (area under the ROC curve [AUC]). Comparison of AUC was performed by the DeLong test. A $p < 0.05$ was considered statistically significant.**

Results: **A total of 107 patients were included. Overall hospital mortality was 29.0% (95%CI: 20.4-37.6%). The best O/E mortality ratio was achieved by the PALSUSE score (1.01, 95%CI: 0.70-1.42), followed by the logistic EuroSCORE (1.3, 95%CI: 0.92-1.87). The logistic EuroSCORE had the highest discriminatory power (AUC 0.77), which was significantly superior to EuroSCORE II ($p = 0.03$), STS-IE ($p = 0.03$), PALSUSE ($p = 0.03$), AEPEI ($p = 0.03$), and RISK-E ($p = 0.02$).**

Conclusions: **Despite the availability of recent IE-specific scores, and considering the trade-off between the indexes, the logistic EuroSCORE seemed to be the best predictor of mortality risk in our cohort, taking calibration (O/E mortality ratio: 1.3) and discrimination (AUC 0.77) into account. Local validation of IE-specific scores is needed to better assess preoperative surgical risk. (Arq Bras Cardiol. 2020; 114(3):518-524)**

Keywords: **Cardiovascular Surgical Procedures/mortality; Endocarditis/complications; Hospital Mortality; Risk Assessment.**

Introduction

Despite advances in medical and surgical treatment, infective endocarditis (IE) is associated with substantial morbidity and risk of death.[1] Surgical correction of active IE is associated with the highest mortality of any valve disease, with overall rates of in-hospital mortality exceeding 20%.[2]

Surgery is currently performed in 50 to 60% of patients with IE.[3] The indications are: heart failure (usually related to valve dysfunction), uncontrolled infection (often associated with perivalvular extension and atrioventricular conduction defects), and prevention of systemic embolism.[4] Although these indications are clear, their practical application relies largely on the patient's clinical status, comorbidities and operative risk.[5]

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Risk prediction models for cardiac surgery have been developed to provide information on risks for both clinicians and patients and to guide decision-making.[6] Assessment of surgical risk helps to measure the quality of healthcare service, and risk profile is essential to differentiate patients by severity of health status. Likewise, being aware of a patient's risk can allow implementation of individualized strategies to prevent complications.[7] Although risk scores are available for use in daily clinical practice, knowing which one to choose is still fraught with uncertainty. Within this context, the aim of the present study was to assess the logistic EuroSCORE,[8] EuroSCORE II,[9] and the IE-specific scores STS-IE,[2] PALSUSE,[10] AEPEI,[11] EndoSCORE[7] and RISK-E,[12] as predictors of hospital mortality in patients undergoing cardiac surgery for active IE at a tertiary teaching hospital in Southern Brazil.

Methods

This retrospective cohort study included all patients aged ≥ 18 years who underwent cardiac surgery for active IE at Hospital de Clínicas de Porto Alegre (HCPA), a tertiary teaching hospital in Southern Brazil, from 2007 to 2016. Only patients

with definite IE based on the modified Duke criteria[13] were enrolled. Patients were identified through surgical schedules and a keyword search of the HCPA electronic medical records system. The present study was approved by the HCPA Research Ethics Committee (protocol 16-0632).

Preoperative risk of death was estimated through the mean logistic EuroSCORE[8] and EuroSCORE II[9], in addition to the IE-specific scores STS-IE,[2] PALSUSE,[10] AEPEI,[11] EndoSCORE[7] and RISK-E[12] (Table 1). Death during hospitalization, regardless of length of stay, was defined as hospital mortality. Creatinine clearance (CC) was estimated through the Cockcroft-Gault formula.[14]

Acute renal insufficiency was defined as any of the following: increase in creatinine by ≥ 0.3 mg/dL within 48 hours or to ≥ 1.5 times baseline, which is known or presumed to have occurred within the past 7 days; or urinary output < 0.5 mL/kg/h for 6 hours.[15] Critical preoperative state was defined if any one or more of the following occurred preoperatively during the same hospital admission as the operation: ventricular tachycardia/fibrillation or aborted sudden death; cardiac massage; ventilation before arrival at the anesthesia suite; administration of inotropes; intra-aortic balloon counterpulsation/ventricular-assist device placement before arrival at the anesthesia suite or acute renal failure (anuria or oliguria < 10 mL/h).[9] Active IE (still on antibiotic treatment for IE at time of surgery), chronic pulmonary disease, extracardiac arteriopathy, poor mobility (severe impairment of mobility secondary to musculoskeletal or neurological dysfunction), recent myocardial infarction (≤ 90 days), severe pulmonary arterial hypertension (systolic pulmonary artery pressure > 55mmHg), severe renal dysfunction (CC < 50mL/min) and urgency of surgery were also defined as in the EuroSCORE II study.[9]

Statistical Analysis

Data were collected directly from the patients' electronic charts and analyzed in IBM SPSS Statistics for Windows, version 21.0; MedCalc, version 12.5; and OpenEpi, version 3.01.[16] Qualitative data were reported as absolute and relative frequency; mean (standard deviation) or median (interquartile range) were used for quantitative variables. The normality of distribution of each variable was evaluated using the Shapiro-Wilk test. Calibration (expressed by the observed/expected [O/E] mortality ratio, i.e., the standard mortality ratio [SMR]) and discriminant ability (by area under the ROC curve [AUC]) of the scores were evaluated. To calculate the SMR with a 95% confidence interval (CI), we used the mid-P exact test with Miettinen's modification. Comparison of AUC was performed by the DeLong test. P-values < 0.05 were considered statistically significant.

Results

During the study period, 107 patients underwent cardiac surgery at the study facility while in the acute phase of IE and were included. Mean age was 58.1 ± 14.5 years and 24.3% were female. Isolated aortic IE was the most prevalent form of IE (43.9%). Patient characteristics and surgical details are described in Table 2.

The median vegetation size was 14.0 (9.25-18.0) millimeters. Thirty-one patients (29.0%) experienced at least one embolic event, diagnosed on the basis of symptoms or by incidental detection: 13 (12.1%) to the central nervous system and 11 (10.3%) to the spleen. Twenty-two (20.6%) were on preoperative dialysis: 14 (13.1%) due to chronic kidney disease, 6 (5.6%) due to acute renal failure, and 2 (1.9%) due to acute-on-chronic renal failure.

Surgery was performed with a median delay of 12.5 (6.0-22.25) days start of antibiotic therapy. The leading indication for surgery was heart failure (76.6%). The most frequently performed procedure was mechanical aortic valve replacement (n = 26, 24.3%), followed by bioprosthetic aortic valve replacement (n = 22, 20.6%) and bioprosthetic mitral valve replacement (n = 22, 20.6%).

Overall hospital mortality was 29.0% (95%CI: 20.4-37.6%). There was a wide variation in expected mortality among the scores, ranging from 10.0% in EndoSCORE to 28.6% in PALSUSE score (Figure 1). The best O/E mortality ratio was achieved by the PALSUSE score (1.01, 95%CI: 0.70-1.42; p = 0.919), followed by the EuroSCORE (1.3, 95%CI: 0.92-1.87; p = 0.123), as seen in Table 3. All other scores significantly underestimated hospital mortality.

The logistic EuroSCORE had the highest discriminatory power (AUC 0.77), as seen in Table 3, which was significantly superior to that of EuroSCORE II (p = 0.03), STS-IE (p = 0.03), PALSUSE (p = 0.03), AEPEI (p = 0.03), and RISK-E (p = 0.02), and non-significantly so when compared to EndoSCORE (p = 0.90). All other comparisons were non-significant, except for EndoSCORE versus AEPEI score (p = 0.03).

Discussion

In this cohort of patients undergoing cardiac surgery for active IE, the best O/E mortality ratio and discriminatory power were achieved by the PALSUSE score (1.01) and the logistic EuroSCORE (AUC 0.77), respectively. The logistic EuroSCORE, which had the second best O/E ratio (1.3), also had significantly better discriminatory power than PALSUSE (AUC 0.68; p = 0.03).

AUC, also known as the c-statistic or c-index, is a marker of overall diagnostic accuracy[17] and an effective and combined measure of sensitivity and specificity.[18] Discriminative power is thought to be excellent if the AUC is > 0.80, very good if > 0.75, and good (acceptable) if > 0.70. We also evaluated calibration using the O/E mortality ratio. Ideally, this ratio will be 1, i.e., the observed mortality equals expected mortality, denoting a perfectly calibrated predictive model. An O/E value > 1 means the model underestimates mortality, while a value < 1 means the model overestimates mortality. If the 95%CI of the O/E mortality ratio crosses 1, the model is well calibrated.[19] Nevertheless, it is possible for a risk model to have good calibration but poor discrimination, and vice versa. Discrimination is more important than calibration; a model can be recalibrated or adjusted as practice improves, but if the model is built on the wrong risk factors, its discrimination cannot be improved.[20] Although the EndoSCORE did not show significantly worse discriminative power than the logistic EuroSCORE, it did significantly underestimate hospital

Table 1 – Infective endocarditis-specific scores analyzed in the present study

NON-SPECIFIC SCORES				
EuroSCORE, 1999[8]			**EuroSCORE II, 2012[9]**	
Active endocarditis			Active endocarditis	
Age			Age	
Critical preoperative state			CCS class 4 angina	
Cr > 200 µmol/L			Chronic pulmonary dysfunction	
Extracardiac arteriopathy			Critical preoperative state	
Female sex			Extracardiac arteriopathy	
LVEF			Female sex	
Neurological dysfunction			IDDM	
Non-coronary surgery			LVEF	
Pulmonary disease			NYHA class	
Previous cardiac surgery			Poor mobility	
Recent MI			Previous cardiac surgery	
sPAP > 60 mmHg			Recent MI	
Thoracic aortic surgery			Renal dysfunction	
Unstable angina			sPAP	
Urgency			Thoracic aortic surgery	
Ventricular septal rupture			Urgency	
			Weight of procedure	
IE-SPECIFIC SCORES				
STS-IE, 2011[2]	**PALSUSE, 2014[10]**	**AEPEI, 2017[11]**	**EndoSCORE, 2017[12]**	**RISK-E, 2017[13]**
Active endocarditis	Prosthetic valve IE	BMI > 27Kg/m^2	Age	Acute renal insufficiency
Arrhythmia*	Age	Critical preoperative state	COPD	Age
Cardiogenic shock	Large intracardiac destruction†	eGFR < 50mL/min	Cr ≥ 2mg/dL	Cardiogenic shock
Chronic lung disease	Staphylococcus spp.	NYHA class IV	Female sex	Periannular complications‡
Systemic hypertension	Urgent surgery	sPAP > 55 mmHg	LVEF	Prosthetic-valve IE
IDDM/NIDDM	Sex (female)		Number of treated valves/ prostheses	Septic shock
Multiple valve procedure	EuroSCORE ≥ 10%		Pathogen isolated on blood specimen culture	Thrombocytopenia§
Preoperative IABP or inotropes			Presence of abscess	Virulent microorganism//
Prior CABG				
Prior valve surgery				
Renal failure (HD) or Cr > 2 mg/dL				
Urgency				

**Sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter or third degree heart block. †Abscesses or other echocardiography findings suggested the infection was invasive (communication between chambers, wall dissection or large valvular dehiscence). ‡Abscess, pseudoaneurysm, fistula or prosthetic dehiscence. § < 150,000 platelets/mm^3. //Staphylococcus aureus or fungi. BMI: body mass index; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; COPD: chronic obstructive pulmonary disease; Cr: creatinine; eGFR: estimated glomerular filtration rate; HD: hemodialysis; IDDM: insulin-dependent diabetes mellitus; NIDDM: non-insulin-dependent diabetes mellitus; IE: infective endocarditis; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure.*

Table 2 – Patient characteristics and surgical details.

VARIABLE	n = 107
Age (years)	58.1±14.5
Female sex	26 (24.3)
Hypertension	60 (56.1)
NYHA III/IV	53 (49.5)
Abscess	40 (37.4)
Previous cardiac surgery	35 (32.7)
Degenerative valve disease	31 (29.0)
Severe PAH	31 (29.0)
Prosthetic endocarditis	31 (29.0)
Acute renal insufficiency	30 (28.0)
Severe renal dysfunction*	25 (26.0)
Dialysis	22 (20.6)
Thrombocytopenia	20 (18.7)
Critical preoperative state	19 (17.8)
LVEF ≤ 50%	17 (15.9)
IDDM	14 (13.1)
Previous infective endocarditis	11 (10.3)
Rheumatic valvulopathy	10 (9.3)
Bicuspid aortic valve	8 (7.5)
Extracardiac arteriopathy	8 (7.5)
Previous MI	8 (7.5)
Chronic lung disease	7 (6.5)
Poor mobility	7 (6.5)
Recent MI	3 (2.8)
CCS class 4 angina	1 (0.9)
Location of infective endocarditis	
Aortic	47 (43.9)
Mitral	35 (32.7)
Aortic + Mitral	20 (18.7)
Tricuspid	4 (3.7)
Tricuspid + Mitral	1 (0.9)
Identified causative microorganism	72 (67.3)
Streptococcus viridans	19 (17.8)
Enterococcus sp.	10 (9.3)
Staphylococcus aureus	9 (8.4)
Magnitude of intervention	
Single, non-CABG	81 (75.7)
Two procedures	25 (23.4)
Three procedures	1 (0.9)
Urgency	
Urgent	98 (91.6)
Emergent	9 (8.4)
Associated CABG	8 (7.5)
Extracorporeal circulation time (min)	84.0 (65.0-110.0)
Cross-clamp time (min)	65.0 (51.0-84.0)

*CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; IDDM: insulin-dependent diabetes mellitus; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction. *We excluded patients on preoperative hemodialysis (n = 22; 20.6%) and those for whom body weight data were unavailable (n = 11; 10.3%), which makes it impossible to calculate the creatinine clearance. Data expressed as mean ± standard deviation, n (%), or median (interquartile range).*

mortality; thus, adjustments are required. In our cohort, the logistic EuroSCORE seemed to be the best predictor of mortality risk.

The causative microorganism was identified in only 67.3% of cases in this cohort, unlike in the validation cohorts of the IE-specific scores, in which the detection rate was 81.0-86.6%.[10-12] Similarly, *Staphylococcus aureus*, which causes an aggressive and often fatal infection,[21] was the causative microorganism in only 8.4% of cases, while in the validation cohorts this percentage ranged from 17.5 to 19.9%.[11,12] These two factors probably explain, at least partly, the low accuracy of IE-specific scores in our cohort. The same occurred with other items included in specific scores, such as NYHA class IV in the AEPEI score[10] (37.7 vs. 20.6%), LVEF ≤ 50% in the EndoSCORE[7] (35.9 vs. 15.9%), cardiogenic shock and thrombocytopenia in the RISK-E score[12] (17.9 and 29.2% in the original study vs. 11.2 and 18.7% in the present study, respectively); although strongly associated with mortality, these factors were not significantly prevalent in our cohort.

EuroSCORE II, the most commonly used score for preoperative risk assessment in current clinical practice, underestimated the observed mortality 2.5-fold and had poor discriminatory power (AUC = 0.69). The original EuroSCORE II study cohort had a very low percentage of patients with active IE (2.2%);[9] therefore, it is difficult to generalize EuroSCORE II results for IE populations. In an analysis of 149 patients undergoing cardiac surgery for active IE at two French referral centers for cardiac surgery, Patrat-Delon et al.[6] observed that, although EuroSCORE II showed good power of discrimination (AUC = 0.78; 95%CI: 0.70-0.84), its results should be interpreted with caution during the acute phase of IE, because it also underestimated postoperative mortality by 5-10% in half of patients with predicted mortality >10%. In Brazil, Oliveira et al.[22] conducted the only other study to date to evaluate a prediction score in patients with active IE undergoing heart surgery. In this study, which included 88 patients, the EuroSCORE II significantly underestimated hospital mortality, with a mortality ratio O/E of 2.31 (95%CI: 1.41-3.58; p = 0.002). ROC curve analysis was not performed.

Patients with active IE were already underrepresented in the EuroSCORE cohort,[8] in which active IE was present in only 3.6% of all valve surgery patients. Madeira et al.[23] in a study including 128 patients who underwent heart surgery for active IE, compared EuroSCORE and EuroSCORE II for perioperative mortality prediction. They observed that the pattern of calibration differed between the scores: EuroSCORE showed a progressive trend towards overprediction, whereas EuroSCORE II tended to underpredict mortality. On the other hand, as in the present study, Mestres et al.[24] in a study including 181 patients with IE (93.2% active), described good discriminatory power (AUC 0.84) and an expected mortality (27.1%) very similar to that observed (28.8%; O/E ratio: 1.1).

The need for a dedicated stratification tool, useful both for preoperative patient information and for bedside decision-making, arises from the peculiarities of IE surgery compared with general cardiac surgery: postoperative outcomes may be influenced not only by cardiovascular anatomic and functional

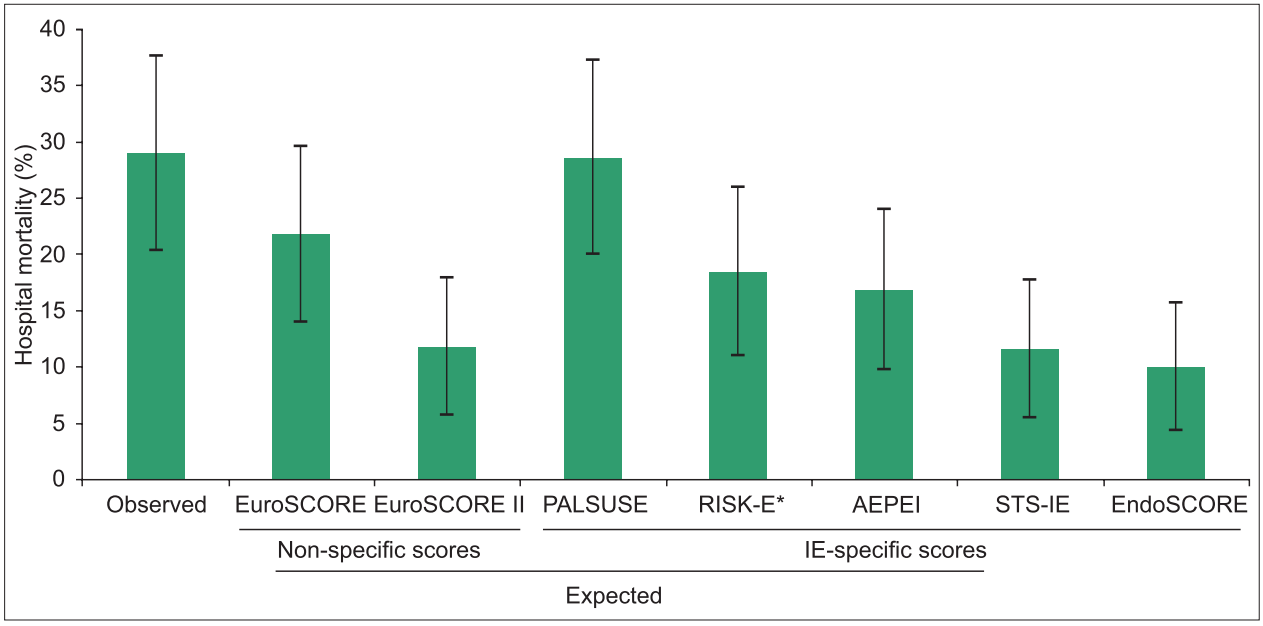

Figure 1 – *Observed and expected hospital mortality according scores. *Observed mortality was 29.0%, except for the RISK-E score, which was 28.4% (5 right-sided infective endocarditis cases were excluded, since they are not included in this score analysis). Error bars represent 95% confidence intervals.*

Table 3 – Observed/expected mortality ratio and ROC curve analysis for the studied scores

SCORE	O/E MORTALITY*	95%CI	p	AUC	95%CI	p
			NON-SPECIFIC SCORES			
Logistic EuroSCORE	1.33	0.92-1.87	0.123	0.77	0.66-0.87	<0.001
EuroSCORE II	2.46	1.70-3.45	<0.001	0.69	0.58-0.80	0.002
			IE-SPECIFIC SCORES			
STS-IE	2.50	1.73-3.50	<0.001	0.67	0.56-0.79	0.005
PALSUSE	1.01	0.70-1.42	0.919	0.68	0.57-0.79	0.003
RISK-E	1.53	1.05-2.18	0.029	0.71	0.60-0.81	0.001
AEPEI	1.71	1.18-2.40	0.006	0.65	0.53-0.77	0.017
EndoSCORE	2.90	2.00-4.06	<0.001	0.76	0.66-0.86	<0.001

**Observed mortality was 29.0%, except for the RISK-E score, which was 28.4% (5 right-sided infective endocarditis cases were excluded, since they are not included in this score analysis). O/E: observed/expected; AUC: area under the curve; CI: confidence interval; IE: infective endocarditis.*

issues, but also by systemic infective and microbiological factors.[25] More recently, new IE-specific risk scores have been developed. They incorporate some IE-specific factors (such as microbiological cultures, abscess formation and sepsis) that are known to be independent predictors of mortality. IE-specific scores have demonstrated greater accuracy for mortality prediction than classical risk scores.[26]

Among the IE-specific scores analyzed, only the PALSUSE[10] and RISK-E[12] scores had derivation cohorts limited to patients with active IE. The PALSUSE score,[10] which incorporates the EuroSCORE in its composition, was derived from a prospective cohort study including 437 patients who underwent surgery in the acute phase of IE. Data were collected in 26 Spanish hospitals. In-hospital mortality was 24.3%, ranging from 0% in patients with a score of 0 to 45.4% in those with a score ≥4. AUC was 0.84 (95%CI: 0.79-0.88), indicating satisfactory discriminatory ability. The RISK-E score[12] was developed from research performed in three tertiary care centers in Spain, which sought to predict in-hospital mortality in 424 patients with active left-sided IE undergoing cardiac surgery. AUC was 0.82 (95%CI: 0.75-0.88). The predicted probability of postoperative mortality ranged from 3% for a patient with a score of 0 to 97% for a patient with the highest possible score of 68. A comparison of AUCs showed a statistically significant superior predictive performance of the RISK-E score ($p = 0.01$) when compared with EuroSCORE, EuroSCORE II, or PALSUSE.

From 2000 to 2015, data from 2,715 patients with endocarditis (70.1% active) who underwent surgery at 26 Italian cardiac surgery centers were collected retrospectively. This large study[7] provided a logistic risk model to predict early mortality (within 30 days of surgery): the EndoSCORE. AUC was 0.84 (95%CI: 0.81-0.86). In our study, this score was tested to predict death during hospitalization, regardless of length of stay, and 5 of 31 deaths (16.1%) occurred beyond 30 days after surgery (early mortality: 24.3%). This difference seemed to have little effect on the performance of the score, which also underestimated early mortality (O/E ratio: 2.4; AUC: 0.77 [95%CI: 0.66-0.88]).

The AEPEI score,[11] despite being IE-specific, does not include IE-specific variables in its final model. It was developed in a prospective study including 361 consecutive patients who had undergone surgery for IE (76.2% active) at eight European cardiac surgery centers. Fifty-six patients (15.5%) died after surgery, and the AUC was 0.78 (95%CI: 0.73-0.82). In the study population, the AEPEI score had equivalent discriminatory power to that of the EuroSCORE II ($p = 0.4$) and was found to be better than the logistic EuroSCORE ($p = 0.0026$) and PALSUSE ($p = 0.047$).

Similarly to the AEPEI score, the STS-IE score[2] does not include IE-specific variables. It was developed from the Society of Thoracic Surgeons (STS) adult cardiac surgery database, which was established in 1989, including data from nearly 3 million cardiac procedures from over 90% of cardiac surgical centers in North America. From 2002 through 2008, 19,543 operations were performed for IE (51.5% active), with a mortality of 8.2%. The STS-IE score demonstrated good predictive ability, with an AUC of 0.76.

Some limitations of our study should be mentioned. First, the retrospective design may have influenced the quality and consistency of the data collected. The relatively small sample size is also a source of concern. Finally, the fact that the study was conducted at a single center can limit the external validity of our findings.

Conclusions

Our results showed that, despite the availability of recent IE-specific scores and considering the trade-off between the indexes, the logistic EuroSCORE seemed to be the best predictor of mortality risk in our 10-year IE cohort, considering calibration (O/E ratio: 1.3) and discriminant ability (AUC 0.77). This finding has clinical implications, as the EuroSCORE II is the score most commonly used score in preoperative evaluation. Local validation of the new IE-specific scores for preoperative risk assessment in this specific group of patients is needed.

Author Contributions

Conception and design of the research, analysis and interpretation of the data and writing of the manuscript: Pivatto Júnior F, Gus M; Acquisition of data: Pivatto Júnior F, Bellagamba CCA, Fernandes FS, Butzke M, Busato SB; Statistical analysis and obtaining financing: Pivatto Júnior F; Critical revision of the manuscript for intellectual content: Pivatto Júnior F, Bellagamba CCA, Pianca EG, Fernandes FS, Butzke M, Busato SB, Gus M.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre under the protocol number 2016-0632. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Prognostic Scores for Mortality in Cardiac Surgery for Infective Endocarditis

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Short Editorial related to the article: Analysis of Risk Scores to Predict Mortality in Patients Undergoing Cardiac Surgery for Endocarditis

The article by Pivatto F Jr et al.[1] allows us to discuss the important issue of prognostic scores in patients who have cardiac surgery for infective endocarditis (IE).[1] The management of left- sided IE often involves surgery during the index admission, and the main challenge is to rapidly and correctly identify patients at high risk and to transfer them to institutions with a surgical team with expertise in endocarditis surgery.

Prognostic scores are important for several reasons: a reasonable estimate of the risk of death is important in clinical decision-making regarding surgical indication; the estimate is necessary to inform patients and their families of the surgical risk; risk stratification permits a fair comparison of cardiac surgery results, so that surgeons and hospitals treating high-risk patients will not appear to have worse results than others.[2] For operative mortality to remain a valid measure of quality of care, it must be related to the risk profile of the patients receiving surgery.[2]

Euroscore I, published in 1999, evaluated 19,030 patients submitted to cardiac surgery in 8 countries in Europe, studying 97 risk factors for death, and among those, the ones that significantly affected surgical prognosis were selected.[2] These variables are presented in Table 1. In this study, only 30% were submitted to valve surgery, and the number of individuals who had endocarditis is not mentioned.[2]

Euroscore II, published in 2012,[3] had the goal of updating the first model by evaluating 22,381 patients from 43 countries in the world, including sites outside Europe, so as to create a more reliable score, incorporating new variables and adjusting others (Table 1). At this time, it was already known that the Euroscore[2] superestimated the surgical risk as technical progress in cardiac surgery along the previous decade had been made, with a mortality decrease adjusted by risk. Improvements to Euroscore were: creatinine clearance as a better measure of renal function than serum creatinine values; unstable angina defined by the use of intravenous nitrates was outdated; weight of intervention was not properly assessed in the previous model (for example, aortic valve replacement with or without concurrent coronary artery bypass grafting had the same weight) and some continuous variables, such as number of previous cardiac surgeries and pulmonary artery systolic pressures were treated as a dichotomic variable.[3]

The receiving operator curve (ROC) of the scores showed an area under the curve (AUC) of 0.78 for the logistic and additive Euroscore and of 0.80 for Euroscore II. A criticism to the model is, that although non-European countries were included, the vast majority of patients were from Spain, France, Italy and the United Kingdom, who contributed with 19, 16, 15 and 12 sites respectively.[3] As for Latin America, Brazil contributed with data from 4 centers, Argentina 1 and Uruguay 1. Also, the model did not analyze valve surgery separately. In fact, only 2.2% of patients (497 in absolute numbers) with active IE had been included.[4] A limitation outlined in the study was that all centers participated voluntarily, what introduces selection bias to the data.[3]

Patients with IE must be thoroughly assessed. If we consider the usual profile of a patient with IE who is operated at Instituto Nacional de Cardiologia, for example, he or she will have a serum creatinine above normal, scoring 2 points; active disease (under antibiotic treatment for IE at the time of surgery), scoring 3 points, and at least moderate left ventricular dysfunction, scoring 1, that is, with a total Euroscore of 6 and anticipated mortality of over 11%. Not infrequently, this patient previously had cardiac surgery (as over a third have rheumatic valvopathy and about 10% previously had IE), which adds 3 points to the total score.[4-6] Therefore, Euroscore I does not discriminate well this subset of patients, as most will probably fall into the 6+ score. Patrat-Delon et al.,[7] studying 149 patients operated for IE in France, between 2002 and 2013, of which in-hospital mortality was 21%, came to a similar conclusion regarding EuroSCORE II: it underestimated mortality in patients with predicted mortality over 10%.[7]

The Society of Thoracic Surgeons–Infective Endocarditis (STS-IE) score, published in 2011,[8] has its variables shown schematically in Table 1. In the subset of North American patients with IE studied in its development, of the 13,617 patients, only over half had active endocarditis at the time of surgery.[8] Overall mortality was 8.2%, although multiple valve surgery had an operative mortality of 13%. Postoperative complications were present in more than half the patients, most common of which were prolonged ventilation in over a quarter.

Keywords

Endocarditis/surgery; Hospital Mortality; Cardiac Surgery/mortalidade; Prognosis; Scores.

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Table 1 – Variables included in prognostic scores for cardiac surgery (Euroscore I and II and STS-IE)

Variables	EuroScore I	EuroScore II	STS-IE Score
Age	■	■	■
Gender	■	■	■
Weight			■
Height			■
Body Mass Index			■
Diabetes Mellitus		■	■
Chronic Pulmonary Disease	■	■	■
Extracardiac arteriopathy	■	■	
Peripheral Arterial Disease			■
Neurological Dysfunction	■		
Low Mobility		■	
Previous cardiac surgery	■	■	■
Number of previous surgeries			■
Previous valvar surgery			■
Renal failure under conservative treatment	■	■	■
Renal Failure under Hemodialysis		■	■
Serum Creatinine / Creatinine Clearance		■	■
Arrythmia			■
Systemic Arterial Hypertension			■
Active infective endocarditis	■	■	■
Immunosuppressive therapy			■
Recent myocardial infarction	■	■	■
Cardiogenic shock			■
Inotropic use			■
Intra-aortic balloon			■
NYHA (New York Heart Association) Classification		■	■
Non-coronary surgery			
Unstable Angina (CCS IV)	■	■	
Preoperative Critical State	■	■	
Left Ventricular Ejection Fraction	■	■	■
Pulmonary Arterial Hypertension	■	■	
Resuscitation			■
Urgency Procedure	■	■	■
Intervention weight:	■	■	■
Single non-coronary procedure	■	■	
2 Procedures	■	■	
3 Procedures	■	■	
Septal rupture after myocardial infarction	■		

Short Editorial

In the STS-IE score, numbers vary from 0-110 points and, according to this model, a patient with 35 points would have an operative risk of at least 10% mortality.[8] Although only patients with IE were studied, this was a voluntary registry of American hospitals only. Important features of IE, such as microbiology, the discrimination between native and prosthetic valves and the presence of intracardiac complications (abscess, fistula) were not analyzed. Surprisingly, 43% of the patients were operated on "electively", which is a different scenario from other series.

Although not specific for endocarditis, Euroscore and Euroscore II take into account active endocarditis as an important variable associated with operative mortality (see Table 1). Importantly, several scores have been created, which are more specific to endocarditis, involving variables that carry a significant weight regarding severity of this condition,[8-13] shown in table 1 of the article by Pivatto Jr F et al.[1] Features specific to IE are prosthetic valve IE, large intracardiac destruction, *Staphylococcus* spp., pathogen isolated from a blood specimen culture (i.e., positive blood cultures), presence of abscess, perivalvar complications, virulent microorganism; besides these, there is atrioventricular block and non-HACEK Gram negatives (the last 2 for INC-Rio model[4]) and perivalvular involvement (ex. annular abscess or aortocavitary fistula).[13] When grouped, in addition to prosthesis involvement, essentially type of microorganism and valve destruction (AV block signaling perivalvular abscess) are the distinctive features in these "IE scores" (see Table 2). We have shown more data on the scores studied by Pivatto Jr F et al.[1] in table 3, and we have added to this the INC-Rio[4] and the DeFeo scores.[13] Mortality and AUC of the scores, relative to their studied population, are shown (Table 3). It is noteworthy that mortality was variable in the different series, and mortality in patients operated with IE was at least double that seen in other types of cardiac surgery (note the lower mortality rates for the populations studied in Euroscore I and II). The present study does not propose a score, and it was added to the table so as to show mortality in their series. In this study [1], the best O/E mortality ratio was achieved by the PALSUSE score, followed by the logistic EuroSCORE, which had the highest discriminatory power and was significantly superior to EuroSCORE II, STS-IE, PALSUSE, AEPEI and RISK-E.

In conclusion, several groups are in search of an adequate score to predict mortality in patients operated for IE. The widely used Euroscore I and II, and the STS-IE have been studied comparatively to the new proposed scores, some of which (for ex., PALSUSE) have included parts of Euroscore to them. In Brazil, only 2 studies (the present one, with 107 patients, and the one by Martins et al.[4] with 154) have addressed the performance of scores in IE, both with small numbers. In the first, the authors concluded that, despite the availability of specific scores, the logistic EuroSCORE was the best to predict mortality in their cohort and no score was proposed; in the second, the mentioned IE scores were not evaluated (most of them published after 2016), but the sensitivity and specificity of Euroscore I was 81.5% and 63%; for Euroscore II , 29.6% and 97.6%, and for STS-IE 7.4% and 98.4%, respectively. AUC values were 0.86 (Euroscore I), 0.90 (Euroscore II) and 0.85 (STS-IE). In the multivariate analysis, the variables found to be statistically significant for death were AV block, cardiogenic shock, insulin-dependent diabetes mellitus, non-HACEK Gram negative microorganisms and inotropic use. These were included in a model, INC-Rio[4] with a calculated sensitivity of 88.9% and specificity of 91.8%; AUC was 0.97. Casalino et al.[14] have studied all-type valvular surgery in 440 patients, in which mortality rate was 16.0% (6.0% in elective surgery and 34.0% in emergency/urgency surgery), and found the AUC was 0.76 for additive and logistic EuroSCORE and 0.81 for EuroSCORE II. They concluded that the EuroSCORE models showed good discriminatory capacity, although calibration was compromised due to mortality underestimation.

We believe a multinational study in Brazil would be of paramount importance, with a greater number of patients, to propose and validate a score, since patients with IE in our country dramatically differ from those in North American or European countries, especially due to the high proportion of rheumatic valvopathy, group *viridans* streptococcal IE, longer delay time to diagnosis, and younger age.

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Table 2– Variables included in prognostic scores for cardiac surgery mortality in patients with infective endocarditis undergoing valve replacement

Variables	PALSUSE2014	AEPEI 2017	INC-Rio 2016	EndoSCORE 2017	RISK-E 2017
Prosthetic valve endocarditis	■				■
Age	■			■	■
Large intracardiac destruction*	■				
Staphylococcus spp.	■				
Urgent surgery	■			■	
Gender (female)	■				
EuroScore ≥10	■				
BMI > 27Kg/m^2		■			
Critical preoperative state		■			
ClearCreat < 50mL/min		■			
Class IV NYHA		■			
PASP > 55mmHg		■			
COPD				■	
Cr ≥ 2mg/dL				■	
LVEF				■	
Number of valves / prostheses treated				■	
Pathogenic microorganism isolated in blood cultures				■	
Presence of abscess				■	
Acute renal failure					■
Cardiogenic shock			■		■
Perivalvar complications‡					■
Septic shock					■
Thrombocytopenia§					■
Virulent microorganism//					■
Atrioventricular block			■		
IDDM			■		
Non-HACEK Gram negatives			■		
Inotropic use			■		

**Abscesses or other echocardiographic findings suggested that the infection was invasive (inter-chamber communication, wall dissection or major valve dehiscence).*
‡Abscess, pseudoaneurysm, prosthetic fistula or dehiscence; § < 150,000 platelets/mm^3.
//Staphylococcus aureus or fungi.
BMI: body mass index; ClearCreat = creatinine clearance (estimated glomerular filtration rate); NYHA: New York Heart Association; PASP = pulmonary artery systolic pressure; COPD = chronic obstructive pulmonary disease; Cr = serum creatinine; LVEF = left ventricular ejection fraction; AVB: atrioventricular block; IDDM = insulin-dependent diabetes mellitus; GN: Gram-Negative; HACEK = Haemophilus spp, Aggregatibacter spp (formerly Actinobacillus), Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.

Table 3 – Areas under the curve (AUC) of the proposed risk scores for assessing mortality in cardiac surgery for infective endocarditis

SCORE	AUC	Postoperative intrahospital mortality	Evaluated IE separately?	N. studied	Country	Author, year
Logistic EuroSCORE	0.79	4.7%	no	14,799	European countries*	Nashef 1999
EuroSCORE II	0.81	3.9%	no	22,381	European countries**	Nashef 2012
STS-IE	0.76	8.2%	yes	13,617	USA	Gaca 2011
"De Feo"***	0.88	9.1%	yes	440	Italy	De Feo 2012
PALSUSE	0.68	24.3%	yes	437	Spain	Martínez-Sellés 2014
INC-Rio	0.97	17.5%	yes	154	Brazil	Martins 2016
RISK-E	0.82	28.6%	yes	671	France and Spain	Olmos 2017
AEPEI	0.78	15.5%	yes	361	France and Italy	Gatti 2017
EndoSCORE	0.85	11%	yes	2,715	Italy	Di Mauro 2017
Not created	Not assessed	29%	yes	107	Brazil	Pivatto Jr F, 2020

*AUC: area under the curve; IE: infective endocarditis. *Participating countries were not discriminated. **Most of the research centers were located in France, Italy and Spain; countries in South and North America, Asia and Africa had a small participation. USA: United States of América. ***Only patients with native valve IE were studied; no name was given to the score.*

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Waist Circumference Percentiles and Cut-Off Values for Obesity in a Large Sample of Students from 6 To 10 Years Old Of The São Paulo State, Brazil

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Abstract

Backgroud: The prevalence of obesity has systematically been increased in the population, including children and adolescents, around the world.

Objectives: To describe reference percentile curves for waist circumference (WC) in Brazilian children and provide cut-off values of WC to identify children at risk for obesity.

Methods: A multicenter, prospective, cross-sectional study was performed with children aged from 6 to 10 years old, enrolled in public and private elementary schools from 13 cities of the São Paulo State. Height, weight, and WC were measured in duplicate in 22,000 children (11,199 boys). To establish the WC best cut-off value for obesity diagnosis, ROC curves with children classified as normal weight and obese were calculated, according to BMI curves, stratified by gender and age, and the Youden Index was utilized as the maximum potential effectiveness of this biomarker. A $p < 0.05$ was considered statistically significant.

Results: WC values increased with age in both boys and girls. The prevalence of obesity in each age group varied from 17% (6 years old) to 21.6% (9 years old) among boys, and from 14.1% (7 years old) to 17.3 % (9 years old) among girls. ROC analyses have shown the 75th percentile as a cut-off for obesity risk, and the diagnosis of obesity is classified on the 85th percentile or more.

Conclusion: Age and gender specific reference curves of WC for Brazilian children and cut-off values for obesity risk may be used for national screening and interventional studies to reduce the obesity burden in Brazil. (Arq Bras Cardiol. 2020; 114(3):530-537)

Keywords: Child; Waist Circunference/physiology; Obesity, Students; Parameters; Anthropometry.

Introduction

The worldwide prevalence of obesity, particularly among children, has been *increasing exponentially*. Over the last 30 years, several national surveys have recorded significant increment in the prevalence of obesity and overweight across Brazilian regions.[1] Childhood obesity is linked to the development of obesity in adults. Moreover, the obese child is exposed to a higher risk of developing type 2 diabetes, hypertension and vascular abnormalities, which are considered precursors of atherosclerosis in adulthood. Left ventricular hypertrophy and kidney problems have also been described in obese children.[2] The increased prevalence of obesity and the strong association with several comorbidities in children provide the relevance for public health.[3] As a result, it is necessary to find a simple anthropometric parameter that may be used to identify obese or at- risk- of- becoming obese children, which may contribute to the appropriate intervention tools to improve this trend.

Obesity and overweight rates across population groups are typically based on body mass index (BMI). However, BMI does not reflect body composition, providing limited information on the central or abdominal adiposity. Waist circumference (WC) measurement is highly sensitive and quite effective in predicting visceral adiposity levels in the pediatric population. Indeed, WC values correlate with obesity-related metabolic disorders, including insulin resistance, dyslipidemia and

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hypertension. It has been suggested that WC measurement could replace BMI in risk assessment for obesity-related comorbidities among young populations.[4-7]

Since WC values are influenced by age, gender, ethnic and geopolitical differences, available studies have presented the distribution of WC percentiles of children and adolescents of a wide range of countries.[8-29] Based on the above-mentioned, we intended to boost the set of information already reported by some national studies on this matter[30-37] by describing the WC percentile distribution and by calculating the WC cut-off values which would be able to predict obesity in a large sample of children aged from 6 to 10 years in the São Paulo State. Moreover, we compared the current WC percentile with data obtained from studies performed in other countries and another Brazilian study evaluating a similar population, according to age and gender.

Methods

Design and study population

This is a longitudinal, prospective, multicenter study, initiated in March 2010 and concluded in July 2010. The study was scientifically supported by the São Paulo Society of Cardiology (Sociedade de Cardiologia do Estado de São Paulo, SOCESP), and was regionally coordinated by the SOCESP Regional Directory Office of Araras, SP.

The current study aimed to include at least 30% of children of both genders, aged from 6 to 10 years old, enrolled at public and private elementary schools of the 13 cities of the Araras District of São Paulo State, Brazil. According to the Statistical and Educational Nationwide Survey Data provided by the National Institute of Educational Studies Anisio Teixeira (INEP), the number of children enrolled in all the cities included in the present study was 63,891 in 2010. In order to exclude children who did not attend school and special needs students older than 10 years of age (which would go beyond the age limit of this study) we used a correction factor of 10% of the total sample. Thus, the total estimated population of children from 6 to 10 years old was 57,501 in these localities.

The Secretariats of Education and the municipal and private schools of all Municipalities were contacted. The study was carried out in places where there was an approval in all instances: 147 public schools and 14 private schools. The Schools' coordination and parent's permission to participate in the evaluation was duly secured and each participating center had to comply with the ethical and data management guidelines of the local institution.

The children´s age was reported by Rousham et al.[38] study. Therefore, 15 June of the year birth was taken as an estimated date of birth.

Anthropometry measurements and WC percentiles comparison

Trained researchers performed the measurements according to standardized procedures.

Anthropometric measurements were undertaken with the children wearing light clothing and no shoes. The height and weight was measured in duplicate with a digital electronic scale provided with a portable stadiometer, to the nearest 0.1 cm and 0.1 kg, respectively. The average of the two measurements was used to calculate the BMI [BMI = weight (kg)/height(cm)^2]. Boys and girls were classified according to the BMI percentile ranges (the BMI curves established for each gender and age), using the parameters of the population curves of NCHS-CDC (National Center for Health Statistics - Centers for Disease Control and Prevention - USA).[39]

The nutritional state of the children was categorized according to the BMI percentiles: obese (BMI > 95%), overweight (BMI between 85 and 95%) and normal weight (BMI < 85%).

Abdominal circumference was measured in duplicate, at half the distance between the lowest rib and the superior border of the iliac crest, with a non-flexible tape, in the upright position, with the abdomen relaxed at the end of gentle expiration.[40]

To compare the actual WC percentiles distribution, we performed a literature review of the population-based studies that had evaluated this parameter in a similar age group. For comparisons among countries, we used the 50th percentiles of WC according to age. Our data has also been compared with a previous Brazilian study, to identify trends in abdominal circumference values in time.

Statistical analysis

Anthropometrical data from the pediatric population are presented as mean ± standard deviation (SD), median, percentiles and minimum and maximum values. The linear (Pearson's correlation coefficient) or non-linear correlation (logarithmic, inverse, quadratic, cubic, compound, power, sigmoid, growth and exponential coefficient) was calculated by regression. If significant, the higher linear or non-linear coefficient was used to identify the best model which explains the phenomenon. To establish the WC best cut-off value for obesity diagnosis, we generated a ROC Curve with normal weight and obese children using the BMI percentiles, stratified by gender and age, and used the highest sum of sensitivity and specificity to set the cut-off point (Youden Index).[41] A $p < 0.05$ was considered significant. The data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 from IBM Corp. Released in 2015. Armonk, NY, USA.

Results

A total of 22,000 children (11,199 boys and 10,886 girls) were included, which represents more than 30% of the estimated population, ranging from 1,606 to 2,610 boys and from 1,612 to 2,502 girls for each of the five periods of age, from 6 to 10 years old. The mean baseline anthropometric characteristics separated by age and gender are presented in Table 1. There was an expected progressive increase in weight, height, BMI and WC in both genders from 6 to 10 years. The prevalence of obesity in each age group varied from a minimum of 17 % (6 years old) to a maximum of 21.6% (9 years old) among boys, and a minimum of 14.1% (7 years old) to a maximum of 17.3 % (9 years old) among girls (Table 1). Approximately 30% of boys and girls had excess of fat, and were classified as either overweight or obese.

6	1.606	24.5 ± 5.85	1.20 ± 0.06	16.7 ± 2.83	58.8 ± 7.63	11.8	17
7	2.223	26.8 ± 6.76	1.25 ± 0.07	16.9 ± 3.14	60.5 ± 8.37	11.6	18.7
8	2.450	29.5 ± 7.81	1.30 ± 0.07	17.3 ± 3.41	62.1 ± 8.80	12.3	18.8
9	2.610	33.1 ± 9.06	1.35 ± 0.07	17.9 ± 3.70	64.4 ± 10.15	13.0	21.6
10	2.310	36.8 ± 10.37	1.40 ± 0.08	18.4 ± 3.92	67.2 ± 10.54	14.0	20.4
Total	11.199						
6	1.612	24.2 ± 5.85	1.19 ± 0.06	16.7 ± 2.95	59 ± 7.95	13.6	15.0
7	2.236	26.0 ± 6.80	1.23 ± 0.06	16.8 ± 3.15	59.8 ± 8.43	12.2	14.1
8	2.284	29.2 ± 7.85	1.29 ± 0.07	17.2 ± 3.49	61.9 ± 9.16	13.5	16.6
9	2.502	32.8 ± 8.92	1.35 ± 0.07	17.8 ± 3.54	64.1 ± 9.75	15.6	17.3
10	2.252	36.9 ± 9.96	1.41 ± 0.08	18.3 ± 3.76	66.8 ± 10.19	14.8	15.7
Total	10.886						

y: years old.

Figure 1 shows the smoothed computed waist circumference percentile curves for the 5th, 10th, 25th, 50th, 75th, 85th, 90th and 95th percentile for boys and girls.

We analyzed the correlation between WC and anthropometric parameters. There was a strong correlation between WC and weight ($r^2 = 0.77$, $p < 0.001$) and WC and BMI ($r^2 = 0.74$, $p < 0.001$), and a weak correlation between WC and height ($r^2 = 0.31$, $p < 0.001$).

The distribution of WC values in percentiles from 5th to 95th, according to age and gender, as well as the best sensitivity and specificity ROC cut-off values of WC, are shown in Table 2.

The cut-off values for WC are slightly below or in the range of 75th. Thus, for children with a WC classified into the 75th percentile the presence of overweigth or obesity must be taken into account. Moreover, the diagnosis of obesity is cleary present in children with a WC classified in the 85th percentile or higher.

In this study, among the eutrophic children, fewer than 7% had a WC value indicating obesity. Among the children categorized as obese by BMI, almost 90% may be characterized as being obese simply by measuring the WC (Table 3).

Figure 2 shows the graphic representation of the 50th percentile values (cm) of the WC set in the current study along with the values obtained from publications of 12 different countries, for boys (A) and girls (B) aged from 6 to 10 years. We detected that six-year-old Brazilian boys had a WC similar to the Mexican boys, the highest of all countries. Seven- to nine-year-old Brazilian boys have WC values lower than those observed in Mexican and Indian boys, and at 10 the values were also lower than the USA boys. Six, seven and ten-year-old Brazilian girls had similar or slightly lower WC values than those detected in Mexican and Indian girls, and 8 and 9 year-old girls also had WC values lower than Mexican girls.

Moreover, Figure 2 presents the 50% percentile of WC values of the Brazilian boys (C) and girls (D) and in a previous study published in 2007. It may be seen that the current WC 50th percentile curves for Brazilian boys was higher than the values of 2007. The current WC 50th percentile curves for Brazilian girls are much higher than the values obtained in 2007, around 2.0 cm at 7 and 8, 2.5 cm at 9 years old, and reaching 4.0 cm at 10 years old.

Discussion

This study presents age and gender specific WC percentile values for a large and representative sample of Brazilian children aged 6-10 years, based on a multicenter longitudinal anthropometric evaluation of school children. Furthermore, it is the first study to propose that WC cut-offs values are associated with obesity, according to BMI for boys and girls from 6 to ten years old. Besides, our study demonstrated that in this school population the prevalence of fat excess was around 30%, with 15% boys and girls overweight and another 15% already obese. Indeed, these findings corroborate previous data pointing out that childhood obesity is an increasingly serious health issue nationwide and worldwide.[42-44]

These data complement the existing set of WC reference values obtained in some other countries and enhance the assessment capabilities of childhood obesity, in the most diverse sites for children care. Since several relationships may be established with the values of waist circumference, such as intra-abdominal fat deposition and cardiovascular disease risk factors in children,[45-48] waist circumference could be adopted as an alternative or additional measurement to BMI in children. The strong correlation found between circumference values and BMI in this study demonstrates that such replacement or its additional use is feasible.

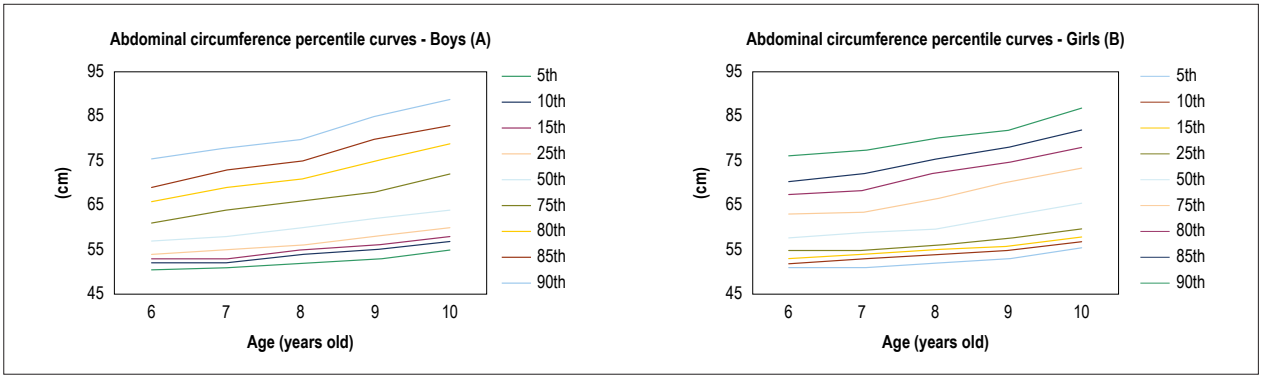

Figure 1 – *WC percentile curves for Brazilian children (aged 6–10 years). Boys (A) Girls (B).*

Table 2 – Distribution of WC percentiles and cut-off points for obesity according to age and gender in the population studied

	Cut-off values (cm) for obesity	WC percentiles								
Boys Age (y)		**5th**	**10th**	**15th**	**25th**	**50th**	**75th**	**85th**	**90th**	**95th**
6	61.2	50.5	52.0	53.0	54.0	57.0	61.0	66.0	69.0	75.8
7	63.2	51.0	52.0	53.0	55.0	58.0	64.0	69.0	73.0	78.0
8	64.8	52.0	54.0	55.0	56.0	60.0	66.0	71.0	75.0	80.0
9	67.7	53.0	55.0	56.0	58.0	62.0	68.0	75.0	80.0	85.0
10	70.5	55.0	57.0	58.0	60.0	64.0	72.0	79.0	83.0	89.0
Girls Age (y)										
6	62.7	50.0	51.0	52.0	54.0	57.0	62.5	67.0	70.0	76.0
7	64.2	50.0	52.0	53.0	54.0	58.0	63.0	68.0	71.7	77.0
8	64.7	51.0	53.0	54.0	55.2	59.0	66.0	72.0	75.0	80.0
9	69.7	52.0	54.0	55.0	57.0	62.0	70.0	74.5	78.0	82.0
10	72.7	54.5	56.0	57.0	59.0	64.8	73.0	78.0	82.0	87.0

y: years old.

Table 3 – Application of the obesity waist cut-off values in the study population classified by BMI as non-obese and obese, according to age and gender

	Non-obese children (%)		Obese children (%)	
Boys Age (y)	**≤ Cut-off ***	**> Cut-off ***	**≤ Cut-off ***	**> Cut-off ***
6	92.9	7.1	11.0	89.0
7	95.7	4.2	8.4	91.6
8	94.1	5.9	9.1	90.9
9	96.7	3.3	12.6	87.4
10	94.2	5.8	10.6	89.4
Girls Age (y)				
6	93.1	6.9	9.9	90.1
7	95.4	4.6	4.7	95.3
8	91.5	8.5	4.9	95.1
9	95.8	4.2	11.8	88.2
10	94.6	5.4	12.1	87.9

*y: years old; *: pre-determined cut-off WC value for each age and gender.*

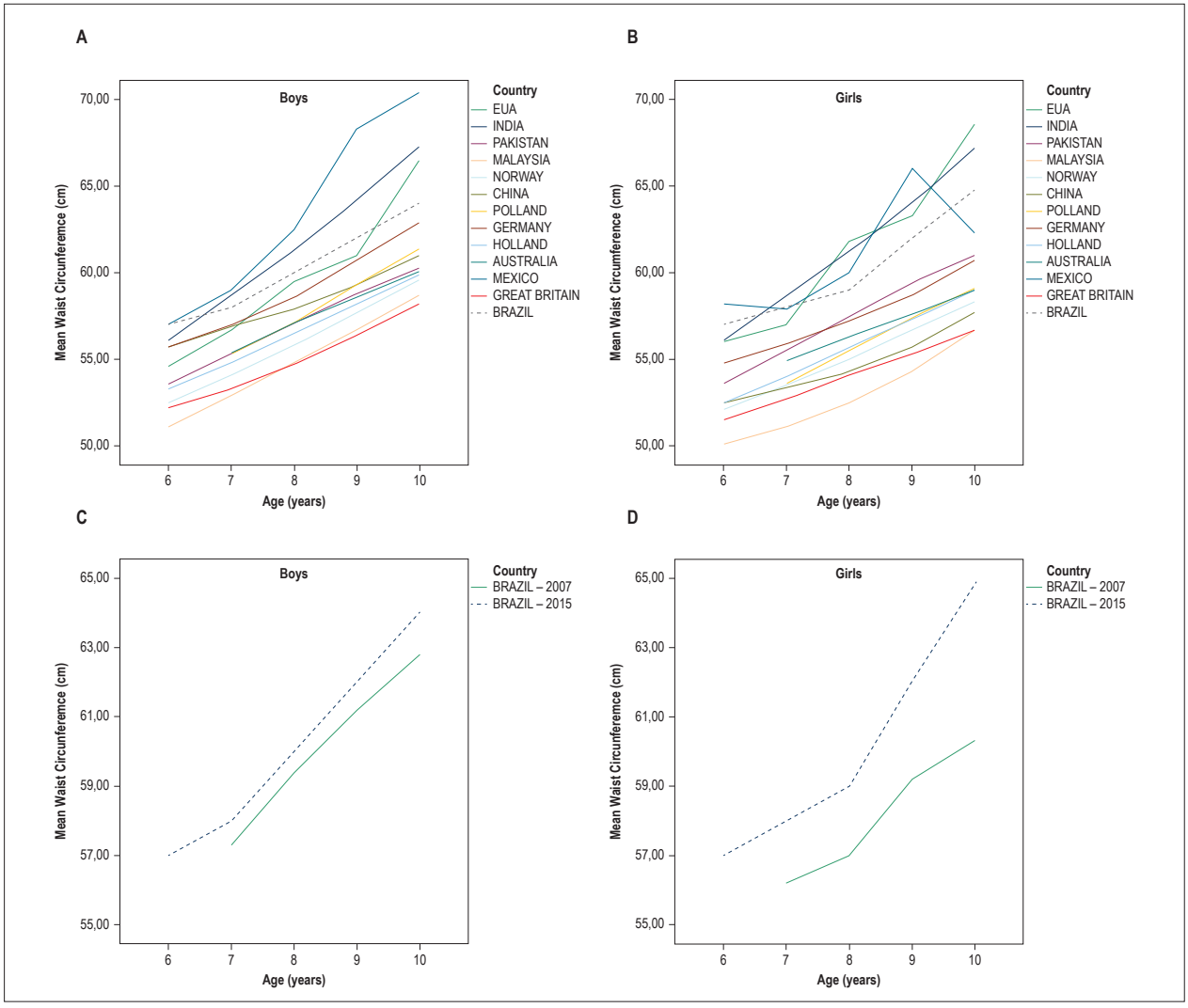

Figure 2 – *Comparison of children 50th WC percentiles curves between 13 different countries. A: Comparison between 6-10 years old boys; B: Comparison between 6-1- years old girls. C: Comparison between boys (C) and girls (D) WC 50th percentiles curves from different Brazilian studies.*

Furthermore, the proposed WC cut-off values for obesity provide a strong approximation of both normal weight (eutrophic) and obesity as defined by the international BMI categorization. No more than 7% of eutrophic children would have a higher WC cut-off value, which would indicate increased BMI. In such cases, other potential explanations may be present, such as initial fat excess caracterized by central obesity or additional clinical alterations (such as gastrintestinal disorders, amongst others). Regarding obese children, almost 87% may have been dignosed with obesity merely by measuring the WC. Moreover, WC is both simple and feasible measurement tool requiring inexpensive and user-friendly equipment, and little technical expertise, making it possible to carry out measurements on a scheduled basis in all schools. Our results demonstrate that Brazilian children present elevated 50th percentile WC values, with boys' values occupying roughly the third top place and girls the forth top place of all countries analyzed. Even more importantly, plotting the 50th percentile WC values obtained in 2007 with the current ones confirms the increment of values across all ages in boys and more intensively in girls.

While The International Diabetes Federation (IDF) suggests that the metabolic syndrome (MetS) should not be diagnosed in children younger than 10 years, weight reduction should be considered in those with abdominal obesity, as measured by waist circumference. The correlation of visceral adipose tissue and waist circumference in children was confirmed and it is an independent predictor of insulin resistance, lipid levels and blood pressure - all components of MetS.

The IDF consensus definition of MetS in children and adolescents was intended to agree upon a universally accepted characterization for facilitating MetS diagnosis and to accelerate preventive measures before the child or adolescent develops diabetes or cardiovascular disease. Obesity, particularly in the abdominal region, is associated with increased risk for cardiovascular disease and type 2 diabetes.[49]

The present study circumscribed an area of 12 cities in the São Paulo State. We believe it may be representative of school children of a large area of Brazil, since it included the most significant number of children of private and governmental schools ever reported in Brazil. Moreover, São Paulo state has a high degree of miscegenation, and its countryside has an economic and social development comparable to the South and Southern Regions and even with many closer areas of the Central-West. As emphasized by several reports, the evaluation of cardiometabolic disorders in children is only feasible when specific references to the association between age, gender and ethnic origin and health risks are available. With a sample of 9,713 subjects from 2 to 18 years old, including 3,414 African-American, 2,746 European-American, and 3,553 Mexican-American (MA), Fernandez et al.[14] have described and provided estimates of the distribution of WC percentiles curves widely used in different countries, the well-known NHANES data. On the 75th and 90th percentiles, MA girls showed the fastest overall increase among all girls. At any of the percentiles considered, MA persons showed the highest overall WC and the fastest overall rate of WC increase with age. This data supports the high WC percentiles among Brazilian children and the most significant increase among Brazilian girls.

Based on the robust data they collected, Fernandez et al.[14] stressed that careful attention should be concentrated to children whose WC values fall in the 75th and 90th percentile, since this drop help identify children at risk for various comorbidities and they strongly suggest prevention actions [against these situations]. All percentiles values found in our study were higher than those described by Fernandez et al.[14] Among German children (6-10-year-old boys and girls), the 97th WC percentile was associated with abdominal obesity.[50]

Healthy lifestyle habits, including engaging in a healthy diet and physical activity, may lower the risk of becoming obese and developing related diseases.[51,52] The dietary and physical activity behaviors of children and adolescents are influenced by many societal environments, including families, communities, schools, child care settings, medical care providers, faith-based institutions, government agencies, the media, and the food and beverage industries and entertainment businesses.[53-56] Schools play a particularly critical role in establishing a safe and supportive environment with policies and practices that support healthy behaviors. They also provide opportunities for students to learn about and practice healthy eating and physical activity behaviors.[56] Therefore, the importance of the present study was to provide representative values of WC of our children that may be used as an assessment tool to help meet public health recommendations.

Another significant contribution in the development of national epidemiological data is the Study of Cardiovascular Risks in Adolescents - (Portuguese acronym "ERICA" - Estudo de Riscos Cardiovasculares em Adolescentes).[57] It is a large cross-sectional study at the national and school-based levels and a pioneering study that aimed to assess the prevalence of cardiovascular risk factors, including metabolic syndrome components in approximately 85,000 students, aged 12 to 17 years. A recent publication of ERICA described that the prevalence of metabolic syndrome was around 2,6% and that the most common combinations of elements, referring to 3/4 of combinations, were: enlarged waist circumference (WC), low HDL-cholesterol (HDL-c) and high blood pressure; followed by enlarged WC, low HDL-c and high triglycerides; and enlarged WC, low HDL-c, high triglycerides, and blood pressure. Therefore, the results of ERICA reinforce the importance of WC as a potential indication of a more global disarrangement that could determine the metabolic syndrome.

The main limitation of the present study is the described percentile curves based on a sample of children from only one state, São Paulo, and not derivated from randomly selected regions across Brazil. This fact may restrict the generalization of our results to children across the entire country. Furthermore, to validate the cut-off points for overweight and obesity, it is necessary to test the respective values in a different coorte of children.

Conclusion

Age and gender specific reference curves of WC for Brazilian children and cut-off values for obesity risk may be used for national screening and interventional studies to reduce the obesity burden in Brazil.

Author contributions

Conception and design of the research: Santos JLF, Consolim F; Acquisition of data: Valério VP, Fernandes RN, Duarte L, Assumpção AC, Guerreiro J, Sickler AL, Lemos AAR, Goulart Filho JG; Analysis and interpretation of the data: Hussid MF, Camacho C, Sangaleti C, Consolim F; Statistical analysis: Camacho C; Writing of the manuscript: Camacho C, Sangaleti C, Consolim F; Critical revision of the manuscript for intellectual content: Santos JLF, Valério VP, Fernandes RN, Cesar LAM, Pinto IM, Magalhães C, Sangaleti C, Consolim F.

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

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Waist Circumference: A Simple Measure for Childhood Obesity?

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Short Editorial related to the article: Waist Circumference Percentiles and Cut-Off Values for Obesity in a Large Sample of Students from 6 To 10 Years Old Of The São Paulo State, Brazil

Childhood obesity has been increasing all over the world and considered one of the major challenges in public health. The prevalence increased from less than 1% in 1975 to 5.6% and 7.8% among girls and boys, respectively, in 2016.[1] No less worrying are the recent data from the Brazilian Institute of Geography and Statistics (IBGE) showing that in 2008-2009, 51.4% of boys and 43.8% of girls aged between 5 and 9 years were overweight or obese.[2]

Obese children and adolescents are five times more likely to become obese adults.[3] Besides, childhood obesity has been associated with hypertension, insulin resistance, diabetes mellitus, dyslipidemia, and increased morbidity and mortality in adult life.[4] Therefore, it is important to screen for excess body fat in this population and create strategies to prevent the development of chronic diseases in the future.

Anthropometric indicators have been suggested as epidemiological screening tools to detect children and adolescents with high cardiometabolic risk, because of their non-invasiveness, low cost, and easy application.[5,6] Waist circumference (WC), for example, is an indicator of central adiposity associated with metabolic complications of obesity in the pediatric population.[7,8] However, the cut-off points of WC for classification of abdominal adiposity in children and adolescents have not been established yet, which limits its use.

Studies describing percentile values of WC have reported different results; WC measurements may be affected by age, sex and ethnicity,[9-11] which makes the establishment of global reference values difficult.

In the current issue of Arquivos Brasileiros de Cardiologia, Santos et al.[12] published a longitudinal study with 22,000 children (11,199 boys) aged between 6 and 10 years, attending public and private schools of 13 cities in Sao Paulo state. The authors presented WC reference curves for age and sex and cut-off points to identify children at risk for obesity. The authors described that approximately 30% of the children had excess body fat and classified as overweight according to body mass index. ROC curve analysis revealed that the 75th percentile was the optimal cut-off point for overweight and obesity, and that obesity was easily diagnosed among children with WC values above the 85th percentile.[12]

When the WC curves (50th percentile) were compared with results of another Brazilian study with 2,919 students aged 7 to 10 years carried out in Florianopolis, Brazil, in 2007,[13] Santos et al.[12] observed that the current percentile curves are higher, with an increase of up to 4.0 cm among girls at the age of 10. These discrepancies may be explained by methodological differences, although the method used for WC measurements was the same in both studies. However, it is known that the Brazilian population is highly mixed and, as above mentioned, WC can be influenced by ethnicity, which may explain the difference between the results.

Again, few studies have addressed cut-off values for WC in a large population including different ethnical groups in Brazil, which reinforces the importance of these investigations to contribute to the scientific literature. However, as the authors mentioned as limitation of the study, the percentiles curves were established based a sample of children in the State of Sao Paulo, and hence it is advisable that representative samples of all geographic regions of the country be studies for generalization of results. Besides, the values proposed need to be validated in other populations with similar characteristics.

Recently, Xi et al.[14] proposed international WC percentile cut-off points, specific for age and sex, to define central obesity based on data of 113,453 children and adolescents aged 4-20 years from eight countries in different regions (Bulgaria, China, Iran, Korea, Malaysia, Poland, Seychelles, and Switzerland). The 90th percentile was established as WC cut-offs to detect central obesity in this population, with good performance in predicting cardiovascular risk in normal weight children and was suggested to be used in the assessment of abdominal adiposity in children and adolescents in different countries.

Keywords

Child; Adolescent; Pediatric Obesity; Overweight; Risk Factors; Body Weights and Measures.

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Original Article

Determination of Myocardial Scar Tissue in Coronary Slow Flow Phenomenon and The Relationship Between Amount of Scar Tissue and Nt-ProBNP

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Abstract

Background: Pathophysiology and prognosis are not clearly determined in patients with the coronary slow flow phenomenon (CSFP). These patients present with various clinical conditions ranging from being asymptomatic to being admitted with sudden cardiac death.

Objectives: We aimed at assessing the findings of late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (CMR) as an indicator of myocardial fibrosis. We also aimed at determining the relationship between the presence of myocardial fibrosis and NT-proBNP levels in patients with CSFP in the left anterior descending coronary artery (LAD).

Methods: A total of 35 patients were enrolled within an age range of 31-75. The study patients (n=19) had normal epicardial coronary arteries at angiography, but they presented with CSFP in the LAD. The control group patients (n=16) had normal epicardial coronary arteries and TIMI scores at normal levels in angiography. In both groups, the patients were examined with CMR for the presence of myocardial fibrosis. In addition, plasma NT-proBNP levels were measured. A p-value < 0.05 was considered significant.

Results: The rate of myocardial fibrosis was significantly higher in CMR in the patients with CSFP (p=0.018). A variable amount of myocardial scar tissue was detected at the left ventricular apex in 7 patients and at the inferior and inferolateral regions in 3 patients. There was no difference in the level of NT-proBNP in patients with CSFP. However, the NT-proBNP levels were higher in patients with CSFP, who had scar tissue in CMR (p=0.022).

Conclusions: In conclusion, LGE in CMR showed that ischemic myocardial scarring may exist in patients with CSFP. These results indicate that CSFP may not always be innocent. (Arq Bras Cardiol. 2020; 114(3):540-551)

Keywords: Heart Failure; Fractional Flow Reserve, Myocardial; Cicatrix, Hypertrophic; Prognosis; Natriuretic-Peptide, C-Type; Endomyocardial Fibrosis, Magnetic Resonance Spectroscopy.

Introduction

There is limited information in the literature regarding the prognosis of slow coronary flow phenomenon (CSFP). The preexisting data indicates that slow flow-related myocardial ischemia may cause angina and the prognosis is worse in these patients.[1] Acute myocardial infarction,[2] sudden cardiac death and malignant ventricular arrhythmia were also reported to be associated with CSFP.[3] The occurrence of recurrent episodes of chest pain or chest pain developing at rest, as well as high rates of emergency admissions, and hospitalizations are reported.[4,5]

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Thus, this phenomenon is not as innocent as it appears to be, bearing a potential to cause serious deterioration in the quality of life. It is not clearly known today whether organic injuries exist in these patients, due to the lack of further investigation and findings.

The level of N-terminal proB-type natriuretic peptide (NT-proBNP) has been shown to increase after exercise in patients with slow coronary artery flow.[6] There is a correlation between ischemia or infarct size on magnetic resonance imaging (MRI) and this correlation can be observed in the NT-proBNP levels in patients with acute coronary syndrome as well.[7] As a result of the advances in cardiac magnetic resonance imaging (CMR), microvascular ischemia and cardiac fibrosis can be demonstrated using this technique.[8,9] The relation between the extent of fibrosis and NT-proBNP levels in these patients has been revealed by several MRI studies performed in patients with acute coronary syndrome.[10,11] However, there are no studies in the literature evaluating patients with CSFP for the

presence of fibrosis in the myocardial tissue according to the findings of late gadolinium enhancement in CMR. This study aimed at investigating the presence of myocardial fibrosis in patients with slow flow in the left anterior descending coronary artery by using the late gadolinium enhancement technique in CMR. In addition, it aimed at evaluating the relationship between myocardial fibrosis and NT-proBNP levels.

Materials and Methods

Study Population

Among the patients who were admitted to our department between January 2015 - August 2016 and who underwent coronary angiography for chest pain, 19 patients with the coronary slow flow phenomenon in LAD were included in this prospective cohort study. The control group included sixteen patients whose epicardial arteries were entirely normal with a normal coronary flow.

This study was approved by the ethics committee of the Gazi University Hospital and was conducted in accordance with the principles of the Helsinki declaration.

Exclusion Criteria

The following patients were excluded from the study: patients with coronary artery ectasia or atherosclerotic lesions in left main and left anterior descending coronary arteries; patients who underwent percutaneous coronary intervention; patients scheduled to undergo coronary artery intervention; patients with >50% stenosis in any coronary artery; patients with a prior history of MI; patients with <50% left ventricular systolic function; patients with claustrophobia, heart failure or valve dysfunction, ventricular extrasystoles or atrioventricular conduction abnormalities, and branch block or atrial fibrillation; patients with positive treadmill test; patients with restrictive, hypertrophic or dilated cardiomyopathies; patients with known systemic disease (hyperthyroidism, hypothyroidism, malignancy, autoimmune disease, infection or any of the pulmonary, hepatic, renal, hematologic disorders); patients with a history of myocarditis, whose GFRs are <80 ml / min and patients who refused to participate in the study.

Patient Data

The study patients were measured for height, weight, and body mass index (BMI). Patients' age, gender, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking and family history), demographic characteristics and comorbid diseases were recorded. Electrocardiography (ECG) was obtained for all patients and all of them demonstrated a sinus rhythm. All study patients were examined on the right lateral decubitus position with a Vivid 7-Pro Ultrasound system (Vingmed Electronic, GE, Horten, Norway), equipped with a 2.5 MHz probe, through simultaneous one-lead ECG recording. M-mode and Doppler measurements were performed in accordance with the recommendations of the American Echocardiography Association.[12]

Exercise test was performed at an average of 3 days before angiography in all patients (GE medical system, Milwaukee, USA), according to the standard Bruce protocol test, with standard ECG, blood pressure and heart rate measurements performed at prespecified time points, as per relevant guidelines.[13]

Blood samples for the quantification of NT-proBNP were collected through the angiography sheath immediately before its removal. After the collection, they were centrifuged for 10 min at 4500 rpm and stored at -20 ºC until the time when the isolated serum was analyzed. On the day of the analysis, after the samples reached room temperature, an electrochemiluminescence immunoassay was performed with the Roche Cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The results were presented in picograms per ml (pg/ml). The coefficent of variation value for the NT-proBNP was found below 5% via this method.

Coronary Angiography and Timi Frame Count

Coronary angiography was performed using the standard Judkins technique with a femoral approach and at 30 frames per second, using Toshiba Infinix cardiac angiography (Toshiba Corporation, Tochigi, Japan). Iopromide (Ultravist-370; Bayer Pharma AG, Berlin, Germany) was used as contrast agent during coronary angiography. An average of 6 to 8 ml of contrast agent was injected manually for each exposure. Coronary arteries were visualized through left and right oblique views with appropiate cranial or caudal angles. The speed of flow at LAD was assessed in right or left anterior oblique views often with caudal angle. The images were evaluated by two clinical specialists who were blind to the clinical findings of the patients.

Quantitative evaluation of coronary flow was performed in accordance with the TIMI-4 study, by counting cine frames, starting from the time of contrast agent administration, until it reached to a certain distal point.[14] The methodology of frame count was standardized for each epicardial vessel. TIMI frame counting started with the first frame in which the dye completely filled in the artery. The complete filling of the artery was determined by meeting the following three criteria: (1) A column of almost or fully concentrated dye should extend across the entire width of the origin of the artery; (2) The dye should touch both borders of the origin of the artery; and (3) there should be an antegrade motion of the dye. The last frame counted was the one in which the dye first enterered the end-point branch of the target artery. A complete opacification was not required at the distal segment.

LAD and TIMI frame counts were 1.7 times longer than the mean of the RCA and CX counts. Therefore, the longer LAD frame counts were corrected by dividing by 1.7 to derive the corrected TIMI frame count (CTFC).

In our study, coronary flow for LAD was accepted to be normal when the TIMI frame count was <23 and it was accepted as slow when the TIMI frame count was ≥ 23.[15,16]

Magnetic Resonance Imaging Technique

CMR was performed after a median of 8 days (range 0-21 days) after coronary angiography. Standard sequences of cardiac MR perfusion studies were used in all patients. The left antecubital vein was used for intravenous contrast injection.

MRI scans of patients were obtained using a 3 Tesla MRI device (Siemens MAGNETOM® Verio, Erlangen, Germany) with a gradient power of 45 mT/m. A 6-channel body coil was placed on the front chest wall while the patient was lying in the supine position with ECG pads placed properly. Multiplanar scout images were obtained with the phase-sensitive inversion-recovery (PSIR) turbo FLASH sequence using a repeated breath-hold MRI-technique. Standart long-axis, 2-chamber, 4-chamber and short- axis images of heart were obtained by aligning the mitral valve and the apex. Imaging parameters were: repetition time (TR) = 800ms; echo time (TE) = 6.66ms; slice thickness = 8 mm; matrix = 128x256 and field of view (FOV) = 400 mm. T1, T2 weighted images accompanied by 'inversion recovery' pulse for the suppression of blood signals (dark blood) and the turbo spin echo sequence were obtained in order to evaluate the myocardial morphology (TR/TE/ thickness/ matrix/ FOV: 698/6.6/ 8 mm/ 128x256, 360 mm).

Dynamic first-pass myocardial perfusion imaging with SR Turbo FLASH (TfI) pulse sequence was acquired after 0.025 mmol/kg Gd-DTPA (Magnevist; Bayer Healthcare, Wayne NJ, USA) was administered intravenously. In eight-minute resting intervals, cine short axis gradient echo sequences for functional imaging of the ventricles were obtained throughout cardiac cycle using the breath-hold technique (TR/TE/ thickness/ matrix/ FOV: 40,24/ TE/ 8 mm/128x256/ 360 mm). Short-axis and 4-chamber images were obtained with T1-weighted PSIR technique, approximately in the 8th minute after the contrast was applied (TR/TE/ thickness/ matrix/ FOV: 756/ TE: 1,15/ 6 mm/ 128x256/360 mm). Total imaging duration lasted 35 minutes on average.

The cost of CMR and plasma NT-proBNP testing were covered by the Scientific Research Projects Unit of the Gazi University.

Magnetic Resonance Image Analysis

All CMR images were transferred to the work station for analysis (Siemens multimodality workplace, Leonardo, Siemens Healthcare). All evaluations were performed visually. CMR studies were retrospectively evaluated by a radiologist experienced for more than 15 years in cardiac imaging, who was blind to the results of echocardiography and coronary angiography examinations. When any perfusion defects or late enhancement were observed during these examinations, they were precisely recorded. Contrast enhancement in perfusion sequences was defined as accomplishing all of the 5 phases after obtaining the highest signal intensity in the left ventricle. CMR results were then compared with the patients' echocardiography and coronary angiography results.

Statistical Analysis

The study data were analyzed by using the SPSS (SPSS Inc., Chicago, version 21.0) program. The variables were examined using visual (histograms, probability plots) and analytical methods (the Kolmogorov-Simirnov test) to determine whether or not they were normally distributed. Descriptive analyses were presented with the values and standard deviations for the normally distributed variables, and with the median (interquartile range), for the non-normally distributed variables. Categorical variables were presented using percentages. Independent samples t-test and the Mann-Whitney U test were used to compare the numerical variables. Pearson's Chi-square analysis was used to compare the categorical data, but Fisher's exact test was performed when two of the expected values were below 5 or one of the expected value was below 2. A difference with a p-value <0.05 was considered statistically significant.

Results

A total of 35 patients were included in the study. Patients were divided into 2 groups as the patient group and the control group. Nineteen patients were identified comprising the group with slow flow in LAD, and 16 patients with normal coronary flow were included in the control group (Figure 1). The patients in the control group were matched for their risk factors to the individuals in the patient group. The mean age of the patients was 50.3 ± 10.7, and 6 out of 35 patients (17%) were females. Eleven patients (31%) were diabetic, 9 patients (25%) were hypertensive, 5 patients (14%) were dyslipidemic, 18 patients (51%) were smokers and 8 patients (22%) had a positive family history (Table 1).

The main complaint was chest pain in all study patients. ECG of all patients was sinus rhythm. Heart rates were between 64/min - 92/min. The average heart rate was 74/min. In addition, there was no sign of ischemia, hypertrophy or arrhythmia in the ECG. Left ventricular ejection fraction and other echocardiography findings of the patients were normal. In addition, all patients' treadmill tests were negative. High sensitivity troponin was measured before and after coronary angiography in all patients. All values were below the threshold and there was no increase in troponin values after angiography.

The time interval between the CMR examinations and catheter coronary angiography of the patients was scheduled not to be longer than 21 days.

When patients with slow flow were compared with the control group, no significant differences were found in NT-proBNP values (p=0.247). The positive CMR results were significantly more common in the patients with the slow flow (p=0.001) (Table 1). Scar tissue was found at varying levels in the cardiac apex of 7 patients (Figures 2 and 5) and at the inferior and inferolateral regions in 3 patients (Figures 3,4,6,7 and 8). No scar tissues were found in 9 patients (Figure 9).

Demographic characteristics and TIMI grade flow were not different in the CMR positive group compared to the MRI negative group (Table 2). NT-proBNP levels were statistically significant in patients with slow flow and scar tissue in CMR (p=0.022) (Table 2).

All subjects completed treadmill exercise testing using the Bruce protocol. All patients had exercise capacity over 7 mets. Treadmill tests were terminated on the patients' own request. There was no significant ST depression (≥1 mm) or T negativity in any exercise test. Metabolic equivalent (MET) values were different in the control, slow flow, and MR positive groups (11.15 ± 1.43; 9.74 ± 2.05; 9.27 ± 2.15, respectively; p=0.027 for the control group vs. the slow flow group; p=0.013 for the group control vs. the MR positive group). There were no differences in MET values between

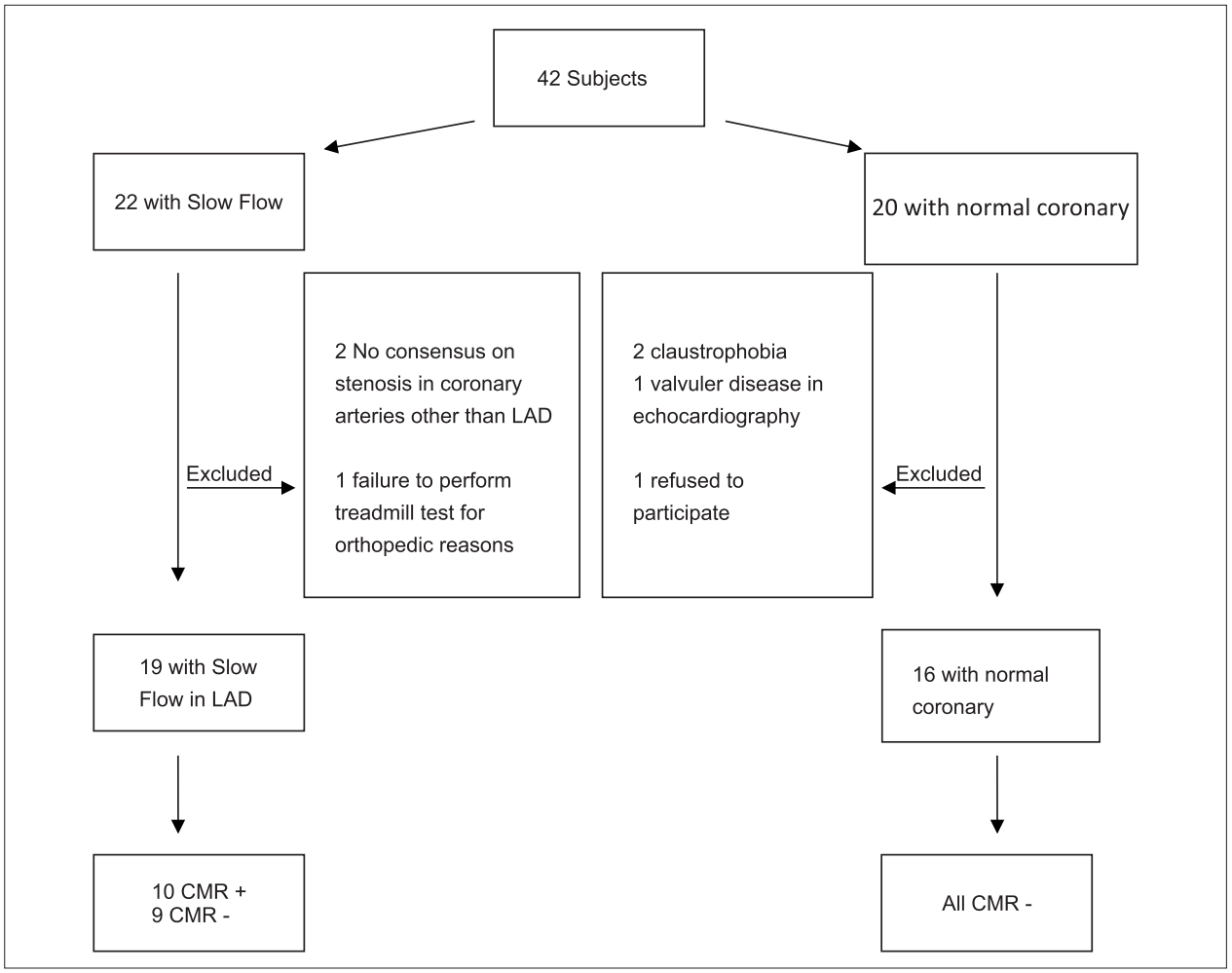

Figure 1 – *Patient selection. CMR: cardiac magnetic resonance imaging.*

the control group and the MR negative group (11.15 ± 1.43 vs 9.74 ± 2.05; p=0.201) (Table 3).

Discussion

The main finding of this study was the detection of scar tissue in CMR in the patients with slow flow in the LAD. NT-proBNP values were higher in patients with slow flow and scar tissue in CMR. In addition, the exercise capacity of these patients was lower compared to the control group. Coronary slow flow patients have not previously been evaluated with CMR to detect any presence of myocardial fibrosis in the literature. In our study, we detected scar tissue in the myocardium in the LAD field in about half of patients with CSFP in the LAD. This finding was statistically and clinically significant when compared to the control group. However, we did not evaluate the patients with serial MRI examinations or serial NT-proBNP measurements. The absence of scar tissue in the remaining patients may be explained by this limitation of our study. The development of scar tissue in the myocardium requires a progressive process occurring as a result of continuous damage over years. Thus, the absence of scar tissue might have been due to timing of the assessment. As it is very well known, the process of atheromatous plaque formation takes many years, depending on the presence of cardiovascular risk factors, environmental conditions, genetic factors and the time period. The same factors may also apply to coronary slow flow. We have shown with this study that the CSFP is not harmless at all and that it can lead to scarring in the myocardial tissue at the end of the respective pathological process.

The role of NT-proBNP in the pathophysiology of CSFP is not clear. It has been shown that B-type natriuretic peptide is secreted from cardiomyocytes in response to ischemia and that its secretion can also be independent of left ventricular wall stress.[17-20] Also, in addition to cardiac myocytes, fibroblasts can secrete BNP and cause fibrosis by induction of matrix metalloproteinases by releasing BNP.[21] In our study, the levels of NT-proBNP were not significantly high in patients with slow flow. However, they were found to be high in patients with slow flow, in whom scars were detected in CMR. It may be suggested that NT-proBNP levels are elevated only in the presence of sufficient fibrosis in response to coronary slow flow, which has led to the development of myocardial scar

Table 1 – Comparison of Clinical Characteristics between both Groups

Parameters	Total (N=35)	Slow Flow (N= 19)	Control (N= 16)	p value
Age, mean (SD), years	50.3 ± 10.7	51.3 ± 8.2	49.44 ± 12.8	0.62
Sex (Male), n (%)	29 (82)	15 (78.9)	14 (87.5)	0.50
Hypertension, n (%)	9 (25)	6 (31.6)	3 (18.8)	0.38
Diabetes mellitus, n (%)	11 (31)	6 (31.6)	5 (31.3)	0.98
Smoker, n (%)	18 (51)	9 (47.4)	9 (56.3)	0.60
Family history, n (%)	8 (22)	4 (21.1)	4 (25)	0.78
Dyslipidaemia, n (%)	5 (14)	3 (15.8)	2 (12.5)	0.78
BMI, mean (SD) (kg/m²)	27.7 ± 2.3	28.1 ± 2.5	27.3 ± 2	0.39
NT-proBNP (pg/ml)	29,5 (17.7-66.2)	47.8 (22.6-121.5)	26.0 (10.9-58.1)	0.246
cTIMI flow (frame/second)	34.6 ± 16.2	28.0 ± 8.6	13.1 ± 1.2	<0.001
METs, mL/kg/dk	10.38 ± 1.91	9.74 ± 2.05	11.15 ± 1.43	0.027
Positive results of MRI n (%)	10 (28)	10 (52.6)	0 (0)	0.001

BMI: body mass index ; cTIMI: corrected Thrombolysis in Myocardial Infarction; METs: metabolic equivalents; MRI: magnetic resonance imaging.

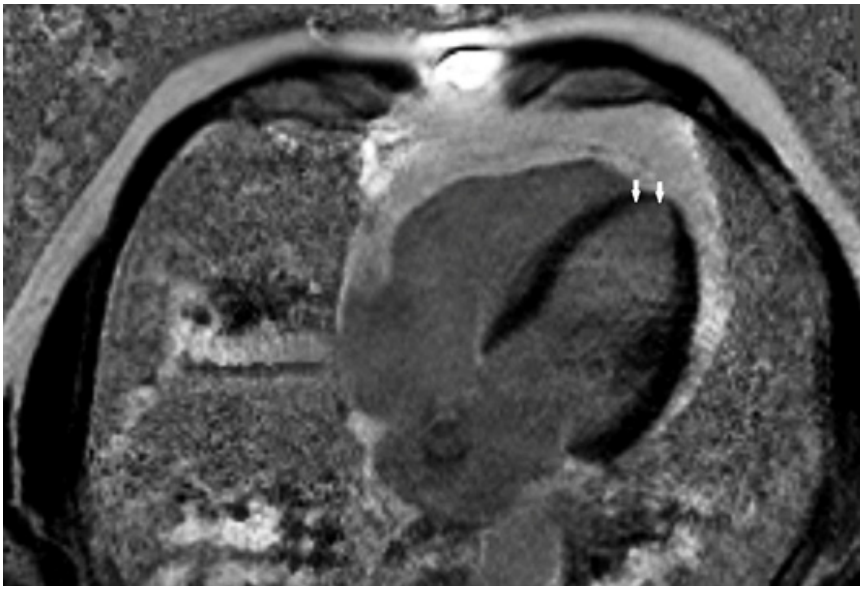

Figure 2 – *Four-chamber delayed-enhancement Phase Sensitive Inversion Recovery (PSIR) image, showing delayed subendocardial circumferential enhancement in the apical region (arrows) of the left ventricle.*

Figure 3 – *Short- axis delayed contrast-enhanced PSIR cardiac MR image, showing focal subendocardial transmural and subepicardial enhancement areas, mostly in the inferior and inferolateral left ventricular walls.*

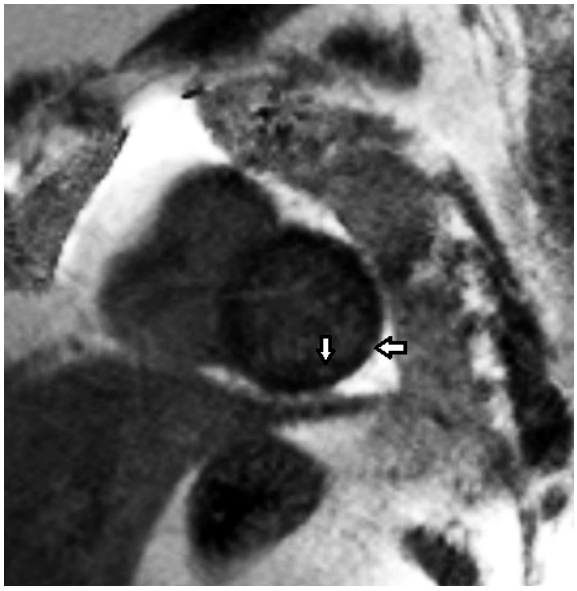

Figure 4 – *Short- axis delayed contrast-enhanced PSIR cardiac MR image, demonstrating focal subendocardial and subepicardial enhancement areas localized into the inferior and inferolateral left ventricular walls (arrows). These hyperintense areas reflect scattered fibrotic scar tissues in the LAD territory.*

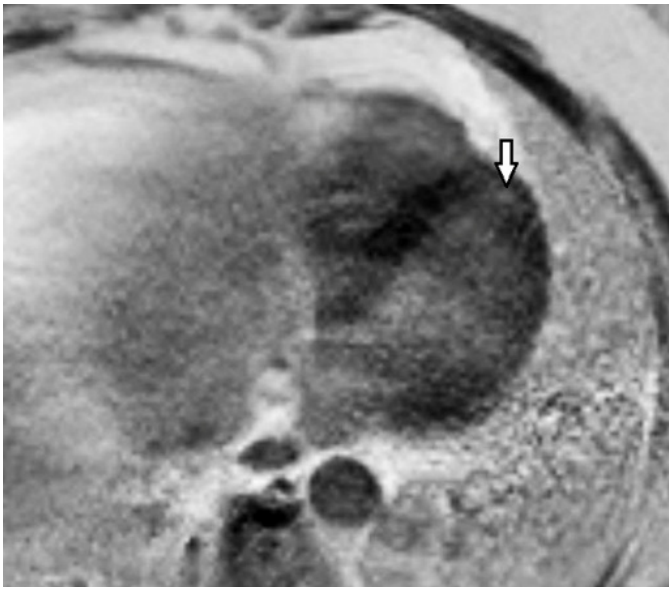

Figure 5 – *There is a focal lesion in four-chamber PSIR prepared gadolinium-enhanced T1-weighted image. Focal lesion localized to the apical region of the left ventricle, showing late subendocardial- myocardial enhancement compatible with fibrosis.*

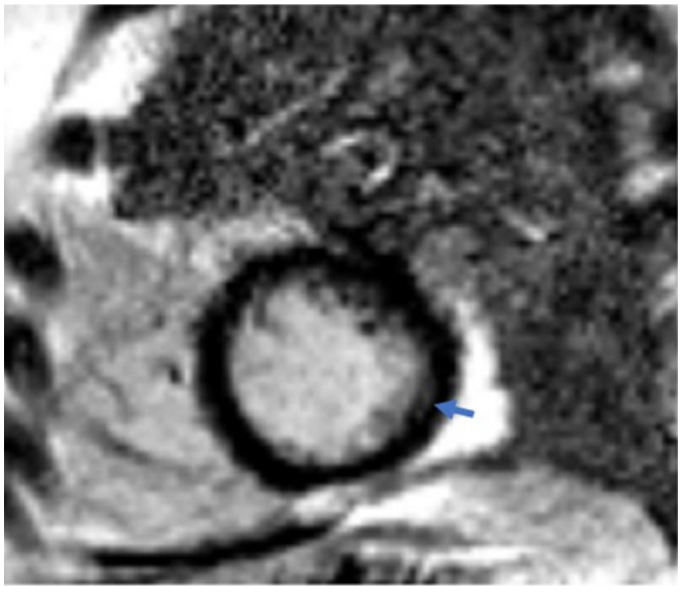

Figure 6 – *Short-axis delayed contrast-enhanced PSIR image represents sub-endocardial enhancement areas, mostly in the inferorolateral left ventricular wall. Scar tissue spanning in nearly 25-50% of wall thickness.*

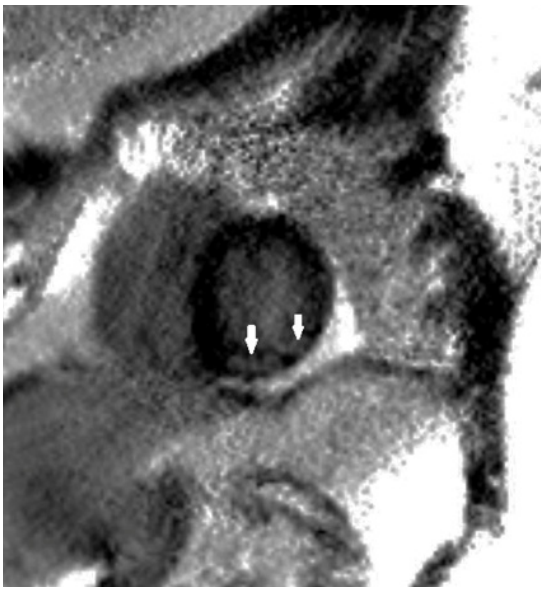

Figure 7 – *Short- axis delayed contrast-enhanced PSIR cardiac MR image, showing focal subendocardial transmural and subepicardial enhancement areas, mostly in the inferior and inferolateral left ventricular walls (arrows), indicating scar tissues in the distribution of the LAD.*

Table 2 – Clinical characteristics in patients with slow flow

Parameters	Slow Flow (N= 19)		
	Cardiac MRI (+) (N=10)	Cardiac MRI (-) (N= 9)	p value
Age, mean (SD), years	54.1 ± 9.6	49.4 ± 7.1	0.29
Sex (Male), n (%)	6 (60)	9 (100)	0.08
Hypertension, n (%)	4 (40)	2 (22.2)	0.62
Diabetes mellitus, n (%)	3 (30)	3 (33.3)	1.0
Smoker, n (%)	6 (60)	3 (33.3)	0.37
Family history, n (%)	1 (10)	3 (33.3)	0.30
Dyslipidaemia, n (%)	3 (30)	0 (0)	0.21
BMI, mean (SD) (kg/m²)	28.2 ± 3.0	28.0 ± 2.4	0.81
NT-proBNP (pg/ml)	147.10	28.0 (21.5-56.2)	0.03
cTIMI flow (frame/second)	(41.57-734.57)	26.4 (22.9-35.0)	0.67
METs, mL/kg/dk	24.1 (23.8-28.9)	10.26 ± 1.92	0.304

BMI: body mass index ; cTIMI: corrected Thrombolysis in Myocardial Infarction; METs: metabolic equivalents; MRI: magnetic resonance imaging.

Table 3 – Exercise test results for groups

Parameter	Control (N= 16) (1)	Cardiac MRI (+) (N=10) (2)	Cardiac MRI (-) (N= 9) (3)	p value (1-2)	p value (1-3)
METs, mL/kg/dk	11.15 ± 1.43	9.27 ± 2.15	10.26 ± 1.92	0.013	0.201

METs: metabolic equivalents; MRI: magnetic resonance imaging.

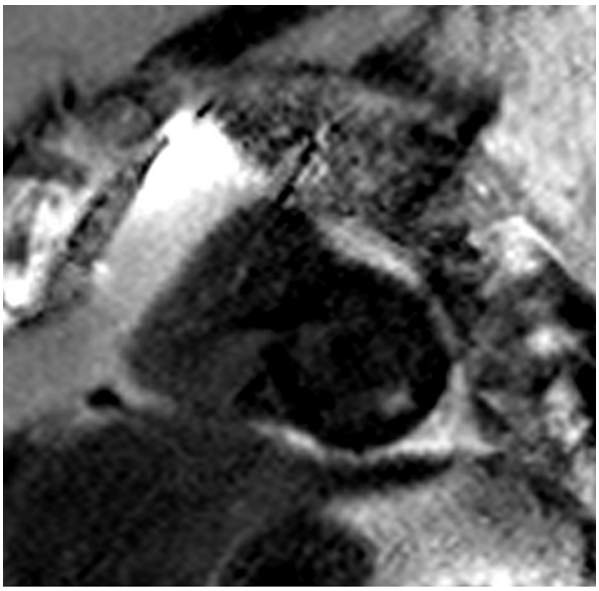

Figure 8 – *Short- axis delayed contrast-enhanced PSIR cardiac MR image, demonstrating focal subendocardial and subepicardial enhancement areas localized into the inferior and inferolateral left ventricular walls.*

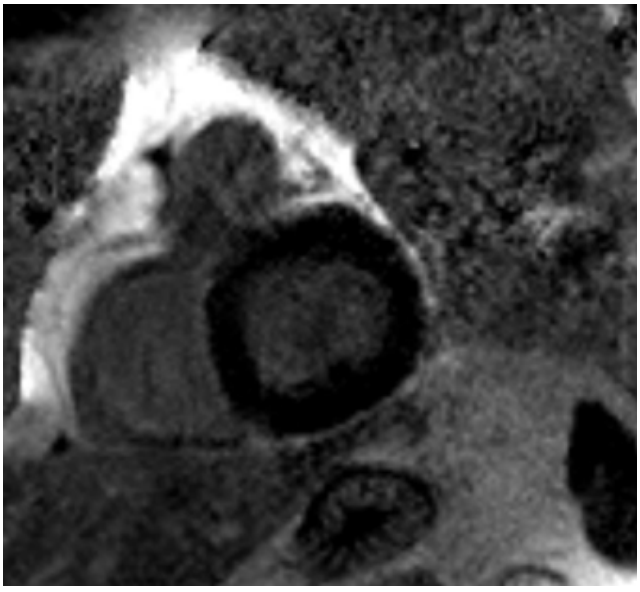

Figure 9 – *This image shows the appearance of normal myocardium. This particular image was obtained using Phase Sensitive Inversion Recovery (PSIR). There is no abnormal enhancement.*

tissue. The etiology of CSFP has not been clearly understood since it was first described. Although CSFP may be the result of microvascular alterations, increased microvascular resistance and early stage widespread atherosclerosis have also been shown to play a role in the etiology.[22,23] In addition, histological and pathological changes in the coronary arteries have been tried to be used for elucidating the etiology. In a study conducted in patients with CSFP, Mangieri et al.[17] found changes such as cellular edema, fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, irregular fibrosis, capillary damage and decreased capillary lumen, as a result of myocardial biopsy, and claimed that these pathological changes slowed blood flow by increasing vascular resistance.[22,23] Moreover, in CSFP, intravascular ultrasonography (IVUS) has shown diffuse intimal thickening and widespread calcification, and coronary angiography has shown atheromatous plaques that do not cause luminal irregularity.[24]

Although coronary slow flow has been reported to be associated with many pathologic conditions, it appears to be the onset of a widespread atherosclerotic disease that is coincidental with a microvascular disease in which endothelial dysfunction is in the forefront. It can be considered that microvascular ischemia and fibrosis may develop in the myocardial tissue in patients with CSFP as a result of changes that take place at the microvascular level and our study supports this view.

The deteriorated coronary microvascular function in CSFP has been shown to be associated with increased risk of cardiovascular events.[25-27] It has also been reported that, in patients with microvascular dysfunction, the prognosis is similar to that observed in obstructive coronary artery disease, and that this dysfunction is not as benign as it is thought to be.[28-30] Clinical manifestations of this pathology are also associated with significant findings. Atypical chest pain,[16-31] typical chest pain[32] and resting chest pain that require urgent intervention[4,33] frequently occur in patients with coronary slow flow. Similarly, patients with CSFP were found to be more symptomatic and their hospital admissions were found to be more frequent.[34] Based on this, CMR may be considered a good choice for investigating whether the myocardial tissue is affected or not, as well as providing a favorable option to evaluate the extent of the injury in patients with CSFP. Delayed contrast-enhanced CMR has high spatial resolution. With this method, the boundary between the infarcted tissue on the LV wall and the viable myocardium can be identified by examining the area of coronary slow flow. In addition, the transmural spread of the infarction area can be determined with this method. It is also possible to distinguish between vascular and non-vascular ischemia owing to the diffusion of gadolinium.[8] In non-ischemic cardiomyopathy, gadolinium involvement is independent of vascular perfusion and occurs in the subendocardial region. Gadolinium involvement is directly associated with vascular feeding in ischemic cardiomyopathy. In addition, this involvement is in the subendocardial or transmural region.[35]

Panting et al.[31] demonstrated subendocardial hypoperfusion with CMR in patients with syndrome X, which is believed to be associated with microvascular dysfunction.[36] In the same way, Lanza et al.[32] detected perfusion defects in the LAD region of the myocardium in syndrome X patients.[37] It is also shown that there is an important relationship between a myocardial perfusion reserve, which is examined with CMR and coronary microvascular dysfunction, and is a precursor of early atherosclerosis.[38]

NT-proBNP may be considered after an effort test in patients with coronary slow flow. It can give information about cardiac fibrosis, although it may be affected by several conditions. However, it is not possible to perform a CMR in all patients with low TIMI frame count due to cost effectiveness. CMR may be considered in patients with severe coronary slow flow degree, severe chest pain and high biomarker values after exercise. Because of the small number of patients in our study, we cannot make any recommendations about treatment, CMR or biomarker control. However, this study will shed light on studies on both treatment (anti-fibrotic drugs) and examination (CMR, NT-ProBNP, among others).

Study Limitations

Our study had a few limitations. First, the number of patients was low. Second, coronary angiographies were performed by different clinicians and, although angiographic images were standardized, there were negligible differences between the projections. Finally, the intravascular ultrasound (IVUS) technique, which can show the structure and functions of coronary arteries in detail, fractional flow reserve (FFR) and intracoronary pressure (pressure-wire) measurements, and acetylcholine testing were not performed in our study. However, performing these invasive tests, with their potential complications, in patients with no epicardial stenosis is not appropriate due to ethical reasons.

Conclusion

In this study, which was conducted to demonstrate scar tissue related to CSFP, CMR with delayed gadolinium enhancement technique has been found to yield valuable results. CMR showed scar tissue in patients with slow flow. These results suggest that the slow flow phenomenon may result in irreversible changes in myocardial tissue. The probable consequences of these changes should be investigated in further studies.

Author Contributions

Conception and design of the research: Candemir M, Şahinarslan A, Yazol M, Boyacı B; Acquisition of data and analysis and interpretation of the data: Candemir M, Şahinarslan A, Yazol M, Öner YA, Boyacı B; Statistical analysis and obtaining financing: Candemir M, Boyacı B; Writing of the manuscript: Candemir M; Critical revision of the manuscript for intellectual content: Şahinarslan A, Öner YA.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of Doctoral submitted by Mustafa Candemir, from Gazi University.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Gazi University under the protocol number 83. 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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Coronary Slow Flow Phenomenon - Adding Myocardial Fibrosis to the Equation

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Short Editorial related to the article: Determination of Myocardial Scar Tissue in Coronary Slow Flow Phenomenon and The Relationship Between Amount of Scar Tissue and Nt-ProBnpBNP

Initially described more than 40 years ago by Tambe et al.,[1] coronary slow flow phenomenon (CSFP) is characterized by delayed contrast medium progression in the absence of obstructive coronary epicardial disease during invasive coronary angiography.[2] CSFP typically affects young male smokers, who often presents with acute coronary syndrome (ACS) or recurrent refractory resting angina requiring hospital admission.[2-4] Moreover, life-threatening arrhythmias and sudden cardiac death have also been associated with CSFP.[5]

Despite increased awareness and research, CSFP remains an elusive and poorly understood condition, with many proposed pathogenic mechanisms including endothelial, vasomotor and microvascular dysfunction.[2,6] Indeed, an abnormal regulation of microvascular tone that occurs only during resting conditions, while coronary flow reserve is within normal range, has been described in CSFP.[7]

In this issue of *Arquivos Brasileiros de Cardiologia*, Candemir et al.,[8] add an important contribution to this field of knowledge. The authors studied 35 patients with chest pain referred for a diagnostic invasive coronary angiography (ICA). All had negative troponin levels and no evidence of ischemia on exercise stress testing. A comparison was made between patients who presented with CSFP in the left anterior descendant artery (n=19) and matched controls with normal coronary arteries and no coronary flow abnormalities (n = 16). They sought to investigate if myocardial scarring identified using cardiac magnetic resonance imaging (CMR) and/or if N-terminal Pro B-type Natriuretic Peptide (NT-Pro-BNP) levels elevation were more frequent in the CSFP group. Importantly, to the best of our knowledge, this was the first study to use CMR to evaluate the presence of myocardial fibrosis in the CSFP population.

Noteworthy, CMR using the delayed enhancement (or late gadolinium enhancement) technique is now a widely available and a powerful tool that allows the precise identification and quantification of myocardial fibrosis, with multiple studies demonstrating its utility in the diagnosis and prognosis of both ischemic and non-ischemic cardiomyopathies.[9-15] Interestingly, the authors demonstrate that delayed enhancement was present in up to 52.5% (n = 10) of the patients with CSFP as opposed to none in the control group. The authors thus concluded that CSFP may result in irreversible changes in the myocardial tissue.

However, we do not believe the presented data can be used to establish causality between CSFP and myocardial fibrosis. For instance, in a subset of patients (n = 3) the myocardial injury was seen in the inferior and inferolateral walls, and not in the typical left anterior descendant coronary artery territory where CSFP was present. Moreover, the authors do not describe whether the delayed enhancement pattern observed in their study was predominantly ischemic (e.g., subendocardial or transmural) or non-ischemic (midwall or epicardial). Most importantly, as the authors point out during the discussion, they performed a transversal study and, thus, no temporal relationship between CSFP and myocardial fibrosis can be established. One of the many possible explanations is that these patients with myocardial fibrosis by CMR might have previously presented with a myocardial infarction with normal coronary arteries (MINOCA) and the CSFP is but a consequence of this previous event. Although the authors did find an association between CSFP and myocardial fibrosis, we believe that further research is needed to determine whether there is a causal relationship between them.

Interestingly, higher NT-pro-BNP levels, a well-known marker of prognosis in ACS,[16] were also seen in patients with CSFP when myocardial scarring was detected by CMR, as compared to CSFP without evidence of fibrosis by CMR (NT-pro-BNP = 147.10 pg/ml vs . 28.0 pg/ml, p = 0,03).

Importantly, in a previously published study by Yurtdaş et al.,[6] elevated NT-pro-BNP levels were shown to correlate with angina and ST-segment depression in patients with CSFP during exercise treadmill testing. However, no abnormalities were seen during exercise testing in any patient of this study. Again, although the authors demonstrate an association of NT-pro-BNP with CSFP and myocardial fibrosis, we believe that no definitive causal relationship can be established based on the presented data.

Altogether, this an interesting work by Candemir et al.[8] using CMR to study a still obscure condition. We find it very interesting that CMR allowed the detection of myocardial fibrosis in a subgroup of patients with CSFP without history of prior myocardial infarction. Myocardial scarring identification

Keywords

Heart Failure; Fractional Flow Reserve; Cicatrix, Hypertrophic; Prognosis; Natriuretic-Peptide C-Type; Endomyocardial Fibrosis; Magnetic Resonance Spectroscopy.

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using delayed enhancement imaging is a powerful prognostic tool in multiple cardiomyopathies, both ischemic and nonischemic. Although small in size, this study by Candemir et al.[8] opens up new research possibilities to answer whether there is causality in the association between CSFP and myocardial fibrosis and if the presence of myocardial fibrosis in these patients have any prognostic implication or, for instance, is associated with a higher likelihood of malignant arrhythmias. Conversely, future research using novel CMR techniques for tissue characterization, including T1 and T2 mapping, may also help shed light into this still poorly understood condition.

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Effects of added salt reduction on central and peripheral blood pressure

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Abstract

Background: Although the effects of salt intake reduction on casual blood pressure have been extensively studied in hypertensive individuals, data on reductions of added salt on arterial stiffness in both normotensive and prehypertensive subjects are scarce.

Objective: To evaluate the effects of progressive reduction in added salt intake (from 6 grams to 4 grams per day) on peripheral and central blood pressure and arterial stiffness in normotensive, prehypertensive and hypertensive individuals.

Methods: This was a single-blinded clinical trial with 13 weeks of follow-up. Normotensive (≤ 130/85 mmHg), prehypertensive (≥ 130 e < 139/≥ 85 e < 90 mmHg) and stage 1 hypertensive individuals (< 139/≥ 85 and < 90 mmHg) were assessed. Casual blood pressure measurements and ambulatory blood pressure monitoring were performed using the automated OMRON 705CP device, and central blood pressure was measured using the Sphygmocor®. Twenty-four-hour urinary sodium excretion and the amounts of added salt consumed were measured. Statistically significance level was set at p < 0.05 for all analysis.

Results: A total of 55 participants (18 normotensive, 15 prehypertensive and 22 hypertensive), median age 48 years (IQR:39-54) were studied. The groups were not different in age or sex. No difference was observed in blood pressure or sodium excretion levels before and after the intervention. No significant changes in arterial stiffness parameters were observed.

Conclusion: The progressive reduction in added salt intake during a period of 13 weeks did not cause significant reductions in peripheral and central blood pressure. (Arq Bras Cardiol. 2020; 114(3):554-561)

Keywords: Cardiovascular Diseases; Arterial Pressure; Prehypertension; Hypertension; Sodium Chloride; Diet, Sodium-Restricted; Health Policies

Introduction

Systemic arterial hypertension is one of the most prevalent cardiovascular risk factors, affecting nearly 970 million people in the world. It is the (direct or indirect) cause of more than nine million deaths every year,[1] accounting for 62% of the cases of cardiovascular diseases (CVD) and 49% of ischemic heart disease.[2] Prehypertension (PH) is also associated with increased incidence of CVD.[3,4]

Compared with other methods of blood pressure (BP) measurement, casual BP measurement is inferior in predicting cardiovascular risk and shows lower diagnostic accuracy.[5,6] Ambulatory blood pressure monitoring (ABPM) has high diagnostic accuracy and excellent cost-benefit relationship.[7,8] Central blood pressure (CBP) provides information of more elastic, central arteries; it has lower values compared with casual pressure and is better associated with lesions in target organs. Therefore, CPB is the best predictor of cardiovascular events,[8] in addition to allowing the analysis of arterial stiffness and vascular resistance parameters.[9-12]

Although the etiology of increased BP is multifactorial, excessive salt intake is a common and important factor. It causes elevations of BP levels and cardiovascular complications. Therefore, salt restriction is an important strategy for prevention and control of systemic arterial hypertension and CVD.[13,14]

Mean daily amount of salt intake recommended is 5 g, or 2 g of sodium. However, Brazilians eat on average up to 12 g/day, i.e., more than the daily amount recommended.[15] Government policies of many countries have been implemented to reduce salt intake by 30% by the year of 2025 with the aim to reduce BP values in the population.[16]

Assessment of salt intake, interventions for its reduction, and the use of instruments capable of identifying this reduction are important strategies in primary prevention of CVD.

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Therefore, this study evaluated the effect of reducing the intake of added salt on central and peripheral BP in normotensive, prehypertensive and hypertensive individuals after 13 weeks of follow-up.

Methods

This is a substudy of the phase II, single-blinded, controlled clinical trial with different amounts of added salt in individuals grouped by BP levels. For the initial sample, a total of 1,000 workers were recruited at a Brazilian public university. A questionnaire on dietary habits was administered, and anthropometric and casual BP measurements were performed. Of the subjects recruited, 678 agreed to participate (Figure 1).

The study was approved by the ethics committee (CAEE: 00790712.3.0000.5078) and all participants signed an informed consent form.

The study population was a convenience sample and was composed of men and women aged between 20 and 60 years. All participants had at least four main meals (lunch and/or dinner) a week at home.

Individuals with casual BP ≥ 160/100 mmHg, diabetes, history of chronic disease and hypertension taking two or more antihypertensive were excluded.

Participation of the study consisted of five visits with an interval of 30 ± 7 days between them. The first visit was divided into two parts, Visit 1A (V1A) and Visit 1B (V1B). In all visits, measurements of casual BP, CBP, ABPM and BMI were performed, and request for urinalysis, and 24-hour urine creatinine, sodium and potassium was made. In V1A, in addition to these procedures, participants also signed the informed consent form, were evaluated for eligibility criteria and a request for serum creatinine was made.

In V1B, participants were grouped according to mean casual BP, in normotensive (NG) (BP < 130/85 mmHg), prehypertensive (PHG) (BP ≥ 130 < 140/≥85 < 90 mmHg) and stage 1 hypertensive (HG) (BP ≥ 140 and < 160/≥ 90 and < 100 mmHg) not using antihypertensive medication.[1]

For casual BP, three measurements were taken with a minimum interval of one minute between them. When a difference greater than 4 mmHg was found between the measurements, further measures were taken until the differences between them were smaller.

Both casual BP and ABPM were measured using a semiautomated device (OMRON, model HEM-711 ACINT), with a cuff size according to the arm circumference. BP was measured in the sitting position after a resting period of five minutes, in a calm environment in the arm with the highest BP value.[1]

ABPM was performed according to the II Brazilian Guidelines for Ambulatory Blood Pressure Monitoring.[17] In each visit, the ABPM device was given to each participant, who was instructed to obtain BP measures following specific protocol, to write down the values in a proper document and to return the device at the next visit.

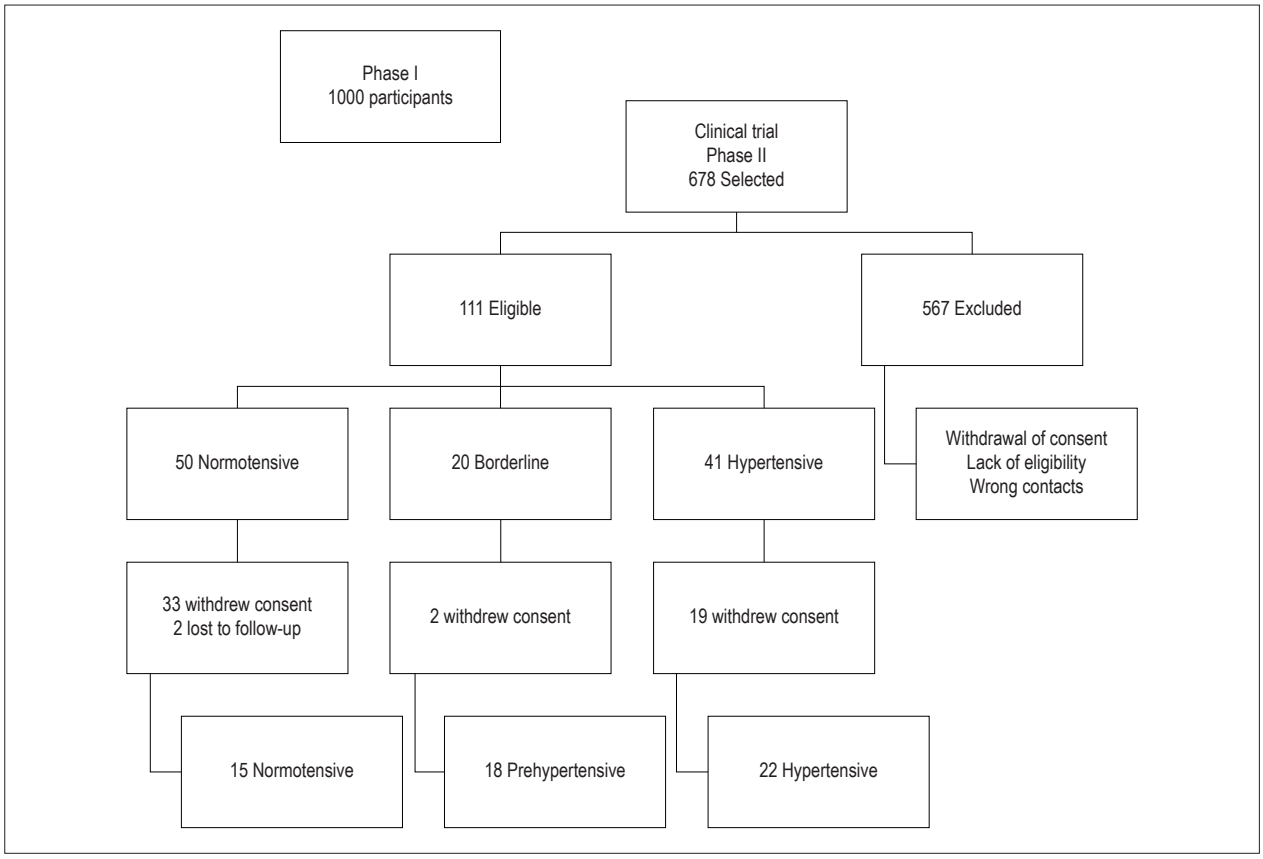

Figure 01 – *Flowchart of the phase II clinical trial.*

CBP measurements were obtained by applanation tonometry, using a calibrated and validated device (Sphygmocor®).[12] Each patient refrained from alcohol, coffee and tobacco use for some hours before the exam, which was performed with empty bladder, after a five-minute rest. The variables analyzed from CBP were central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), central pulse pressure (cPP) and augmentation index (AIx).

Collection of the 24-hour urine sample was conducted following the information contained in an explanatory leaflet. The 24-hour urine test was performed at the laboratory of the Federal University of Goias, and an ion-selective membrane was used to quantify urinary sodium at baseline, before the intervention and in the intervals between the visits (total of four collections).

During V1B, the NG, PHG and HG received the same instructions regarding the amount of salt intake (6g/day). In visits 2 (V2) and 3 (V3), 5 g/day and 4 g/day of salt, respectively, were given to each participant. Interval between the visits was of 30 ± 7 days.

The amount of salt given to each participant was estimated based on the number of people living in the residence and the meals (lunch and dinner) prepared. The salt was delivered properly packed, without weight identification. Also, an additional 10% of salt was given to each participant, to be used in exceptional cases (e.g. visitors at home).

In the return visits (V2, V3 and visit 4, V4), all packages of salt were collected and other packages containing the amount of salt planned for the subsequent period were given. In all visits, it was emphasized to participants the importance of cardiovascular health and of a low-sodium diet, and that the amount of added salt consumed by participants should be limited to that established in the study protocol.

The salt packages (empty or full) returned were weighed and used for assessment of adherence to the protocol, which was also evaluated by 24-hour urinary excretion.

Statistical analysis

Statistical analysis was performed using Stata, version 12. An intention-to-treat analysis was used, and for those who dropped out the study before V4, the data of the last visit were considered for analysis. Continuous variables with normal distribution were presented as mean and standard deviation, and those with a non-normal distribution were presented as median and interquartile range. Categorical variables were presented as absolute and relative frequency. Normal distribution of data was tested using the Shapiro-Wilk test.

Between-group comparisons in V1A were made using the Kruskal-Wallis test and the Fisher's exact test. Within-group comparisons before (V1B) and after (V4) intervention were performed by Wilcoxon test or the paired Student's t-test. Comparison of delta sodium excretion was made by ANOVA followed by Bonferroni post hoc test. Delta sodium excretion was calculated by subtracting sodium excretion at V4 from that obtained in V1B. Correlation between BP (ABPM, and casual and central BP) and the levels of urinary sodium was performed by Spearman's test. A $p < 0.05$ was considered statistically significant.

Results

Fifty-five individuals participated in the study, 32 (58.2%) were male, median age of 48 years (IQ:39-54). Eighteen (32.7%), 15 (27.3%) and 22 (40.0%) individuals were included in the NG, PHG and HG, respectively. There was no difference in age and sex between the groups, but a significant difference was observed in BMI ($p = 0.03$) (Table 1).

No difference was observed in CBP and AS between V1 and V4 in any of the groups. However, there was a trend of reduction in both cSBP and cDBP from V1 to V4 in all groups (Table 2). There was no difference in delta sodium excretion between the groups (Figure 2).

In addition, no differences were found in ABPM, casual BP or urinary sodium from V1B to V4 in NG and PHG (Table 3).

Urinary sodium correlated with CPB and peripheral BP in the HG (Table 4).

Discussion

Based on the methods used for SBP and DBP assessment in the study, the progressive reduction of salt intake was not associated with significant changes in SBP. Also, the authors expected to find a higher sensitivity of CBP in detecting small changes in tension, since this parameter reflects the behavior of more elastic arteries, which did not occur.

Data from the literature have associated the reduction in salt intake with a reduction in BP in hypertensive, normotensive and prehypertensive individuals and have shown a higher sensitivity of CBP to detect these changes. However, a large part of these studies was based on interventions or evaluated reductions in the consumption of salt in packaged food and total intake.[18,19]

In a systematic review, a mean reduction of 4.4 g/day was associated with a reduction by 2.4mmHg in SBP and 1.0 mmHg in DBP in normotensive subjects, and by 5.4 mmHg in SBP and 2.8 mmHg in DBP in hypertensive subjects. These findings indicated a reduction of 0.72 mmHg ad 1.8 mmHg in BP levels in normotensive and hypertensive individuals, respectively, for each gram of salt reduction daily.[18]

Improvements in BP levels lead to lower cardiovascular events, including cardiovascular mortality, which reinforces the importance of adopting effective measures to reduce salt consumption. A study conducted in England between 2003 and 2011 evaluated the relationship of reductions in total salt intake with BP and mortality for stroke and acute myocardial infarction and showed a reduction by 2.7 mmHg in SBP and 1.1 mmHg in DBP. Therefore, a fall of BP of 2.7 mmHg led to a decrease in mortality for stroke by 42% and acute myocardial infarction by 40%.[19]

In our study, the variables cPP and AIx75% did not show statistically significant reductions, which is in contrast to what the authors expected, since these variables are also related to vascular resistance and arterial stiffness. Again, in our opinion, this may be achieved by an intervention aimed at reducing total salt intake, as previous studies have already demonstrated.[20]

In a study conducted with South African hypertensive individuals, the authors evaluated the relationship between salt

Table 01 – Sociodemographic and clinical characteristics of the study sample (n = 55), Goiânia, Brazil, 2014

Variables	Normotensive (n = 18)		Prehypertensive (n = 15)		Hypertensive (n = 22)		p*
	Median	IQ	Median	IQ	Median	IQ	
Age	45.0	30-52	46.0	43-54	52.0	41-56	0.08
BMI	25.1	23.5-27.2	27.6	25.7-31.1	28.4	25.6-31.8	0.03
Sex	N	%	N	%	N	%	p†
Male	09	50.0	11	73.3	12	54.5	0.424
Female	09	50.0	04	26.7	10	45.5	

**Kruskal-Wallis test; † Fisher's exact test; p-value < 0.05 was considered significant; BMI: body mass index (kg/m²); IQR: interquartile range.*

Table 02 – Within-group comparisons (Visits 1B and 4) of central blood pressure parameters (n = 55)

Variables	Normotensive group (n = 18)		p	Prehypertensive group (n = 15)		p	Hypertensive group (n = 22)		p
	V1b	V4		V1b	V4		V1b	V4	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean± SD	Mean ± SD	
cSBP	107.2 ± 9.2	103.4 ± 10.4	0.24	119.2 ± 8.5	115.0 ± 9.9	0.22	119.0 ± 12.6	113.4 ± 9.0	0.10
cDBP	73.3 ± 4.7	70.6 ± 7.0	0.18	82.3 ± 8.9	74.7 ± 19.6	0.17	83.3 ± 11.6	78.5 ± 8.3	0.12
cPP	34.1 ± 6.6	32.3 ± 7.5	0.45	36.9 ± 6.5	35.1 ± 4.9	0.41	35.6 ± 6.7	34.9 ± 6.0	0.70
AIx 75%	22.5 ± 15.3	21.8 ± 13.0	0.87	23.4 ± 10.4	19.7 ± 11.7	0.36	25.0 ± 10.5	23.3 ± 10.5	0.59

*SD: standard deviation; *paired Student's t-test or Wilcoxon test; cSBP: central systolic blood pressure (mmHg); cDBP: central diastolic blood pressure (mmHg); cPP: central pulse pressure (mmHg); ALx 75%: augmentation index 75%.*

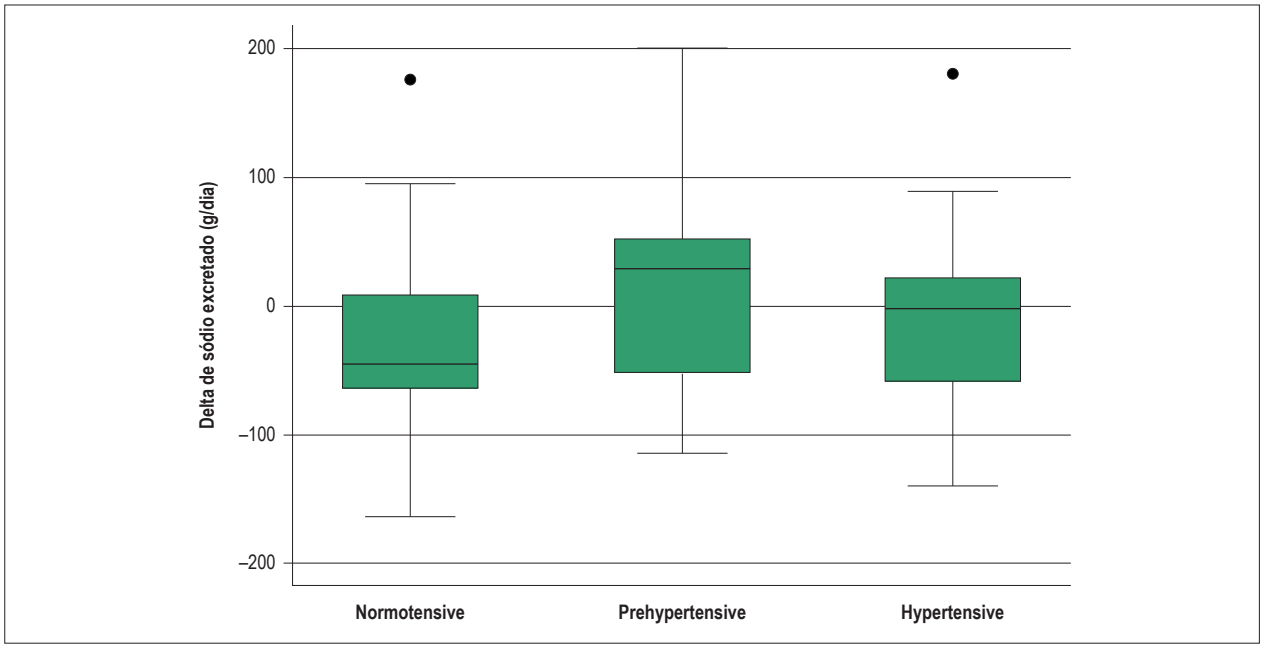

Figure 2 – *Comparison of delta sodium excretion between normotensive, prehypertensive and hypertensive groups; ANOVA with Bonferroni post-hoc test.*

intake (assessed by 24-hour urinary sodium) and central dynamics and found a correlation with arterial stiffness parameters – cPP, AIx75%, cSBP and central mean arterial pressure.[20]

A study conducted in China evaluated the association between salt intake (24-hour urinary excretion) with CBP in three groups of untreated hypertensive patients divided into three groups according to mean urinary sodium excretion – group A, 76.9 mmol, group B, 146.6 mmol and group C 258.6 mmol, corresponding respectively to 4.7 g, 9.6 g and 15.8 g of salt per day. The mean 24-h urinary sodium of all patients was 166.6 mmol, or 10.1g of salt. Parameters of arterial stiffness (cSBP, cDBP and AIx75%) worsened from group A to group C.[21]

Table 03 – Within-group comparison (Visits 1B and V4) of ambulatory blood pressure monitoring, casual blood pressure, serum creatinine and urinary sodium (n = 55)

Variables	Normotensive group n = 18			Prehypertensive group n = 15			Hypertensive group n = 22		
	Mean	SD	p	Mean	SD	p	Mean	SD	p
ASBPM V1b	115.7	9.7	0.87*	125.0	8.2	0.88*	128.6	10.3	0.63*
ASBPM SBP V4	115.1	11.8		125.5	11.8		127.0	11.6	
ADBPM V1b	69.3	6.6	0.86*	76.1	7.7	0.72*	80.0	7.3	0.81*
ADBPM V4	69.7	7.2		77.3	10.8		79.5	8.0	
casual SBP V1B	116.3	10.6	0.44*	125.9	8.4	0.94*	128.5	11.1	0.18*
casual SBP V4	113.8	9.3		126.1	7.5		124.2	10.1	
Casual DBP V1B	71.1	7.4	0.58*	79.3	8.8	0.87*	81.4	8.5	0.10*
Casual DBP V 4	69.8	7.2	0.44*	78.8	7.3		77.3	73.8	
Sodium V1B	163.2	71.7	0.20*	158.4	68.7	0.60*	156.8	52.7	0.63*
Sodium V4	135.2	58.1	0.20**	172.7	80.8	0.60**	147.3	75.9	0.63**

*SD: standard deviation; *paired Student's t-test; **Wilcoxon test; ASBPM: ambulatory systolic blood pressure monitoring (mmHg); ADBPM: ambulatory diastolic blood pressure monitoring (mmHg); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); V1b: visit 1b; V2: visit 2; V3: visit 3; V4: visit 4.*

Table 4 – Correlation of blood pressure parameters with 24-hour urinary sodium excretion, n = 55

Variables	Normotensive group n = 18		Prehypertensive group n = 15		Hypertensive group n = 22	
	r	p	r	p*	r	p
cSBP x sodium V4	0,208	0,40	0,282	0,30	0,276	0,21
cDBP x sodium V4	0,397	0,10	0,328	0,23	0,458	0,03*
PPc x sodium V4	-0,024	0,92	0,023	0,93	-0,174	0,43
AIx 75% x sodium V4	0,201	0,42	0,014	0,95	0,116	0,60
ASBPM x sodium V4	0,241	0,33	0,216	0,43	0,298	0,17
ADBPM x sodium V4	0,188	0,45	0,205	0,46	0,369	0,09
casual SBP x sodium V4	0,010	0,96	0,294	0,28	0,157	0,48
Casual DBP x sodium V4	0,156	0,53	0,413	0,12	0,480	0,02*

*Spearman test; r: rho value; * ≤ 0.005; ASBPM: ambulatory systolic blood pressure monitoring (mmHg); ADBPM: ambulatory diastolic blood pressure monitoring (mmHg); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); V4: visit 4.*

A meta-analysis evaluating the effect of salt intake reduction on intermediate outcomes, including BP, detected mean BP reductions of 3.39 mmHg in SBP and 1.54 mmHg in DBP. Such effect was greater in hypertensive (4.06 mmHg in SBP and 2.26 mmHg in DBP) than normotensive individuals (1.38 mmHg in SBP and 0.58 mmHg in DBP). In addition, greater reductions in BP was observed in individuals with sodium intake < 2 g/day versus ≥ 2 g/day, and in those with a reduction in daily salt intake ≥ 1/3 versus < 1/3.[22]

A controlled dietary intervention consisting of 7.6 g/day sodium supplementation versus placebo (no supplementation) caused a significant increase in CBP measurements – 8.5 mmHg in SBP, 3.6 mmHg in cDBP and 4.8 mmHg in PPa.[23]

It is therefore clear that strategies towards reductions in salt intake (salt in packaged foods or total salt consumption) are an effective nonpharmacological approach for the prevention and treatment of hypertension.

Since reducing the amount of added salt in the diet is commonly recommended by healthcare professionals, we decided to investigate whether such strategy, adopted for a short period of time, would be effective in reducing BP levels. It is worth pointing out that the World Health Organization recommends the reduction in salt intake to less than 5 grams per day to reduce BP.[15]

It is possible that an intervention towards lowering added salt intake in more meals and for a longer period would lead to more effective results than those obtained in this study. A meta-analysis of studies on interventions of salt intake reduction showed that reductions in salt intake for up to five weeks in hypertensive individuals and for up to four weeks in normotensive individuals are ineffective to cause significant falls in BP.[18] In our study, intervals between the different levels of salt reduction were of four weeks, aiming to achieve good adherence to the intervention proposed.

Based on scientific evidence, European countries have established population-wide recommendations to lower salt intake to less than 5 grams per day. In the United Kingdom and Finland, there are government policies focusing on reducing salt intake to less than 3 grams per day by the year of 2025.[24]

These governmental measures are crucial for preventing many diseases related to excessive salt intake. Lowering salt intake to up to 2,300mg per day could prevent 11 million cases of systemic arterial hypertension and save billions of dollars in health care costs.[24] A meta-analysis showed that a drastic reduction in salt intake (up to 3g/day) was effective in preventing CVD. A major part of this prevention is explained by reductions of BP that occur in both hypertensive and prehypertensive individuals.[18]

Another interesting strategy may be the replacement of conventional salt with low-sodium salt. A randomized trial with patients with uncontrolled hypertension showed reductions in BP and urinary sodium in the group of individuals that received 3 grams of light salt compared with the group that received regular salt.[25]

All these strategies are important, but ineffective if used alone. Our results reinforce the need to sharply reduce the amount of salt intake, especially through packaged foods that usually contain great amounts of sodium. Processed foods are very present in post-modern society and the main sources of salt in the diet.[26]

It is also important the use of clear and objective information about salt content in packaged foods, so that consumers can deliberately change or make adaptations in their habitual diet.[27]

Also, although quantification of urinary sodium is the gold standard method to estimate sodium intake, it has a sensitivity of 86% in detecting urinary sodium excretion. Considering that interventions towards lowering added salt affect only 15% of total salt intake, the sensitivity of the method to detect changes in sodium excretion in these interventions is probably low, as may have occurred in our study. Besides, adherence to interventions like this varies between individuals and may be low. In our sample, we did not detect significant reductions in urinary sodium excretion in any of participants.

Another factor to be considered is that we cannot assure that the 24-hour urinary excretion test was performed correctly, since we did not verify how urine sample was collected and stored. However, this method has been used by different researchers in Brazil[28] and in the world.[29,30]

The meta-analysis of trials with a modest reduction in salt intake and duration of four weeks to three years evaluating the effects on 24-hour urinary sodium excretion and BP showed that a reduction of 4.4g per day of salt was associated with a fall in SBP of 5.4 mmHg in normotensive individuals. Therefore, a moderate reduction in salt intake for longer periods was effective in reducing BP levels.[18]

One of the limitations of our study was the difficulty in ensuring that participants had at least four main meals at home per week and that the salt added during food preparation was only that received during the study. Out-of-home meals were not controlled also. The strategy used was to involve the whole family in lowering the amounts of added salt and to emphasize the importance of identifying high-sodium foods in restaurant and of choosing low-sodium foods.

Conclusions

The intervention proposed, to gradually reduce the amount of added salt from 6 grams to 4 grams per day for 13 weeks, did not show significant reductions in the 24-hour urinary sodium excretion. However, the amount of sodium excretion showed a positive, moderate correlation with CBP and casual DBP in the HG.

Author contributions

Conception and design of the research: Arantes AC, Sousa ALL, Jardim PVBV, Jardim TSV, Rodrigues RB, Souza WKSB. Acquisition of data: Arantes AC, Rodrigues RB, Souza WKSB. Analysis and interpretation of the data: Arantes AC, Sousa ALL, Vitorino PVO, Rezende JM, Rodrigues RB, Souza WKSB. Statistical analysis: Arantes AC, Vitorino PVO, Rezende JM, Lelis ES, Souza WKSB. Obtaining financing: Arantes AC, Sousa ALL. Writing of the manuscript: Arantes AC, Sousa ALL, Vitorino PVO, Rezende JM, Souza WKSB. Critical revision of the manuscript for intellectual content: Arantes AC, Vitorino PVO, Jardim PVBV, Jardim TSV, Rezende JM, Coca A, Souza WKSB.

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 da Universidade Federal de Goiás CAEE: 00790712.3.0000.5078. 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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Dietary Salt Reduction: Illusion or Reality?

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Short Editorial related to the article: Effects of added salt reduction on central and peripheral blood pressure

In spite of ample knowledge regarding systemic arterial hypertension as the main risk factor for cardiovascular diseases, the rates of control have shown a modest progressive increase, especially in Brazil. Brazilian studies have provided evidence that 50% to 60% of people with hypertension are receiving treatment, while only 20% to 30% of all people with hypertension are controlled.[1]

The main difficulty in controlling systemic arterial hypertension lies in managing long-term patient adherence, given that the majority of patients are asymptomatic, and they eventually begin to have symptoms as a result of antihypertensive medication use.

While adherence to medical treatment is low, adherence to lifestyle changes is even lower. Among these changes, dietary salt reduction has posed a major challenge. The benefits of moderate salt reduction to blood pressure, especially for patients with hypertension, are undeniable, as are its effects on preventing cardiovascular events, even if the reduction is by at least one third of the salt regularly ingested or a goal of no more than 5 grams of salt daily, according to the World Health Organization.[2] Current salt consumption is very high, especially among patients with hypertension, ranging from 9 to 12 grams daily.[3]

Among different strategies for successfully reducing dietary salt, the one most commonly employed by multidisciplinary teams, which include a physician, consists of advising patients to avoid processed foods (sausages, canned foods, etc.), giving preference to unprocessed foods, in combination with reducing salt when preparing meals and removing the salt shaker from the table.[4] The use of spices such as garlic, onion, and oregano is also frequently recommended, given that they may enhance the taste of food, thus lowering the need to use salt. A recent study found that the use of oregano in common bread dough changed the preferences of young and elderly hypertensive and normotensive individuals with respect to consumption of reduced-sodium bread, by improving the flavor.[5] Maintaining this preference over a long time, however, is a major challenge, and this intervention has not yet been tested. Middle-aged individuals who, in a randomized cross-over manner, used low-salt bread (0.3 g of salt per 100 g) or bread with the conventional level of salt (1.2 g of salt per 100 g) showed a decrease in systolic blood pressure and a decrease in urine excretion of sodium after 5 weeks of consuming the low-salt bread, when compared to the moment 5 weeks after consuming the conventional bread.[6]

When patients are advised to make lifestyle changes, what is generally observed is that initial adherence is good, but the changes do not continue over time. It is not correct to assume that patients are the only ones responsible for poor adherence. Modern life has led to habits of eating meals outside of the home, with little time available; salt is, furthermore, the preservative most widely used by the food industry. Even with individualized advice within a well structured protocol, where all the salt for adherence was given in a package, Arantes et al.[7] did not observe a reduction in the total quantity of salt ingested by middle-aged volunteers, all of whom were employs of a public university, over three months of follow-up. Notwithstanding advice to prepare at least four main meals at home, in addition to advice regarding the importance of choosing foods with less salt, the total quantity of sodium excreted in 24 hours, which estimates the quantity of salt ingested during the same period, was probably not reduced due to the consumption of saltier foods outside of the house or even due to the choice of saltier foods at home. It was possible to verify an association of greater salt excretion in hypertensive patients with higher central diastolic blood pressure and casual measurement.

The actions implemented to reduce salt intake in processed foods so far have promoted the reduction of 17 tons of salt in foods between 2011 and 2016, especially in mixtures for soup, instant soup, sausage, cheese, and cottage cheese. In 2017, the target of a new agreement between the Ministry of Health and the food industries was to reduce salt in bread and instant pasta.

Reducing the quantity of salt in processed foods, without compromising their taste or jeopardizing their preservation, makes the industry's work complex, but the reduction of salt in processed foods needs to advance, as does the education of the population. It is necessary to consider that individuals who are already used to higher salt consumption may add salt to processed foods if they consider that doing so makes these foods taste better and if they are unaware of the risks associated with this practice.

An interesting Dutch study performed a simulation of two different strategies for reducing salt consumption, with a goal of up to 6 grams of salt daily, based on data from the Dutch population. One of the strategies would be substituting high-salt foods with similar low-salt foods that are already commercially available, while the other proposed reducing the salt content of processed foods to the extent that it was possible. They observed that the reduction in salt consumption, with either of these strategies, would be

Keywords

Hypertension/prevention and control; Developing Countries; Medication Adherence; Sodium Chloride, Dietary; Cardiovascular Diseases/mortality.

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approximately 30%, decreasing systolic blood pressure by 1.6 mmHg, with a potential 4.8% reduction in the incidence of acute myocardial infarction.[8]

Education that promotes healthy measures is important. Unfortunately, there is still a lack of association between what is good for our health and what is most accepted by society, especially when we observe young people's behavior at parties or on weekends, when they further face the difficulty of ingesting lower amounts of alcoholic beverages or giving preference to healthier foods without suffering discrimination.

An Italian study found that both knowledge regarding salt ingestion (foods with more salt, the habit of reading labels, etc.) and behavior based on this knowledge were primarily lower in adolescents and individuals with lower levels of schooling.[9]

Education for lower salt consumption will have to be widely supported by government agencies, industries, schools, healthcare professionals, and the advertising industry, in order to create a culture different from the current one. This process will have to start in early childhood, but the whole family will need to be integrated, and elderly people may be important agents of habit change within their communities.

Evaluating strategies for salt reduction in different countries in all world regions, one study identified that the regions with the fewest initiatives were Africa, South East Asia, and the Eastern Mediterranean.[10] Only the implementation of diverse strategies for reducing salt conception, in a concomitant and organized manner, as well as the monitoring of their effects, will be able to have a real impact on the reduction of cardiovascular diseases.

Dietary salt reduction will therefore be possible when it truly becomes the objective of national and regional health and education policies. As long as this reality, however, appears to be far off, even though efforts are growing, what remains is the impression of an illusion.

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The Top 10 Original Articles Published in the *Arquivos Brasileiros de Cardiologia* and in the *Revista Portuguesa de Cardiologia* in 2019

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Introduction

For centuries, Portugal and Brazil have shared a tradition of cooperation, which applies to medicine. In cardiology, for example, their national scientific societies – the Brazilian Society of Cardiology and the Portuguese Society of Cardiology – have a long history of collaboration, which extends to their journals.

The *Arquivos Brasileiros de Cardiologia* (*Arq Bras Cardiol*), the official scientific publication of the Brazilian Society of Cardiology, with an impact factor of 1.679 in 2018 (JCR), is the most influential cardiology journal in Brazil and Latin America. This can be exemplified by the increasing number of submissions to the *Arq Bras Cardiol* (650 in 2017, 771 in 2018, and 734 in 2019), and by its h5 index of 31 and h5 median of 39, with acceptance rate lower than 20%.

The *Revista Portuguesa de Cardiologia* (*Rev Port Cardiol*) is the official journal of the Portuguese Society of Cardiology, an institutional member of the European Society of Cardiology. It has been continuously published since 1982, has global impact, being indexed in PubMed, Elsevier, ScienceDirect and SCOPUS, with an impact factor of 0.79 in 2018.

In that year, for the first time, both journals got together to issue a review of the most relevant original papers published in both journals in 2018.[1] Because of the great success of that initiative, the editorial bodies of those two journals decided to cooperate again to select their best 2019 publications. The articles of the *Arq Bras Cardiol* listed here were those selected for the Brazilian Society of Cardiology Publication Award. It is worth noting that Nuno Cardim, author of the best article published in the *Rev Port Cardiol* in 2019, attended the award ceremony of the 74th Brazilian Congress of Cardiology, in the city of Porto Alegre, in 2019. We aim to strengthen the cultural ties of the major cardiology journals published in Portuguese, which represent the best publications directed to a growing population of around 250 million people worldwide.

Given the overall high quality of the articles published, this selection was a hard, possibly imperfect task, which allowed us to highlight several relevant papers in cardiology. Tables 1 and 2 list the top ten articles published in each journal in 2019.

Keywords

Cardiovascular Diseases; Periodicals as Topic; Portals for Scientific Journals; Journal Impact Factor; Periodical; System for Evaluation of Publications; Scientific and Technical Publications; Periodical; System for Evaluation of Publications.

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Cardiovascular prevention

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide. Although several strategies to treat CVD are currently available, the control of cardiovascular risk (CVR) factors remains below the desired degree. The DISGEN-LIPID[2] study, an observational study conducted in 24 centers in Portugal, has aimed at assessing the degree of control of dyslipidemia, one of the major CVR factors for the development of coronary artery disease (CAD). That study has shown that, although most patients were at high or very high CVR, more than 50% of those on lipid-lowering therapy did not achieve the recommended target levels for LDL-C, a large proportion being on low-intensity statins or low-dose therapy. Another study, assessing data from the DISGEN-LIPID study, has shown a significant disparity between genders, with lipid profile values significantly higher in women than in men.[3] That relevant study evidences the need for public health policies that can overcome both the current obstacles to implementing the guidelines in clinical practice and the problems of low statin dose, therapeutic inertia and lack of patient's adherence to treatment.

In 2019, the *Rev Port Cardiol* published the PRECISE study[4] to help understand the control of CVR factors in the Portuguese population. That epidemiological, cross-sectional study has assessed the prevalence of several CVR factors in 2848 hypertensive patients followed up in primary health care centers. The study has shown that only 56% of those patients had good blood pressure control and more than 80%

Table 1 – List of the top ten articles published in the *Arquivos Brasileiros de Cardiologia* in 2019

Author	Title of the article and link
Faria AP et al.[7]	Proposta de um Escore Inflamatório de Citocinas e Adipocinas Plasmáticas Associado à Hipertensão Resistente, mas Dependente dos Parâmetros de Obesidade http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000400383&lng=pt&nrm=iso&tlng=pt
Dippe Jr. et al.[18]	Estudo de Perfusão Miocárdica em Obesos sem Doença Cardíaca Isquêmica Conhecida http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000200121&lng=en&nrm=iso&tlng=pt
Reuter CP et al.[5]	Relação entre Dislipidemia, Fatores Culturais e Aptidão Cardiorrespiratória em Escolares http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000600729&lng=en&nrm=iso&tlng=pt
Villela PTM et al.[9]	A Preferência ao Sal está Relacionada à Hipertensão e não ao Envelhecimento http://www.scielo.br/scielo.php?pid=S0066-782X2019005015104&script=sci_arttext&tlng=pt
Barros MVL et al.[27]	Alteração Contrátil Segmentar Ventricular Esquerda é Preditor Independente de Cardiotoxicidade em Pacientes com Câncer de Mama em Tratamento Quimioterápico http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000100050&lng=pt&nrm=iso&tlng=pt
Kiyose AT et al.[28]	Comparação de Próteses Biológicas e Mecânicas para Cirurgia de Válvula Cardíaca: Revisão Sistemática de Estudos Controlados Randomizados http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000300292&lng=en&nrm=iso&tlng=pt
Eickemberg M et al.[6]	Indicadores de Adiposidade Abdominal e Espessura Médio-Intimal de Carótidas: Resultados do Estudo Longitudinal de Saúde do Adulto - ELSA-Brasil http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000300220&lng=en&nrm=iso&tlng=pt
Effting PS et al.[8]	Exercício Resistido Modula Parâmetros de Estresse Oxidativo e Conteúdo de TNF-α no Coração de Camundongos com Obesidade Induzida por Dieta http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019000500545&lng=es&nrm=iso&tlng=pt
Avila WS et al.[29]	Gravidez em portadoras de cardiopatias congênitas complexas. Um constante desafio http://www.scielo.br/scielo.php?pid=S0066-782X2019005019101&script=sci_arttext&tlng=pt
Barbosa JE et al.[17]	Perfil da Expressão do mRNA do Nrf2, NF-κB e PPARβ/δ em Pacientes com Doença Arterial Coronariana http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2019005001205&lng=en&nrm=iso&tlng=pt

of them had three or more concomitant CVR factors. These data show the importance of the overall assessment of CVR in hypertensive patients, and, once again, the urgent need to implement preventive strategies to improve the control of CVR factors in Portugal.

The first author of both studies was our colleague Pedro Marques da Silva, a remarkable physician, who left an indelible mark on Cardiovascular Medicine. His passing in early 2020 brought us great sorrow. This was a tremendous loss for cardiology in Portugal.

Difficulty controlling CVR factors in children and adolescents has also been observed. A study with 1254 children and adolescents from southern Brazil (female sex, 55%; age range: 7-17 years) has assessed the relationship between dyslipidemia, cultural factors and cardiorespiratory fitness (CRF). The cultural factors were assessed by use of a self-reporting questionnaire, and the CRF levels, by use of the 12-minute walk/run test, which consisted in covering the longest possible distance on a previously established track for 12 minutes. The authors have reported a dyslipidemia prevalence of 42%, which was associated with female sex and low CRF levels. On multivariate analysis, dyslipidemia was associated with children, but not with adolescents, as well as with overweight and obesity. In addition, sedentary commuting to and from school, too much time spent watching TV, female sex, and overweight/obesity were associated with isolated components of the lipid profile. The authors have emphasized the need for early interventions that promote healthy life habits among children.[5]

The ELSA-Brazil study,[6] assessing 15105 public servers (age range: 35-74 years) from six teaching and research institutions of the Brazilian southern, southeastern and northeastern regions, has assessed the magnitude of the association between abdominal adiposity, defined based on different diagnostic indicators [waist circumference (WC), waist-to-hip ratio (WHR), conicity index , lipid accumulation product (LAP), visceral adiposity index (VAI)], and carotid intima-media thickness (cIMT), a marker of subclinical atherosclerosis and predictor of myocardial infarction and stroke. By using multiple logistic regression, the authors have shown an important association of abdominal adiposity, diagnosed by use of WC, with cIMT in both sexes (men: OR = 1.47; 95% CI: 1.22-1.77; women: OR = 1.38; 95% CI: 1.17-1.64). Abdominal adiposity, identified by the indicators WC, WHR, LAP and VAI, in women showed a 0.02-mm effect on cIMT (WC: 0.025, 95% CI: 0.016-0.035; WHR: 0.026, 95% CI: 0.016-0.035; LAP: 0.024, 95% CI: 0.014-0.034; VAI: 0.020, 95% CI: 0.010-0.031). The results observed reinforce the importance of abdominal adiposity, represented by WC, especially in men, as a simple marker of abdominal adiposity associated with subclinical atherosclerosis.

In addition, subclinical atherosclerosis seems to be associated with systemic inflammation in patients with resistant arterial hypertension (RAH). In a convenience sample of 224 hypertensive patients, half of them with RAH, an inflammatory score (IS) was established, comprising the measurement of plasma pro-inflammatory and anti-inflammatory cytokines and adipokines, TNF-alpha, interleukins (IL)-6, -8, -10, leptin

Table 2 – List of the top ten articles published in the *Revista Portuguesa de Cardiologia* in 2019.

Author	Title of the article
P Marques Silva et al.[2]	Suboptimal lipid levels in clinical practice among Portuguese adults with dyslipidemia under lipid-lowering therapy: Data from the DISGEN-LIPID study
P Marques Silva et al.[4]	Prevalência de fatores de risco cardiovascular e outras comorbilidades em doentes com hipertensão arterial assistidos nos Cuidados de Saúde Primários: estudo PRECISE
R Calé et al.[12]	Time to reperfusion in high-risk subgroup patients with myocardial infarction undergoing primary percutaneous coronary intervention
J Pinto Monteiro et al.[13]	KAsH: Uma nova ferramenta para previsão de mortalidade hospitalar em doentes com Enfarte Agudo do Miocárdio
D Bento et al.[16]	Short and medium-term prognosis of Takotsubo syndrome in a Portuguese Population
D Bonhorst et al.[20]	Implantação de dispositivos de ressincronização e/ou desfibrilhação em doentes com insuficiência cardíaca: dados da vida real – o Estudo Síncrone
L Fernandes et al.[19]	Acidente vascular cerebral isquémico em doentes previamente anticoagulados por fibrilhação auricular não valvular: por que acontece?
C Ruivo et al.[25]	The SHIFT model combines clinical, electrocardiographic and echocardiographic parameters to predict Sudden Cardiac Death in Hypertrophic Cardiomyopathy
A Sousa et al.[23]	Molecular characterization of Portuguese patients with dilated cardiomyopathy
C Ruivo et al.[22]	Myocardial deformation measures by cardiac magnetic resonance tissue tracking in myocarditis: relationship with systolic function and myocardial lesion

and adiponectin. The IS correlated positively with body mass index ($r = 0.40$; $p < 0.001$), WC ($r = 0.30$; $p < 0.001$) and fat mass, assessed by use of bioimpedance ($r = 0.31$; $p < 0.001$) in all hypertensive individuals. It may provide complementary information on CVR stratification in obese individuals with RAH. However, it requires validation in other populations to be recommended for clinical use, which is limited by the high cost of measuring cytokines and adiponectin.[7]

Obesity, which was associated with inflammation, is also associated with the excessive production of reactive oxygen species. Aiming to assess the effects of an 8-week resisted training on oxidative stress and inflammatory parameters in 24 Swiss mice with obesity induced by a 26-week lipid-rich diet, insulin tolerance testing was performed and body weight was monitored, as were oxidative stress markers and inflammatory parameters on cardiac tissue. The results of the study have shown body weight control despite the excessive calory intake, reversing the lipid damage and the production of reactive oxygen species, and positively modulating the major cytokines responsible for activating the inflammatory process. Thus, resisted exercise can aid the treatment of obesity, but how it promotes those effects on cardiac tissue requires clarification.[8]

In another study, 118 individuals, 77 of whom were hypertensive, received random samples of bread with three different salt contents at the beginning of the study. After two weeks, the individuals received the same breads, then added with oregano, and had their arterial blood pressure and 24-hour urine sodium and potassium excretion measured. The hypertensive elderly and young individuals preferred and consumed more salt than the normotensive individuals, and the bread added with oregano decreased the preference for salt in hypertensive elderly and young individuals. The variables that significantly influenced the preference for saltier bread samples were: hypertension, male sex, and alcohol consumption. Public policies to reduce the sodium content of meals, such as those implemented in Portugal, might associate with better control of arterial hypertension and its outcomes, such as stroke, chronic kidney disease and CAD.[9]

Chronic coronary artery disease and acute coronary syndromes

The introduction of direct access to primary angioplasty has allowed for a significant reduction in mortality due to acute coronary syndrome (ACS).[10] However, the organization of the primary angioplasty system requires continuous improvement to reduce system-dependent delay times. *The Rev Port Cardiol* has published two relevant studies about that. The first study,[11] assessing 1222 patients with ST-segment elevation myocardial infarction (STEMI), has shown that, as compared to patients admitted directly to a catheterization laboratory, the inter-hospital transfer of patients with STEMI significantly increased ischemic time. The second study,[12] part of the Stent for Life initiative, has assessed data on 1340 patients with STEMI admitted to 18 Portuguese hospitals, aiming at evaluating the performance indicators in the high-risk population, namely elderly, diabetic and female patients. The authors have reported that the elderly have longer patient and system delays, regardless of gender and presence of diabetes, suggesting that the elderly subgroup should be the target of new sensitization strategies.

There are several scores for the risk stratification of patients with myocardial infarction, many of which are difficult to use. On the October edition of the *Rev Port Cardiol*, Monteiro Pinto et al.[13] have proposed a new simple to use clinical score, the KAsH score, which is calculated according to the following formula: KAsH = (Killip class x age x heart rate)/systolic blood pressure. In 1504 consecutively admitted patients with myocardial infarction, the new score has shown a better predictive value than the existing scores, specially the GRACE score. Although promising, the KAsH score requires better

validation in other cohorts of patients to be then implemented in clinical practice.[14]

The Takotsubo syndrome is a differential diagnosis for patients suspected of having ACS, and has gained increasing attention.[15] This year, the *Rev Port Cardiol* published the results of a Portuguese multicenter study that has assessed the characteristics of 234 patients diagnosed with Takotsubo syndrome.[16] That study has shown that the Takotsubo syndrome has a good short- and medium-term prognosis (in-hospital mortality of 2.2%), but the rate of in-hospital complications (namely heart failure, atrial fibrillation, ventricular arrhythmias and stroke) is high (33%).

Aiming at assessing the expression of the transcriptional factors NF-κB and Nrf2 and PPARβ/δ in chronic coronary syndrome (CCS), 35 patients with CAD (17 men; mean age, 62.4 ± 7.55 years) and 12 patients without CAD (5 men; mean age, 63.50 ± 11.46 years) were studied. Peripheral blood mononuclear cells (PBMC) were isolated and processed for the mRNA expression of Nrf2, NF-κB, NADPH:quinone oxidoreductase 1 (NQO1) and PPARβ/δ by use of real-time quantitative polymerase chain reaction. The authors have reported a higher mRNA expression of PPARβ/δ in the PBMC of patients with CAD as compared to that of the control group, while the mRNA expressions of Nrf2 and NF-κB did not differ. Such findings might indicate possible target-therapies for future research in CCS.[17]

Another study on CCS has evaluated 5526 obese patients without known CAD referred for CPM-SPECT assessment between January 2011 and December 2016. The factors associated with abnormal myocardial perfusion in obese patients without known ischemic heart disease after adjusting for the relevant variables (multivariate analysis) were: age (2% risk increase for each year of age); diabetes mellitus (57% risk increase); typical angina (245% risk increase in patients with typical angina as compared to asymptomatic patients); need for pharmacologic stress during testing (61% risk increase as compared to physical stress by use of exercise testing); less physical effort evaluated in metabolic equivalents (METs - 10% risk reduction for each additional MET during exercise testing); and left ventricular ejection fraction (LVEF) after stress (1% risk reduction for each 1% addition in LVEF). Such data support the association of obesity and CCS.[18]

Cardiac arrhythmias and devices

The association between atrial fibrillation and the risk of stroke is complex and multifactorial. Even more challenging is understanding the mechanisms involved in the occurrence of stroke in patients undergoing anticoagulation. In a very interesting study, Fernandes et al.[19] have assessed 60 consecutive patients with nonvalvular atrial fibrillation, chronically medicated with an oral anticoagulant and admitted due to ischemic stroke. For most of those patients, stroke occurrence despite anticoagulation appears to be explained by subtherapeutic dosage, poor treatment adherence or non-cardioembolic etiology, and not by inefficacy of the anticoagulants, because 90% of the patients on vitamin K antagonists had an admission INR < 2, and subtherapeutic prescriptions were found in 43% of those on novel oral anticoagulants.

Implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) reduce the risk of death and hospitalization and promote an improvement in the quality of life of patients with heart failure and reduced LVEF. Bonhorst et al. have published in the *Rev Port Cardiol* the results of the Síncrone study,[20] an observational, prospective, multicenter registry conducted in 16 centers in Portugal that included 486 patients with a diagnosis of heart failure, LVEF < 35% and indication for ICD or CRT devices. In that study, most patients treated with devices had a class I recommendation of the guidelines, the overall mortality at one year being low (3.6%), as was the number of hospitalizations (11%). That study helps understand the reality of the treatment with devices for heart failure in Portugal. In addition, it evidences the need to improve the pharmacological treatment of those patients, because the drug use rates were suboptimal (76% angiotensin-converting-enzyme inhibitor/aldosterone receptor antagonist; 77% beta-adrenergic blockers; 34% aldosterone antagonist).

Heart failure and cardiomyopathies

For patients with hypertrophic cardiomyopathy (HCM), the European guidelines recommend assessing the risk of sudden death according to the ESC-SCD score.[21] However, that score has come under criticism, and new risk stratification models are required for those patients. Ruivo C et al.[22] have published in the *Rev Port Cardiol* a study based on data from the Portuguese National Registry of HCM, which includes 1022 patients with HCM. After identifying the major determinants of the risk of sudden death, the authors have built a new risk model, the SHIFT score, which includes four variables: unexplained syncope; signs of heart failure; septal thickness ≥ 19 mm; and fragmented QRS complex. In that population of patients, the SHIFT score, which includes relatively simple clinical, electrocardiographic and echocardiographic parameters, showed a better predictive value (C-index, 0.81) than the ESC-SCD score. Thus, that new score might play an important role in selecting patients with HCM with indication for ICD in primary prevention.

Regarding dilated cardiomyopathy, the *Rev Port Cardiol* published in 2019 a multicenter study aimed at providing the molecular and genetic characterization of 107 patients with dilated cardiomyopathy.[23] The authors have reported large genetic complexity and diversity in those patients, having identified 31 rare variants in eight different genes, mainly involving sarcomeric genes (MYBPC3, TNNT2 and LMNA). That study emphasizes the importance of the new genomic analysis techniques, mainly next-generation sequencing techniques, to better understand the etiology of dilated cardiomyopathy.

Cardiovascular magnetic resonance has played an increasing role in the assessment of patients with myocarditis, being currently the non-invasive test of choice to diagnose that pathology.[24] A study[25] published in the *Rev Port Cardiol* in 2019 has assessed the role of quantifying myocardial deformation by using tissue tracking as an objective measure of myocardial function quantification in 78 patients with myocarditis. Significant correlations were found between all deformation parameters (strain, strain rate, velocity and displacement) and LVEF, regional wall motion abnormalities,

and the extent of late gadolinium enhancement. The challenge now is to understand how those results can influence the clinical approach of patients with myocarditis.[26]

Assessing the risk of cardiotoxicity of anthracycline chemotherapy and humanized monoclonal antibodies is a clinical challenge that stimulates the search for predictors of left ventricular regional wall motion abnormalities (LVRWMA) that are easy to use and allow reassessment throughout treatment. Barros et al.,[27] evaluating 112 patients (mean age, 51.3 ± 12.9 years) with breast cancer and treated with doxorubicin and/or trastuzumab, have carried out an echocardiographic study to assess cardiotoxicity, which was defined as a 10% decrease in LVEF. Cardiotoxicity was observed in 18 (16.1%) patients. On multivariate analysis, LVRWMA (OR = 6.25 [95% CI: 1.03; 37.95], $p < 0.05$), left ventricular systolic diameter (OR = 1.34 [95% CI: 1.01; 1.79], $p < 0.05$) and global longitudinal strain by speckle tracking (OR = 1.48 [95% CI: 1.02; 2.12], $p < 0.05$) were significant and independent predictors of cardiotoxicity. Those authors have concluded that LVRWMA is an independent predictor of cardiotoxicity and can be useful in the early detection of myocardial dysfunction.[27]

Heart Surgery

A meta-analysis of four controlled randomized studies, aimed at determining the clinical outcomes of 1528 patients with old-generation and contemporary mechanical and biological valvular prostheses, followed up for 2-20 years, showed no difference between patients with mechanical and biological valvular prostheses regarding the outcomes death (relative risk, RR = 1.07; 95% CI: 0.99-1.15), systemic arterial embolism (RR = 0.93; 95% CI: 0.66-1.31), and infective endocarditis (RR = 1.21; 95% CI: 0.78-1.88). However, the risk of bleeding was one-third lower (RR = 0.64; 95% CI: 0.52-0.78) and the number of reoperations (RR = 3.60; 95% CI: 2.44-5.32) was three times higher in patients with biological valvular prostheses. Three studies had included old-generation valvular prostheses with results similar to those of the new generation ones. The authors highlight the lack of studies on the new generation valvular prostheses, emphasizing the need to compare contemporary mechanical and biological valvular prostheses.[28]

Congenital heart diseases

Pregnancy in patients with complex congenital heart disease (CCHD) has become a reality, maternal-fetal management being a current clinical challenge. Avila et al. have studied, for 10 years, 435 pregnant women with CCHD, included in the registry of the Instituto do Coração (Registro-InCor). They have selected 42 pregnancies in 40 women with CCHD (24.5 ± 3.4 years), who had been advised not to get pregnant. The CCHD listed were as follows: transposition of the great arteries, pulmonary atresia, tricuspid atresia, single ventricle, double right ventricular outflow tract, and double left ventricular inlet. Those CCHD had been treated with the Rastelli, Fontan, Jatene, Senning and Mustard surgeries, and other procedures combined, such as tunneling, Blalock Taussig and Glenn. Of the 40 women with CCHD, 8 had not undergone surgery and 48% were hypoxemic. Despite the individualized and frequent follow-up, with hospitalization from the 28th week onward, most pregnancies (60%) had maternal or fetal complications, as follows: maternal complications reported in 31% of the pregnancies, including two deaths caused by post-partum hemorrhage and severe pre-eclampsia; 7 fetal losses; 17 premature babies; and 2 newborns with congenital heart disease. Despite the improvement in the prognosis of CCHD and the need to respect a woman's intention to conceive, the authors highlight the current recommendations that maternal and fetal complications advise against pregnancy, especially in hypoxemic patients.

Final Conclusions

From the perspective of the editors of the *Arq Bras Cardiol* and the *Rev Port Cardiol*, this review of the best articles of the year is a small sample of what such scientific publications have to offer regarding updating and spreading of innovations to their readers. This review evidences the relevance of science in the Portuguese language. We aimed to provide the readers with the best information, in a brief, precise and efficient way.

Science only moves forward when knowledge is shared. The role of the *Arq Bras Cardiol* and the *Rev Port Cardiol* is to publish, circulate and disseminate science, as well as to contribute to the global scientific progress. And why should we not do that elegantly and efficiently in our beloved mother language, with the accent that pleases us most? We hope everybody enjoys this review of the 2019 best articles and we are looking forward to the 2020 best ones. In addition, we invite our readers, members of our societies of cardiology, cardiologists, physicians and scientists in general to remain constantly connected to our scientific publications by using the traditional digital way (webpage), social media (Facebook, Twitter and LinkedIn), and smartphone apps. Enjoy the reading!

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The Evolving Landscape of the Geriatric Cardiology Field in Brazil: New Challenges for a New World

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"Do we practice Geriatric Cardiology?". It was with this editorial, published in the *Journal of the American College of Cardiology* (JACC),[1] in 1997, that Dr. William W. Parmley highlighted the need to develop specialized care for the geriatric population worldwide. Two decades later, it is considered by some as the starting point for the growth of Geriatric Cardiology in America. Even though the Society of Geriatric Cardiology was founded in 1986, it was not bonded to either the American College of Cardiology or the American Heart Association, and it lacked major impact in the field. With the global phenomenon of aging, cardiologists were involved in the care of elderly patients more frequently, thus initiatives were developed to fulfill their needs. For instance, in 2007, an online curriculum of continuing medical education (CME) was developed by the ACC/SGC and provided for its members, as well as published in a new editorial in the JACC.[2] In 2011, the SGC was extinguished and added to the Geriatric Cardiology chapter of the ACC.

By that time, the world had already recognized the inevitability of population aging and had already realized the importance of both giving professionals a super specialized competence (specialization in this age group) and of providing the potentially aging population with the possibility of having their demands answered by taking into account their individual characteristics, rather than the conditions they suffered from.

In Brazil, under Prof. Dr. Luís Gastão Costa Carvalho do Serro Azul's pioneering leadership, the Heart Institute (InCor) Cardio Geriatric Clinical Unit was founded in 1982 (4 years before the foundation of the American Society of Geriatric Cardiology), a movement that placed our country at the forefront of this issue. In the 90s, Geriatric Cardiology was recognized by the Brazilian Cardiology Society, initially as a study group in Cardiogeriatrics (GEBRAC) and, since 2005, as a department (DECAGE). In 2006 and 2014, two articles were published which reinforced the importance of Geriatric Cardiology among the Brazilian medical society. The first article, by Prof Dr. Maurício Wajngarten,[3] listed the challenges ahead and the need for preparing for the elderly population care. The second article, by Prof Roberto Franken and Dr. Ronaldo Fernandes Rosa,[4] highlighted the contribution of the DECAGE for the education and training in Geriatric Cardiology, by means of a partnership with the ACC, as well as the advances in scientific evidence generated by the department. In addition, it listed essential abilities for full care of the elderly. Due to those needs, the Brazilian Cardiology Society published specific Geriatric Cardiology guidelines: the first, in 2002,[5] and the second, in 2010,[6] which was updated in 2019.[7] The necessary contents of training professionals for due care of cardiovascular disease in elderly patients were also listed in the 1st Guidelines on Processes and Competences for Cardiology Training in Brazil.[8]

Keywords

Geriatrics/trends; Geriatric Assessment; Population Dynamics; Cardiology/trends; Aged; Delivery of Health Care; Frail Elderly; Health Services for the Aged.

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The essence of geriatric cardiology

Because it is a recent and not widespread specialty, Geriatric Cardiology is often confused with Geriatrics that is practiced by a cardiologist or simply with Cardiology that is applied to elderly patients. Although this is part of the discipline's core, it does not represent the whole picture. It would be more adequate to define it as integrated and age-adequate cardiovascular care, centered on the patients[9] and their functionalities – a concept previously presented by our colleagues[3,4]- that has been evolving and taking shape, as a result of the use of specific and predetermined tools.

Objectively, one could consider it as cardiology practice integrated with the Geriatric's 5 Ms: medication (focusing on prescribing the absolutely necessary, targeting at reducing polypharmacy, minimizing interactions and adverse reactions; following Beers criteria to select appropriate medication for the elderly), mentation (vigilance, prevention and treatment of cognitive disturbances), mobility (valuing and implementing strategies that seek to maintain the patient's mechanical functionality), multimorbidity (approaching the patient not only by looking up the cardiovascular system, but also by considering the occurrence of multiple comorbidities to be the rule, not the exception, in these individuals), and last, but literally not least is matters most (always consider the patient's opinion regarding the benefits and burdens of the treatment, taking into account the biography and personal values, bringing the patient into the center of decision making). We would also add a sixth and last M, multidisciplinary, for the care of the elderly, remembering it must be coordinated in a horizontal fashion by a professional, but never concentrated in only one person, giving due importance to the participation of other specialists and healthcare professionals. At our institute, in the Geriatric Cardiology Unit, we perform in all patients

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a Comprehensive Geriatric Assessment with the aid of the 10-TaGA (10-Minute Targeted Geriatric Assessment) tool.[10,11]

Trends in geriatric cardiology

Over the years, medical, scientific and life conditions advances have caused individuals to reach advanced ages in large numbers, in physical conditions and future expectations that exceed what was once observed, changing concepts of what "getting old" means.[12] We observe that, save for a few exceptions, cardiovascular diseases are aging-related diseases. In the 17th century, Dr Thomas Sydenham had already declared that "a man is as old as his arteries". Therefore, the typical cardiology patient is an older person who has, beyond more expectations and aspirations, also an increasingly number of comorbidities and age-related deteriorations that complicate traditional guideline directed management.[13] It is also known that aging provides the cardiovascular system with characteristics diverse from those of young people,[14-16] which makes the care of the elderly even more unique.

The traditional dogma that "after a certain age, the patient is too old for being submitted to invasive cardiac procedures" has no longer room in the current scenario. Notably, with the technological progress, we have seen the joining of the cardiologist's therapeutic arsenal options that have allowed for the care of cardiovascular affections that disproportionally affect the elderly. The forthcoming of Direct Oral Anticoagulants, Cardiac Resynchronization Therapy, Left Ventricular Assist Devices, TAVR and Mitral Clips open up new therapeutic horizons. Paradoxically, interventional risks (clinical or surgical) remain high in the very elderly, making geriatric and frailty evaluation useful and necessary tools for therapeutic decision making, including distinguishing those individuals who might benefit from a certain procedure from those who will not.[9,17]

We live in a multimorbidity age: Medicare data shows that, among its users, it occurs in 63% of those between 65 and 75 years old, progressing with age until it occurs in 83% of users over 85 years of age.[18] Its economic impact is equally impressive, for only 14% of beneficiaries (those who report 6 or more chronic conditions) consume 46% of the programs annual budget (over $500 billion).[13]

Current treatment paradigms for treating cardiovascular disease are limited for elderly patients. Usual approach for cardiological care is widely driven by clinical practice single disease guidelines – largely based on Randomized Clinical Trials that often deliberately and systematically exclude elderly patients with multimorbidity; they evaluate predominantly hard endpoints and do not consider physical preservation, cognition or life quality associated with health in their analysis, which would be much more relevant for evaluating the patients in their last decades or years of life. Another limitation for applying those guidelines is that focus on disease may inadvertently cause harmful effects in the multimorbidity context – this issue is extremely complex, since a treatment often entails the emergence of a new disease or decompensation of another preexisting condition.[19]

The Sliding Doors[20] phenomenon was proposed to describe how, in the current model of care, patients with multiple comorbidities may have different outcomes, depending on the door through which they go first. For example, a patient with an occult colorectal cancer and coronary artery disease, by going first to an Oncologist, is diagnosed with neoplasia, goes under surgery/chemotherapy and during treatment develops heart failure; by going first to a Cardiologist, the same patient has a severe coronary obstruction diagnosed, has an angioplasty made, uses dual antiplatelet therapy and, after a few months, presents significant gastrointestinal bleeding, and is diagnosed with cancer at a more advanced stage. We believe, as Forman DE,[19] in a new model: in which multimorbidity elderly patients care is centered on one professional with a geriatric point of view, who coordinates the care in a horizontal fashion, with specialists acting punctually and under communication, preferably with shared electronic medical records. In such model, our hypothetical patient would have had both diseases evaluated and treated in an opportune moment.

It is, indeed, a new look on illness, with the patients as the primary focus, not only with their multiple biological components, but also within their biography, which makes each of them unique, but not really excluded from the benefits of technological advances that have proven effective for other age groups and were also tested and proven in this advanced life stage.

Since we were given the invaluable opportunity of living longer, may it also be an option for a better life.

Conclusion

Geriatric Cardiology is an evolving field, still in the process of forming its identity and defining which training is mandatory and fundamental. In a couple of decades only, we have evolved a lot. Gaps within the knowledge of the elderly were identified, we took the first steps to establish a Geriatric Cardiology curriculum and develop specific tools for evaluating the eldery with cardiovascular diseases – initial steps for a subspecialty that is still in the making. Formal clinical training is still rare – to our knowledge, in North America, it is only offered in New York University, Vanderbilt University, University of Pittsburgh – in the United States – and McGill University – in Canada. In Brazil, we have fellowships at the InCor (Heart Institute), Instituto Dante Pazzanese and Escola Paulista de Medicina, open to Cardiologists and Geriatricians. Gladly, this year we have 6 professionals under training in our institution – the greatest number since the program was opened. We expect that this represents the evolution of Geriatric Cardiology and an incentive on the long journey we have ahead. After all, the challenges are not few: i) narrowing the gaps on the knowledge of the elderly; ii) increase the participation of the elderly included in clinical trials; iii) evaluate endpoints that are relevant for our patients – cognition and quality of life; iv) increase the ability to form professionals with specific training in Geriatric Cardiology.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Tavares CAM, Cavalcanti AFW, Jacob Filho W; Writing of the manuscript: Tavares CAM, Cavalcanti AFW.

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Response to "Readmission of Patients with Acute Coronary Syndrome and its Determinants": An Overview of PHC

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The study by Oliveira et al.[1] shows extremely important data on readmissions of patients within one year after hospitalization for ACS and its determinants. In their study, a number of variables were evaluated. The most determinant one includes the type of health service used by patients during hospitalizations.

Thus, for a better understanding of the reality portrayed not only in the host city of the study, but in many other cities throughout Brazil, and in order to allow a greater understanding of the variables addressed, we would like to highlight issues previously discussed in the literature.

The article shows that, of 21.46% of the patients who required readmission, the majority used private health services, highlighting one of the risk factors used in the study: the socioeconomic profile of the participants. Among those who depended on the public health system, the readmission rate was lower, because, as the spots are limited, not all of them are admitted, as opposed to what is seen in the private service.

The study reports that the demand for hospital service is because it is difficult to make an appointment at the primary care level, evidencing failure in communication between primary health care and the population, which, in the long term, affects hospital admissions and their high — potentially avoidable — costs. According to Cecílio et al.,[2] when it comes to the population's access to health services, primary health care is the gateway to this system, highlighting one of the fundamental roles of basic health units: prevention, whether primary, secondary or tertiary.

For Starfield,[3] it is Primary Health Care that must coordinate the flow of users between the multiple health services, in order to ensure greater equity in access to health services. However, this requires an informed and supported community that is encouraged to prevent cardiovascular or other diseases, both before and after hospitalizations. This reality can be made possible with campaigns, projects, tracking and monitoring by the health unit in charge in each region.

Thus, it is extremely important that health professionals inform the population about the services offered by Primary Health Care and its role in disease prevention and prevention of hospitalization. In doing so, they can provide an alternative potentially capable of reducing hospitalization rates by the public health service during and after the duration of ACS. This way, it will be possible to enforce Law 8080,[4] of 19/9/1990, of the Brazilian Constitution, which aims to promote health for all.

Keywords

Primary Health Care; Hospitalization/economy; Patient Readmission/economy; Health Services; Acute Coronary Syndrome; Socioeconomics Factors.

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Reply

We are thankful to the comments and for the interest in our study, which is about a relevant topic, i.e., readmission of patients with acute coronary syndrome (ACS) and its determinants to both public hospitals (Brazil's public health system — SUS) and private hospitals. A better understanding of the findings we reached, which certainly reflect what happens in the country, will result in benefits for the therapeutic approach of those who have this major disease.

The expressive rate of readmissions observed, which certainly has a significant impact on health costs, results not

Letter to the Editor

only from clinical factors, but also from the type of assistance received by the patient, both during hospitalization and after discharge. It is worth noting that about 72% of the Brazilian population depends exclusively on the public health system. Therefore, as we said, Primary Health Care (PHC) can play a pivotal role in the adoption and reinforcement of secondary prevention measures that will surely be successful for those particularly affected by ACS. According to Ordinance No. 2436 of the Ministry of Health, published on 21/9/2017, Brazil's Policy on Primary Health Care provides for the longitudinality of care, with monitoring of the effects of health interventions and coordination of care. Therefore, person-centered care, also advocated in this ordinance, places PHC in a fundamental role of helping patients to develop knowledge, skills and competence to better take care of their own health. Health education actions are essential to stress self-care and the prevention of subsequent readmissions. Finally, co-responsibility between health professionals and patients in the implementation of actions to prevent complications of the disease, health promotion and proper therapeutic adherence can positively influence the reduction of readmission rates.

Sincerely,

Larissa Marina Santana Mendonça de Oliveira
Danielle Góes da Silva
Antônio Carlos Sobral Sousa

Brazilian Position Statement on Resistant Hypertension – 2020

Development: Department of Hypertension (DH) of the Brazilian Society of Cardiology

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Note: These statements are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Statement

Declaration of potential conflict of interests of authors/collaborators of the Brazilian Position Statement on Resistant Hypertension – 2020
If, within the last 3 years, the author/collaborator of the statement:

Names of statement collaborators	Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this guideline	Spoke at events or activities sponsored by industry related to this guideline	Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry	Participated in normative committees of scientific research sponsored by industry	Received personal or institutional funding from industry	Wrote scientific papers in journals sponsored by industry	Owns stocks in industry
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Andrea Araújo Brandão	No	Abbott, EMS, Merck	No	No	Servier, Medley	Servier, Abbott	No
Annelise Machado Gomes de Paiva	No	No	No	No	No	No	No
Armando da Rocha Nogueira	No	No	No	No	No	No	No
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Statement

Content

1. Definition and Epidemiology

Coordinator: Heitor Moreno Júnior.

Authors: Juan Carlos Yugar-Toledo, Heitor Moreno Júnior, Miguel Gus, Guido Bernardo Aranha Rosito, and Luiz César Nazário Scala.

1.1. Definition/New Concepts

Resistant hypertension (RHTN) is defined as blood pressure (BP) persistently above the recommended target values despite the use of three antihypertensive agents of different classes, including one blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB]), one long-acting calcium channel blocker (CCB), and one long-acting thiazide diuretic (TZD) at maximum recommended and tolerated doses, administered with appropriate frequency and doses and with proven adherence.

Other drugs may be added if the above ones fail (aldosterone antagonists, beta-blockers, and α-methyldopa). Experts disagree on issues related to dose/potency, although the main discussion occurs around the use of chlorthalidone or hydrochlorothiazide as the main TZD.[1]

The definition above includes a subgroup of patients with RHTN whose BP is controlled with four or more antihypertensive medications, known as controlled RHTN (C-RHTN).[2,3] A proposal to classify the disease into C-RHTN and uncontrolled RHTN (UC-RHTN),[4] including refractory RHTN (Ref-RHTN), an extreme UC-RHTN phenotype involving use of five or more antihypertensive agents,[5] has gained space in the literature.[6,7]

Thus, UC-RHTN is defined by BP levels that remain above the desired level (140/90 mmHg) despite the concomitant use of four or more antihypertensive agents of different classes and a fourth drug, which is generally a mineralocorticoid receptor antagonist or a central sympathetic inhibitor (Chart 1).

1.2. Control of Hypertension in Brazil and Worldwide

An analysis of 135 population studies with 1 million individuals indicated that 31.1% of the adult population is hypertensive (95% CI; 30 to 32%), with an estimated rate of 28.5 and 31.5% in countries with the highest and lowest socioeconomic status, respectively. BP control varies according to socioeconomic status, reaching 28.4% in more developed countries and only 7.7% in those with a lower degree of development.[8] In Brazil, the control rate varied from 10.4 to 35.2% in populations studied in three regions of the country.[9]

A study conducted in 291 centers in all five Brazilian regions including 2,810 patients evaluated the control rates of hypertension according to risk profile and target BP. For patients with lower risk and target levels < 140/90 mmHg, the control rate was 61.7%, while for those with high risk and target levels < 130/80 mmHg, the corresponding value was 41.8%.[10]

Chart 1 – Classification of resistant hypertension

Number of antihypertensive agents		
Controlled resistant hypertension	N 6 5 4	Uncontrolled resistant hypertension
	3	Resistant hypertension
	2 1	
< 140/90	Blood pressure (mmHg)	≥ 140/90
Normotension		Hypertension

1.3. Incidence and Prevalence of Resistant Hypertension

The prevalence of RHTN among individuals with hypertension is estimated at 10 to 20% worldwide, resulting in approximately 200 million individuals with RHTN.[11] This variability is mainly due to differences in RHTN criteria and characteristics of the studied populations.

The National Health and Nutrition Examination Survey (NHANES) reported a prevalence of RHTN of about 9% in individuals with hypertension, corresponding to 12.8% of the individuals using antihypertensive agents in the US.[12]

Still, the actual prevalence of RHTN is unknown. A meta-analysis by Achelrod et al.[11] evaluating populations of individuals with treated hypertension found a prevalence of 13.72% (95% CI; 11.19 to 16.24%), according to 20 observational studies, and 16.32% (95% CI; 10.68 to 21.95%), according to four randomized controlled trials.[11] In Brazil, a multicenter study (ReHOT) including ambulatory BP monitoring (ABPM) showed a prevalence of RHTN of 11.7%.[13]

Daugherty et al.[14] analyzed the incidence of RHTN in 205,750 patients with hypertension who initiated antihypertensive treatment between 2002 and 2006. The authors found a rate of 1.9% at 1.5 years of follow-up (0.7 per 100 patients per year), leading to a 1.47 higher cardiovascular (CV) risk at 3.8 years.[14]

1.4. Factors Related to Resistant Hypertension

RHTN is more prevalent in elderly, obese, and African descent individuals, as well as in patients with left ventricular hypertrophy (LVH), diabetes mellitus, chronic nephropathy, metabolic syndrome, increased alcohol and/or salt intake, and sedentary lifestyle.[1,15-17] Aspects related to RHTN include the following: 1) diagnostic factors – inadequate BP measurement technique, white-coat effect;[1,15] 2) causal factors – increased salt sensitivity, volume expansion due to excessive salt intake or chronic kidney disease (CKD), use of nonsteroidal antiinflammatory drugs, anabolic steroids, oral contraceptives, sympathomimetic agents (nasal decongestants, appetite suppressants, cocaine), chemotherapeutic agents, antidepressants, erythropoietin, immunosuppressants, alcohol;[1,15] 3) secondary causes of hypertension, including primary hyperaldosteronism, obstructive sleep apnea (OSA), CKD, renal artery stenosis, thyroid diseases;[15] 4) therapeutic factors – medications that are either inappropriate or are used

in insufficient doses, medical inertia, low adherence.[16,17] Both systolic and diastolic hypertension may be resistant, the former being more prevalent.[1]

2. Prognostic Aspects

Coordinator: Elizabeth Silaid Muxfeldt.

Authors: Alexandre Alessi, Andrea Araújo Brandão, Osni Moreira Filho, and Elizabeth Silaid Muxfeldt.

2.1. Introduction

RHTN is associated with high CV morbidity and mortality, increasing the risk of CV events by 47% in patients affected by this condition when compared with individuals with incident hypertension.[14]

2.2. Office Blood Pressure and Ambulatory Blood Pressure Monitoring

True RHTN, diagnosed by ABPM, is associated with twice the CV risk compared with RHTN due to a white-coat effect.[18] Overall, the average BP measurements obtained in all three ABPM periods are strong predictors of CV risk, while office BP has shown no prognostic value.[18,19] Longitudinal studies have highlighted high BP during sleep and the absence of nocturnal dipping as important predictors of CV risk.[18-20] Prognostic importance of the nighttime BP pattern has also been shown in meta-analyses.[21]

2.3. Target-Organ Damage

2.3.1. Central Arterial Pressure and Arterial Stiffening

Pulse wave velocity (PWV) has an independent predictive value in several subgroups of patients with hypertension.[22] Reduced arterial relaxation and elasticity have been observed in patients with RHTN compared with individuals with well-controlled hypertension, being a marker of prognosis and response to antihypertensive therapy.[23] In hypertensive patients, PWV provides additive value when incorporated into CV risk scores.[24]

2.3.2. Left Ventricular Hypertrophy

The electrocardiographic diagnosis of LVH has emerged as a predictor of risk for coronary disease (Cornell index) and cerebrovascular disease (Sokolow-Lyon index), and the regression of both indices reduces the risk of CV events by 35 and 40%, respectively.[25]

2.3.3. Albuminuria

Both baseline and serial changes in albuminuria have prognostic implications in RHTN. In a large prospective cohort of 531 patients with RHTN, the occurrence of moderately increased albuminuria (MIA) at baseline was an independent predictor of composite events and all-cause mortality.[26] A later analysis by the same group, this time including 1,048 patients, showed that MIA increased by 40% the risk of fatal and nonfatal CV events and all-cause mortality.[27]

During follow-up, the persistence of MIA at 2 years was a risk factor for CV events, while persistent normoalbuminuria emerged as a protective factor.[26] Another cohort of 143 patients with RHTN assessed at baseline and after 6 years of follow-up showed that the development or persistence of MIA was associated with an increased risk of CV events. In contrast, the persistence of normoalbuminuria or regression of MIA was associated with a lower risk of major events.[28]

2.3.4. Inflammatory Biomarkers

Elevated C-reactive protein is an independent predictor of coronary and cerebrovascular disease, and a more important marker in patients with RHTN who are younger, obese, and have uncontrolled ABPM and a non-dipping pattern (absent or attenuated nocturnal decline).[29]

3. Flowchart of Assessment of Resistant Hypertension

Coordinator: Audes Diógenes de Magalhães Feitosa.

Authors: Oswaldo Passarelli Júnior, Dilma do Socorro Moraes de Souza, and Audes Diógenes de Magalhães Feitosa.

3.1. Flowchart of the Diagnostic Approach in Resistant Hypertension

On clinical suspicion of RHTN, diagnostic confirmation is required, and the first step in the investigation is the exclusion of causes of pseudoresistance, such as lack of treatment adherence (pharmacological and non-pharmacological), inadequate dosing, improper BP measurement technique, and white-coat effect[1] (Figure 1). Lack of BP control should be confirmed by ABPM and home blood pressure monitoring (HBPM).[30-32]

Once pseudoresistance is excluded, the occurrence of RHTN is confirmed and a diagnostic investigation should be initiated with specific tests, according to recommendations of hypertension guidelines regarding the involvement of target-organ damage (TOD) and secondary hypertension.[33,34] The occurrence of associated comorbidities should be evaluated with specialized tests according to clinical suspicion.

Out-of-office BP measurement is fundamental since such readings are usually higher than those measured at home, reflecting the frequent occurrence of the white-coat effect in this population. Treatment adherence is always challenging, especially in public centers.

Patient-related problems that may occur include rejection to the excessive number of medications in complex dosing (excessive doses and tablets), medication side effects, sociocultural issues and lack of knowledge of the natural history of the disease, as well as other problems related to the physician, including poor doctor-patient relationship, non-synergistic dosing or wrong doses and omission or lack of knowledge in the investigation of treatable secondary causes. A potential problem related to health care services is difficulty in access to physicians, medications, and complementary tests.

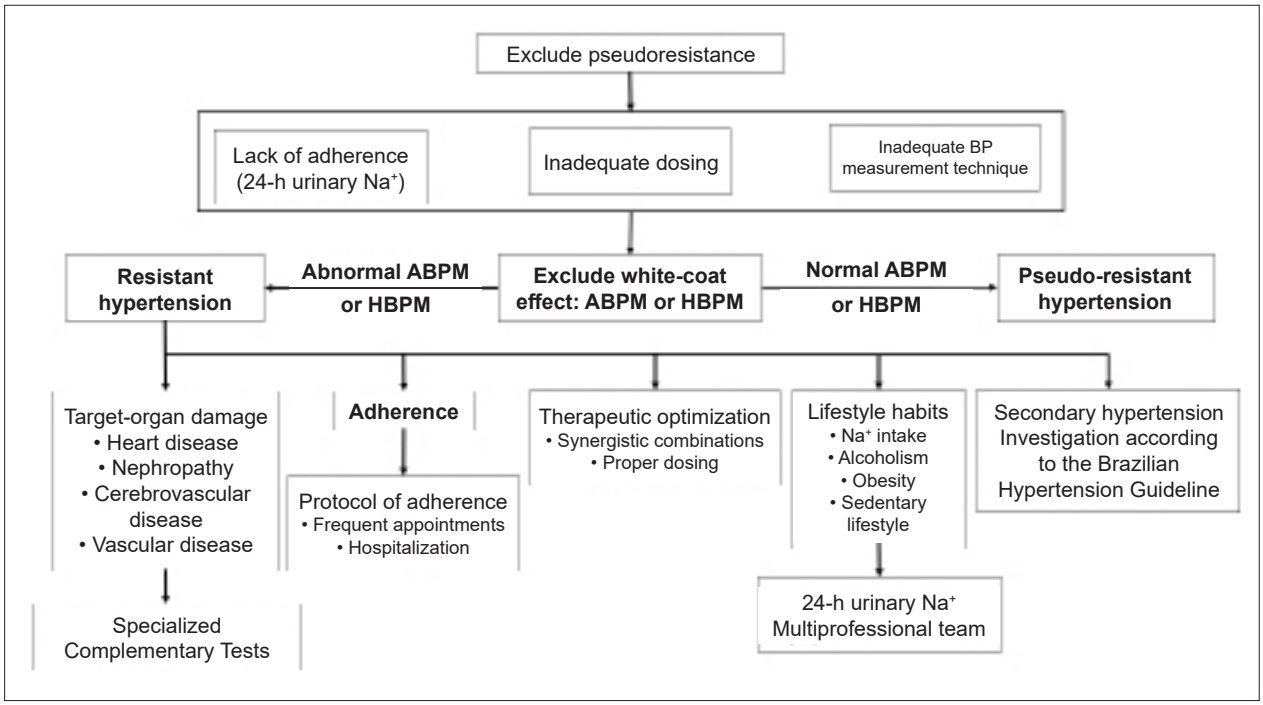

Figure 1 – *Flowchart of the evaluation of resistant hypertension. ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; Na+: sodium; BP: blood pressure.*

All these factors hinder the adherence to pharmacological and non-pharmacological treatment and must, therefore, be verified and circumvented.

Salt intake should always be verified, if possible with a 24-hour urinary sodium measurement, as intake is often excessive due to the consumption of processed foods and lack of knowledge by the patients about excessive salt intake.

Treatment should be optimized, preferably with the same physician and for a minimum of 6 months to strengthen the doctor-patient relationship. Added to that are regular recommendations regarding healthy lifestyle habits and continuous verification of treatment adherence, with synergistic dosing schedules and appropriate medication adjustments, respecting the occurrence of comorbidities indicating or contraindicating certain antihypertensive drug classes.

4. Blood Pressure Measurement

Coordinator: Celso Amodeo.

Authors: Weimar Kunz Sebba Barroso, Marco Antônio Mota Gomes, Annelise Machado Gomes de Paiva, and Eduardo Costa Duarte Barbosa.

4.1. Office Blood Pressure in Resistant Hypertension

Although not diagnostic of RHTN, office BP should be verified, and the measurement procedure should follow the guidelines of the 7th Brazilian Guideline of Arterial Hypertension.[33] The BP can be measured with a manual, semiautomatic, or automatic sphygmomanometer. Several measurements are recommended, with the patient sitting in a calm and comfortable environment to improve reproducibility and bring the values obtained in the office close to those obtained on ABPM during daytime.

Consideration must be given to the occurrence of the white-coat effect, a phenomenon involving two situations. The first is a white-coat hypertension, in which BP is elevated in isolated office measurements but normal during ABPM or HBPM. The second is a white-coat effect, which is characterized by increased office BP in relation to the mean BP during daytime in the ABPM or the weekly average HBPM, without changing the diagnosis of hypertension or normotension.[35]

These two situations can lead to a false diagnosis of RHTN, resulting in unnecessary test requests and medication use. White-coat hypertension may be referred to as a cause of pseudo-resistant hypertension.[36]

4.2. Ambulatory Blood Pressure Monitoring in Resistant Hypertension

This test is necessary to rule out the hypothesis of white-coat hypertension, which falsely suggests RHTN.[37] The diagnosis is confirmed when the mean BP during daytime and over 24 hours is below 135/85 mmHg and 130/80 mmHg, respectively. Compared with casual BP measurements, the values obtained are more strongly related to the risks arising from hypertension, especially during ABPM evaluation, when an absence or attenuation of the BP reduction during sleep is identified, along with an increase in the difference between systolic and diastolic BP.[37] Chart 2 presents the main applicability in hypertension of the ABPM, a fundamental test in RHTN evaluation, diagnosis, and follow-up.

Chart 2 – Key information obtained from ambulatory blood pressure monitoring

- Multiple measurements over an observation period
- Blood pressure assessment during daytime
- Correlation of daytime measurements with activities and symptoms
- Blood pressure assessment during sleep
- Possibility of correlating blood pressure variability with symptoms, activities, and medications
- Complement to the patient's diagnosis and prognosis
- Evaluation of the antihypertensive effect

4.3. Home Blood Pressure Monitoring and Blood Pressure Self-Measurement

Home BP measurements are more accurate than casual BP measurements and offer a better prediction of risk for CV outcomes, contributing to greater adherence to drug treatment.[35,38,39] In this context, HBPM and BP self-measurement (BPSM) are viable and effective alternatives for proper diagnosis and improved adherence.[40,41]

4.4. Measurement of Central Arterial Pressure

Arterial stiffness is recognized as an important prognostic index and potential therapeutic target in patients with hypertension. As a result, central systolic blood pressure (cSBP) and PWV have been recently investigated in a population of patients with RHTN.[42] The mean age of the population was 58.7 ± 15.3 years, and 65% (n = 53) were women. Brachial and central blood pressures were elevated in all patients. Additionally, the PWV value was higher than the reference value for age, and the difference was statistically higher for PWV in women.

Another study[23] analyzing associations between RHTN and arterial stiffness has shown that patients with RHTN have increased vascular stiffness compared with patients with well-controlled hypertension. PWV increased with arterial stiffness and correlated with BP levels, justifying the need for adequate BP control.

5. Target-Organ Damage

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5.1. Introduction

Both C-RHTN and UC-RHTN are associated with a higher prevalence of TOD and higher CV risk and mortality compared with controlled hypertension.[43-45] Therefore, the investigation of TOD in RHTN is fundamental to complement the risk stratification and establish the prognosis.[44]

5.2. Vascular Changes

Patients with RHTN present structural and functional vascular changes resulting not only from uncontrolled hypertension but also from early vascular aging. This is a complex process involving biochemical, enzymatic, and cellular changes that modify the function and structure of the artery, culminating in early and progressive degeneration of the arterial health.[43-47]

Pathophysiological mechanisms include increased oxidative stress, endothelial dysfunction, vascular remodeling, smooth muscle cell hypertrophy, increased arterial stiffness due to changes in collagen/elastin distribution, vascular inflammation, and increased expression of inflammatory mediators and matrix repair metalloproteinases, in addition to increased advanced glycation end-products and parietal calcification.[48,49]

The molecular mechanisms of vascular aging include genetic alterations in segments involved in DNA protection and repair[50] and mitochondrial metabolic activity.[51]

In the microcirculation, endothelial dysfunction promotes vasoconstriction, eutrophic remodeling (increased media/lumen [M/L] ratio without external changes), decreased vasodilatory reserve and vascular rarefaction, the latter evaluated by *in vivo* capillaroscopy,[52] gluteus biopsy, or yet, measurement of the M/L ratio with laser Doppler flowmetry of retinal arteries[53] and optical videomicroscopy. In large arteries, parietal remodeling leads to increased arterial stiffness.[49,54-56]

Arterial stiffness is estimated by carotid-femoral PWV (c-f PWV) and calculation of the augmentation index (AIx) by applanation tonometry.[57,58] These changes in arterial stiffness hemodynamic parameters and cellular biomarkers are associated with increased morbidity and mortality.[59,60]

The macrovascular involvement is further characterized by carotid, cerebral, coronary, and peripheral atherosclerotic diseases.[61,62]

5.3. Cerebral Changes

The cerebrovascular involvement in RHTN is subtle and insidious. Microscopic white matter lesions begin early and may progress irreversibly, leading to cognitive impairment and progression to vascular dementia.[63,64]

Patients with RHTN have a higher risk of cerebral infarction and transient cerebral ischemia, a fact that has been pointed out by the Kaiser Permanente[16] and REGARDS studies,[65] which showed risk increases of 17 and 14%, respectively. Atherosclerosis of the carotid and small cerebral vessels is responsible for ischemic and thromboembolic phenomena. Retinal artery occlusion is a marker of small vessel injury and has been associated with an increased risk of cerebral events.[66]

Uncontrolled hypertension is the leading cause of hemorrhagic stroke. Patients with RHTN have microangiopathy (Charcot-Bouchard aneurysms), which affect the penetrating arteries in the brain and cause intraparenchymal hemorrhage.[67]

Changes in large artery stiffness are also associated with increased occurrence of microvascular changes and a greater predisposition to cerebrovascular events.[68]

5.4. Cardiac Changes

Several cardiac changes may be observed in patients with RHTN, including LVH, left ventricular diastolic dysfunction (LVDD), and myocardial ischemia.[69] LVH is an independent

predictor of heart failure, coronary artery disease (CAD), arrhythmias, and stroke.[70]

In Brazil, the prevalence of LVH assessed by echocardiography in patients with RHTN ranges from 68 to 87%,[71,72] with concentric LVH being the most common geometric pattern in these individuals.[72,73]

LVDD predisposes to cardiovascular events and heart failure, regardless of cardiac mass and BP levels.[74] The exact prevalence of LVDD in patients with RHTN is uncertain, but the strong association between this condition and LVH[74] suggests that LVDD is very frequent in this population. About one third of the patients with RHTN are diagnosed with CAD.[71] However, even in the absence of overt CAD, up to 28% of the patients with RHTN have myocardial ischemia,[72] which may result from decreased coronary reserve and increased myocardial oxygen consumption, particularly in patients with LVH, and increased arterial stiffness.[70,74]

5.5. Renal Changes

The association between RHTN and CKD is well established and may be causal or consequential. The anatomopathological substrate is hypertensive nephrosclerosis, resulting from hemodynamic abnormalities (glomerular hyperfiltration and hypertrophy), culminating in glomerulosclerosis. Nephrosclerosis (erroneously termed "benign") is characterized by arteriosclerosis and arteriolosclerosis, hyalinosis, tubulointerstitial lesions, global glomerulosclerosis, and focal segmental glomerulosclerosis.

Known risk factors for CKD progression include age > 50 years, male sex, genetic predisposition, family history, African descent, hypertension duration and stage, low socioeconomic status, intensity of albuminuria, degree of renal dysfunction, dyslipidemia, obesity, diabetes, lifestyle habits (diet with excessive salt and/or protein, smoking), and use of nephrotoxic substances, among others.[75] Albuminuria and reduced estimated glomerular filtration rate (eGFR) identify patients at high CV and renal risks, and the reduction in albuminuria may be a therapeutic objective in RHTN.[26-28]

Recommended tests for evaluation and follow-up of renal damage include urinalysis, serum creatinine for eGFR calculation using the equations MDRD or CKD-EPI, available at http://ckdepi.org/equations/gfr-calculator/, renal and urinary tract ultrasonography, and calculation of the albuminuria or urinary protein/creatinine ratio for CKD staging[75] (Figure 2).

6. Phenotype of the Patient with Resistant Hypertension

Coordinator: Luciano Ferreira Drager.

Authors: Heitor Moreno Júnior, Juan Carlos Yugar-Toledo, and Luiz Aparecido Bortolotto.

6.1. Introduction

This section describes initially the characteristics that distinguish patients with RHTN from those with non-resistant hypertension. Subsequently, it discusses the differences between patients with C-RHTN and UC-RHTN, and finally, addresses the approach to the extreme phenotype of the RHTN patients, i.e., patients with refractory hypertension.

6.2. Phenotype of the Patient with Resistant Hypertension

Patients with RHTN often present some characteristics that distinguish them from those with non-resistant hypertension, including older age, obesity, a profile of increased salt intake, CKD, diabetes, presence of TODs such as LVH, female sex, and african descent.[1] The Brazilian multicenter study ReHOT has shown that diabetes, prior stroke, and BP at study entry ≥ 180/110 mmHg (hypertension stage 3) were independent predictors of true resistance.[13] While some of these

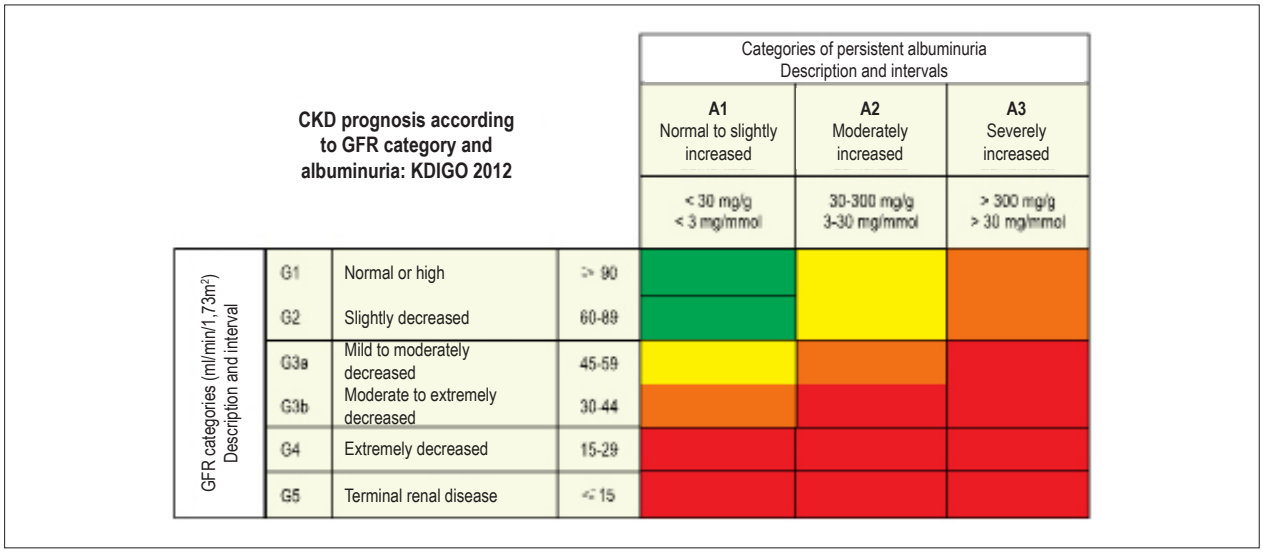

Figure 2 – *Prognosis of chronic kidney disease according to degrees of albuminuria and decline in estimated GFR.[76] Green: low risk; yellow: moderate risk; orange: high risk; red: very high risk.*

characteristics are intuitive, others, including the female sex, still lack well-defined rationales in predicting RHTN.

6.3. Phenotype of Controlled and Uncontrolled Resistant Hypertension

6.3.1. Pathophysiological Aspects

C-RHTN shows greater dependence on volume status than UC-RHTN, due to critical persistence of water retention, increased sodium sensitivity, hyperaldosteronism, and renal dysfunction. Additionally, these individuals present increased plasma volume expansion measured by thoracic bioimpedance,[77] higher plasma and urinary aldosterone concentrations, suppression of renin activity,[78] high plasma aldosterone/renin ratio (ARR), and increased levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).[79-83] This relationship between increased volume and pressure is the pathophysiological basis demonstrated in several studies[81,84,85] and justifies the use of diuretics in patients with C-RHTN.[86,87]

In contrast, patients with UC-RHTN often have sympathetic hyperactivity, evidenced by increased (24-hour) urinary metanephrines and resting heart rate, reduced 24-hour variability (spectral analysis), in addition to increased vascular stiffness (increased PWV).[88,89] These markers of increased sympathetic activity, together with other factors linked to hyperaldosteronism,[78,90-92] are related to mechanisms that maintain high BP even with administration of four or more antihypertensive agents, characterizing UC-RHTN. Higher PWV values reflect exacerbated arterial stiffness,[4] while elevated levels of cytokines, including tumor necrosis factor-alpha (TNF-α),[48,56,93] probably indicate vascular damage in patients with RHTN.[49]

Other factors and mechanisms, such as age, obesity, OSA,[4,94,95] African descent, adipokine deregulation,[96] endothelial dysfunction, and increased activity of metalloproteinases-2, metalloproteinases-9 and adhesion molecules[97-99] are also involved in this process.

Genetic polymorphisms, especially those involving the renin-angiotensin-aldosterone system and the endothelial nitric oxide synthase (eNOS), have been correlated to RHTN[100,101] (Figure 3). However, large studies conveniently characterized in individuals with the disease are needed to define the importance of genetics in this group of patients.

6.3.2. Clinical Differences

In 2011, Martins et al. published a comparative study in patients with C-RH and UC-RHTN[4] specifically assessing biological factors contributing to resistance to antihypertensive agents. Body mass index (BMI), arterial stiffness (PWV), left ventricular mass index (LVMI), and plasma aldosterone concentration (PAC) were higher in the UC-RHTN group when compared with the C-RHTN group. Additionally, the authors demonstrated using multivariate analysis that PWV was dependent on age in both groups, although this influence was more pronounced in patients with UC-RHTN. They also showed that the UC-RHTN group had higher values of carotid intima-media thickness (cIMT) and PWV.[102] Finally, the drop in nocturnal BP (dipping pattern) was less pronounced in the UC-RHTN group.[103]

6.3.3. Prognosis

Pierdomenico et al.[104] evaluated CV outcomes in subjects with C-RHTN and UC-RHTN. The occurrence of fatal and nonfatal CV events was investigated in 340 patients with C-RHtN (BP < 140/90 mmHg or daytime BP < 135/85 mmHg) and 130 patients with UC-RHTN (BP ≥ 140 or 90 mmHg and daytime BP > 135 or 85 mmHg). During follow-up (4.98 ± 2.9 years), the event rates per 100 patients/year were 0.87 and 4.1, respectively. These data also show that patients with UC-RHTN have a greater risk of CAD, stroke,

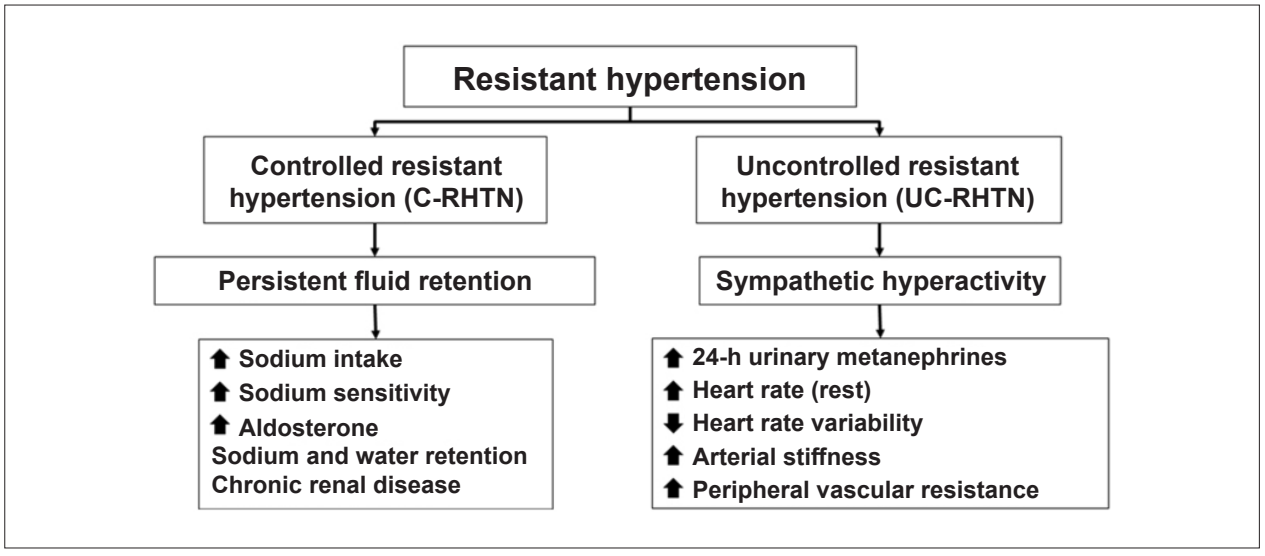

Figure 3 – *Predominant pathophysiological mechanisms in controlled (C-RH) and uncontrolled (U-RH) resistant hypertension. Refractory hypertension (uncontrolled with five or more medications) is included in the U-RH group.*

arterial disease, congestive heart failure (CHF), kidney disease, and all-cause death compared with patients with C-RHTN.

6.4. Phenotype of the Patient with Refractory Hypertension

Refractory hypertension appears to be an extreme phenotype of patients with RHTN. Recently, phenotypic characterization has shown that these patients are younger than those with RHTN in general, are more commonly women, have a higher frequency of heart failure, and have particularly higher sympathetic activity than patients with RHTN.[5] These findings are important pillars for the pathophysiology of refractoriness, potentially constituting a therapeutic target for procedures such as renal denervation. Studies in this area are currently under development.

7. Secondary Causes of Resistant Hypertension

Coordinator: Fernanda Marciano Consolim-Colombo

Authors: Márcio Gonçalves de Sousa, Flávio Antonio de Oliveira Borelli, Cibele Isaac Saad Rodrigues, and Fernanda Marciano Consolim-Colombo.

7.1. Introduction

Secondary hypertension (SecHTN) is defined as increased BP due to an identifiable cause.[33,105] Patients with RHTN should be investigated for the most prevalent causes of "non-endocrine" and "endocrine" SecHTN after exclusion of use of medications that may interfere with BP values: antiinflammatory drugs, glucocorticoids, nasal decongestants, appetite suppressants, antidepressants, immunosuppressants, erythropoietin, contraceptives, and illicit drugs.[33,105]

7.2. Secondary Hypertension due to Non-Endocrine Causes

7.2.1. Obstructive Sleep Apnea

Defined as a total or partial cessation of respiratory flow during sleep, this syndrome promotes oxyhemoglobin desaturation and microarousals during sleep. OSA is estimated to have a prevalence of 17%[106] among American adults and 30% among hypertensive individuals and may affect 60 to 80% of the patients with RHTN.[94] A recent meta-analysis[107] has concluded that the presence of OSA is related to a higher risk of RHTN.[107]

Activation of the sympathetic nervous system and humoral abnormalities are responsible for changes in vascular endothelial integrity, and their consequences in patients with OSA include increased BP, development of atherosclerotic disease, and cardiac arrhythmias, among others.[108] Clinical suspicion can be verified with the Berlin questionnaire.[109]

The diagnosis is established with polysomnography, which records apnea/hypopnea indices greater than five events/hour.

Treatment should include recommendations on sleep hygiene and weight loss, among others. For airway clearance, the use of equipment producing continuous positive airway pressure (CPAP) is the most recommended. However, the impact of this treatment on reducing BP values is still debatable.[110,111]

7.2.2. Renal Parenchymal Disease

Renal parenchymal disease (RPD) is one of the most prevalent causes of SecHTN. The diagnosis of this condition is relatively simple since the assessment of renal function is part of the routine approach in patients with hypertension. Patients on dialysis and renal transplant recipients have a high prevalence of hypertension, and CV events are responsible for high morbidity and mortality in this population.[112]

The progression of renal dysfunction in patients with RPD is directly related to BP values, and target BP levels should be achieved to reduce CV morbidity and mortality. In patients with RPD and renal transplant recipients, ACEIs and angiotensin-II receptor blockers have been shown to offer renal protection additional to that obtained by BP reduction, and are, therefore, the preferred medications.[33,105,113]

7.2.3. Renal Artery Stenosis

Renovascular disease is a term used to define renal artery involvement by different pathologies, including atherosclerotic disease, fibromuscular dysplasia, and vasculitis, which can lead to arterial obstruction. Usually, no symptoms are associated with mild arterial obstruction. However, with obstructions affecting more than 70% of the artery, severe hypertension and even ischemic nephropathy may occur.

Renal artery stenosis (RAS) of atherosclerotic origin is present in 12.5% of the patients with RHTN older than 50 years of age.[114] The diagnosis should always be determined, but the treatment of this condition is still much discussed in the literature.[115,116] Adequate BP control and interruption of progressive renal function deterioration are the primary treatment goals in these patients. To achieve that, two therapeutic possibilities are available for this population: clinical and interventional (surgical or percutaneous, with or without stent implantation).

Interventions are recommended for patients with RHTN or accelerated hypertension with progressive loss of renal function, bilateral RAS or stenosis in a "single" kidney, or with severe complications (CHF and recurrent acute pulmonary edema).[33,115,116]

Other potential surgical indications include total renal artery obstruction, large arteriovenous fistulas, aortic lesion encompassing the renal arteries, and failure in clinical or endovascular treatment.[117]

7.3. Secondary Hypertension due to Endocrine Causes

7.3.1. Primary Hyperaldosteronism

Considered in the past to be a rare type of SecHTN (with a prevalence of about 1%), hyperaldosteronism is currently believed to occur in up to 22% of the cases in populations with RHTN.[118,119] The most frequent cause of hyperaldosteronism is adrenal adenoma, while unilateral or bilateral hyperplasia is less frequently detected. Carcinomas (albeit infrequent) and genetic forms of the disease may also be responsible for the occurrence of hyperaldosteronism.

Aldosterone, through activation of mineralocorticoid receptors, is related to insulin resistance and endothelial

dysfunction and, consequently, participates in the development of metabolic syndrome and CV and renal lesions associated with RHTN. Thus, mineralocorticoid receptor blockade improves endothelial dysfunction and contributes to a better response to RHTN and TOD therapies.[118,119]

During the diagnostic evaluation, all patients with RHTN (not only those with hypokalemia) should be evaluated for the occurrence of hyperaldosteronism.[33] Screening should include the assessment of the plasma aldosterone concentration (PAC expressed in ng/dL) to plasma renin activity (PRA expressed in ng/mL/hr) called aldosterone/renin ratio (ARR). This method has excellent sensitivity but may yield false-positive results. Therefore, adoption of the minimum PAC and PRA values of 15 ng/dL and 0.5 ng/mL/h, respectively, are recommended. An ARR ≥ 100 establishes the diagnosis of hyperaldosteronism, while values < 20 to 30 indicate a low probability of the disease, and values in between detect "individuals potentially affected" by this condition.[120] In the latter case, tests assessing the renin-aldosterone axis (saline infusion test, walking, use of diuretics) may be performed.

Tomography or magnetic resonance imaging is used for imaging identification of adrenal adenomas or hyperplasia. The absence of a visible tumor on tomography does not exclude the presence of a microadenoma, hence the importance of searching for excessive aldosterone production. Functional images, obtained by adrenal scintigraphy, may be useful in detecting adenomas and may differentiate them from nodular hyperplasia in up to 90% of the cases. Adrenal vein blood sampling can be used to confirm lateralization in aldosterone secretion and the presence of unilateral adenoma.[120,121]

In terms of treatment, unilateral resection usually corrects excessive aldosterone production and potassium loss in unilateral adenomas. The BP response to surgical treatment varies. Cases of hyperplasia benefit from aldosterone receptor blockade.[121]

7.3.2. Pheochromocytoma

Pheochromocytoma is a rare neuroendocrine tumor that originates from chromaffin cells (cells producing catecholamines). The most common clinical manifestation of this condition is elevated BP, and the disease may arise from the adrenal medulla or extra-adrenal paraganglia (paragangliomas). Clinical exacerbation peaks between the third and fourth decades of life, but 10% of the cases arise in childhood.

These tumors may be sporadic or associated with genetic syndromes.[122,123] They are usually unilateral; however, in familial syndromes, they may be bilateral, multiple, or extra-adrenal, and benign or malignant (5 to 26% of the cases). This etiology should be investigated in all patients presenting with RHTN and/or symptoms or signs suggestive of hyperadrenergic spells. Paroxysmal hypertension occurs in 30% of the cases, triggered by regular physical activity, exercises with increased intensity, surgical procedures, and use of certain substances such as tricyclic antidepressants, histamine, and opioids. Paroxysms may be accompanied by headache (60 to 90%), sweating (55 to 75%), and palpitations (50 to 70%). Symptoms of heart failure and electrocardiographic abnormalities may indicate myocarditis induced by catecholamine excess.

At diagnosis, measurement of metanephrines (catecholamine metabolites) in plasma and 24-hour urine has higher sensitivity and specificity than direct catecholamine measurement. When laboratory tests are not elucidative, clonidine suppression test may be performed (administration of clonidine 0.2 mg and measurement of catecholamines 1 hour before and 2 hours after the medication).

For a topographic diagnosis of the tumors and, eventually, the metastases, the recommended imaging methods are computed tomography and magnetic resonance imaging, both of which have sensitivity close to 100% for adrenal tumors. Whole-body 131 or 123 metaiodobenzylguanidine (MIBG) has sensitivity of 56 to 85% (malignant tumors) and high specificity. Octreoscan, bone mapping, and PET scan (with different markers) can be decisive when previous localization tests are negative or in the investigation of malignant disease.

Treatment is surgical. However, in preoperative or chronic medication therapy, alpha-blockers (prazosin, doxazosin, and dibenzyline) are initially used, combined or not with other agents such as beta-blockers (after effective alpha blockade), ACEIs, and CCBs. Control of BP levels and volume replacement are recommended before the surgical intervention.[124] Sodium nitroprusside can be used in acute crises and during surgery.[124]

7.3.3. Hypothyroidism and Hyperthyroidism

Hypertension may affect 40% of the patients with thyroid disorders, while correction of the glandular dysfunction usually results in BP control.[125] If BP levels remain high after correction of the hypothyroidism or hyperthyroidism, use of antihypertensive drugs is indicated.[32,126]

Causes of SecH in patients with RHTN are summarized in Table 1.

8. Non-Pharmacological Treatment

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Authors: Gil Fernando Salles, Maria de Fátima de Azevedo, and Lucélia Batista Neves Cunha Magalhães.

8.1. Weight Loss

Several mechanisms contribute to maintain high BP in obese patients with hypertension, including OSA, sympathetic hyperactivity, endothelial dysfunction, and modification of the intestinal microbiota – all these factors can promote an inflammatory phenotype and perpetuate a vicious cycle.[130] Patients with BMI ≥ 30 kg/m^2 are 50% more likely to have uncontrolled BP than those with normal BMI (< 25 kg/m^2).[131] A BMI > 40 kg/m^2 triples the chances of the requirement of multiple drugs for BP control.[132]

A weight loss of 10 kg is associated with mean reductions of 6.0 mmHg in systolic BP and 4.0 mmHg in diastolic BP.[133] Surprisingly, there is no consistent evidence on the effect of diet-induced weight loss in patients with RHTN, but this recommendation meets the common sense and the evidence available in other subgroups. There are also no data on the effect of bariatric surgery on BP in this subgroup. A recent randomized trial showed a reduction of at least 30% in the

Table 1 – Prevalence, clinical findings, and additional tests for the most common causes of secondary hypertension in patients with resistant hypertension

Secondary cause	Overall prevalence	Prevalence in RHTN	Clinical findings	Diagnostic investigation
Obstructive sleep apnea[94,107,109]	> 5 to 15%	> 30%	Snoring, daytime sleepiness, morning headache, metabolic syndrome	Berlin questionnaire, STOP-Bang questionnaire, Epworth sleepiness scale, polysomnography (gold standard) or home polysomnography with five or more episodes of sleep apnea and/or hypopnea per hour of sleep
Renal parenchymal disease[113]	1.6 to 8%	2 to 10%	Edema, anorexia, nocturia, fatigue, anemia, increased urea and creatinine, changes in urinary sediment	Urinalysis (low density, glomerular hematuria or albuminuria), calculation of estimated GFR, renal US, screening for albuminuria and protein/creatinine ratio in random urine sample
Renal artery stenosis[115,116]	1 to 8%	2.5 to 20%	Abdominal murmur, acute pulmonary edema, impaired renal function by RAAS blockers, asymmetric kidneys	Screening: renal artery Doppler US (operator dependent) and/or renogram with or without captopril, magnetic resonance angiography, computed tomography, conventional renal arteriography (gold standard)
Primary hyperaldosteronism[119-121]	1.4 to 10%	6 to 23%	Mostly asymptomatic RH hypokalemia (not required and unusual) Incidental adrenal nodule	ARR > 30 in the absence of aldosterone antagonists. Confirmatory tests (suppression with fludrocortisone or saline infusion) Imaging tests: thin-slice helical computed tomography (preferred) or resonance magnetic imaging
Thyroid diseases[32] Hypothyroidism	1 to 2%	1 to 3%	Fatigue, weight gain, hair loss, systolic hypertension, muscle weakness.	TSH and free T4
Hyperthyroidism			Heat intolerance, weight loss, diastolic hypertension, palpitations, exophthalmos, tremors, tachycardia	
Cushing's syndrome[32]	0.5%	< 1%	Weight gain, fatigue, hirsutism, amenorrhea, "moon facies," "buffalo hump," purple striae, central obesity, hypokalemia	Salivary cortisol 24-hour urinary cortisol Morning cortisol (8 AM) and 8 hours after administration of dexamethasone (1 mg) at 12 AM. Magnetic resonance
Pheochromocytoma[127,128]	0.2 to 0.5%	< 1%	Episodic, labile or resistant hypertension, episodic headache, profuse sweating and palpitations, pallor	Free plasma and/or 24-hour urinary metanephrines (values twice or thrice above the normal), 24-hour plasma and/or urinary catecholamines and/or computed tomography and magnetic resonance
Coarctation of aorta[129]	< 1%	< 1%	SBP/DBP difference > 20/10 mmHg between upper and lower limbs; ejection murmur in the interscapular region	Lower rib notching on chest X-ray, screening with Doppler echocardiography, magnetic resonance imaging or thoracic aorta angiography

Adapted from Rimoldi SF et al.[105] PA/PRA: plasma aldosterone/plasma renin activity; RHTN: resistant hypertension; DBP: diastolic blood pressure; SBP: systolic blood pressure; GFR: glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system; US: ultrasonography.

number of antihypertensive drugs in 84% of operated patients, compared with 12.4% in the clinically treated group.[134]

8.2. Salt Restriction

Control of salt intake is especially effective in the elderly, in individuals of African descent, and in those with decreased glomerular filtration.[135] These situations restrict the ability of water and sodium excretion by the kidneys, and BP becomes more dependent on volume variations. Not surprisingly, sodium sensitivity and volume overload account for the primary pathophysiological mechanism in most cases of RHTN.[136] A systematic review and meta-analysis involving 34 studies with 3,230 participants on the effect of long-term reduction in sodium intake revealed a decrease in systolic BP of 5.8 mmHg (2.5 to 9.2; p = 0.001) associated with a decrease in urinary sodium excretion of up to 100 mmol in 24 h, which corresponds to a reduction in salt intake of approximately 6 g/day.[137] In patients with RHTN, a low-sodium diet with 2.5 g of salt daily reduced BP by up to 23.0/9.0 mmHg, clearly demonstrating the efficacy of this measure, despite the possibility of compromising the long-term adherence to such markedly restricted salt consumption.[79]

8.3. Alcohol Intake

Due to the direct relationship between the amount of alcohol consumed and BP levels, excessive alcohol consumption

contributes significantly to hinder BP control.[138] After all, daily consumption of more than two drinks (about 24 g/day) is associated with increased BP levels.[139] A recent meta-analysis of 36 studies with 2865 participants revealed that a 50% reduction in daily alcohol intake among consumers of six or more drinks (72 g) led to a decrease of 5.50 mmHg in systolic BP (95% CI; 6.70 to 4.30) and 3.97 mmHg in diastolic BP (95% CI; 4.70 to 3.25).[140] No studies have been published on patients with RHTN; however, based on available information, daily alcohol consumption is recommended to be restricted to less than two standard drinks (about 24 g) or even interrupted.

8.4. Physical Activity

Despite having been evaluated only in small groups of patients with RHTN, physical activity is probably as much – or even more – beneficial in these individuals compared with those with non-resistant hypertension.[40,141] Regular aerobic exercise decreases office and ambulatory BP in patients with RHTN[142-145] and attenuates the characteristic neurohumoral activation.[146] Despite the lack of studies on resistance exercise in this subgroup, it is assumed that there is at least an advantage similar to that observed in patients with non-resistant hypertension.[147] Furthermore, the improved cardiorespiratory capacity obtained with physical activity appears to reduce mortality in patients with RHTN.[148] Therefore, this category of patients should be encouraged to perform regular physical activity of moderate intensity under proper supervision. In patients with very high BP (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg), physical activity should be delayed until the optimization of pharmacological treatment promotes BP reduction.[40,141]

9. Pharmacological Treatment of Resistant Hypertension

Coordinator: Rui Manoel dos Santos Póvoa.

Authors: Marcus Vinícius Bolívar Malachias, Armando da Rocha Nogueira, and Paulo César Brandão Veiga Jardim.

The objective of pharmacological treatment in RHTN is to identify the causes of lack of control and find the best combination of drugs, aiming at achieving the target BP with few adverse effects and greater adherence.

In general, triple treatment optimization is attempted with preferred drugs, namely, ACEIs or ARBs, dihydropyridine CCBs, and TZDs.[33,149]

Because they are better tolerated, ACEIs or ARBs must be increased to maximum doses in RHTN. Long-acting, higher potency TZDs, such as chlorthalidone instead of hydrochlorothiazide, should be used at appropriate doses for volume control, from 12.5 to 50 mg in a single dose in the morning.[1,33,40,150] Indapamide is a second TZD option in RHTN.[150] Furosemide should be used in cases of CKD with a eGFR of 30 mL/min or less.[1,33] In RHTN, CCB should preferably be taken at night to alternate the peaks of action of the antihypertensive drugs.[40]

Intolerance to CCBs due to side effects is often one of the causes of treatment resistance. In such cases, lipophilic CCBs (manidipine, lercanidipine, manidipine) or levamlodipine, at low doses, may be attempted or, in selected cases, a non-dihydropyridine CCB such as diltiazem and verapamil.[33] If a CCB cannot be used, introduction of a beta-blocker may be considered, preferably one with vasodilatory action, such as nebivolol or carvedilol.[33,151] Beta-blockers may also be considered in association with one or more preferred antihypertensive drugs – ACEI or ARB, TZD, CCB – in special conditions such as heart failure, CAD, and increased basal heart rate, among others.[33,150,151]

Failure to reach the target BP with triple therapy requires the use of a fourth drug, which current preferred option is spironolactone, 25 to 50 mg daily.[13,152-154] In cases of intolerance to spironolactone, which main adverse effect is gynecomastia in men, 12.5 mg daily may be attempted. As eplerenone is not available in our country, if intolerance to spironolactone persists even at low doses, replacement with a central sympatholytic agent should be considered, preferably clonidine, between 0.100 and 0.200 mg twice daily,[152] or a potassium-sparing diuretic, preferably amiloride (only available sparingly in our country in compounded formulations), from 10 to 20 mg;[155] or a beta-blocker, preferably with vasodilatory action, if not yet used;[40] or an alpha-blocker, preferably doxazosin 1 to 16 mg in one (nighttime) or two daily doses.[33,40,155]

All these antihypertensive agents may be used in combination when necessary for BP control.[33] When no control is obtained with the addition of the fourth drug or combinations of the following options, a direct vasodilator must be used, preferably hydralazine, at doses between 50 and 150 mg administered twice or thrice daily.[40] Due to frequent adverse effects, the vasodilator minoxidil should be reserved for situations of extreme resistance when all previous alternatives fail[40,150] (Figure 4).

In RHTN treatment, attention must be given to possible adverse effects of each drug used, along with their possible interactions.

10. New Treatments of Resistant Hypertension

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10.1. Introduction

In recent years, new types of interventional treatment have been evaluated in patients with RHTN, including:

10.2. Direct Carotid Sinus Stimulation

Stimulation of carotid baroreceptors increases their activity and, consequently, reduces sympathetic flow, resulting in decreased BP.[156] Interventions promoting this stimulation have been used to treat patients with RHTN lacking response to clinical treatment.[156-159] Baroreflex activation therapy (BAT) is a surgical procedure in which electrodes are surgically implanted on the external portion of the carotid sinus unilaterally or

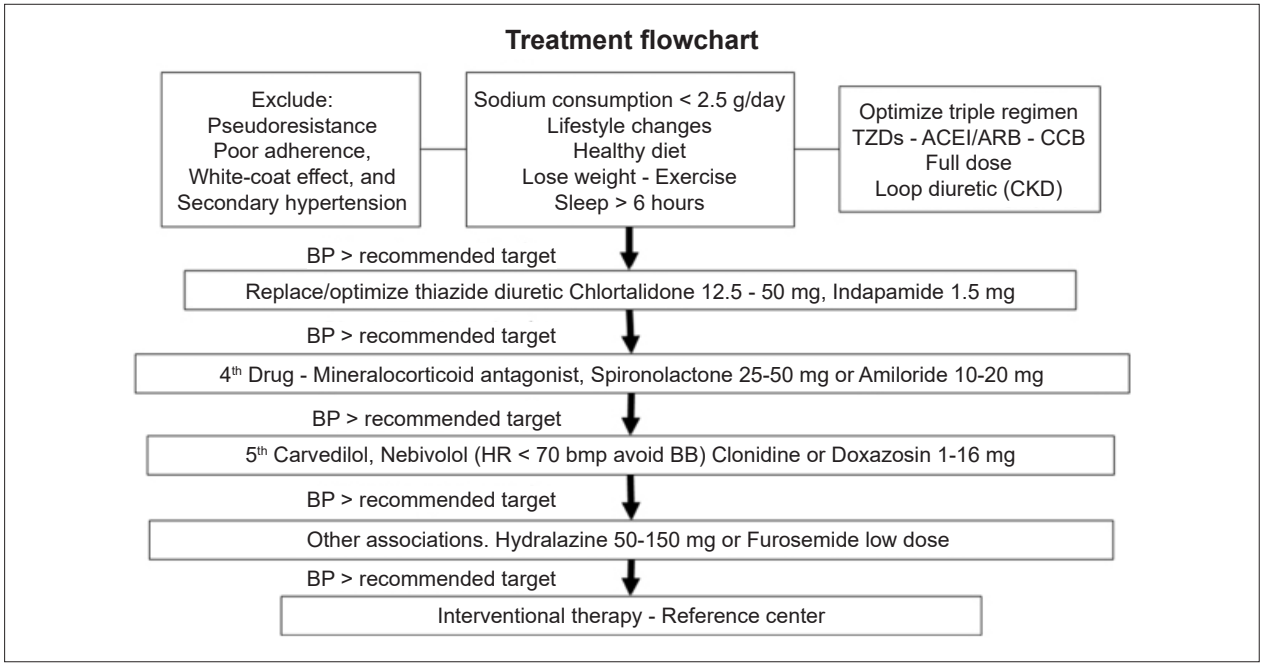

Figure 4 – *Flowchart of RH treatment. CCB: calcium channel blocker; ARB: angiotensin receptor blocker; HR: heart rate; ACEI: angiotensin-converting enzyme inhibitor; CKD: chronic kidney disease; BP: blood pressure.*

bilaterally.[157,159] BAT has shown significant reductions in BP persisting for up to 3 years in randomized controlled trials.[157,159] However, this procedure is invasive and expensive and is associated with side effects, limiting its indication in clinical practice.[156,159] Another form of stimulation is the amplification of the endovascular baroreflex (implantation of an expandable device within the carotid artery), which has shown promising results with greater safety in controlling BP in RHTN.[156] These procedures are not available in Brazil.

10.3. Renal Sympathetic Denervation

Renal sympathetic denervation (RSD) by ablation catheter reduces renal efferent activity and, consequently, increases renal blood flow and decreases activation of the renin-angiotensin-aldosterone system, water retention, and renal afferent activity, which through brain signaling, decreases sympathetic action on heart and vessels.[160]

Data from uncontrolled studies have shown reductions of up to 30 mmHg in office systolic BP in patients with RHTN, without complications related to the procedure.[161] However, the SYMPLICITY HTN-3 trial,[162] a randomized sham-controlled study, showed no significantly superior effect of BP reduction after 6 months from RSD. A meta-analysis of 11 controlled studies comparing RSD with optimized pharmacological treatment or sham procedure in patients with RHTN showed that RSD was not superior in reducing BP, with heterogeneity of responses in the studies, mainly due to lack of a sham control in most publications and heterogeneity in assessment of treatment adherence.[163]

The development of new circumferential catheters with distal renal artery applications may promote a more complete RSD, and their effects on BP reduction have been demonstrated in patients with untreated hypertension.[164]

The 2018 European Society of Hypertension position paper does not recommend RSD for treatment of hypertension in general but includes a recommendation of this procedure in the context of controlled clinical studies with sham procedures and optimized therapy for safety and efficacy assessment in populations with a large number of individuals.[160]

Based on this evidence, RSD is currently an alternative only for patients with UC-RHTN with optimized pharmacological treatment and proven therapeutic adherence or with important drug-related adverse effects, to be always performed at referral centers trained for the procedure.[164]

10.4. Use of Continuous Positive Airway Pressure

OSA is a clinical condition affecting more than half of the patients with RHTN[94] and is mainly treated with CPAP, an air compressor that applies continuous positive pressure to the patient's airway. To date, seven randomized trials have analyzed the effect of treatment of OSA with CPAP in patients with RHTN.[165-171] Except for one of these studies,[170] the others found significant reductions in BP (5 mmHg on average; one study showed reductions ≥ 10 mmHg after CPAP use).[169]

However, the proportion of patients who achieved the target BP (< 140/90 mmHg) with CPAP was low, possibly due to poor CPAP adherence. In clinical practice, the BP response to CPAP varies, even in patients with good adherence. A recent study showed predictive biomarkers of better BP response to CPAP in patients with RHTN.[172] Validation and large-scale application of these biomarkers could help select better those patients who benefit most from BP reduction.

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10.5. Arteriovenous Fistula

The creation of an arteriovenous fistula (AVF) can decrease BP by reducing total peripheral resistance and blood volume and inducing baroreflex inhibition and release of natriuretic peptides.[173] In a prospective randomized controlled trial, the creation of a central iliac AVF by an implantable device in 44 patients with RHTN led to significant reductions in 24-hour office and ambulatory systolic BP compared with pharmacological treatment.[174] However, there was a high rate of complications due to ipsilateral venous stenosis, requiring intervention in the AVF group.

Further studies with a greater number of patients and with a comparison of AVF versus sham procedure are being conducted to verify the benefits of AVF in RHTN.[173]

Erratum

In the Statement "Posicionamento Brasileiro sobre Hipertensão Arterial Resistente – 2020" with DOI number: https://doi.org/10.36660/abc.20200198, published in the periodical Arquivos Brasileiros de Cardiologia, 114(3): 576-596, on page 582: in the figure 1 of the Portuguese version, where "hipertensão segundária" is mentioned, the correct is "Hipertensão arterial pseudorresistente". In the English version, where "abnormal" is mentioned, right side of the figure 1, the correct is "normal".

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