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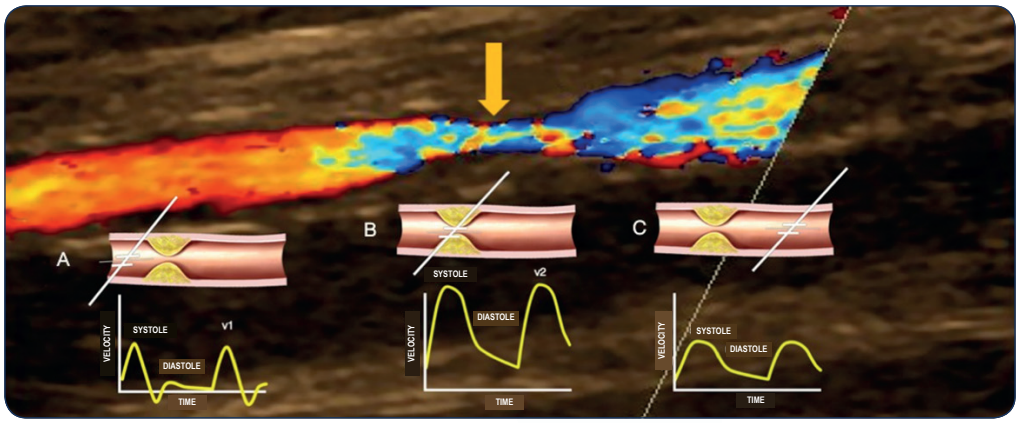

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Editorial

Ganglionated Plexi Ablation to Treat Patients with Refractory Neurally Mediated Syncope and Severe Vagal-Induced Bradycardia

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Neurally mediated syndrome (NMS) is the most common cause of and transient loss of consciousness and usually causes anxiety and concerns for patients and their families. Clinical investigation and explanations about benignity, in association to lifestyle modifications and teaching methods to abort the vagal reflex are the initial and effective approaches to manage the majority of patients.[1-3]

However, in some cases, the loss of consciousness occurs suddenly, without prodromal symptoms and the patient does not have the opportunity to prevent falls, which may lead to severe physical trauma. Specific medications have been proposed trying to control the symptoms and pacemaker implantation has been recommended in the refractory cases of cardioinhibitory reflexes.[1-3]

In 2005, Pachón et al.[4] proposed using a catheter ablation technique to attenuate vagal activity on the sinus and AV nodes, through radiofrequency (RF) ablation of the sites related to vagal inputs to the atria. This procedure aimed to promote better quality of live for patients with refractory NMS and severe bradycardia, avoiding pacemaker implantation, especially in young individuals.[4] Since that time, many reports have confirmed that atrial vagal modulation by catheter ablation is feasible in clinical settings, for patients with vagal induced marked and symptomatic bradycardia.[5-20]

However, those studies came from relatively few centers, such as case reports,[5-13] or from non-randomized series involving a limited number of patients.[14-20] Additionally, until now, there is no consensus about the criteria for patient selection, about how to perform an autonomic evaluation prior and post ablation, the best technique to be applied, the endpoints to conclude the procedure and what to expect during the outcome. These are the main reasons why vagal attenuation by catheter ablation has not been considered a possible treatment in the international guidelines of NMS management.[1-3]

Almost 50 years ago, experimental studies demonstrated that the sinus and atrioventricular nodes receive specific autonomic innervation, which can be surgically destroyed.[21] However, current techniques to promote vagal denervation have been based on a more recent descriptions of atria innervation.[22,23] It has been demonstrated that cardiac parasympathetic neurons get together with postganglionic sympathetic fibers and fat tissue (fat pads), in specific areas of the epicardium, adjacent to the posterior walls of left and right atria. Such ganglionated plexi (GP), working together, coordinate a sophisticated network that regulates cardiac functions, and more precisely the cardiac rhythm.[24]

The Oklahoma group has worked intensively to understand GP functional activities and has observed, in experimental studies, that despite the intense interconnections among GP, the sinus node is mainly innervated by the plexi, anatomically situated in the superior portion of the posterior interatrial septum, between the superior vena cava and anterior to the right superior PV. The AV node is manly innervated by the right inferior plexi, located behind the coronary sinus ostium and between the inferior vena cava and right inferior PV. The sinus node and AV node still receive fiber connections from the left superior and left inferior GP located nearby the left pulmonary veins. However, these interconnections necessary cross the right superior and right inferior PV GP to reach the sinus and AV nodes.[24] Additionally, extra GPs connections might influence the sinus and AV node innervation.[22-24] It has also been suggested that the intrinsic autonomic nervous system of the heart receives inputs from mechanical and chemosensory receptors located in both ventricles.[25] Those autonomic nervous interconnections could have an important role in the pathophysiology of NMS and might explain some behaviors observed in patients submitted to GPs ablation, who showed additional improvement in the peripheral vasovagal reflex.

Sinus node vagal denervation was a fortuitous observation detected by the occurrence of an augmented vagal response triggered during catheter ablation of atrial fibrillation and also, the subsequent increase in heart rate observed soon after the procedure. Those findings were more evident when extensive ablation of the PV antrum, where GPs are frequently located, was performed.[26,27] Autonomic tests performed after PV isolation confirmed an effect of the vagal denervation of the sinus node in many patients; however, a controversy still persists regarding the effect of persistent atrial vagal denervation on the long term outcome.[28,29] Those serendipity findings opened a new possibility for the treatment of the negative effects of excessive vagal activity in some patients.

Different techniques have been used for sinus and AV node vagal denervation: one is based on the hypothesis that autonomic innervation can be recognized by the characteristics of the endocardial fractionated electrograms (AF Nests), and detected by Fast-Fourier transform analysis.[4] The original report from Pachón et al.[5] in 2005, described twenty-one patients with a mean age of 48 years, six with neurally mediated reflex syncope, and 15 with sinus node dysfunction or functional high-degree atrioventricular block, who underwent vagal denervation. In a mean follow-up

Keywords

Ganglia, Autonomic; Catheter Ablation; Syncope,Vasovagal; Bradycardia; Autonomic Nervous System.

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of 9.2 months, no patient showed syncope recurrence, or complications. In 2011, the authors reported the late outcome of 43 patients with recurrent NMS, submitted to ablation. Forty patients remained asymptomatic during a mean follow-up of 45.1 ± 22 months and no significant complications were observed.[5]

More recently, Yan et al.[14] performed vagal denervation in ten consecutive patients with a mean age of 50.4 ± 6.4 years and recurrent episodes of NMS, in which traditional therapies were not effective. The authors used the high-frequency stimulation (HFS) technique, described by the Oklahoma group, in order to locate GP based on induced vagal response.[30] The endpoint of the procedure was the inhibition of the vagal response at the target sites. During a mean follow-up of 30 ± 16 months, no patient had syncope episodes, but 5 patients reported transient symptoms. There were no complications.[14]

Sun et al.[15] reported the long-term outcome of 57 consecutive patients (aged 43.2 ± 13.4 years; 35 women) with refractory vasovagal syncope, who underwent left atrium GP ablation. The GP were located based on the combination of anatomic features obtained by the electroanatomic mapping and positive response (vagal hyperactivity) during HFS, on expected GP locations. During a mean follow-up of 36 ± 22 m, 52 (91.2%) patients had no syncope. However, 16 patients showed prodromal symptoms. Autonomic evaluation revealed reduced vagal activity, persistent for at least 12 months after the procedure. The only side effect was sinus tachycardia observed in one patient.[15] Zhao et al.[16] performed catheter ablation in 11 patients (8 men, with mean age of 45 ± 10 years) with a long history of symptomatic bradycardia. All anatomic locations of the GP were confirmed by HF stimulation before ablation. The procedure endpoint was the elimination of vagal response at the ablation sites. During a mean follow-up of 18 ± 6 months, all patients reported significant symptom improvement. There was a significantly increase in the mean sinus heart rate, which persisted for 12 months.[16] The main limitations of these studies are the absence of control groups and randomization. The already known placebo effect of interventions in patients with NMS does not allow considering their good results as definitive to regularly apply the GP ablation in clinical practice.

Despite such limitations many other authors have reported selected cases in which patients had advanced atrioventricular block induced by excessive vagal activity and had indication for pacemaker impantation.[6-13] Although the GP mapping and ablation technique were not identical, no patient had complications and pacemaker implantation was avoided. Some authors delivered RF pulses guided by a positive vagal action induced by HFS. Others delivered RF pulses based on the characteristics of the electrograms, or at the anatomic sites where the presence of GP clusters was highly probable, based on previous anatomical reports. [17-20]

We investigated the effectiveness of vagal ablation in 14 patients (7 men, mean age of 34 ± 13 years) with symptomatic cardioinhibitory syncope, severe sinus bradycardia or advanced AV block, no structural heart disease, and pacemaker indication. The GP were identified and ablated based on the anatomy obtained by the electroanatomical mapping analysis. During a mean follow-up period of 22 ± 11 months, 10 patients (71.4%) showed significant clinical and ECG improvement: no syncope recurrence or symptomatic bradycardia were observed at daytime Holter monitoring during the follow-up. However, transient second-degree atrioventricular block was still detected, exclusively at night. The remaining four patients (28.6%), despite showing acute vagal activity attenuation, had syncope recurrence or symptomatic bradycardia and underwent pacemaker implantation. No significant complications were observed during or after the procedure.[18]

Therefore, until now, no consensus has been achieved about the ideal electrophysiological technique to perform vagal activity attenuation: if through extensive ablation areas based on fragmented electrograms, or by anatomical landmarks; if ablating all right and left atrial GP areas, or those that directly innerve the sinus and AV nodes, in both sides of the septum; or only the right side of the septum, or even spots in the superior vena cava.[9,10,20] Another important controversial point is how to establish the procedure endpoint, whether reaching an expected heart rate elevation such as 20% of basal cardiac frequency, shortening the P-P interval > 120 ms; eliminating prior vagal response induced by HFS on the target GP or absence of an additional heart rate elevation after GP ablation with the atropine test. Recently, an extracardiac vagal stimulation with high frequency pulses, performed directly on the right or left cervical vagal trunk through retrograde jugular vein catheterization was suggested to evaluate vagal response before, during and at the end of the procedure. This method has been proposed to obtain an objective, faster and reproducible evaluation of the ablation effect during the procedure.[31]

Finally, it is important to define a reproducible autonomic evaluation in patients considered for vagal denervation. The most frequent analysis prior to the procedure has been the analysis of time-domain and frequency-domain heart rate variability (HRV), during 24h Holter monitoring. Small segments of the ECG are also evaluated during the tilt table test, in the last 5 minutes of supine position and the first 5 minutes of orthostatic exposure. It is also important to identify patients with the vasodepressor component, in which prodromal symptoms will probably persist, even after effective sinus and/or AV node denervation. The atropine test (0.04 mg/Kg), complemented with exercise stress test, have been performed to evaluate the vagal reserve and to rule out a possible sinus node dysfunction. Such autonomic evaluation should be repeated during the follow-up aiming to identify the long-term outcome of the autonomic modulation.

In summary, the experimental and clinical background suggest that RF ablation of GP may promote significant vagal withdrawal in the sinus and AV nodes, in patients with very symptomatic neurally mediated bradycardia syndromes. However, its effectiveness, safety and reproducibility need a more thorough evaluation. Different techniques have been proposed to successfully identify and ablate the sites of vagal inputs to the atria. Therefore, a randomized multicenter study is fundamental not just to establish the effectiveness of vagal denervation and the long-term clinical impact on symptoms and safety to the patient but also to identify the best techniques to obtain vagal response attenuation, with smaller areas of ablation.

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Brazilian Society of Cardiology – The Women's Letter

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Objective

The primary objective of this document is to stimulate improvements in women's health conditions in Brazil, with a focus on cardiovascular disease (CVD), which is responsible for 17.5 million premature deaths yearly worldwide. This number is predicted to increase to 23 million by 2030. CVD are responsible for one third of all deaths in Brazil, with similarities between men and postmenopausal women. These data assume even greater importance when we consider that 80% of premature deaths could have been avoided by controlling four risk factors: tobacco use, inappropriate diet, physical inactivity, and harmful alcohol use.[1]

Keywords

Women; Medicine/ trends; Demography; Cardiovascular Diseases/prevention and control; Societies, Medical; Management Quality Circles; Risk Factors; Prevalence; Education, Medical.

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This document further aims to create a permanent discussion group that will play a leadership role in Brazilian healthcare policies, providing administrators with an overall view of the relevance of CVD to women so that they may establish strategic actions to reduce the prevalence of risk factors and improve diagnosis and therapeutic approach, thus reducing mortality and morbidity.

Foreword

Considering that the burden of chronic noncommunicable diseases (CNCD), of which CVD are the main component, will continue to grow significantly in Brazil and worldwide; in line with the global target of a 25% reduction in premature mortality from noncommunicable diseases by 2025 as established by the World Health Assembly (WHA);[2] and in accordance with the United Nations High-level Meeting on the Prevention and Control of Noncommunicable Diseases, we endorse the measures proposed by this Assembly which reunited the cardiology societies of the Rio de Janeiro Letter,[3] also highlighting the importance of goals to be met for women, who currently represent 48% of the 7.7 billion inhabitants of the world and 47% of the 202,768,562 individuals who compose the population of Brazil, as of April 2019.[4]

In recognition of the fact that, predominantly among younger doctors, the proportion of women doctors has increased over the past years, going from 22% in 1910 to 45.6% in 2018, and considering the fact that this increase

has been less accelerated among women cardiologists, where women currently represent approximately 30% of the total,[5] we highlight the importance of promoting activities whose aim is to multiply healthcare opportunities from women's point of view, allowing for the integration and exchange of experience which will amplify improvements in daily clinical practice.

Emphasizing that the presence of women in science today corresponds to 28% of researchers worldwide, according to UNESCO, and 49% in Brazil,[6] with less than one quarter of speakers at scientific events being women, in addition to the low representation of women in clinical trials which determine therapies to be used, we propose that forums be held, wherein it will be possible to discuss cost-effective, short- and long-term measures to decrease these inequalities, as well as affirmative policies which may accelerate women's representation in science and clinical research.

In conclusion, knowing the relevance of the role which medical societies and their associates play as critical agents for paradigm change and the establishment of multiple partnerships, we call on these entities to be protagonists in the elaboration of documents which will act as tools to accelerate these results.

Deliberations

1. To work collectively to defend global goals for the prevention and control of CNCD, especially CVD, in Brazilian women.
2. To establish cardiovascular prevention campaigns, promoting efforts consistent with the global goal of 25% reduction in mortality rates by 2025.
3. To perform critical analyses of health statistics and to implement registers capable of evaluating and measuring cardiovascular health issues, so that there may be improvements in strategic health actions.
4. To elaborate and suggest government policies to promote appropriate environments for reducing exposure to risks, facilitating the population's adoption of healthy habits in school, work, and leisure environments, with the aim of combating CVD in women.
5. To work and act together with governments for the development and application of cardiovascular prevention programs, in addition to incorporating cost-effective technologies to reduce CVD morbidity and mortality.
6. To involve patients with CVD and diverse segments of civil society in formulating, implementing, and reviewing policies, legislation, and discussion on strategies which may lead to improvements in women's healthcare.
7. To develop collaborative projects through scientific societies which may aggregate different forms of knowledge in order to reduce genders inequalities.
8. To provide the highest level of continuing medical education, to promote technical, scientific, cultural, and social exchanges between cardiologists in Brazil and worldwide, and to cultivate the scientific knowledge necessary to increase women's participation in science, scientific events, and health and related sciences.
9. To mobilize means of communication in order to bring continual information on the importance of CVD in women, as well as its primary risk factors and forms of prevention, thus amplifying the transmission of the importance of early diagnosis to the general population.
10. To create an international permanent discussion forum in order to monitor actions with the aim of preventing, diagnosing, and treating cardiovascular risk factors.
11. To stimulate actively the greater participation of women cardiologists in Executive Boards of Representative Bodies, so that they may have the same rights and remuneration in the diverse aspects of their medical careers.

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Clinical Significance of Platelet Volume and Other Platelet Parameters in Acute Myocardial Infarction and Stable Coronary Artery Disease

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Abstract

Background: Platelets are important in the initiation of thrombosis, and their morphological and functional changes are closely related with the occurrence and development of coronary artery thrombosis. Platelet parameters might be valuable in distinguishing between acute myocardial infarction (AMI) and stable coronary artery disease (SCAD).

Objective: This study was designed to detect and compare changes in platelet parameters, such as mean platelet volume (MPV) in patients with acute myocardial infarction (AMI) and stable coronary artery disease (SCAD) and to investigate their roles in these diseases.

Methods: Specimen collection: Between January 2011 and December 2013, 2 mL of elbow vein blood was drawn from each of 31 patients primarily diagnosed with AMI, 34 SCAD patients and 50 healthy subjects; and placed in EDTA-K2 anticoagulant tubes. Platelet count (PLT), MPV, plateletcrit (PCT), platelet distribution width (PDW), white blood cell (WBC) and neutrophil (NEU) counts were determined using an STKS automated hematology analyzer (Beckman Courter).

Results: Compared with the control group, MPV levels were significantly higher in the AMI and SCAD groups ($p < 0.05$), while PLT was significantly lower ($p < 0.05$).

Conclusion: These results suggest that MPV and other related parameters have a certain value in the diagnosis of SCAD and AMI. (Arq Bras Cardiol. 2019; 112(6):715-719)

Keywords: Acute Coronary Syndrome/physiopathology; Coronary Thrombosis; Mean Platelet Volume; Myocardial Infarction.

Introduction

Acute coronary syndromes (ACS) are a group of clinical syndromes, of which pathological bases are coronary atherosclerosis plaques rupture or erosion,[1] followed by complete or incomplete occlusive thrombosis. ACS include acute myocardial infarction (AMI) and unstable angina pectoris. Among these, AMI refers to acute focal myocardial necrosis caused by prolonged and severe myocardial ischemia.[2]

In 2013, the European Society of Cardiology issued the management guidelines for stable coronary artery disease (SCAD).[3] These guidelines clearly pointed out that SCAD also include situations of no symptoms or stable symptoms after the stabilization of acute coronary syndrome, besides stable angina pectoris. These situations cannot be clearly distinguished from ACS. Previous studies have revealed that platelet is an important medium in the initiation of thrombosis, and its morphological and functional changes are closely correlated with the occurrence and development of coronary artery thrombosis.[4,5]

Additionally, mean platelet volume (MPV), one of the platelet parameters in AMI, is significantly higher than in normal subjects, hence MPV is considered as a predictor for AMI.[6] However, the value of platelet parameters in distinguishing between AMI and SCAD has not been reported in China. It has been reported that the supersensitive troponin level was elevated in patients with SCAD.[7] Although it did not reach the threshold for the diagnosis of myocardial infarction, the prognosis was poorer, when compared with SCAD patients without an elevated troponin level. In our study, differences in platelet parameters such as MPV in AMI patients, SCAD patients and healthy subjects were analyzed, and the significance of these parameters for predicting the disease was investigated.

Methods

General Information

A total of 31 patients primarily diagnosed with AMI were enrolled in this study. All patients had been diagnosed for the first time, did not undergo anticoagulation or stent percutaneous coronary intervention, and met the international and Chinese guidelines for the diagnosis of AMI. Of these patients, 23 patients were males and eight patients were females; and the mean age of these patients was 64.4 ± 11.6 years. Thirty-four patients were diagnosed with SCAD. These patients were required to meet the following criteria: (1) patients diagnosed with AMI for more than two months; (2) patients without pectoralgia; (3) patients who were receiving anticoagulation drug treatment. Of these patients, 28 patients were males and six patients were females; the mean age of these patients was 60.6 ± 13.1 years. The control group comprised 50 healthy subjects who underwent physical examinations at the Outpatient Department.

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Among these subjects, 38 were males and 12 were females, and their mean age was 60.9 ± 6.9 years.

None of the abovementioned patients had severe liver or kidney disease, malignant tumors, idiopathic thrombocytopenia, or thrombocytopenia caused by other primary diseases.

Sample collection

In the early morning, 2 mL of elbow vein blood was withdrawn from each of these subjects under a fasting state, without receiving any hemostasis, coagulation and anticoagulation drugs. The collected blood was placed in EDTA-K2 anticoagulant tubes.

Detection method

Platelet count (PLT), plateletcrit (PCT), MPV, platelet distribution width (PDW), white blood cell (WBC) and neutrophil (NEU) counts were determined using an STKS automated hematology analyzer (Beckman Courter).

Statistical analysis

Statistical analysis was performed using the GraphPad Prism 5 software. Measurement data were presented as mean± standard deviation (x ± SD). Comparison of the means in multiple samples was performed using unpaired t-test. $p < 0.05$ was considered statistically significant. The prediction value of platelet parameters and the total leukocyte count for AMI and SCAD were evaluated using the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). Correlations between parameters were analyzed using Pearson's correlation statistical method.

Results

Results of the four platelet parameters and the total WBC count in AMI patients, SCAD patients and normal healthy subjects (Table 1).

As shown in Table 1, compared with the control group, the MPV levels were significantly higher ($p < 0.01$), while the PLT and the PDW were significantly lower ($p < 0.05$) in the AMI and SCAD groups. Moreover, compared to the control group, the WBC and NEU levels were also significantly higher ($p < 0.01$) in the AMI group, but there was no significant difference in the SCAD group. However, the PCT levels had no significant difference between the patient groups and the control group.

Evaluation of the diagnostic efficacy of each index by the diagnostic test

As shown in Figure 1, in the AMI group, the AUC of PLT (95% CI) was 0.6474 (0.5206-0.7742) and the p-value compared with controls was < 0.05, which shows that the differences were statistically significant. The AUC of MPV (95%CI) was 0.9032 (0.8232-0.9832) and the p-value compared with controls was < 0.01, which revealed that the differences were statistically significant. Furthermore, the AUC of PDW (95% CI) was 0.6529 (0.5239-0.7819) and the p-value compared with controls was < 0.05; the AUC of PCT (95% CI) was 0.5687 (0.4364-0.701) and the p-value compared with controls was < 0.05, and the AUC of WBC (95% CI) was 0.9190 (0.8475-0.9906) and the p-value compared with controls was < 0.01. Finally, the AUC of NEU (95% CI) was 0.9310 (0.8678-0.9942) and the p-value compared with controls was < 0.01. These differences were all statistically significant. These results imply that the diagnostic value of PLT, MPV, WBC and NEU was significantly higher in the AMI group.

As shown in Figure 2, in the SCAD group, the AUC of PLT (95% CI) was 0.6176 (0.4907-0.7445) and the p-value compared with controls was > 0.05. The AUC of PDW (95% CI) was 0.6818 (0.5554-0.8081) and the p-value compared with controls was < 0.01, with the differences being statistically significant. The AUC of PDW (95% CI) was 0.5609 (0.4268-0.6949) and the p-value compared with controls was >0.05, whereas the AUC of PCT (95% CI) was 0.5332(0.3994-0.6671) and the p-value compared with controls was > 0.05, and the AUC of WBC (95% CI) was 0.5635 (0.4368-0.6903) and the p-value compared with controls was > 0.05. Finally, the AUC of NEU (95% CI) was 0.5447 (0.4138-0.6756) and the p-value compared with controls was > 0.05. These results imply that the diagnostic value of MPV was significantly higher in the SCAD group.

Correlation analysis of MPV with PLT, PCT and PDW in patients with myocardial infarction

Pearson's correlation coefficient between MPV and PLT was 0.3817; Pearson's correlation coefficient between MPV and PCT was 0.1103. Pearson's correlation coefficient between MPV and PDW was 0.0726. It indicates that the MPV and PLT in patients with myocardial infarction have a strong correlation.

Table 1 – Platelet parameters and total number of white blood cells and neutrophils in the AMI, SCAD and the control groups

Parameters	AMI (n = 31)	SCAD (n = 34)	control group (n = 50)
PLT (x 10^9)	185.84 ± 61.26	193.62 ± 47.1	206.28 ± 36.17
MPV (fL)	10.42 ± 1.26	9.16 ± 1.28	8.42 ± 0.72
PCT (%)	0.1777 ± 0.0464	0.1709 ± 0.0393	0.1693 ± 0.0287
PDW (%)	16.2 ± 0.65	16.0 ± 1.37	16.5 ± 0.32
WBC (x 10^9/L)	10.60 ± 2.53	6.61 ± 1.54	6.37 ± 1.25
NEU (x 10^9/L)	8.34 ± 2.66	3.99 ± 1.25	3.79 ± 0.93

Compared with the control group, the MPV levels were significantly higher ($p < 0.01$), while the PLT and the PDW were significantly lower ($p < 0.05$) in the AMI and SCAD groups. Besides, compared to the control group, the WBC and NEU levels were also significantly higher ($p < 0.01$) in the AMI group, but there was no significant difference in the SCAD group. However, the PCT levels showed no significant difference between the patient groups and the control group.

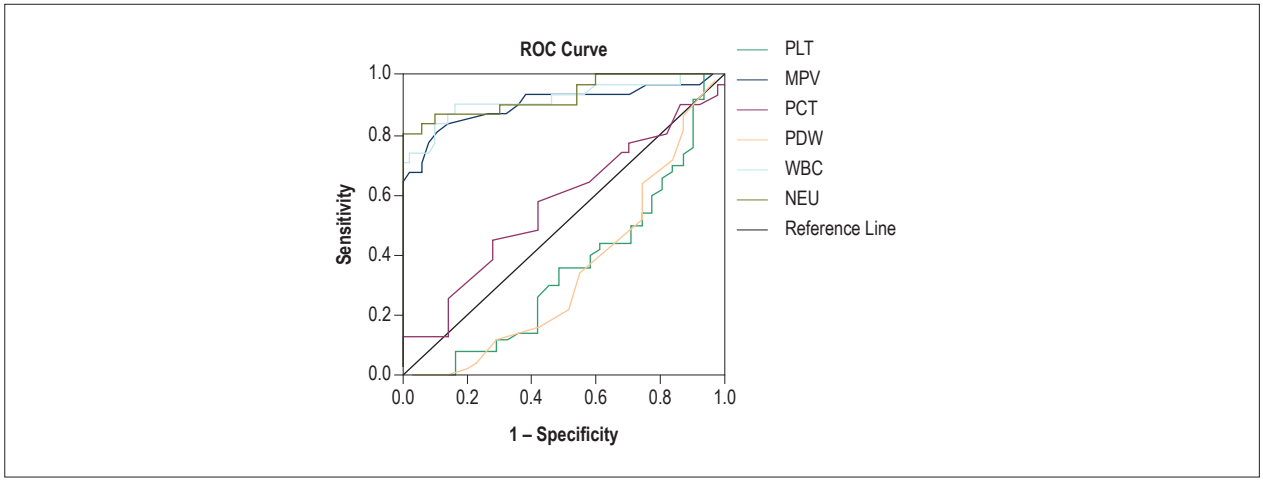

Figure 1 – *ROC curves of PLT, PDW, MPV, PCT, WBC and NEU for predicting AMI. PLT: platelet count; MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width; WBC: white blood cell; NEU: neutrophils; AMI: acute myocardial infarction.*

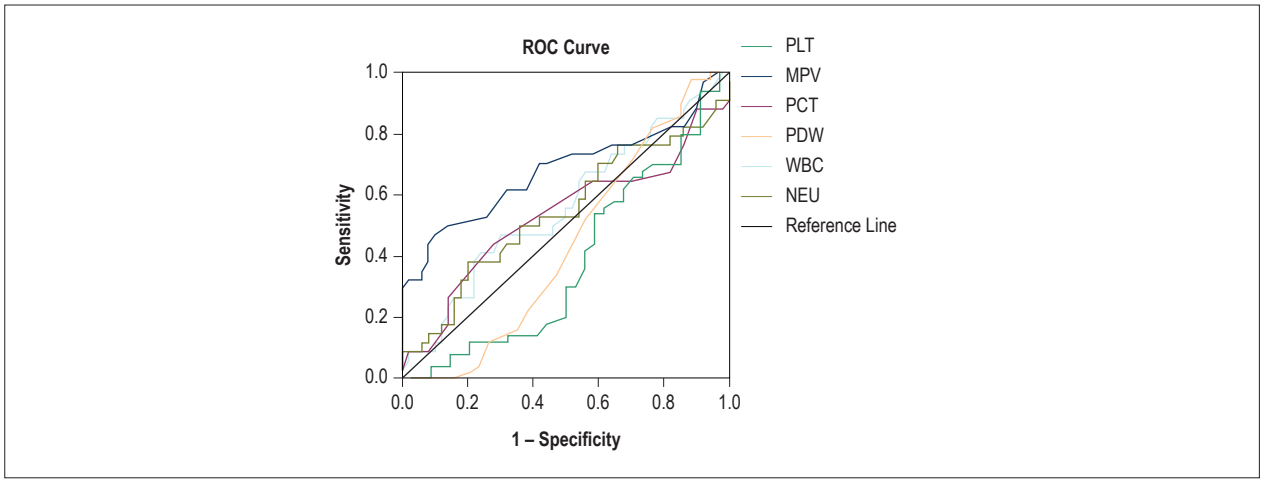

Figure 2 – *ROC curves of PLT, PDW, MPV, PCT, WBC and NEU for predicting SCAD. ROC, receiver operating characteristics; PLT: platelet count; MPV: mean platelet volume; PCT: plateletcrit; PDW: platelet distribution width; WBC: white blood cell; NEU: neutrophils; SCAD: stable coronary artery disease.*

Discussion

The key mechanisms of ACS include coronary plaque rupture, platelet aggregation and thrombus formation. Mounting evidence has revealed that inflammation is an important precipitating event in the pathogenesis of ACS.[8] Inflammatory response plays an important role in the process of the occurrence, development and prognosis of coronary heart diseases. As markers of inflammatory response, WBC and NEU are closely correlated to cardiovascular system diseases. Studies have revealed that both can directly reflect the level of inflammation in coronary artery lesions, thereby further reflecting the severity of coronary artery lesions.[9,10] Studies have confirmed that the NEU/lymphocyte ratio could serve as a predictor of major adverse cardiovascular events.[11-13] This study revealed that there was a leukocyte-mediated inflammatory response in patients with AMI and that serum leukocyte levels were higher in SCAD and AMI patients than in normal healthy subjects. Furthermore, serum NEU levels were significantly abnormal in AMI patients, suggesting that inflammatory response is more intense in AMI patients. Hence, we consider that the reason may be that the range of inflammation is broader in myocardial infarction.

MPV reflects the degree of activation of platelets to a certain extent and is considered an important marker of cardiovascular disease.[14] Furthermore, it can be used in risk prediction, diagnosis and prognosis assessment of cardiovascular diseases.[15-17]

A recent study revealed that MPV significantly increased in patients with AMI, and the increase in MPV was correlated to the long-term prognosis of AMI patients to a certain extent.[18] Our study also revealed that MPV was significantly increased in patients in the AMI and SCAD groups. The increase in MPV is likely correlated to the intensity of inflammatory response in the body.

MPV has important significance in the evaluation of arterial thrombotic diseases such as cardiovascular thrombotic diseases. Therefore, MPV can act as an independent factor for the diagnosis and assessment of conditions and the curative effect of ACS. MPV levels in both the AMI and SCAD groups were significantly higher than normal levels, while PLT levels were significantly lower. These indicators are worthwhile in practice for disease diagnosis. In addition, based on the assessment of the diagnostic efficacy of the ROC curve for these parameters, the predicting value of MPV and PLT in AMI was superior to that in SCAD. In summary, the present study revealed that MPV- and PLT-related indicators are valuable for AMI and SCAD diagnostic prediction. However, there are two shortcomings of our study: one is that the study design is cross-sectional, because of the difficulty in keeping contact with these patients; the other is that there are only about 30 patients in the AMI and SCAD groups. There is no doubt that these two problems constitute limitations of our study. Further studies need to be carried out in a larger cohorts of patients with AMI and SCAD, with a more appropriate design to confirm its value as a diagnostic marker.

Author contributions

Conception and design of the research: Ding L, Hua F; acquisition of data: Ding L, Sun L, Wang F, Zhu L; analysis and interpretation of the data: Ding L, Sun L, Wang F, Zhu L, Zhang T; statistical analysis: Ding L, Sun L, Wang F, Zhang T, Hua F; writing of the manuscript: Ding L, Zhu L, Zhang T, Hua F; critical revision of the manuscript for intellectual content: Hua F. Supervision: Hua F.

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 Jinshan Hospital, Fudan University under protocol number 785. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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The Search for New Prognosis Markers for Coronary Artery Disease

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Short Editorial related to the article: Clinical Significance of Platelet Volume and Other Platelet Parameters in Acute Myocardial Infarction and Stable Coronary Artery Disease

There is growing evidence that platelets play a key role in vascular atherothrombosis associated with endothelium and inflammation.[1] Platelet activation leads to abnormalities in the surface glycoprotein expression of these cells, with subsequent aggregation and degranulation, which greatly contribute to thrombus formation.[2] Corroborating these facts, the role played by antiplatelet agents in the treatment of atherosclerotic vascular disease[3] is of note. In this context, a study by Ding et al.[4] shows the association between hematological parameters, with emphasis on leukocyte and platelet indicators, and stable coronary artery disease (SCAD). The authors evaluated platelet count, total platelet mass, mean platelet volume (MPV), platelet amplitude and white blood cell and neutrophil counts of 34 patients diagnosed with SCAD and compared two groups: 50 healthy patients (control) and 31 patients with acute myocardial infarction (AMI). The diagnostic criteria used for SCAD were those established by the European Society of Cardiology guidelines from 2013.[4] The authors mainly highlighted the association between higher values of MPV and the presence of SCAD compared with the control group.[4]

Some previous studies have outlined the relationship between MPV and the presence of cardiovascular risk factors or acute myocardial infarction.[5,6] The findings are not always consistent. In a systematic review of 2010, evaluating 16 cross-sectional studies, 14 presented a positive association between higher MPV values in patients with AMI compared with groups without AMI.[7] The association between high platelet volume value and coronary artery disease (CAD) was also shown in another meta-analysis on this matter in 2014. In this last systematic review, the authors found that patients with MPV values greater than 7.3 were more likely to present CAD than those with lower values.[8] On the other hand, Wada et al.[9] found an association between lower MPV values and the presence of stable CAD.[9]

Another reason for discussion among the researchers is the use of MPV as a parameter of platelet function, as MPV is not associated with platelet aggregation by turbidimetry. This latter method is considered a gold standard for evaluating platelet aggregation.[10]

The pursuit for new risk markers and prognosis for coronary disease is ongoing. In this context, MPV can be added to high-sensitivity C-reactive protein, to coronary calcium score and to the carotid intima-media thickness. However, in different countries, MPV may be a measure with a better profile, since it is inexpensive, technically easy and little invasive.[9] The new study by Ding et al.[4] adds more data to assist in the choice of MPV as a prognostic method in one of the CAD categories.

Keywords

Acute Coronary Syndrome, Biomarkers; Prognosis; Blood Platelets; Platelet Aggregation.

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Original Article

Behavioral Influence of Known Prognostic Markers on the Cardiologist's Decision following Acute Coronary Syndrome: the GRACE Score Paradox

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Abstract

Background: **Behavioral scientists consistently point out that knowledge does not influence decisions as expected. GRACE Score is a well validated risk model for predicting death of patients with acute coronary syndromes (ACS). However, whether prognostic assessment by this Score modulates medical decision is not known.**

Objective: **To test the hypothesis that the use of a validated risk score rationalizes the choice of invasive strategies for higher risk patients with non-ST-elevation ACS.**

Methods: **ACS patients were consecutively included in this prospective registry. GRACE Score was routinely used by cardiologists as the prognostic risk model. An invasive strategy was defined as an immediate decision of the coronary angiography, which in the selective strategy was only indicated in case of positive non-invasive test or unstable course. Firstly, we evaluated the association between GRACE and invasiveness; secondly, in order to find out the actual determinants of the invasive strategy, we built a propensity model for invasive decision. For this analysis, a p-value < 0.05 was considered as significant.**

Results: **In a sample of 570 patients, an invasive strategy was adopted for 394 (69%). GRACE Score was 118 ± 38 for the invasive group, similar to 116 ± 38 for the selective group (p = 0.64). A propensity score for the invasive strategy was derived from logistic regression: positive troponin and ST-deviation (positive associations) and hemoglobin (negative association). This score predicted an invasive strategy with c-statistics of 0.68 (95%CI: 0.63-0.73), opposed to GRACE Score (AUC 0.51; 95%CI: 0.47-0.57).**

Conclusion: **The dissociation between GRACE Score and invasive decision in ACS suggests that the knowledge of prognostic probabilities might not determine medical decision. (Arq Bras Cardiol. 2019; 112(6):721-726)**

Keywords: **Acute Coronary Syndrome; Prognosis; Non-ST Elevation Myocardial Infarction.**

Introduction

The risk-treatment paradox is a common phenomenon in which, contrary to what is expected, patients with higher risk receive less aggressive treatment as compared with individuals with lower risk.[1] One of the causes of this paradox is an equivocal risk evaluation based on the physician's intuitive impression. Probabilistic risk models have shown to be more accurate than intuitive judgment, suggesting that the use of such models theoretically facilitates prognosis-based treatment choice.[2-4]

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However, behavioral scientists have demonstrated that knowledge does not modulate decisions as expected.[5] In economy, people tend to make irrational decisions, which is not different in health-related issues. For example, it is well known smoking or obesity are risk factors for serious diseases, but habits of smoking, or eating improperly are common. Therefore, whether the use of a risk score actually modulates the physician's decision is unknown.

Non-ST-segment elevation acute coronary syndromes (ACS) present with a wide spectrum of risks, and patients can be treated in a conservative or aggressive manner.[6,7] This is one of the main clinical scenarios in which the risk-treatment paradox has been described.[8] Even though GRACE Score is a well-validated risk model for patients with ACS, its actual impact on providing a more reasonable approach according to risk, and on its relationship with medical judgment, has yet to be demonstrated.[9,10] Our aim was to test the hypothesis that the utilization of a risk score rationalizes the choice for invasive strategies towards higher risk patients with with non-ST elevation acute coronary syndromes.

Methods

Sample selection

Patients consecutively admitted to the coronary care unit (CCU) of a tertiary-care hospital due to non-ST elevation acute coronary syndromes between August 2007 and October 2014 were included in the study. Inclusion criteria was typical chest discomfort plus at least 1 of the 3 objective criteria: electrocardiographic changes consisting of transient ST-segment depression (0.05 mV), or T wave inversion (0.1 mV); troponin change to a level beyond the 99th percentile threshold of a healthy reference population, with 10% coefficient of variability;[11] or previous documentation of coronary artery disease, defined as a definitive history of myocardial infarction, or coronary obstruction ≥ 50% at angiography. Patient's option not to participate in the Registry was the sole exclusion criteria. All participants provided written informed consent.

Study protocol

Patients included were classified as for invasive or selective strategies according to medical decision. Management strategy was decided by the cardiology team in the CCU and was not influenced by the study protocol. Invasive strategy was prospectively defined by a decision to perform invasive coronary angiography, followed by a revascularization procedure if anatomically indicated. Selective strategy was defined as an indication of angiography conditioned to a positive non-invasive test, or clinical instability.

GRACE Score was used for evaluation of baseline risk, defined by tertiles of the original study (low risk: 1-108; intermediate risk: 109-140; high risk: 141-372). Death during hospitalization was the outcome of interest.

Statistical analysis

In order to evaluate whether baseline risk influenced the physician's decision regarding management strategy, GRACE Score was compared between the groups undergoing invasive versus selective strategy by the Mann-Whitney statistic. Secondly, in order to understand the determinants of medical decision, logistic regression was utilized to assess independent predictors of the invasive strategy. The selection of variables for this analysis was based on their univariate association with the invasive strategy ($p < 0.10$). A propensity score for the invasive strategy was derived from the logistic regression. Thirdly, in order to evaluate whether medical decision was correctly driven by prognosis, the value of the propensity score for predicting death during hospitalization was tested by the C-statistics (area under the ROC curve). C-statistics of the propensity score was compared with the c-statistics of GRACE Score by Hanley-Mcneil's test.

The analysis of normality was done through the combination of histogram and Q-Q plots visualization, description of skewness and kurtosis with confidence intervals and normality tests (Shapiro-Wilk and Kolmogorov-Smirnov). Numeric variables were expressed by means (standard deviation) or medians (interquartile range), and compared by unpaired student's t test or Mann-Whitney test. Categorical variables were described by frequencies and compared by Pearson's chi-square test, or Fisher's exact test. SPSS Statistical Software (Version 21, SPSS Inc., Chicago, Illinois, USA) was utilized for data analysis.

Results

A sample of 570 consecutive patients admitted with non-ST-segment elevation ACS was studied, aged 69 ± 14 years, 50% males. GRACE Score had a normal distribution, with mean of 118 ± 38. According to GRACE definition, 46% of patients were defined as low risk, 30% as intermediate risk, and 24% as high risk. Management through an invasive strategy took place in 69% of the patients.

GRACE Score of patients who underwent an invasive strategy was 118 ± 38, similar to patients managed conservatively (116 ± 38; $p = 0.64$). Seemingly, the area under the ROC curve for GRACE Score predicting an invasive strategy was not significant (0.51; 95% CI = 0.47 - 0.57; $p = 0.51$) - Figure 1A. There was no difference in the frequency of invasive strategy among patients with low, intermediate and high risk according to GRACE (68%, 77%, 73%, respectively; $p = 0.48$).

Table 1 depicts univariate association between patients' characteristics and management strategies. Among GRACE variables, Killip class, systolic blood pressure, heart rate, and creatinine did not have any association with the strategy chosen. On the contrary, positive troponin (OR = 2.7; 95% CI = 1.8 - 3.8; $p < 0.001$), ST-deviation (OR = 2.0; 95% CI = 1.2 - 3.2; $p = 0.006$), and the numeric value of hemoglobin at admission (OR = 1.2; 95% CI = 1.1 - 1.4; $p < 0.001$) predicted an invasive strategy. Conversely, age as a numeric variable had an inverse relationship with invasive strategy (OR = 0.98; 95% CI = 0.97 - 0.99; $p < 0.013$). Finally, the risk of bleeding according to CRUSADE Score was protective against invasive strategy (OR = 0.98; 95% CI = 0.97 - 0.99; $p < 0.018$).

A logistic regression model was used to build a propensity score for invasive strategy. The 5 variables associated with the invasive strategy in a univariate analysis were included. Positive troponin (OR = 2.5; 95% CI = 1.7 - 3.7; $p < 0.001$), ST-deviation (OR = 1.8; 95% CI = 1.1 - 3.1; $p = 0.026$), and hemoglobin on admission remained positively associated (OR = 1.2; 95% CI = 1.1 - 1.4; $p < 0.001$). Age and CRUSADE Score lost statistical significance ($p = 0.09$ and 0.29, respectively) - Table 2. This propensity model was statistically significant (chi-square = 48; $p < 0.001$; $R^2 = 0.2$), calibrated (H-L $\chi^2 = 12$; $p = 0.17$), and had an area under the ROC curve (AUC) of 0.68 (95% CI = 0.63 - 0.73; $p < 0.001$) for predicting an invasive strategy. This AUC was significantly better than GRACE Score area for the strategy prediction ($p < 0.001$) - Figure 1A.

A secondary model was built only with variables commonly utilized as part of a risk profile in ACS patients. In this model, hemoglobin and CRUSADE were not included, making age an inversely associated independent predictor of invasive strategy, and positive troponin and ST-deviation positively associated with invasive strategy - Table 2.

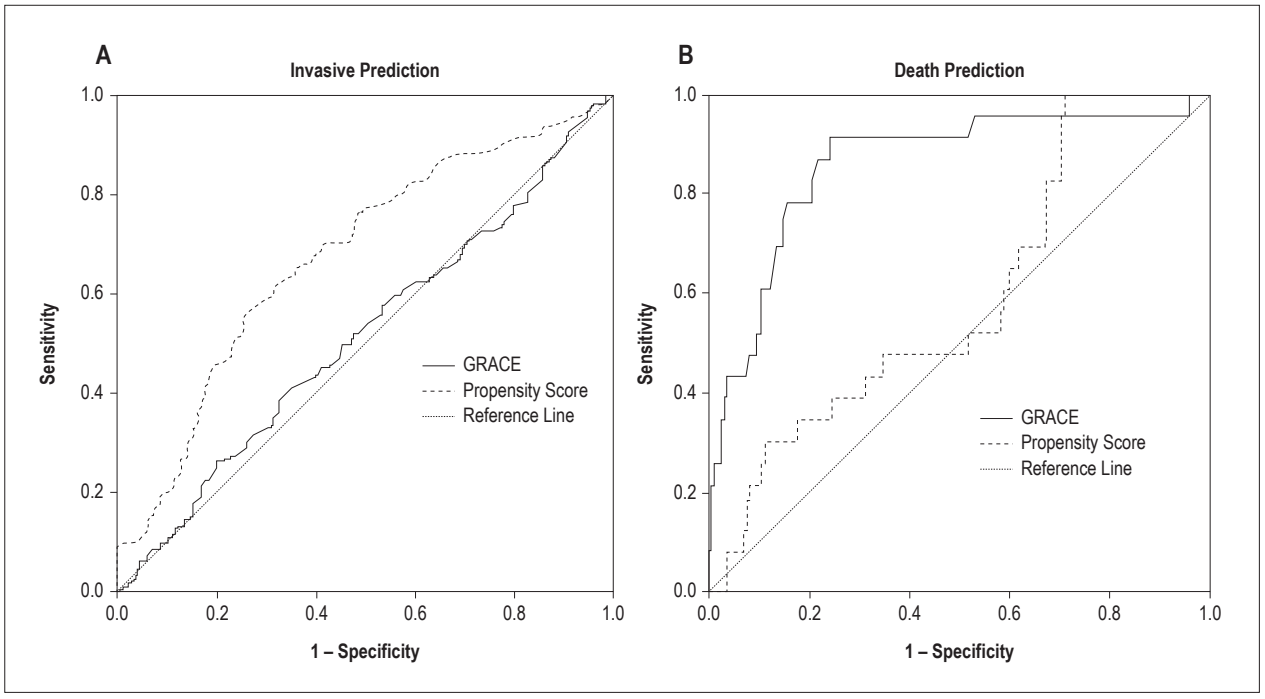

Figure 1 – *According to the area under the curve, GRACE Score does not predict an invasive strategy, as opposed to the propensity score (Panel A, p < 0.001 for curve comparison). Conversely, GRACE Score is better than the propensity Score for the prediction of mortality (Panel B, p < 0.001).*

Table 1 – Exploratory analysis of variable associates with strategy

	Chosen Strategy		p value
	Invasive	Selective	
Sample Size	394	176	
Male Gender	204 (52%)	82 (47%)	0.25*
Age (years)	66 ± 14	69 ± 14	0.01†
Positive Troponin	249 (63%)	69 (39%)	< 0.001*
ST Depression	94 (24%)	24 (14%)	0.005*
Killip > 1	57 (15%)	24 (14%)	0.81*
LV Ejection Fraction < 45%	26 (7.3%)	12 (7.8%)	0.84*
Systolic BP (mmHg)	154 ± 28	155 ± 33	0.68†
Heart Rate (bpm)	79 ± 20	77 ± 16	0.30†
Creatinine (mg/dl)	1.1 ± 0.84	1.2 ± 1.1	0.35†
Diabetes	143 (36%)	62 (35%)	0.79*
Smoking	33 (8.4%)	11 (6.3%)	0.38*
Number of Risk Factors	2.2 ± 1.0	2.1 ± 1.1	0.21†
Known Coronary Artery Disease	209 (53%)	104 (59%)	0.19*
Hemoglobin	13.4 ± 1.8	12.7 ± 2.1	< 0.001†
CRUSADE Bleeding Score	38 ± 15	41 ± 14	0.02†

*Known Coronary Artery Disease =Definitive history of myocardial infarction or coronary obstruction ≥50% at angiography; LV: left ventricle. BP: blood pressure. *Pearson's chi-square test p-values; † Unpaired Student's T test p-values.*

Table 2 – Logistic regression univariate and multivariate associations between the candidate's predictive variables and invasive strategy

	Univariate Analysis		Multivariate Analysis			
			Model 1		Model 2	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Positive Tn	2.7 (1.8 - 3.8)	< 0.001	2.5 (1.7 - 3.7)	< 0.001	2.6 (1.8 - 3.8)	< 0.001
ST-deviation	2.0 (1.2 - 3.2)	0.006	1.8 (1.1 - 3.1)	0.026	1.8 (1.1 - 2.9)	0.026
Hemoglobin	1.2 (1.1 - 1.4)	0.001	1.2 (1.1 - 1.4)	< 0.001		--
Age	0.98 (0.97-0.99)	0.013	--	0.09	0.98 (0.96 - 0.99)	0.002
CRUSADE	0.98 (0.97-0.99)	0.018	--	0.29		--

The 5 variables on this table are the ones that reached statistical significance in univariate analysis. Model was derived by the initial inclusion of all 5 variables (full model) and Model 2 only included typical risk prediction variables (did not include hemoglobin and CRUSADE Score). Positive Tn = Troponin change to a level beyond the 99th percentile.

The incidence of death during hospitalization was 5.1% (29 individuals). GRACE Score accurately predicted mortality, with an AUC of 0.87 (95% CI = 0.80 - 0.94; p < 0.001). The propensity score for invasive strategy also predicted mortality (AUC = 0.64; 95% CI = 0.56 - 0.72), but had a lower accuracy in comparison with GRACE Score (p < 0.001) - Figure 1B.

Discussion

The present study found a dissociation between the risk predicted by a probabilistic model and the physician's choice towards invasive strategy in patients with non-ST-elevation acute coronary syndromes. GRACE Score was the probabilistic model utilized in this analysis, a well-validated and accurate tool for prediction of death in ACS.[9,10] The study took place in an environment whose team of physicians has the duty to calculate GRACE Score for risk stratification and decision making. In spite of that, GRACE Score was not higher in individuals who underwent an invasive strategy, in comparison with patients of a selective strategy. Our findings reproduce behavioral science experiments where decisions are not well driven by knowledge.[5]

Contrary to GRACE Score, some patients' characteristics were independently associated with decision and were utilized to build a propensity score for invasive strategy. This score had a prognostic value lower than GRACE Score. Therefore, we found a paradox in which the variables that determined an invasive approach had a weaker association with prognosis in comparison with a true prognostic model that was not related to this decision.

Our findings are in line with previous evidences of dissociation between risk and intensity of treatment, the so-called risk-treatment paradox.[12-14] This phenomenon takes place when management has a risk/benefit trade-off, and the size of beneficial effect correlates with risk of unintended consequences. In this case, individuals who mostly need the treatment are the ones who most discourage the physician's decision .[15] For example, older ages were associated with a more conservative strategy, despite being the most important risk predictors in GRACE Score.[16,17]

Traditionally, medical judgment is based on intuition and experience, the so-called *gestalt*. This non-structured method of decision is vulnerable to cognitive bias.[18,19] Possibly, in elderly patients, a kind of nihilistic view makes the sense of risk surpass the sense of beneficial effect, while there is more enthusiasm towards young individuals, making the sense of benefit surpass the sense of risk. The utilization of a probabilistic model tends to avoid under- or overestimation of probabilities due to cognitive bias. Instead, it allows the quantification and balance of the risk/benefit ratio. Secondly, it is proved in different scenarios that the estimation of probabilities under uncertainty is more accurate when a probabilistic model is utilized instead of gestalt.[19] Indeed, in acute coronary syndromes, GRACE Score has shown to have better accuracy than the physician's opinion.[20,21] Our data validates this concept, since GRACE Score was more accurate in relation to the propensity score for invasiveness.

However, a mental reluctance of specialists to utilize a mathematical model, at the expense of unstructured judgment, has been reported.[22] Our observation is peculiar because it arises from an environment in which GRACE Score is systematically calculated and registered in the chart. In spite of that, physicians did not seem to be influenced by the predictive model, a phenomenon illustrated by GRACE Score being virtually identical in invasive and non-invasive groups. One could find only natural that physicians sometimes overrule GRACE Score based on patients' individualities and preferences. However, this should not be frequent enough to totally blunt the contrast of risk between the selective and invasive groups.

In our observations, positive troponin and ST-deviation were independent predictors of invasive strategy. They are both part of the 8 variables in GRACE Score, which were not associated with decision. This may be an indication that medical decision tends to be more univariate than multivariate, more deterministic than probabilistic.[14] Probably, either a positive troponin or an ST-deviation would lead them to opt for the invasive strategy, as opposed to a multivariable probabilistic approach. Also, in our first model, low hemoglobin was independently associated with a more conservative strategy. Considering that hemoglobin is not a

traditional prognostic marker, it may be acting as a proxy to a more fragile patient or one with more co-morbidities.

The limitation of our study is the generalization from a single CCU. Actually, we utilized our Unit as a model to test the hypothesis that the use of GRACE Score influences decision towards a more aggressive approach. While our study should not be generalized as a demonstration that decision-making has not been properly based on risk, it is an evidence that the utilization of a risk model does not guarantee risk-based decision. Moreover, our observation is in line with previous evidences of risk-treatment paradox.[14,23] Finally, our findings only generate hypotheses to be further validated by a clinical trial, in which individuals would be allocated to utilization or no utilization of GRACE Score, and the frequency of the invasive strategy would be compared between the groups.

Conclusion

In conclusion, the dissociation between GRACE Score and invasive decision in ACS suggests that the utilization of a prognostic model does not guarantee a risk-based decision.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Carvalhal MC, Souza TMB, Suerdieck J, Lopes F, Correia VCA, Lacerda YF, Sá N, Sodré GS, Rabelo MMN, Correia LCL; Acquisition of data: Carvalhal MC, Souza TMB, Suerdieck J, Lopes F, Correia VCA, Lacerda YF, Sá N, Sodré GS, Correia LCL; Critical revision of the manuscript for intellectual content: Correia LCL.

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 Hospital São Rafael under protocol number 35/11. All procedures involved in this study are in accordance with the Declaration of Helsinki of 1975, updated in 2013. Informed consent was obtained from all participants included in the study.

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Rational Use of Evidence-Based Medicine: Why We Resist So Much?

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Short Editorial related to the article: Behavioral Influence of Known Prognostic Markers on the Cardiologist's Decision following Acute Coronary Syndrome: the GRACE Score Paradox

"Man is a rational animal who always loses his temper when he is called upon to act in accordance with the dictates of reason"
Oscar Wilde

Patients expect three things during a medical consultation: To know what they have, how they should be treated and what is the prognosis of the illness. For all these relevant questions physicians apply their clinical judgement. This term, as vague as it sounds, has been largely utilized and research has recently been developed to clarify its meaning and intend to develop techniques to improve it. Many biases (actually more than thirty have been described) or non-rational decisions can occur during the entire decision-making process and were extensively studied in non-medical areas like economics, granting a Nobel Prize to Daniel Kahneman. Although commonly observed in diagnostic reasoning, the first question of the patient, it has also a significant role in therapeutic decisions, the second question and ultimately, both previous questions affect the third one.

A therapeutic decision solely based on clinical judgement is certainly influenced by previous personal experiences and acquired knowledge, even if not recent or up to date. In most cases, those decisions must respect 3 fundamental principles of rational decision making - the principle of dominance, the principle of invariance and the sunk-cost principle of fallacy.[1] Briefly, the first one states that a person should choose the option that is never worse than the others available and may provide a better outcome. The principle of invariance holds that same data-information should be considered and used the same way despite how it is presented. Finally, because decisions influence the future not the past, so those making decisions should not consider previous outcomes and behaviors - the sunk-cost principle/fallacy.

Carvalhal et al.,[2] in this issue of the Arquivos Brasileiros de Cardiologia, made an observational study in a coronary care unit where the GRACE score was applied to every admission. Contrary to the GRACE study they included only patients with an acute coronary syndrome without ST-segment elevation in their study cohort. They verified that despite the risk score category (low, intermediate or high), the therapeutic decision of intervention was made in equal proportions. Additionally, a propensity score based on physicians preferences was less prognostic than the GRACE score.

So, why physicians choose not to use the GRACE score? The GRACE study from nearly 25 years ago, using a large sample of acute coronary syndrome patients from 94 representative hospitals in 14 countries, obtained data about all aspects involving the care of those patients and proposed some guidance to better select interventions[3,4] based on prognostic factors identified. The proposed score has been validated in other cohorts.[5,6]

The three principles above mentioned were apparently not considered. Since the invasive option was selected equally for all risk score categories, the principle of dominance was ignored because non-invasive exams were the choice for those at least in those with a low-risk score. Also, the principle of invariance was not considered since similar risk scores (same information) were distinctly treated. The third principle, also known as a sunk-cost fallacy, was not observed since, despite knowledge of the validation of the GRACE score for predicting future events, it was not used, probably based on previous misleading information or personal experiences. In this situation, people tend to remember worse outcomes even if they are very few compared to those who evolved well. Here it may also apply other biases such as default bias and bandwagon effect.[1] The propensity score used in the study was less predictive of mortality than the GRACE score. It would be interesting to know if based on these results any change in the decision process was done.

Some aspects were not addressed by the authors. Bias due to race, gender and economic status may be present in some settings.[7] They did not specify if the sample was exclusively from the public health system or private. This information may have also an influence in the decision process (availability bias) since some exams may not be available in the public health care system, for example.

To reduce bias, the simplest approach is to have doctors aware of the various biases present in daily practice. Another very important solution for bias and heuristics behavior is adherence to Evidence-Based Medicine (EBM). It provides accurate information from multiple sources and suggests those more validated and identify those considered harmful.[8] The GRACE score is an excellent example of EBM. Nowadays, another relevant area for research in this field is the prescription of the new oral anticoagulants.[9] As in Oscar Wilde quote, we must resist being non-rational and follow straight and balanced guidelines in order to improve our results in daily practice.

Keywords

Acute Coronary Syndrome; Prognosis; Myocardial Infarction; Clinical Decision Making; Health Knowledge, Attitudes Practice, Evidence-Based Medicine.

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Original Article

Relationship between Dyslipidemia, Cultural Factors, and Cardiorespiratory Fitness in Schoolchildren

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Abstract

Background: **The presence of dyslipidemia and behavioral aspects are determinants of cardiovascular risk, especially in childhood and adolescence.**

Objective: **To verify possible relationships between dyslipidemia, cultural factors, and cardiorespiratory fitness (CRF) in schoolchildren.**

Methods: **This cross-sectional study evaluated a sample of 1,254 children and adolescents between the ages of 7 and 17 from the South of Brazil, 686 of whom were female. Dyslipidemia was defined as increased levels of at least one of the following lipid profile parameters: triglycerides (TG), total cholesterol (TC) and fractions of high (HDL-c) and low-density lipoprotein (LDL-c). Cultural aspects were evaluated by a self-reported questionnaire. Data were analyzed by logistic regression, considering the odds ratios (OR) and confidence intervals (CI) at 95%.**

Results: **The results revealed a high prevalence of dyslipidemia (41.9%), which was associated with female sex (OR: 1.56; IC: 1.24–1.96) and overweight/obese status (OR: 1.55; IC: 1.20–2.00). When lipid profile parameters were evaluated separately, high levels of LDL-c were observed to be associated with sedentary school transport (OR: 1.59; IC: 1.20–2.09). Schoolchildren who were overweight/obese had higher chances of elevated levels of TC (OR: 1.40; IC: 1.07–1.84) and TG (OR: 3.21; IC: 1.96–5.26). HDL-c was shown to be related to high television time (OR: 1.59; IC: 1.00–2.54).**

Conclusion: **Alterations in lipid parameters are associated with cultural factors, especially those related to sedentary lifestyle and low levels of CRF. (Arq Bras Cardiol. 2019; 112(6):729-736)**

Keywords: **Dyslipidemias/physiopathology; Child; Adolescent; Life Style; Risk Factors; Atherosclerosis.**

Introduction

Dyslipidemia in childhood and adolescence has been the object of diverse studies, owing to its high prevalence in these age groups and to the fact that it is a predictor of atherosclerosis in adulthood.[1-3] Data from a study conducted in the United States during the period 2011–2012 indicate that approximately 1 in every 5 children and adolescents between the ages of 6 and 7 had adverse blood lipid concentrations.[4]

Subsequent studies have indicated that the occurrence of dyslipidemia during childhood and adolescence is associated with cardiovascular events[5] and cardiorespiratory fitness (CRF).[6] Similarly, behavioral aspects involving eating habits and a sedentary lifestyle, with reduced caloric expenditure and physical activity, as well as more time spent using television (TV), computers, and cellular phones, have been introduced as important determining factors for cardiovascular risk in children and adolescents.[7]

From this point of view, analyzing changes related to these conditions during childhood and adolescence is a strategy capable of reducing the incidence of injuries and preventing the occurrence of chronic diseases in subsequent years of life,[8,9] thus proposing subsidies for the development of programs that aim to maintain and promote health. With the aim of contributing to efforts to overcome these deficiencies, the objective of this study was to verify possible relations between dyslipidemia, cultural factors (eating habits, TV, school transport) and CRF in schoolchildren.

Methods

This cross-sectional study involved the participation of 1,254 children and adolescents (ages 7 to 17), 686 of whom were female, from 19 public and private school in the municipality of Santa Cruz do Sul, Rio Grande do Sul, Brazil, selected by conglomerate sampling from a population of 20,540 schoolchildren from rural and urban areas.

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Participating schools were randomly selected in the year 2004, in the beginning of the "Schoolchildren's Health" longitudinal study, in line with the population density of schoolchildren in the municipality. During the following cross-sectional analyses, all of the schoolchildren from the previously selected schools were invited to participate in the study. The initial sample was made up of 1,949 schoolchildren. However, 695 schoolchildren were excluded for the following reasons: refusal/impossibility of blood collection, non-completion of fasting period before blood collection, failure to perform the CRF test, or incomplete filling out of questionnaire form. This study is part of the "Schoolchildren's Health" study, which was approved by the Human Research Ethics Committee under certificate number 2525/10. This study follows the principles set forth by the Declaration of Helsinki. The schoolchildren's parents or legal guardians signed free and informed consent forms.

The sample size was calculated using the program G*Power 3.1 (Heinrich-Heine-Universität, Düsseldorf, Germany), using logistic regression as a statistical test (presence versus absence of dyslipidemia as dependent variable). Considering a statistical power of $(1 - \beta) = 0.95$, a significance level of $\alpha = 0.05$ and an odds ratio of 1.30, the minimum sample size estimated was 988 schoolchildren.

Blood samples were collected after a 12-hour fasting period. Serum samples were used to determine triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c). The tests were carried out using Miura One automated equipment (I.S.E., Rome, Italy). Low-density lipoprotein cholesterol (LDL-c) levels were calculated using the Friedewald, Fredrickson, and Levy formula.[10] International cutoff points were used to classify the lipid profile.[11] Dyslipidemia was considered as the presence of alterations in at least one component of the lipid profile (increased TG, TC, or LDL-c or decreased HDL-c, without considering borderline cases).

Levels of CRF were evaluated by the 12-minute run/walk test, recommended by the Projeto Esporte Brasil (Brazil Sport Project; PROESP-BR),[12] which consists of covering the longest distance possible in 12 minutes on a previously marked track. Researchers with degrees in Physical Education who are a part of this study applied the test, with assistance from previously trained students of Physical Education receiving scholarships. Schoolchildren were instructed to wear light clothing and tennis shoes on evaluation day. Data were classified using cutoff points defined by PROESP-BR.[12]

Cultural habits were evaluated using the adapted Barros and Nahas questionnaire,[13] which was self-reported by the schoolchildren. Amount of time spent watching TV was categorized into two categories: 1) less than two hours per day and 2) two hours per day or more. School transport was considered either active (by foot or by bike) or sedentary (car, motorcycle, or collective transport). Eating habits were evaluated by the weekly frequency with which schoolchildren consumed the following foods: 1) sweets, 2) soft drinks, 3) fried salty snacks, and 4) pizza/lasagna. Consumption was classified as "never/sometimes" (not at all/once a week) and "almost always/always" (twice or more than twice weekly).

Statistical Analysis

Data analysis was carried out using the statistical program SPSS v. 23.0 (IBM, Armonk, USA). Descriptive data were expressed in absolute and relative frequency. The association between dependent variables (dyslipidemia and increased levels of any lipid profile parameter) and cultural habits was tested via logistic regression. Values were described in odds ratios (OR) and confidence intervals (CI) at 95%. Initially, univariate analysis of data was conducted. Subsequently, adjusted analysis of variables that showed significance was applied. Data with $p < 0.05$ were considered significant.

Results

Descriptive data are shown in Table 1. Dyslipidemia was observed in 41.9% of schoolchildren. The condition was more prevalent in females, adolescents, and schoolchildren with low CRF levels ($p < 0.05$).

The data described in Table 2 indicate that dyslipidemia was significantly associated with female sex and overweight/obese status. Adolescents had lower chances of developing dyslipidemia, in comparison with children. In the univariate analysis, low levels of CRF were associated with dyslipidemia. This association, however, was not maintained in the multivariate analysis. Furthermore, cultural aspects were not associated with dyslipidemia.

When comparing data for lipid profile components, in as isolated manner, high levels of TC were observed to be associated with female sex. Adolescents had higher chances of increased TC and TG levels than children. Overweight/obese status is associated with increased TC and TG (Table 3).

Low levels of HDL-c are associated with the habit of watching TV for 2 or more hours per day. Female sex, adolescent age range, and sedentary school transport were associated with increased LDL-c (Table 4).

Discussion

A high prevalence of dyslipidemia in schoolchildren has constituted increasingly frequent alterations in Brazilian children and adolescents. Studies conducted in Recife, Pernambuco (29.7%),[14] Florianópolis, Santa Catarina (22.0%),[15] and Londrina, Paraná (20.8%)[16] indicate a growing prevalence of dyslipidemia in schoolchildren in different regions of the country. In Birjand, Iran, similar estimates indicated that the prevalence of dyslipidemia has affected 31% of children between 6 and 11 years of age, with girls presenting a higher prevalence of hypertriglyceridemia and boys a higher prevalence of hypercholesterolemia.[17] It is worth highlighting, however, that the high prevalence found in this study (41.9%) exceeds these already high estimates. Furthermore, data from a 10-year trend study (2004–2014) of serum lipid levels and dyslipidemia, conducted with 3,249 schoolchildren between the ages of 6 and 18 from several schools in Beijing, demonstrated that the prevalence of dyslipidemia, based on elevated levels of TG and TC and reduced HDL-c, significantly increased during the period. This suggests an upward trend in this prevalence and constitutes a warning that continuous measures are necessary to curb this condition.[18]

Table 1 – Description of results regarding variables studied in schoolchildren in Santa Cruz do Sul, RS

Variables	Total (n = 1,254)	Presence of dyslipidemia (n = 526)	Absence of dyslipidemia (n = 728)	p
	n (%)	n (%)	n (%)	
Sex				
Male	568 (45.3)	208 (39.5)	360 (49.5)	0.001
Female	686 (54.7)	318 (60.5)	368 (50.5)	
Age range				
7 to 9 years old (children)	344 (27.4)	166 (31.6)	178 (24.5)	0.005
10 to 17 years old (adolescents)	910 (72.6)	360 (68.4)	550 (75.5)	
TV				
Less than 2 hours	697 (55.6)	303 (57.6)	394 (54.1)	0.221
2 hours or more	557 (44.4)	223 (42.4)	334 (45.9)	
School transport type				
Active	558 (44.5)	234 (44.5)	324 (44.5)	0.995
Sedentary	696 (55.5)	292 (55.5)	404 (55.5)	
Avoids eating fatty or sweet foods				
Never/sometimes	917 (73.1)	377 (71.7)	540 (74.2)	0.324
Almost always/always	337 (26.9)	149 (28.3)	188 (25.8)	
4 to 5 varied meals per day				
Never/sometimes	583 (46.5)	249 (47.3)	334 (45.9)	0.609
Almost always/always	671 (53.5)	277 (52.7)	394 (54.1)	
Consumption of soft drinks				
Never/sometimes	492 (39.2)	220 (41.8)	272 (37.4)	0.110
Almost always/always	762 (60.8)	306 (58.2)	456 (62.6)	
Consumption of fried salty snacks				
Never/sometimes	639 (51.0)	273 (51.9)	366 (50.3)	0.570
Almost always/always	615 (49.0)	253 (48.1)	362 (49.7)	
Consumption of pizza and lasagna				
Never/sometimes	897 (71.5)	391 (74.3)	506 (69.5)	0.061
Almost always/always	357 (28.5)	135 (25.7)	222 (30.5)	
Consumption of sweets				
Never/sometimes	500 (39.9)	211 (40.1)	289 (39.7)	0.882
Almost always/always	754 (60.1)	315 (59.9)	439 (60.3)	
Cardiorespiratory fitness				
At risk	637 (50.8)	285 (54.2)	352 (48.4)	0.042
Normal	617 (49.2)	241 (45.8)	376 (51.6)	

TV: television.

Regarding factors that contribute to high rates of dyslipidemia, our findings showed an association with the presence of overweight/obese status and sedentary behavior. On the other hand, various factors have been indicated as contributing to the occurrence of altered blood lipid concentrations. Alcântara Neto et al.[19] indicate that there is a positive association between inadequate food intake and dyslipidemia. Body mass index (BMI) is also an important variable, given that obesity has been evidenced as an important risk factor for dyslipidemia and cardiometabolic risk. This suggests that obese adolescents have elevated levels of TG, TC, LDL-c, increased insulin resistance, and reduced levels of HDL-c.[20] Moreover, a cross-sectional study of 173 schoolchildren ages 10–18, demonstrated that greater adherence to a diet high in fat and sugar was associated with the presence of hypercholesterolemia (OR: 1.6; 95% CI: 1.1–2.3) and increased LDL-c (OR: 1.7; 95% CI: 1.0–2.9). Furthermore, children who exercised less than 3 times/week were less likely to have low levels of HDL-c than children who exercised 7 times/week or more (OR: 0.4; 95% CI: 0.2–0.7).[21]

Table 2 – Association between dyslipidemia and demographic data, cardiorespiratory fitness, and cultural habits in Santa Cruz do Sul, RS

Variables	Dyslipidemia Crude OR[1] (95% CI)	Dyslipidemia Adjusted OR[2] (95% CI)
Sex		
Male		
Female	1.50 (1.19–1.88)*	1.56 (1.24–1.96)*
Age range		
7 to 9 years		
10 to 17 years	0.70 (0.55–0.90)*	0.72 (0.56–0.93)*
TV		
Less than 2 hours		–
2 hours or more	0.87 (0.69–1.08)	
School transport type		
Active		–
Sedentary	1.00 (0.80–1.25)	
Cardiorespiratory fitness		
Normal		
At risk	1.26 (1.01–1.58)*	1.18 (0.93–1.48)*
BMI classification		
Underweight/normal		
Overweight/obese	1.60 (1.25–2.05)*	1.55 (1.20–2.00)*
Avoids eating fatty or sweet foods		
Never/sometimes		–
Almost always/always	0.88 (0.68–1.13)	
Varied meals		
Never/sometimes		–
Almost always/always	1.06 (0.85–1.33)	
Soft drinks		
Never/sometimes		–
Almost always/always	0.83 (0.66–1.04)	
Pizza or lasagna		
Never/sometimes		–
Almost always/always	0.79 (0.61–1.01)	
Sweets		
Never/sometimes		–
Almost always/always	0.98 (0.78–1.24)	
Fried salty snacks		
Never/sometimes		–
Almost always/always	0.94 (0.75–1.17)	

*Logistic regression. OR: odds ratio; CI: 95% confidence interval; TV: television; BMI: body mass index. [1]Univariate analysis; [2]analysis adjusted for variables that showed significance ($p < 0.05$). *Significant data ($p < 0.05$).*

A study of 1,805 Chinese children and adolescents evaluated the different between metabolically healthy and metabolically unhealthy schoolchildren. The findings revealed that BMI and sedentary behavior were the factors with the greatest impact on metabolic health. In addition, excessive consumption of junk food was strongly associated with unfavorable metabolic profiles in schoolchildren.[22] Similarly, a study of 227 preschool children conducted in Diamantina, Minas Gerais, Brazil demonstrated that preschoolers who reported less balanced diets, with more frequent consumption of foods rich in lipids and carbohydrates, as well as higher BMI and lower levels of maternal education, had a higher association with the occurrence of lipid profile

Table 3 – Association between altered triglycerides and total cholesterol and demographic data, cardiorespiratory fitness, and cultural habits in Santa Cruz do Sul, RS

Variables	CT Crude OR[1] (95% CI)	CT Adjusted OR[2] (95% CI)	TG Crude OR[1] (95% CI)	TG Adjusted OR[2] (95% CI)
Sex				
Male				–
Female	1.29 (1.01–1.66)*	1.36 (1.05–1.75)*	1.53 (0.94–2.51)	
Age range				
7 to 9 years				
10 to 17 years	0.63 (0.48–0.83)*	0.66 (0.50–0.86)*	0.39 (0.34–0.62)*	0.47 (0.28–0.76)*
TV				
Less than 2 hours				–
2 hours or more	0.81 (0.63–1.04)	–	1.31 (0.81–2.10)	
School transport type				
Active				–
Sedentary	0.83 (0.64–1.06)	–	0.98 (0.61–1.58)	
Cardiorespiratory fitness				
Normal				–
At risk	1.24 (0.97–1.59)	–	1.50 (0.93–2.44)	
BMI classification				
Underweight/normal				
Overweight/obese	1.45 (1.11–1.90)*	1.40 (1.07–1.84)*	3.82 (2.36–6.20)*	3.21 (1.96–5.26)*
Avoids eating fatty or sweet foods				
Never/sometimes				–
Almost always/always	0.91 (0.69–1.20)	–	1.10 (0.66–1.87)	
Varied meals				
Never/sometimes				–
Almost always/always	0.92 (0.72–1.18)	–	0.70 (0.44–1.13)	
Soft drinks				
Never/sometimes				
Almost always/always	0.86 (0.67–1.11)	–	0.48 (0.30–0.78)*	0.63 (0.38–1.04)
Fried salty snacks				
Never/sometimes				
Almost always/always	0.96 (0.75–1.23)	–	0.49 (0.30–0.81)*	0.58 (0.34–0.98)*
Pizza or lasagna				
Never/sometimes				–
Almost always/always	0.93 (0.70–1.23)	–	0.58 (0.32–1.05)	
Sweets				
Never/sometimes				–
Almost always/always	0.89 (0.69–1.15)	–	0.95 (0.59–1.53)	

*Logistic regression. TC: total cholesterol; TG: triglycerides; TV: television; BMI: body mass index; OR: odds ratio; CI: 95% confidence interval. [1]Univariate analysis; [2]analysis adjusted for variables that showed significance (p < 0.05). *Significant data (p < 0.05).*

alterations, especially higher levels of LDL-c, with these variables being identified as determinants of dyslipidemia in the preschoolers evaluated.[5] It is thus understood that this condition, largely due to dietary habits, is affecting schoolchildren at increasingly early ages.

In detail, this study indicated an associated between dyslipidemia and low levels of CRF, increased LDL-c, and sedentary school transport, as well as low levels of HDL-c and more time in front of the TV. It is thus proposed that sedentarism and low CRF are associated with metabolic

Table 4 – Association between altered high and low-density lipoprotein cholesterol and demographic data, cardiorespiratory fitness, and cultural habits in Santa Cruz do Sul, RS

Variables	HDL-c Crude OR[1] (95% CI)	LDL-c Crude OR[1] (95% CI)	LDL-c Adjusted OR[2] (95% CI)
Sex			
Male			
Female	0.87 (0.54–1.38)	1.68 (1.28–2.20)*	1.65 (1.25–2.18)*
Age range			
7 to 9 years			
10 to 17 years	1.14 (0.67–1.95)	1.52 (1.11–2.09)*	1.50 (1.08–2.07)*
TV			
Less than 2 hours			–
2 hours or more	1.59 (1.00–2.54)*	0.88 (0.67–1.15)	
School transport type			
Active			1
Sedentary	0.92 (0.58–1.48)	1.63 (1.24–2.15)*	1.59 (1.20–2.09)*
Cardiorespiratory fitness			
Normal			–
At risk	1.28 (0.80–2.05)	1.08 (0.83–1.40)	
BMI classification			
Underweight/normal			–
Overweight/obese	1.55 (0.96–2.50)	1.13 (0.85–1.51)	
Avoids eating fatty or sweet foods			
Never/sometimes			–
Almost always/always	0.90 (0.53–1.54)	0.89 (0.66–1.21)	
Varied meals			
Never/sometimes			–
Almost always/always	0.81 (0.51–1.30)	1.07 (0.82–1.40)	
Soft drinks			
Never/sometimes			–
Almost always/always	0.88 (0.55–1.41)	0.78 (0.60–1.03)	
Fried salty snacks			
Never/sometimes			–
Almost always/always	0.98 (0.62–1.57)	0.88 (0.67–1.14)	
Pizza or lasagna			
Never/sometimes			–
Almost always/always	0.55 (0.30–0.99)	0.97 (0.73–1.31)	
Sweets			
Never/sometimes			–
Almost always/always	0.96 (0.60–1.54)	1.10 (0.84–1.44)	

*Logistic regression. HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; TV: television; BMI: body mass index; OR: odds ratio; CI: 95% confidence interval. [1]Univariate analysis; [2]analysis adjusted for variables that showed significance (p < 0.05). *Significant data (p < 0.05).*

alterations. In the same manner, results from the *National Health and Nutrition Examination Survey* (NHANES) demonstrated that screen time appears to be a potential moderator of the relationship between physical activity and cardiovascular fitness in male adolescents with dyslipidemia.[23] Furthermore, previous data, involving a sample of 1,243 children and adolescents from our municipality, demonstrated that lipid profile alterations are more prevalent among obese/unfit children and adolescents in comparison with schoolchildren with normal or low weight, in both sexes. These results reinforce the findings of the present study and indicate a direct relation between the prevalence of dyslipidemia, obesity, and low levels of CRF.[6]

Thus faced with this increasing impact of dyslipidemia on health conditions in the pediatric population, recommendations suggest that children be screened for risk factors in order to promote early identification of high levels of LDL-c and reduce cardiovascular events in young adults.[24] This notwithstanding, it is assumed that only 18% of this population receives this form of primary care.[25] The National Academy of Medicine of the United States recommends that children have access to healthy food and that parents and guardians offer nutritious foods that promote fullness. It is also necessary to increase time dedicated to practicing physical activities and reduce activities that stimulate sedentary behavior in the pediatric population.[26] With respect to treating dyslipidemia, it is estimated that changes involving lifestyle intervention are alternatives with excellent results and that they provoke positive response and adaptation, with treatment involving medication being used only in rare cases.[27] In the same manner, the results of our study suggest that these recommendations should continue during subsequent years to include the periods of adolescence and adulthood.

We recognize the fact that the questionnaire was self-reported by the schoolchildren as a limitation to this study, given that these reports may not be compatible with reality. Additionally, due to the cross-sectional design, it was not possible to show causality. The study includes the evaluations of schoolchildren in a municipality in the South of Brazil, which may not be representative of the reality of children and adolescents in other contexts. At the same time, this may be considered a strong point of our study, to the extent that it indicates that the high prevalence of dyslipidemia found corresponds to and even exceeds those which were indicated in studies in other territories of Brazil, providing a current estimate that the occurrence of this condition tends toward a growing increase. Furthermore, the study structurally explores variables that are relevant to schoolchildren's cultural context, proposing estimates and describing factors that are apparently associated with the high prevalence of dyslipidemia in children and adolescents. The data thus permit health management organizations dedicated to children and adolescents to establish more precise guidelines for this population.

Conclusion

The results of this study show that there is a high prevalence of dyslipidemia in schoolchildren and that this is related to low cardiorespiratory fitness and cultural factors, especially those related to sedentary behavior. These findings highlight the need for interventions that promote healthy habits and lifestyles, beginning with the first years of childhood.

Author contributions

Conception and design of the research: Reuter CP, Brand C, Renner JDP, Franke SIR, Burgos MS; Acquisition of data: Reuter CP, Silva PT, Reuter EM, Renner JDP, Franke SIR, Burgos LT, Schneiders LB, Burgos MS; Analysis and interpretation of the data: Reuter CP, Brand C, Silva PT, Reuter EM, Renner JDP, Franke SIR, Mello ED, Burgos LT, Schneiders LB, Burgos MS; Statistical analysis: Reuter CP, Silva PT; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Reuter CP, Brand C, Silva PT, Reuter EM, Renner JDP, Franke SIR, Mello ED, Schneiders LB, Burgos MS.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Santa Cruz do Sul under the protocol number 2525/10. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Cardiovascular Risk Factors in Childhood Claim for Public Health Policies

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Short Editorial related to the article: Relationship between Dyslipidemia, Cultural Factors, and Cardiorespiratory Fitness in Schoolchildren

Obesity is presently a pandemic public health problem not only in developed countries but also in developing ones. As its incidence is increasing in childhood and adolescence as well this issue becomes alarming considering its evolution and associations. The multiple comorbidities such as hypertension, hyperlipidemia and insulin resistance that accompany obesity increase the risk of cardiovascular mortality whilst worsening quality of life in adults.[1] It is always appropriate to reinforce the fact that the atherosclerotic process starts at an early stage in life[2-5] as demonstrated in autopsies of children with strong association between LDL cholesterol levels prior to death and the presence of fatty streaks in the aorta.[2] This observation has been documented in various reports in Brazil demonstrating that public health policies must be reinforced towards this problem.[6-8]

In different approaches in schoolchildren of a city in Sao Paulo for over ten years we have been studying the impact of biochemical, anthropometric, nutritional status, clinical, socio-cultural and economic conditions.

Interesting enough was the positive correlation between minimum wage salary and its multiples per family, indicating that probably expenses went up on unhealthy food in the richer groups.[9,10] Passive smoking at home correlated with lower ranges of HDL Cholesterol.[11] The distance between the urban and rural areas was divided into eight categories for comparison with Total Cholesterol values. The closer to rural areas the lower the Cholesterol and our understanding is that their diets were more adequate in terms of vegetables intake and less processed food. For these conclusions, we needed a new statistical approach, a multilevel hierarchical model.[12,13] Continuous intervention is given by means of weekly talks on the local radio, press releases, TV programs, participation in parents and teachers' meetings and periodically having ludic and playful camping with the students. Comparison of Total Cholesterol levels in the students of the same grades as of ten years earlier showed a statistically significant difference for the better, lower levels.[14]

Besides the already mentioned surveys in Brazil, programs with some slight differences are being carried out in other cities, such as Campinas[15] and Sao Caetano do Sul.

The Brazilian Society of Cardiology enrolled the major part of the above-mentioned investigators in a unique program- Brazilian Cardiology Society Goes to the Schools-, launched in 2017 together with the State of Sao Paulo Education Ministry. As from 2020, the plan is to have reached the five regions of Brazil.

The paper presented in this issue - Relationship between Dyslipidemia, Cultural Factors, and Cardiorespiratory Fitness in Schoolchildren - broadens importantly the spectrum of elements as to cardiovascular risk, mainly in the overweight or obese students. The Brazilian Society of Cardiology Goes to the Schools will contemplate incorporating the PROESP-BR test in its program. The hyperlipidemia finding of 41.9% is really alarming and close to 100 % higher than the data that has been published. This really calls for immediate actions joining Ministeries of Health and of Education. Looking further into the article the attention is called to the investigators having a large range of spectrum to amplify their research as it is a relatively new observation among documentation of association with risk factors for atherosclerotic diseases.[16]

Articles on criterion-referenced cut points for cardiorespiratory fitness in children,[17] sleep patterns, augmentation index, pulse wave velocity, insulin resistance, preschool children testing, cognition, arterial stiffness and so many others can be expected in the near future from the authors of this relevant and well-conducted paper.

Keywords

Cardiovascular Diseases/physiopathology; Child; Obesity; Risk Factors; Hypertension; Diabetes Mellitus; Hyperlipidemias; Insulin Resistance.

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Sympatho-Vagal Imbalance is Associated with Sarcopenia in Male Patients with Heart Failure

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Abstract

Background: **Resting sympathetic hyperactivity and impaired parasympathetic reactivation after exercise have been described in patients with heart failure (HF). However, the association of these autonomic changes in patients with HF and sarcopenia is unknown.**

Objective: **The aim of this study was to evaluate the impact of autonomic modulation on sarcopenia in male patients with HF.**

Methods: **We enrolled 116 male patients with HF and left ventricular ejection fraction < 40%. All patients underwent a maximal cardiopulmonary exercise testing. Maximal heart rate was recorded and delta heart rate recovery (ΔHRR) was assessed at 1st and 2nd minutes after exercise. Muscle sympathetic nerve activity (MSNA) was recorded by microneurography. Dual-energy X-ray absorptiometry was used to measure body composition and sarcopenia was defined by the sum of appendicular lean muscle mass (ALM) divided by height in meters squared and handgrip strength.**

Results: **Sarcopenia was identified in 33 patients (28%). Patients with sarcopenia had higher MSNA than those without (47 [41-52] vs. 40 [34-48] bursts/min, p = 0.028). Sarcopenic patients showed lower ΔHRR at 1st (15 [10-21] vs. 22 [16-30] beats/min, p < 0.001) and 2nd min (25 [19-39] vs. 35 [24-48] beats/min, p = 0.017) than non-sarcopenic. There was a positive correlation between ALM and ΔHRR at 1st (r = 0.26, p = 0.008) and 2nd min (r = 0.25, p = 0.012). We observed a negative correlation between ALM and MSNA (r = -0.29, p = 0.003).**

Conclusion: **Sympatho-vagal imbalance seems to be associated with sarcopenia in male patients with HF. These results highlight the importance of a therapeutic approach in patients with muscle wasting and increased peripheral sympathetic outflow. (Arq Bras Cardiol. 2019; 112(6):739-746)**

Keywords: **Heart Failure; Sarcopenia; Sympathetic Hyperactivity; Blunted Vagal Reactivation.**

Introduction

Changes in body composition play an important role in the pathogenesis and progression of chronic heart failure (HF).[1] Sarcopenia, which is characterized by a decrease in skeletal muscle mass and strength, affects 19.5% of ambulatory patients with HF,[2] and is associated with several alterations such as impaired endothelial function, reduced 6-minute walking distance, and attenuated peak VO_2.[2, 3] Although sarcopenia has been frequently described in elderly patients as a consequence of the ageing process, it can also be present in younger patients with HF.[4]

Resting sympathoexcitation is a hallmark in chronic HF.[5] In addition, accumulated evidence shows that this autonomic dysregulation is highly associated with increased morbidity and mortality.[5] In normal conditions, sympathetic nervous system exerts anabolic action via β_2-adrenoceptors on skeletal muscle,[6] but in experimental model of HF, the exacerbated sympathetic nervous activity contributes to downregulation of β_2-adrenoceptors favoring skeletal muscle atrophy and weight loss.[7]

Reduced parasympathetic activity has also been reported in patients with HF.[8,9] Binkley and colleagues[10] showed impaired parasympathetic activity in patients with HF evaluated by heart rate variability. Moreover, heart rate recovery (HRR), an important cardiac deceleration mechanism after maximum effort, can also be used to assess parasympathetic activity immediately after maximal exercise testing.[11] Furthermore, HRR is an easy, low-cost, and clinical assessment of vagal reactivation, and provides additional prognostic information.[12-14]

Muscle sympathetic nerve activity (MSNA) and HRR, as measures of sympathetic and parasympathetic activity, respectively, have not been studied in sarcopenic patients with HF. Therefore, the aim of this study was to evaluate the impact of autonomic modulation assessed by MSNA (by microneurography technique) and HRR immediately after maximal exercise testing in patients with HF and sarcopenia.

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Methods

Study population

Between May 1, 2016 and December 31, 2017, we prospectively enrolled 116 male outpatients with stable chronic HF. Inclusion criteria were: (1) age between 18 and 65 years old; (2) at least 1 year of HF diagnosis; (3) left ventricular ejection fraction (LVEF) lower than 40% measured by echocardiography; (4) non-ischemic and ischemic etiologies; (5) compensated HF with optimal medication for at least three months prior the study; and (6) New York Heart Association (NYHA) class I to IV.

Patients with autonomic diabetic neuropathy, chronic renal failure with haemodialysis, heart transplantation, pacemaker, muscular dystrophy (i.e. Duchenne muscular dystrophy), any hormonal treatment, history of cancer, ongoing infection, and myocardial infarction with percutaneous coronary intervention or revascularization up to 6 months prior to the study entry, were not included.

Muscle sympathetic nerve activity

MSNA was directly recorded from the peroneal nerve using the microneurography technique.[15,16] Multiunit post-ganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode placed in the peroneal nerve near the fibular head. Nerve signals were amplified by a factor of 50,000 to 100,000 and band-pass filtered (700 to 2000 Hz). For recording and analysis, nerve activity was rectified and integrated (time constant 0.1 second) to obtain a mean voltage display of sympathetic nerve activity. MSNA was expressed as burst frequency (bursts per minute).

Maximal cardiopulmonary exercise test

All patients underwent symptom-limited cardiopulmonary exercise test (Vmax Encore 29 System; VIASYS Healthcare Inc., Palm Springs, California, USA) performed on a cycle ergometer (Ergometer 800S; SensorMedics, Yorba Linda, California, USA), using a ramp protocol with workload increments of 5 or 10 Watts per minute. Oxygen consumption (VO_2) and carbon dioxide output (VCO_2) were measured by means of gas exchange on a breath-by-breath basis and expressed as 30-s averages. The patients were initially monitored for 2 minutes at rest when seated on the ergometer; then they were instructed to pedal at a pace of 60-70 rpm and the completion of the test occurred when, in spite of verbal encouragement, the patient reached maximal volitional fatigue. A respiratory exchange ratio (RER) higher than 1.10 was reached for all patients. Heart rate (HR) was monitored continuously at rest, during the test and recovery phase, using a 12-lead digital electrocardiogram (CardioSoft 6.51 ECG/CAM-14, GE Medical Systems Information Technologies, Wisconsin, USA).[17]

After achieving peak workload, the patients continued to pedal at 10 watts for 2 minutes, followed by 4 minutes seated on the ergometer, this 6-min period was considered the recovery phase. Delta (Δ) HRR was calculated by subtracting the HR values at 1st (ΔHRR1) and 2nd (ΔHRR2) minutes of the recovery phase from the peak HR.[12]

Body composition and muscle strength

Body composition measurements – total lean and fat mass – were performed using dual-energy X-ray absorptiometry (DXA) (Lunar iDXA; GE Medical Systems Lunar, Madison, USA). Then, skeletal muscle mass index (SMI) was calculated as the sum of appendicular lean muscle mass of both arms and legs divided by height in meters squared.[18]

After adjusting handle position, muscle strength was assessed by handgrip dynamometer (Model J00105; Jamar Hydraulic Hand Dynamometer) using the dominant hand in a supinated position with elbow flexed at 90º. There was 1-min rest interval between efforts and the maximum value of three attempts was used.[19]

Sarcopenia was defined as SMI and muscle strength lower than 7.26 kg/m^2 and 30 kg, respectively.[20]

Laboratory Measurements

Blood samples were drawn in the morning after 12h overnight fasting. The laboratory tests included B-type natriuretic peptide (BNP; pg/mL) plasma level, serum sodium (mEq/L), serum potassium (mEq/L), creatinine (mg/dL), haemoglobin level (g/dL), high-sensitivity C-reactive protein (hs-CRP; mg/L), lipid profile (triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein; mg/dL), and fasting glucose (mg/dL).

Statistical analysis

Data are presented as mean ± standard deviation and median with lower and upper quartile (95%CI). One-sample Kolmogorov-Smirnov test was used to evaluate the distribution normality of the studied variables. Student's t-test and Mann-Whitney U test were used to compare parametric and nonparametric variables, respectively. Chi-square test and Spearman's correlation were used as appropriate. The Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, Illinois, USA) was used to perform all the statistical analysis. P value lower than 0.05 was considered statistically significant.

Results

Clinical-demographic data

We prospectively enrolled 116 male patients (Table 1) with stable chronic HF, 33 of whom were identified to have sarcopenia (28%). Patients with sarcopenia were older, had higher BNP concentration, and lower hemoglobin compared with patients without sarcopenia. No difference was found between sarcopenic and non-sarcopenic patients regarding the dosage of β-blocker medication (20 ± 9.6 vs. 23 ± 10.5 mg b.i.d., p = 0.39; respectively) and medication in general (Table 1).

Muscle sympathetic nerve activity, heart rate recovery and functional capacity

Patients with sarcopenia had higher MSNA (Figure 1) and lower ΔHRR1 and ΔHRR2 (Figure 2) when compared with non-sarcopenic patients. There was no statistical difference in resting HR and peak HR between sarcopenic and non-sarcopenic patients.

Table 1 – Demographic and clinical characteristics of the study population

Variables	All patients (n = 116)	Patients with sarcopenia (n = 33)	Patients without sarcopenia (n = 83)	P value
Age (y)	55 ± 9	59 ± 6	54 ± 9	0.002
Weight (kg)	71.1 ± 14.4	59.4 ± 7.4	75.8 ± 13.8	< 0.001
Height (m)	1.67 ± 0.07	1.66 ± 0.07	1.67 ± 0.07	0.401
BMI (kg/m^2)	25.5 ± 4.5	21.6 ± 2.5	27.1 ± 4.2	< 0.001
Aetiology (Ischaemic/non-ischaemic)	30/86	8/25	22/61	1.000
NYHA class (I/II/III/IV)	40/41/28/7	9/11/11/2	31/30/17/5	0.500
LVEF (%)	28 ± 8	26 ± 7	29 ± 8	0.124
BNP (pg/mL)	773 ± 877	1159 ± 924	621 ± 816	0.006
Sodium (mEq/L)	139 ± 3	138 ± 4	139 ± 3	0.383
Potassium (mEq/L)	4.6 ± 0.4	4.6 ± 0.3	4.6 ± 0.4	0.535
Creatinine (mg/dL)	1.24 ± 0.39	1.27 ± 0.47	1.23 ± 0.35	0.568
Haemoglobin (g/dL)	13.9 ± 1.7	13.3 ± 1.6	14.1 ± 1.7	0.022
hs-CRP (mg/L)	8.96 ± 16.0	12.4 ± 13.6	7.6 ± 16.7	0.147
Triglyceride (mg/dL)	118 ± 68	96 ± 38	127 ± 75	0.031
Cholesterol (mg/dL)	170 ± 45	159 ± 37	174 ± 48	0.111
HDL (mg/dL)	44 ± 15	47 ± 16	44 ± 14	0.306
LDL (mg/dL)	103 ± 35	95 ± 25	106 ± 38	0.155
Fasting glucose (mg/dL)	108 ± 21	106 ± 24	109 ± 20	0.510
Medication				
β-blocker		33 (100)	78 (94)	0.319
Statins		18 (55)	49 (59)	0.682
ACEI/ARB		31 (94)	76 (92)	1.000
Diuretics		26 (79)	62 (75)	0.811
Anticoagulants		12 (36)	32 (39)	1.000
Hydralazine		6 (18)	18 (22)	0.802
Isosorbide		6 (18)	18 (22)	0.802
Spironolactone		24 (73)	58 (70)	0.824

Data are presented as mean ± SD or %. P value referred to Student's t-test and Chi-square test for medication. ACEI, angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; BNP: B-type natriuretic peptide; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Spearman's correlation showed a positive correlation between appendicular lean muscle mass and ΔHRR1 and ΔHRR2 (Figures 3A and 3B, respectively). In addition, we observed a negative correlation between appendicular lean muscle mass and MSNA (Figure 3C).

Absolute VO_{2peak}, relative VO_{2peak}, and peak workload were significantly lower in patients with sarcopenia than those without. Sarcopenic patients also showed higher ventilatory equivalent for carbon dioxide (VE/VCO_2) slope and dead space to tidal volume (VD/VT_{peak}) than non-sarcopenic patients, whereas VE_{peak} was lower in patients with sarcopenia than those without (Table 2).

Body composition and muscle strength characteristics

Body mass index was lower in sarcopenic patients when compared with non-sarcopenic, with a significant reduction in appendicular lean muscle mass, total lean mass, fat mass, and fat percentage (Table 2). SMI and muscle strength assessed by handgrip dynamometer were also lower in patients with sarcopenia compared with those without sarcopenia.

Discussion

The main and new findings of this study are that sarcopenic patients with HF have increased resting MSNA and blunted vagal reactivation after maximal exercise testing when compared with patients without sarcopenia. Moreover, the appendicular lean muscle mass seems to be associated with higher MSNA and blunted HRR. Additionally, as previously demonstrated,[2] we also confirmed the reduction in exercise tolerance (decreased peak VO_2 and peak workload) in patients with HF and muscle wasting.

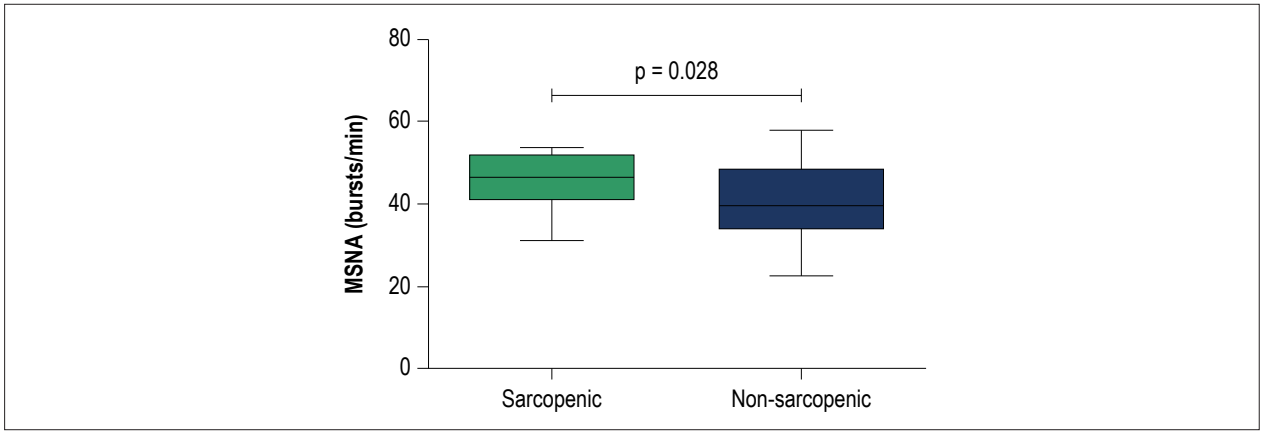

Figure 1 – *Muscle sympathetic nerve activity (MSNA) in bursts/min. Values are presented as medians with lower and upper quartiles (CI 95%). Note that sarcopenic patients showed an increase of 18% in MSNA.*

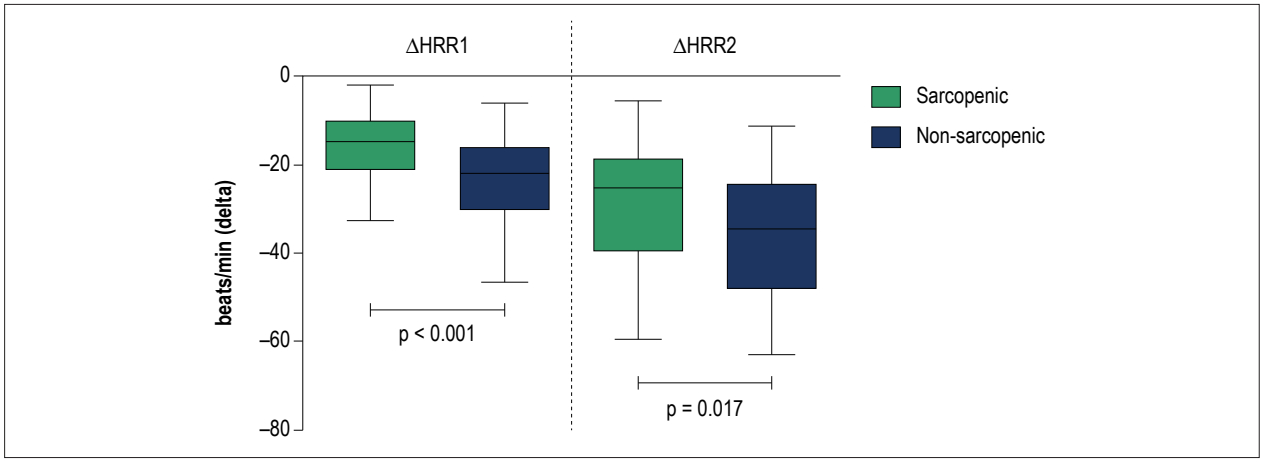

Figure 2 – *Delta heart rate recovery at 1st (ΔHRR1) and 2nd (ΔHRR2) minutes immediately after maximal exercise testing. Values are presented as medians with lower and upper quartiles (CI 95%). Note that sarcopenic patients showed a lower HRR at 1st (47% difference) and 2nd minutes (40% difference).*

HF is a complex disease associated with several comorbidities. One of the major co-morbidities observed in patients with advanced chronic HF is sarcopenia, which is associated with poor prognosis.[21] Although the aetiology of sarcopenia is multifactorial, several mechanisms have been suggested to explain this decrease in muscle mass in patients with HF, such as increased inflammatory profile,[22] increased oxidative stress,[23] overactivation of ubiquitin–proteasome system,[24] and increased C-terminal agrin fragment (CAF).[25] These alterations, acting independently or in combination, may lead to excessive muscle protein degradation and reduced muscle protein synthesis.

Besides the mechanisms mentioned above, exacerbated sympathetic nerve activity seems to be an important pathophysiological feature in HF leading to the loss of skeletal muscle.[6] In an experimental model of HF, Bacurau and colleagues[6] showed that sympathetic hyperactivity contributes to the development of skeletal myopathy by changing muscle morphology.[6] β_2-adrenoceptors play a key role in regulating skeletal muscle mass in both anabolic and catabolic state.[26] However, chronic sympathetic hyperactivity may be toxic to skeletal muscle,[27] which favors weight loss and sarcopenia in patients with HF. Moreover, increased sympathetic outflow is associated with higher chance of arrhythmias,[28] and adverse remodeling of the heart.[29]

Interestingly, pharmacological treatment of HF is focused on blocking sympathetic activity, mainly by using cardio-selective and non-selective β-blockers.[30] Treatment with β-blockers can increase total body fat mass and total body fat content in patients with HF, without apparent improvement in muscle mass.[30,31] In this study, we did not observe differences between groups in β-blocker treatment and dosage. In this context, future randomized clinical trials are required to assess the real impact of β-blocker therapy on skeletal muscle mass in patients with HF.

Previous studies showed that HRR has an important prognostic value in the general population[12] and in patients with HF.[32] In addition, HRR is a very simple and easy way to indirectly evaluate the reactivation of the parasympathetic

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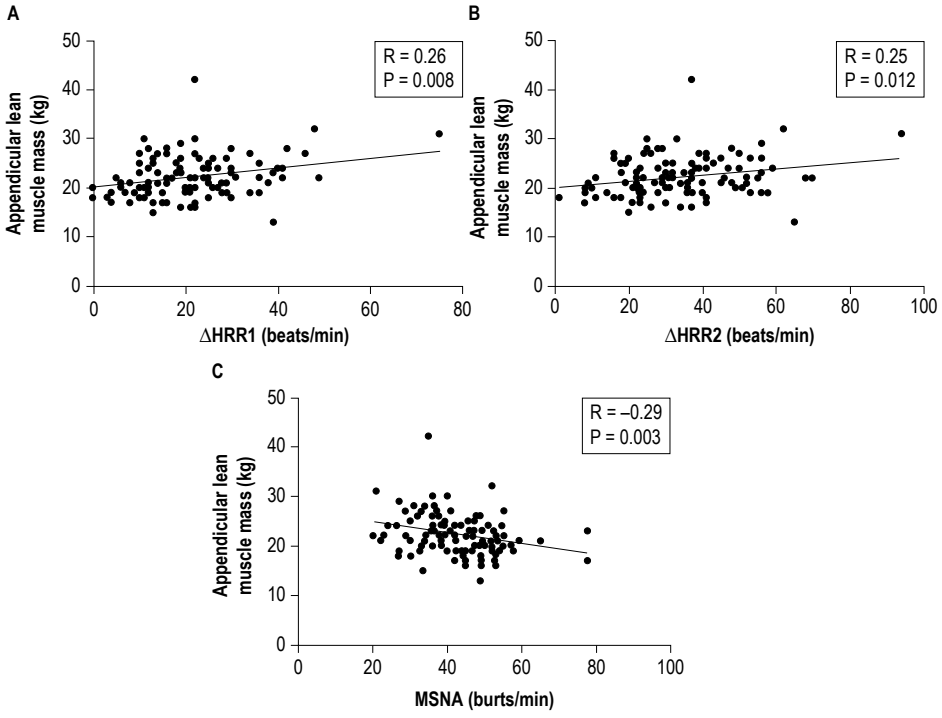

Figure 3 – *(A) Spearman's correlation between appendicular lean muscle mass and delta heart rate recovery at 1st minute (ΔHRR1). (B) Spearman's correlation between appendicular lean muscle mass and delta heart rate recovery at 2nd minute (ΔHRR2). (C) Spearman's correlation between appendicular lean muscle mass and muscle sympathetic nerve activity (MSNA).*

Table 2 – Cardiopulmonary, body composition and strength variables of the patients

Variables	All patients (n = 116)	Patients with sarcopenia (n = 33)	Patients without sarcopenia (n = 83)	P value
Absolute VO_{2peak} (L/min)	1.43 ± 0.48	1.09 ± 0.31	1.58 ± 0.47	< 0.001
Relative VO_{2peak} (ml/(kg/min))	20.1 ± 6.3	18.3 ± 5.3	21.0 ± 6.5	0.036
Peak workload (Watts)	103 ± 47	77 ± 27	115 ± 51	< 0.001
Resting HR (beats/min)	72 ± 13	75 ± 16	71 ± 12	0.254
HR_{peak} (beats/min)	134 ± 27	130 ± 27	135 ± 28	0.323
VE/VCO_2 slope	35 ± 7	37 ± 8	33 ± 7	0.015
VD/VT_{peak}	0.17 ± 0.02	0.19 ± 0.04	0.16 ± 0.04	< 0.001
VE_{peak} (L/min)	62.5 ± 18.3	53.5 ± 14.1	66.4 ± 18.4	< 0.001
Body composition and strength				
Total LM (kg)	49.6 ± 8.4	43.0 ± 5.2	52.5 ± 8.0	< 0.001
ALM (kg)	22.2 ± 4.3	18.3 ± 2.3	23.9 ± 3.8	< 0.001
SMI (kg/m^2)	7.97 ± 1.21	6.63 ± 0.58	8.54 ± 0.92	< 0.001
Fat mass (kg)	18.2 ± 8.5	12.9 ± 4.9	20.5 ± 8.8	< 0.001
Fat (%)	26 ± 8	22 ± 7	27 ± 8	< 0.001
Handgrip strength (kg)	33 ± 8	26 ± 3	36 ± 8	< 0.001

Data are presented as mean ± standard deviation or %. P value referred to Student's t-test. ALM: appendicular lean muscle mass; HR: heart rate; LM: lean mass; SMI: skeletal muscle mass index; VE: ventilation; VE/VCO_2: ventilatory equivalent for carbon dioxide; VD/VT: dead space to tidal volume; VO_2: oxygen consumption.

nervous system immediately after maximum effort in cardiopulmonary exercise testing.[11] Several investigators showed that the kinetic of HRR in a 6-min recovery period was reduced in patients with HF[33] and this reduction seems to be independent of β-adrenergic blocker therapy.[34] Ushijima et al.[35] showed an association between norepinephrine and HRR in patients with myocardial infarction, arguing that increased sympathetic excitation at maximum exercise may suppress the parasympathetic reactivation leading to HRR attenuation.[35]

Taken together, the sympathovagal impairment in patients with HF is associated with poor outcome, and this autonomic imbalance may worsen the loss of muscle mass in these patients. In fact, we showed greater MSNA and lower decrease in HRR at 1st and 2nd minutes post-exercise in sarcopenic patients with HF. Furthermore, reduced appendicular lean muscle mass was correlated with lower HRR1 ($r = 0.26$), HRR2 ($r = 0.25$) and greater MSNA ($r = -0.29$).

We recognize limitations in our study. The present study included only male patients, so we are not able to generalize these results to female patients with HF. Further studies are necessary to investigate the influence of sarcopenia on gender-related differences. The date when HF was diagnosed was not available in patients' medical records, and to compensate for this missing information, we included only patients with at least one year of diagnosis. We assessed parasympathetic activity using the HRR as a marker of vagal reactivation. Although our study has a clinical applicability, more studies using HR variability should clarify the role of cardiac autonomic control on sarcopenia in patients with HF.

Conclusion

Sympatho-vagal imbalance seems to be associated with sarcopenia in male patients with HF. These results highlight the importance of a therapeutic approach in patients with muscle wasting and increased peripheral sympathetic outflow.

Author contributions

Conception and design of the research: Fonseca GWP, dos Santos MR, Alves MJNN; Acquisition of data: Fonseca GWP, dos Santos MR, Souza FR, Costa MJA, Takayama L, Pereira RMR, Alves MJNN; Analysis and interpretation of the data: Fonseca GWP, dos Santos MR, Costa MJA,Souza FR, Pereira RMR, Negrão CE, Alves MJNN; Statistical analysis: Fonseca GWP, dos Santos MR; Obtaining financing: Negrão CE, Alves MJNN; Writing of the manuscript: Fonseca GWP, Souza FR, Alves MJNN; Critical revision of the manuscript for intellectual content: dos Santos MR, von Haehling S, Pereira RMR, Negrão CE, Anker SD, Alves MJNN.

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 Guilherme Wesley Peixoto da Fonseca, from Universidade Federal de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number 0892/07. 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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Heart and Skeletal Muscles: Linked by Autonomic Nervous System

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Short Editorial related to the article: Sympatho-Vagal Imbalance is Associated with Sarcopenia in Male Patients with Heart Failure

The autonomic nervous system (ANS) plays a fundamental role in maintaining cell homeostasis and human life. The functionality of the heart and skeletal muscles is partially modulated by sympathetic and parasympathetic branches of the ANS both in resting and exercising conditions.

Substantial literature attests to the fact that objective indices of muscle strength reflect health status. It is well-established that heart failure is typically accompanied by skeletal muscle abnormalities that contributed to the exercise intolerance and poor health-related quality of life usually seen in these patients.[1,2] Indeed, while a decrease in muscle mass and strength is naturally seen with ageing, especially after the fifth decade of life, this is especially more relevant in middle-aged and older patients with heart failure.

Several decades ago, the term sarcopenia was proposed as a medical expression to describe the universal and involuntary loss in muscle mass that occurs with age.[3] However, despite the fact that several criteria were proposed to characterize it, a growing body of knowledge understanding its pathophysiology and confirming its clinical and epidemiological relevance and being listed in ICD-10,[4] still today, it remains rarely evaluated in daily medical practice.

In a Brazilian and German collaborative research study, Fonseca et al.[5] analyzed data from 116 male patients with heart failure with reduced ejection fraction (HFrEF) that were submitted to a maximal cycling cardiopulmonary exercise testing using a ramp protocol. In addition, using a microneurography technique, muscle sympathetic nerve activity was directly recorded from the peroneal nerve and parasympathetic activity was estimated by the magnitude of heart rate decay in the first two minutes after the maximal cycling exercise test. Measurements were obtained from dual-energy X-ray absorptiometry (DEXA) and handgrip strength to reflect, respectively, body composition and muscle strength. Based on these measurements and applying standard literature criteria, the authors were able to identify the presence or absence of sarcopenia in their set of patients. We acknowledge the authors by their study originality that could add a significant contribution to the existing body of knowledge in the research area.

Combining all these data, they searched for a link between heart-skeletal muscle abnormalities and ANS dysfunction and tried to quantify the association between sympathetic ANS abnormalities and sarcopenia in male patients with clinically stable heart failure. They have identified sarcopenia in 33 (28%) of HFrEF patients and their results indicated that these patients had significantly distinct results to the ANS variables assessed when compared as to the group of patients without sarcopenia.[5] Moreover, they found a significant although quite modest correlation (r = -0.29) between appendicular muscle mass and muscle sympathetic nerve activity. Looking in more details their results, it is possible to note that there is a considerable overlapping between the results of HFrEF patients with and without sarcopenia, which may diminish the clinical value.

Based on their current study by Fonseca et al.,[5] we can speculate that if they have used other assessment methods, like the 4-second exercise test,[6,7] – a very specific one for assessing cardiac vagal activity – and handgrip strength relative to body weight or maximal muscle power[8] or even a simple functional test like the sitting-rising test,[9] all of them, more specific to assess dynapenia, a likely clinically more relevant issue than sarcopenia,[10,11] they could have found additional discriminative values.

Finally, perhaps regular exercise/physical exercise could be the way to improve the health status of HFpEF patients. In acknowledging that this study showed an association between cardiac ANS dysfunction and heart and skeletal muscle abnormalities and knowing that regular aerobic and resistance exercise improves cardiac ANS modulation, including reducing the risk of ventricular fibrillation on the occurrence of a myocardial infarction,[12] and are strongly recommended as part of the medical treatment of patients with sarcopenia and for those with HFpEF;[13] it is quite motivating to think about an expected next step in research: a randomized controlled trial with exercise training intervention. Such study would assess if the ANS dysfunction reported by Fonseca et al.[5] is subject to reversal, and if so, how this would improve quality of life and other major health outcomes in patients with HFpEF.

Keywords

Heart Failure; Myocardium; Muscle,Skeletal; Autonomic Nervous System; Homeostasis; Heart Failure; Sarcopenia; Sympathetic Nervous System.

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Original Article

The Relationship between Lifestyle and Costs Related to Medicine Use in Adults

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Abstract

Background: **The unhealthy lifestyle is growing and this can have repercussions on health status demanding actions on the occurrence of diseases and leads to increased expenses.**

Objective: **To examine the interrelationship between the costs of medicine use and lifestyle behaviors.**

Methods: **A cohort study with 118 participants, age around 51.7 ± 7.1 years old. It was collected personal and anthropometric data and information about medicine of continuous use to calculate the costs. Lifestyle variables included habitual physical activity (PA) assessed by pedometer, sedentary behavior by Baecke questionnaire, sleep quality by mini sleep questionnaire and self-report of smoke and alcohol consumption. Statistical analyses were performed by BioEstat (version 5.2) and the significance level set at p-value < 0.05.**

Results: **In 12 months, 62 subjects bought 172 medicines, representing an overall cost of US$ 3,087.01. Expenditures with drugs were negatively related to PA (r = -0.194, p-value = 0.035 and r = -0.281, p-value = 0.002), but positively related with sleep quality (r = 0.299, p-value=0.001 and r = 0.315, p-value = 0.001) and age (r = 0.274, p-value = 0.003). Four multivariate models were executed considering lifestyle behaviors in different moments of cohort and medicine costs, and all these models identify important relationship between lifestyle behaviors with expenditures with drugs.**

Conclusion: **Worse sleep quality seems to increase the costs related to medicine use in adults, while obesity and ageing play a relevant role in this phenomenon and alcohol consumption seems a variable with relevant economic impact. (Arq Bras Cardiol. 2019; 112(6):749-755)**

Keywords: **Quality of Life; Sedentary Lifestyle; Obesity; Sports Medicine; Longevity; Health Behavior, Exercíse.**

Introduction

Over the last decades, the occurrence of obesity and chronic diseases has increased dramatically among adults worldwide.[1] On the other hand, advances in medical sciences, development of new generation of medicines/therapies, have significantly improved quality of life and longevity.[2,3]

In developing countries, the use of any medicine is reported by 60% of the adult population, while the use of three or more medicines in the last two weeks is reported by about 18% of the population.[4] A similar pattern is observed in Central Eastern Europe where more than 20% of adults (18 years plus) report three or more medicine use.[5] Narayan et al.[3] found that in a period of nine years (from 2005 to 2013) the use of drugs for prevention purposes (aspirin, clopidogrel, statins and bisphosphonates) increased significantly among New Zealand adults aged 65 years or more (about 19.5%, 2.9%, 7% and 2.3%, respectively).

The dramatic rise in the prevalence of obesity and its associations with the development of metabolic and cardiovascular diseases would explain, at least in part, this increase trend.[1,6] In fact, wide access to medicines by population signifies an improvement in the prevention/treatment of diseases.[2] However, the potential adverse drug reactions generated by the use of unprescribed medicines constitute a global public health concern related to high healthcare costs.[7,8]

The economic burden related to medicine use involves not only health care costs resulting from inappropriate medication but also the purchase of prescribed and unprescribed medicines (public and out of pocket expenses).[7,9] For example, in a period of five years from 2000 to 2004, the Brazilian Ministry of Health expended US$ 916 million in programs to provide high-cost drugs to population.[10] Despite the increasing economic burden related to medicines use, little is known about its underlying determinants. We need to know these determinants in order to identify target areas for policy making on managing health budgets, particularly in health systems in developing settings.

Unhealthy lifestyle behaviors (alcohol consumption, smoking, poor sleep habits and sedentary behaviors [SB]) have

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been shown to play an important role in the development of many diseases,[11] but their direct relationship with the costs related to medicines use is unclear. For example, the occurrence of sleep disorders is highly prevalent in adults,[12] but its economic burden is unknown.[13] A longitudinal study carried out with 11,698 American employees identified that how worse were the sleep disorder reported the health care costs to increase in average US$ 725.15.[13] Similarly, in a 12-months study carried out in Taiwan, adults with positive diagnosis to obstructive sleep apnea were 66% more expensive (in terms of physician diagnoses, medications, treatments, surgeries, laboratory tests and diagnostic imaging) than those adults without the same diagnosis (US$ 1,734.10 versus US$ 1,041.30, respectively).[14] Conversely, improved levels of physical activity (PA) could reduce costs related to medicine use in adults,[15,16] but its role in the potential relationship between unhealthy lifestyle behaviors and costs of medicine use has not been studied to date.

In this study, we examine the interrelationship between costs of medicine use and lifestyle behaviors (both healthy and unhealthy).

Methods

Sample

The data comes from a cohort study carried out in the city of Presidente Prudente which presents human development index 0.806,[17] placed on western Sao Paulo State (which is the state of the most industrialized Brazilian federation) from February/June 2014 (baseline) to May/December 2015 (follow-up). Sample size estimation was based on an equation for the correlation coefficient. Due to the absence of specific data about the relationship between lifestyle behaviors and health care costs in Brazil,[16,18] we have adopted a correlation coefficient of 0.30 between PA and health care costs,[16,18] $z = 1.96$ and power of 80% (adopting the above-mentioned parameters, the minimum sample size required for this study was 86 participants). The inclusion criteria for participants were: 40-65 years old, no diagnosis of previous cardiovascular complications (e.g. stroke, heart attack), no diabetes complications (amputation or visual problems), no regular medication use, and no physical disability.

Invitation to participate in the study was conducted using advertisements (ie posters) in the Sao Paulo State University in Presidente Prudente and gyms/fitness centers across the city. Interested participants contacted the research staff, who then checked the profile of the participants against the inclusion criteria (participants who met all the inclusion criteria signed a written consent form). One hundred ninety-eight adults contacted the research staff and were considered eligible and undertook baseline assessment. The analysis herein covered 118 subjects (44 men and 74 women) assessed at both baseline and follow-up (12 months later). The excluded people were due to (a) dropouts (n = 62) and (b) provision of less than seven days of pedometer use at baseline (n = 18).

All procedures (questionnaires, pedometers and body composition assessment) were performed by trained staff of researchers (Professors, MSc and PhD students) following the protocols of the Laboratory of Investigation in Exercise (LIVE), Brazil.[19] The Ethics committee of the Sao Paulo State University (UNESP), campus of Presidente Prudente, approved the study.

Costs of medicines use

At baseline, the participants were given a questionnaire (in diary form) for medicine use and instructions (further clarification offered face to face by research staff) on how to fulfil the questionnaire. The participants reported the following data: (a) number and type of all medicines (prescribed and unprescribed); (b) how they obtained the medicines - through the Brazilian National Health System [BNHS] or out of pocket expenditure. The diary was filled for each of the 12 months of the cohort study. At the end of the follow-up period, the research staff collected back the completed diaries (Table 1). To calculate the cost of medicines, we used national prices presented by BNHS (for medicines delivered by the BNHS) and market prices from drug stores in the study area (medicines obtained via personal expenses). Costs were computed in Brazilian currency (Real$) and converted to US dollar (US$) using the cambial information provided by the Central Bank of Brazil.

Lifestyle behavioral variables

PA was measured using both objective and subjective measures at baseline and follow-up. Objective measure of PA was collected using pedometers (Yamax digiwalker, SW200 model, Japan), and specified in terms of step count. At both assessments periods (baseline and follow-up), pedometers were worn by participants for seven consecutive days. The pedometers were fixed laterally at the hip and were taken off only during periods of sleep and water-based activities. Participants logged (at the end of each day) the total step count. In the present study, PA denoted the number of days (out of 14 days assessed) that ≥7,500 steps were achieved. In line with Tudor-Locke et al.,[20] participants who reached ≥7,500 steps/day were classified as "sufficiently active". The subjective measure of PA was collected using Baecke's questionnaire.[21] The questionnaire is composed of 16 questions about three PA domains (occupational, sports participation and leisure-time PA).

Data on SB at work (both baseline and follow up) were captured using the following question: "At work I sit"...; potential responses were: never [score attributed = 1], seldom [score attributed = 2], sometimes [score attributed = 3], often [score attributed = 4] and very often [score attributed = 5]).

Quality of sleep was assessed at baseline and follow up using the Mini-Sleep Questionnaire,[22] which includes 10 questions, each one with seven possible answers (ranging from never to always). The sum of these 10 answers generates a numerical score ranging from 10 to 70 points (higher scores indicate worse sleep quality).

Participants also self-reported at baseline and follow-up smoking status (yes or no current smoker) and weekly alcohol consumption (number of days per week with alcohol consumption).

Table 1 – Most frequently bought medicines according to anatomical therapeutic chemical code

Anatomical Therapeutic Chemical Code	Types of medicine	Number of medicines bought
Digestive tract and metabolism	18	33
Blood and Blood-forming organs	2	2
Cardiovascular system	31	42
Dermatological	1	1
Genito-urinary system and sex hormones	9	25
Hormones, except sexual and insulin	10	10
Systemic anti-infective agents	1	1
Anti-neoplastics and immune modulators	1	2
Muscle-skeletal system	7	9
Nervous system	28	38
Antiparasitics	1	2
Respiratory system	3	3
Sensory organs	1	1
Other	1	3
Overall	114	172

Covariates

Covariates were data collected via questionnaire (sex [male or female], date of birth [chronological age estimated using the difference between birthday and date of assessment] and formal schooling [in years]). Clinical data also were evaluated (body fatness [dual-energy X-ray absorptiometry], systolic and diastolic blood pressure respectively). Researchers performed the clinical measures in university facilities with controlled temperature and followed standardized procedures.

Statistical analyses

Descriptive statistics were undertaken using mean, 95% confidence intervals (95%CI) and proportions as appropriate. Due to non-parametric distribution (attested by Kolmogorov-Smirnov test), the costs of medicine use were converted into base-10 logarithms.

Both the Pearson correlation and linear regression were conducted to assess the relationship between the costs of medicines and the independent variables. In the former approach, Pearson correlation (expressed as standardized coefficients ["*r*" values]) analyzed the relationship of the costs of medicine use with lifestyle behaviors (sleep quality, PA, SB at work, smoking and alcohol consumption) and covariates (sex, age, schooling, blood pressure and body fatness) separately. In the latter, linear regression models (expressed as unstandardized coefficients [β values]) were fitted to examine the relationship between the costs of medicine use and lifestyle behaviors controlling for all covariates. For each approach, four models were fitted based on different specifications of lifestyle behaviors ([A] only baseline values, [B] only follow-up values, [C] difference between follow-up and baseline and [D] sum of baseline and follow-up), to explore the differential relationship these specifications may present. Diagnosis of multicollinearity and homoscedasticity were assessed and the linear regression models were considered adequately fit.

All analyzes were performed using BioEstat (version 5.2) and the significance level was set at p-value < 0.05.

Results

At baseline, the mean age of the sample was 51.7 ± 7.1 years, ranging from 40 to 68 years (Table 2). Alcohol was consumed on average 2.1 days per week, while 5.1% of the sample were smokers. Expenses on medicine use were reported by 52.5% of the sample. During 12-months of follow-up, 62 subjects bought 172 medicines (Table 2), representing an overall cost of US$ 3,087.01 for the entire sample. There was no missing data.

PA decreased significantly from baseline to follow-up (p-value = 0.024), while the score for SB at work (p-value = 0.396), sleep quality (p-value = 0.951) and alcohol consumption (p-value = 0.100) remained stable between baseline and follow-up.

In the bivariate analysis, costs of medicine use were negatively related to $PA_{baseline}$ (r = -0.194; p-value = 0.035), $PA_{follow\text{-}up}$ (r = -0.281; p-value = 0.002), but positively related with sleep quality $_{baseline}$ (r = 0.299; p-value= 0.001) and sleep quality $_{follow\text{-}up}$ (r = 0.315; p-value = 0.001), and age $_{baseline}$ (r = 0.274; p-value = 0.003). Gender, education, SB at work, alcohol consumption and smoking were not significantly related with costs of medicine use. There was no interrelationships among the lifestyle behaviors.

In the multivariate model considering lifestyle behaviors at baseline (Model-A), sleep quality and body fatness were positively related to higher 12-months medicine costs, while alcohol consumption was negatively related to it. Model-A explained 19.1% of all variance in the outcome (Table 3). In the multivariate model considering lifestyle behaviors at follow-up (Model-B), only sleep quality was positively related to higher 12-months medical costs. Model-B explained 21.9% of all variance in the medicine costs.

Table 2 – Summarized characteristics of the sample (n = 118)

Variables	Descriptive Statistic	
	Mean (95%CI)	Median (IR)
Age (years)$_{baseline}$	51.7 (50.4 to 53.1)	51.1 (10.1)
Body weight (kg)$_{baseline}$	74.6 (71.7 to 77.4)	72.6 (16.6)
Height (m)$_{baseline}$	1.65 (1.63 to 1.67)	1.65 (0.15)
BMI (Kg/m^2)$_{baseline}$	26.92 (26.3 to 27.5)	26.41 (5.98)
Costs with medicine (US$)$_{follow-up}$	26.16 (17.7 to 34.62)	1.19 (42.91)
Alcohol consumption (days)$_{baseline}$	2.1 (1.9 to 2.3)	2 (2)
Alcohol consumption (days)$_{follow-up}$	1.9 (1.7 to 2.2)	1 (2)
Sleep quality (MSQ score)$_{baseline}$	26.6 (24.7 to 28.4)	25 (13)
Sleep quality (MSQ score)$_{follow-up}$	26.8 (24.8 to 28.7)	26 (15)
PA (≥7,500 steps/day)$_{baseline}$	2.3 (1.8 to 2.7)	1 (5)
PA (≥7,500 steps/day)$_{follow-up}$	1.9 (1.5 to 2.3)	1 (4)
SB at work (score)$_{baseline}$	3.2 (2.9 to 3.4)	3 (2)
SB at work (score)$_{follow-up}$	3.1 (2.9 to 3.3)	3 (2)
Smoking (yes [%])$_{baseline}$	5.1% (1.1% to 9.1%)	---
Smoking (yes [%])$_{follow-up}$	5.9% (1.6% to 10.1%)	---
Medicine use (yes [%])$_{follow-up}$	52.5 (43.5% to 61.5%)	---

95% CI: 95% confidence interval; IR: interquartile range; BMI: body mass index; MSQ: mini-sleep questionnaire; PA: physical activity; SB: sedentary behavior.

Table 3 – Linear regression describing the relationship between 12-months medicine costs (dependent variable) and lifestyle behaviors (n= 118)

Independent variables	Model - A	Model - B	Model - C	Model - D
	Baseline	Follow-up	Follow-up minus Baseline	Baseline plus Follow-up
	β (β$_{95\%CI}$)	β (β$_{95\%CI}$)	β (β$_{95\%CI}$)	β (β$_{95\%CI}$)
PA (steps)	-0.011 (-0.078 to 0.056)	-0.048 (-0.122 to 0.027)	-0.18 (-0.092 to 0.056)	-0.017 (-0.058 to 0.025)
Sleep quality (MSQ score)	0.018 (0.001 to 0.034)	0.018 (0.002 to 0.033)	0.004 (-0.017 to 0.026)	0.011 (0.002 to 0.019)
Alcohol consumption (days)	-0.137 (-0.272 to -0.002)	-0.111 (-0.241 to 0.019)	0.034 (-0.140 to 0.208)	-0.073 (-0.145 to -0.001)
Smoking (yes)	0.157 (-0.514 to 0.828)	0.424 (-0.224 to 1.072)	0.819 (-0.376 to 2.014)	0.170 (-0.172 to 0.513)
SB at work (frequency)	0.021 (-0.114 to 0.157)	0.017 (-0.123 to 0.157)	0.023 (-0.154 to 0.201)	0.006 (-0.070 to 0.082)
Sex (female)*	-0.447 (-0.900 to 0.007)	-0.341 (-0.780 to 0.098)	-0.302 (-0.731 to 0.126)	-0.421 (-0.872 to 0.029)
Age (years)*	0.021 (-0.004 to 0.047)	0.020 (-0.004 to 0.044)	0.029 (0.003 to 0.056)	0.019 (-0.005 to 0.044)
Body fatness (%)*	0.023 (0.003 to 0.043)	0.019 (-0.002 to 0.039)	0.027 (0.007 to 0.048)	0.020 (-0.001 to 0.040)
SBP (mmHg)*	-0.005 (-0.028 to 0.019)	-0.005 (-0.028 to 0.017)	-0.004 (-0.028 to 0.020)	-0.005 (-0.028 to 0.018)
DBP (mmHg)*	0.017 (-0.010 to 0.044)	0.021 (-0.005 to 0.047)	0.014 (-0.014 to 0.043)	0.020 (-0.007 to 0.046)
Schooling (years)*	0.084 (-0.024 to 0.193)	0.091 (-0.020 to 0.202)	0.080 (-0.026 to 0.187)	0.092 (-0.019 to 0.202)
Linear regression parameters				
R	0.527	0.549	0.473	0.548
r ^{2}	0.278	0.301	0.224	0.300
r ^{2} $_{adjusted}$	0.191	0.219	0.131	0.217

**: only baseline values were used; Model-A: lifestyle behaviors inserted as baseline values; Model-B: lifestyle behaviors inserted as follow-up values; Model-C: lifestyle behaviors inserted as follow-up minus baseline values; Model-D: lifestyle behaviors inserted as baseline plus follow-up values; 95%CI: 95% confidence interval; PA: physical activity; MSQ: mini-sleep questionnaire; SB: sedentary behavior; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

In the multivariate model considering changes over time in lifestyle behaviors (Model-C), age and body fatness were positively related to higher 12-months medicine costs. Model-C explained 13.1% of all variance in the medicine costs. In Model-D (sum of baseline and follow-up values), sleep quality had a positive relationship with medicine use (Table 3). On the other hand, alcohol consumption was negatively related to costs of medicine use. Model-D explained 21.7% of all variance in the medicine costs.

Discussion

This study shows that lifestyle behaviors particularly worse sleep quality leads to higher costs related to medicine use. Body fatness was also found to be an important predictor – positive effect on costs. In overall, 52.5% of adults reported any medicine use during the cohort period, while 20.5% (n = 24) of these same adults reported the use of three or more medicines. These rates are similar to Brazilian (18%) and European (20%) surveys, in which population-based samplings were carried out.[4,5]

Another similarity with previous studies observed in our findings is that drugs for the treatment of cardiovascular diseases were the most reported by the participants. A study carried out in New Zealand examining the trends of medicine use in adults aged ≥ 65 years from 2005 to 2013 identified that the use of drugs to prevent cardiovascular events (aspirin and statins) increased significantly.[3] The dynamics observed for medicines to the treatment of cardiovascular diseases seems affected by aging as well (in our study, a relevant covariate in the multivariate models). Previous data have identified that consumption of aspirin and dipyridamole increased in older adults at a higher rate than observed in younger ones.[3]

The increased amount paid by older adults can be supported by the natural effects that ageing exert over organs of the human body and their functions,[23] but also boosted by the reduced PA observed in older groups.[24] In the analyzed sample, although the effect of age on costs with medicine use was not mediated by PA, they were related with other in crude analyzes, denoting the relevance of actions targeting the improvement of PA practice mainly in population groups composed of older adults.[23,24]

In this sample, the higher cost with medicines in adults with sleep disorders can represent not only the treatment of the sleep disorders itself, but also the use of medicines to relief its symptoms and hence to maintain the daily activities, such as work.[13,25]

The findings related to alcohol consumptions were surprising because usually the higher alcohol consumption is linked to higher health care costs,[26,27] and not the opposite as observed in our study. In fact, the linkage between alcohol consumption and health care costs can be direct (e.g. diseases directly linked to alcohol consumption) and indirect (e.g. traffic car accident), but it is important to take into account that some kinds of alcoholic drinks have healthy characteristics, such as anti-inflammatory properties observed in the red wine.[28] Therefore, the explanation for our interesting finding could be due to both the type and amount of alcohol consumed. However, our study looked at only the number of days per week with alcohol consumption, and not amount and type of alcohol consumed, which characterizes a limitation in our study.

Other limitations of the study are worth mentioning. The first limitation of the study is the small sample size. The current study has statistical power of 80% to detect coefficient of correlation of 0.256 or higher, while the relationship between some behaviors and costs with medicine are around r = 0.110.[16] Even considering the fact that the inclusion of covariates increases the power of multivariate models,[29] the reduced sample size may have been responsible for the absence of significant relationship between PA and costs with medicine. Another limitation related to objective measures of PA is the logging of data by the participants because every day they had to note the number of steps displayed in the pedometer. Although this method is widely used,[19] it could have led to misreporting. As above mentioned, the absence of measures of amount and kind of alcoholic drinks and sedentary behavior (by screen time on TV or computer) constitute limitations as well. Further studies could explore the impact of these.

Conclusions

Worse sleep quality seems to increase the costs related to medicine use in adults, while obesity and ageing play a relevant role in this phenomenon. Moreover, alcohol consumption seems a variable with relevant economic impact, but further studies are necessary to identify clearly the direction of its relationship with medicine costs.

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Author contributions

Conception and design of the research: Fernandes RA; Acquisition of data and Analysis and interpretation of the data: Mantovani AM; Statistical analysis: Mantovani AM, Anokye N; Writing of the manuscript: Codogno JS, Turi-Lynch BC, Anokye N; Critical revision of the manuscript for intellectual content: Codogno JS, Turi-Lynch BC, Pokhrel S.

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 Faculdade de Ciências e Tecnologia da Universidade Estadual Paulista under the protocol number 349.306/2013. 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

Lifestyle and Medication Costs May Be Associated with Consequences for Adult Patient Health

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Short Editorial related to the article: The Relationship between Lifestyle and Costs Related to Medicine Use in Adults.

The increase in health costs can be explained by several factors, such as the aging of the population, changes in the morbidity and mortality structures of the population and the introduction of new medical technologies in the diagnosis and treatment of diseases.[1]

Moreover, the guarantee of the appropriate and safe use of the medications also covers clinical, economic, legal, regulatory, and cultural aspects that must be taken into account in the decision-making process in the health sector. The first study on the economic analysis of medications was published in 1979 by Bootman et al.[2]

In recent years, drug costs have become a threat to the sustainability of public health systems in many countries. These costs have affected other major priorities in the health sector, and these costs have not resulted in significant health indicator improvements. Medication-related economic expenses involve not only the cost of treatments resulting from inappropriate drug use but also the purchase of prescription or non-prescription drugs.[3]

According to the World Health Organization (WHO)[4] lifestyle is the set of habits and customs that can be influenced, modified, encouraged or inhibited by the prolonged process of socialization. These habits and customs include the use of substances such as coffee, alcohol, tobacco or tea, dietary and exercise habits. These substances are important and have consequences for health and are often investigated through epidemiological studies.

Unhealthy lifestyle behaviors, such as alcohol consumption, smoking, sleep disorders, and sedentary individuals, have been responsible for the development of several diseases. On the other hand, medical, diagnostic advances and modern therapeutics have been responsible for improving quality of life and longevity. Unlike lifestyle, the term "quality of life" involves physical and mental well-being.

Recent studies have shown that lifestyle interventions are as effective as evidence-based medical therapies in reducing mortality.[5]

The reduction in mortality in the USA attributed to the decrease in risk factors, as a result of the improvement in the environmental lifestyle, reached 44%, while those related to medication use were 47%.[6]

There is strong evidence that lifestyle changes have a major impact on the quality of life of individuals and of the population.[7] Lifestyle is considered fundamental and determinant for health, mainly related to individual behavior (eating habits, stress management, preventive behavior and physical activity).[8] Regarding physical activity, the WHO states that physical inactivity is among the four main causes of mortality worldwide.[9]

The article by Fernandes et al.,[10] published in 2018 in *Arquivos Brasileiros de Cardiologia*, evaluated the association of some quality of life-related items with medication costs, an idea that has validity, as it is currently thought-provoking. However, even though a multivariate analysis was performed, it is difficult to establish a causal association. Issues such as quality of sleep and alcohol consumption were associated with costs, while physical activity and smoking did not show an independent association.

The balance of positive and negative variables makes an overall conclusion regarding lifestyle and cost of medications indeterminate. Since it is difficult to mechanistically justify the association with some variables, but not with others, we conclude these associations may result from a residual confounding effect.

Therefore, we consider this article[10] brings reflections, but this question cannot be defined, leaving it in the open for future studies. It is important to have monetary costs in mind in relation to decision-making. But whether lifestyle is the focus to rationalize the system has yet to be defined. First, this causal association is doubtful; second, there are more direct and predictable ways of reducing costs; and, finally, the economic reasoning will not be a determinant of the lifestyle recommendation or quality of life, which should be sought regardless of the costs.

Keywords

Health Education; Drug Costs; Life Style; Exercise; Tobacco and Disorders; Alcoholism; Drug Utilization/economics.

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Subclinical Thyroid Dysfunction was not Associated with Cardiac Arrhythmias in a Cross-Sectional Analysis of the ELSA-Brasil Study

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Abstract

Background: **The association of subclinical thyroid dysfunction (STD) with cardiac arrhythmias remains controversial, particularly in the non-elderly population.**

Objective: **To investigate whether STD was associated with cardiac arrhythmias in a cohort of middle-aged and older adults.**

Methods: **Baseline data of the Longitudinal Study of Adult Health, ELSA–Brasil (35–74 years) were collected from 2008 to 2010. After exclusion of clinical hypothyroidism and hyperthyroidism, participants were categorized as euthyroidism (TSH = 0.4–4.0 μU/mL), subclinical hypothyroidism (TSH > 4.0 μU/mL; FT4 = 0.8–1.9 ng/dL), and subclinical hyperthyroidism (TSH < 0.4 μU/mL; FT4 = 0.8–1.9 ng/dL). The prevalence rates of tachycardia (HR > 100) and bradycardia (HR < 60), atrial fibrillation/flutter, conduction disorders, extrasystoles, low QRS voltage, prolonged QT intervals, and persistent supraventricular rhythms were compared between groups after adjusting for age, sex, comorbidities, lifestyle, body mass index and medications.**

Results: **The HR data of 13,341 participants (52% female; median age, 51 years) and the electrocardiogram readings of 11,795 were analyzed; 698 participants (5.23%) were classified as subclinical hypothyroidism, 193 (1.45%) as subclinical hyperthyroidism, and 12,450 (93.32%) as euthyroidism. The prevalence of rhythm and conduction disorders was similar, as were HR medians, even in the subgroups with TSH < 0.01 UI/mL or > 10.0 UI/mL or in older adults. Conduction disorders were less prevalent in older adults with subclinical hypothyroidism (adjusted OR = 0.44; 95% CI 0.24 to 0.80).**

Conclusion: **In this large, multicenter and cross-sectional study, STD was not associated with cardiac arrhythmias, but a longitudinal assessment is necessary. (Arq Bras Cardiol. 2019; 112(6):758-766)**

Keywords: **Thyroid Diseases/complications; Pathologic Processes; Thyroropin (TSH); Arrhythmias, Cardiac; Adults.**

Introduction

Subclinical thyroid dysfunctions (STD), which include subclinical hypothyroidism (SCHypoTh) and subclinical hyperthyroidism (SCHyperTh), are characterized by elevated or suppressed thyroid-stimulating hormone (TSH), without clinical alterations or abnormalities in thyroid hormone levels.[1] Diagnosis of STD has been increasing with the dissemination of ultrasensitive TSH assays; however, the clinical repercussions of STD and the benefits associated with thyroid dysfunction screening are still the object of scientific debate, and further research is needed.

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The prevalence of SCHyperTh ranges from 1% to 16% in large population-based studies, while that of SCHypoTh varies from 4% to 20%.[1,2] Those prevalence rates can vary according to sex, age, degree of iodine sufficiency, and the TSH reference values adopted in each study.[3] In Brazil, population-based studies have shown prevalence rates of SCHyperTh ranging from 2.4% in older adults[4] to 6.2% in Japanese Brazilians aged > 30 years,[5] while SCHypoTh varied from 6.5% among older adults[4] to 12.3% in women aged > 35 years.[6]

There is no consistent evidence of the clinical relevance of STD, particularly regarding the cardiovascular system. Although some meta-analyses and population-based cohort studies have indicated a higher cardiovascular risk and mortality associated with STD,[5,7] other studies do not corroborate those results.[8-10] Regarding arrhythmias, SCHyperTh has been associated with a two- to three-fold risk of tachyarrhythmias, especially sinus tachycardia, atrial fibrillation (AF) and atrial flutter, extrasystoles, supraventricular and ventricular arrhythmias,[11-17] and prolonged QT intervals (QTi).[18] Fewer studies have explored the relationship between

SCHypoTh and cardiac arrhythmias. Weak evidence, mostly in the form of case reports, suggests that SCHypoTh can lead to bradyarrhythmias, including sinus bradycardia and atrioventricular blocks, atrial arrhythmias, prolonged QTi, and severe ventricular arrhythmias.[19,20] Most of the related studies have focused on older adults.

The aim of the present study was to investigate whether STD was associated with cardiac arrhythmias in a cohort of middle-aged and older adults in the baseline of the Longitudinal Study of Adult Health (ELSA–Brasil), the largest cohort of a Brazilian adult population to date.

Methods

Study population

The present investigation is a subproject of ELSA–Brasil, in which the baseline cohort comprised 15,105 civil servants aged 35–74 years from six Brazilian cities, who were enrolled between August 2008 and December 2010. The majority of participants were young adults (78% aged < 60 years), with 54% female. The ELSA–Brasil protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the research ethics committees at all six centers. All participants provided a written informed consent.[21]

Participants were excluded if they were using any drugs that could interfere with TSH or free thyroxine (FT4) laboratory assays (levodopa, carbidopa, metoclopramide, haloperidol, valproic acid, propranolol, heparin, prazosin, rifampicin, carbamazepine, primidone, phenytoin, and furosemide).[22] Participants with serum TSH and FT4 alterations indicating clinical thyroid dysfunction, including those with normal serum FT4 levels and TSH > 20 μU/mL, or if they were using levothyroxine or antithyroid agents (thiamazole or propylthiouracil) were excluded. All participants who did not present exclusion criteria were included.

Study protocol

Standardized interviews were conducted with participants at their workplaces and at the research center. Clinical examinations and laboratory tests were performed according to standardized protocols developed for the study. Participants were instructed to present all medical prescriptions and medications they had used in the preceding month.[21]

Skin color was self-reported. Anthropometric parameters, including height and weight, were measured using standardized techniques and materials. Resting heart rate (HR) and blood pressure (BP) were measured three times, with the mean values for the second and third measurements considered for analysis.[23]

Standard 12-lead resting electrocardiograms (ECGs) were recorded and analyzed according to the Minnesota code criteria[24] using a digital device (Atria 6100, Burdick, Cardiac Science Corporation, Bothel, WA, USA) with automated readings of HR; duration, range, and axes of P, QRS, and T waves; QT intervals, and QTc (Bazett's correction). The ECG tracings were analyzed at the ECG Reading Center of ELSA-Brasil in Minas Gerais. In total, 11,795 ECGs were available for analysis.

Blood samples were collected after an overnight fast. Participants were instructed to reschedule their appointment at the research center if they had a fever or developed any acute disease symptoms. All laboratory analyses were centralized in a single research center (University of São Paulo).[25] The quality and management of data collection and storage were ensured through training sessions, certifications, and renewal of certifications of the interviewers and technicians in charge of the clinical examinations and laboratory tests of the study protocol.[21]

The methods, reagents, and equipment used in the assays conducted at the central laboratory were as follows: 1) TSH: immunoenzymatic bead-based technique, Siemens reagent L2KTS2, analytical sensitivity of 0.004 mU/L, conducted for all participants; 2) FT4: immunoenzymatic bead-based technique, analytical sensitivity of 0.3 ng/dL, only for those patients with abnormal TSH levels (both the TSH and FT4 assays were performed using a Siemens IMMULITE 2000 Immunoassay System® – Siemens Healthcare Diagnostics, Deerfield, IL, USA); 3) Total cholesterol: enzymatic colorimetric method, Siemens reagent (code 99301390); 4) Triglycerides: enzymatic colorimetric method with glycerol phosphate peroxidase according to Trinder; 5) HDL cholesterol: homogeneous enzymatic colorimetric method without precipitation; 6) LDL cholesterol: Friedewald equation for triglycerides < 400 mg/dL; otherwise, measured directly using a homogeneous enzymatic colorimetric assay without precipitation; 7) Serum blood sugar: enzymatic hexokinase method; 8) Hemoglobin A1C: high-pressure liquid chromatography (HPLC), Bio-Rad D-10 Hemoglobin A1c Program (Bio-Rad Laboratories, Inc., Hercules, CA, USA). All biochemical tests were analyzed using the ADVIA 1200 Chemistry System (Siemens Healthcare Diagnostics, Deerfield, IL, USA); and 9) Chagas disease serology: ELISA method using a solid-phase microplate (CHAGATEST, Wiener Laboratorios S.A.I.C., Rosario, Argentina).[25]

Definition of cases

Participants were allocated into one of three groups: euthyroidism (TSH = 0.4–4.0 μU/mL), SCHypoTh (TSH > 4.0 and ≤ 20 μU/mL with FT4 = 0.8–1.9 ng/dL), and SCHyperTh (TSH < 0.4 μU/mL and FT4 = 0.8–1.9 ng/dL). =

Abnormalities on ECG were categorized into rhythm disorders (AF and flutter: Minnesota codes 8.3.1, 8.3.2, 8.3.3, 8.3.4; supraventricular extrasystoles (SVES): 8.1.1; ventricular extrasystoles (VES): 8.1.2; persistent supraventricular rhythm: 8.4.1) and blocks or conduction disorders (complete right and left bundle branch block: 7.2.1, 7.2.2, 7.1.1, 7.1.2; incomplete right and left bundle branch block: 7.3 and 7.6; nonspecific intraventricular block: 7.4, and atrioventricular blocks: 6.1; 6,2,1; 6.2.2; 6.2.3; 6.3). The presence of long QTi (> 115%) and low QRS complex voltage (9.1) was also investigated.[24, 26]

Abnormalities on heart rate measured by clinical examination were classified as bradycardia (HR < 60 or < 50 beats per minute [bpm]) and tachycardia (HR > 100 or >110 bpm).

Diabetes mellitus was defined by abnormal laboratory findings according to American Diabetes Association criteria (fasting blood glucose ≥ 126 mg/dL, blood glucose levels two

hours after a 75 g load of anhydrous glucose ≥ 200 mg/dL, or hemoglobin A1c ≥ 6.5%) or the use of insulin or oral/subcutaneous hypoglycemic drugs. Arterial hypertension was defined by a self-reported medical diagnosis of hypertension, use of anti-hypertensive agents, or blood pressure ≥ 140/90 mmHg. Dyslipidemia was defined as total serum cholesterol ≥ 200 mg/dL or triglycerides ≥ 150 mg/dL or LDL cholesterol ≥ 130 mg/dL, or the use of hypolipidemic medication. Congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease were defined by a self-reported medical diagnosis. Chagas disease was defined by positive serology in the Chagas test – ELISA assay. Excessive alcohol use was defined as the intake of more than 140 g of alcohol per week for women and more than 210 g of alcohol per week for men.

Medications considered for statistical adjustments were those that could interfere with thyroid or cardiac function and included antiarrhythmic drugs, β-blockers other than propranolol (which had been excluded previously), β2-agonists, adrenergic agonists and nondihydropyridine calcium channel blockers, lithium carbonate, potassium iodide, amiodarone, interferon-α, systemic glucocorticoids, dopaminergic agonists, carbamazepine, and oxcarbazepine.[27,28]

Statistical analysis

The statistical analysis was performed using the STATA™ software, v. 12.0. The data are described as medians and interquartile ranges or proportions, since they did not present a normal distribution, according to test of Shapiro-Wilk. The nonparametric tests of Mann-Whitney and Kruskal-Wallis were used to compare medians, Pearson's chi-squared and Fisher's exact tests to compare proportions, and Spearman's correlation coefficient to estimate correlations between continuous variables. Logistic regression analysis was delineated between SCHyperTh or SCHypoTh and serum TSH and FT4 levels and the presence of arrhythmias/electrocardiographic abnormalities. Age, sex, skin color, body mass index (BMI), smoking status, excessive alcohol use, comorbidities (dyslipidemia, diabetes, hypertension, coronary disease, congestive heart failure, chronic obstructive pulmonary disease, and Chagas disease), and medication use were considered for adjustment. The p value < 0.20 was considered for the multivariate model, and statistical significance was $p < 0.05$. Subgroup analyses were performed for older individuals (age 65–74 years) and those with extreme TSH values (< 0.1 μU/mL or > 10 μU/mL).

Results

This study included 13,341 (88.32%) of the 15,105 participants enrolled at the baseline of the ELSA-Brasil study. The 1,764 excluded participants are shown in Figure 1.

The profile of the participants for the overall study population categorized by thyroid function group is shown in Table 1.

STD was found in 891 (6.68%) participants, with a greater prevalence of SCHypoTh (5.23%) over SCHyperTh (1.45%). SCHypoTh was slightly associated with older age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.02-1.04), female sex (OR 1.18, 95% CI 1.01- 1.38), higher BMI (OR 1.03, 95% CI 1.01-1.04), and white skin color (OR 1.30, 95% CI 1.10-1.55) when compared to the euthyroidism. Black skin color (OR 0.56, 95% CI 0.41- 0.75) and smoking (OR 0.72, 95% CI 0.56-0.94) were independently and negatively correlated with SCHypoTh.

SCHyperTh was slightly associated with older age (OR 1.02, 95% CI 1.01-1.04), female sex (OR 1.71, 95% CI 1.26- 2.31), and black skin color (OR 1.61, 95% CI 1.11- 2.33). White skin color (OR 0.71, 95% CI 0.50-0.99) and non-smoking (OR 0.65, 95% CI 0.49-0.88) were independently and negatively associated with SCHyperTh. Increased BMI was associated with SCHyperTh only in the univariate analysis (OR 1.03, 95% CI 1.01-1.04) (Table 1).

There were no significant differences in the HR medians of participants with normal thyroid function (35–130 bpm, median 70), SCHypoTh (42.5–111 bpm, median 70; $p = 0.087$) and SCHyperTh (42–104 bpm, median 71.5, $p = 0.084$).

No correlation was found between HR and serum TSH or FT4 values, whether for the total study population or within each STD group. The multivariate linear regression indicated a relationship between TSH levels and HR in the participants with SCHypoTh ($p = 0.001$, after adjustment). No relationship was found between TSH levels and HR in the SCHyperTh group, or between FT4 levels and HR in any of the groups.

Tachycardia was found in 3.10% of the participants and was not associated with STD, even among older adults or in those with extreme TSH values, as shown in Table 2. Likewise, bradycardia (14,72%) was not significantly associated with STD, even in those subgroups.

The relationship between TSH and FT4 levels and heart rate is shown in Table 3. Median TSH levels were significantly higher for individuals with tachycardia compared to those with normal HR, even after adjustments, and medians for FT4 levels were significantly higher in individuals with tachycardia.

Considering the 11,795 ECGs analyzed in this study, no abnormality was associated with STD (Table 4), even in the subgroup of older adults or those with extreme TSH values. The only correlation found was a lower frequency of branch blocks in older adults with SCHypoTh compared to those who were euthyroid (14.29% vs. 26.13%; adjusted OR 0.44, 95% CI 0.24-0.80; $p = 0.007$).

A sensitivity analysis was performed excluding all participants in use of antiarrhythmic drugs, β-blockers, β2-agonists, adrenergic agonists and nondihydropyridine, calcium channel blockers, lithium carbonate, potassium iodide, amiodarone, interferon-α, systemic glucocorticoids, dopaminergic agonists, carbamazepine, and oxcarbazepine, and most of the results were the same, without any association between STD and abnormalities in ECG, and no correlation or relationship was found between HR and serum TSH or FT4 values, whether for the total study population or within each STD group. The only association found was the lower frequency of bradycardia (HR < 60 bpm) in participants with SCHyperTh compared to those who were euthyroid (8,23% vs. 13,54%; adjusted OR 0.62, 95% CI 0.41-0.93; $p = 0.021$).

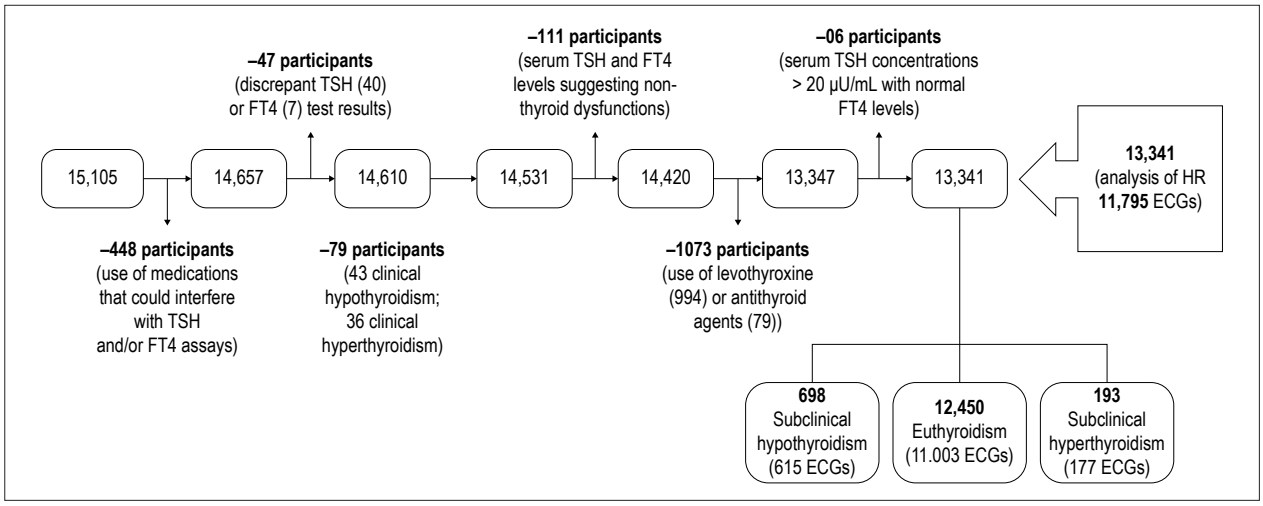

Figure 1 – *Inclusion of participants from the ELSA-Brasil study baseline, 2008-2010. TSH: thyroid-stimulating hormone; FT4: free thyroxine; ECG: electrocardiogram.*

Table 1 – Characteristics of participants categorized by thyroid function group, Longitudinal Study of Adult Health, ELSA–Brasil, 2008-2010

	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Total
N (%)	698 (5.23%)	12,450 (93.32%)	193 (1.45%)	13,341 (100%)
Age, y *	54 (47-61) †	51 (45-58)	53 (46-59) †	51 (45-58)
Female sex (%)	381 (54.58%)‡	6,433 (51.67%)	123 (63.73%)‡	6,937 (52.00%)
BMI (kg/m^2) *	26.80 (24.03-29.96) §	26.27 (23.63-29.48)	26.16 (23.55-29.39) †	26.30 (23.65-29.52)
Education ≥ completed secondary education (%)	589 (84.38%)	10,887 (87.45%)	163 (84.46%)	11,639 (87.24%)
Skin color (%)				
white	426 (61.03%)§	6,283 (50.47%)	72 (37.30%)§	6,781 (50.82%)
brown	177 (25.36%)	3,547 (28.49%)	54 (27.98%)	3,778 (28.32%)
black	60 (8.60%)§	2,032 (16.32%)	54 (27.98%)§	2,146 (16.09%)
others	35 (5.01%)	588 (4.72%)	13 (6.74%)	636 (4.77%)
Hypertension (%)	243 (34.81%)	4,258 (34.20%)	87 (45.08%)§	4,588 (34.39%)
Diabetes mellitus (%)	145 (20.77%)	2,493 (20.02%)	46 (23.83%)	2,684 (20.12%)
Dyslipidemia (%)	547 (78.37%)†	9,338 (75.00%)	138 (71.50%)	10,023 (75.13%)
LDL > 130	395 (56.59%)	7,059 (56.70%)	112 (58.03%)	7,566 (56.71%)
TGC > 150	254 (36.39%)§	3,850 (30.92%)	58 (30.05%)	4,162 (31.20%)
Coronary artery disease (%)	44 (6.30%)†	531 (4.27%)	10 (5.18%)	585 (4.39%)
CHF (%)	14 (2.01%)	170 (1.37%)	4 (2.07%)	188 (1.41%)
COPD (%)	17 (2.44%)†	241 (1.94%)	6 (3.11%)	264 (1.98%)
Chagas' disease (%)	9 (1.29%)	112 (0.90%)	0 (0.00%)	121 (0.91%)
Excessive alcohol (%)	43 (6.16%)	992 (7.97%)	10 (5.18%)	1,045 (7.83%)
Smoking status				
Current smoker	66 (9.46%)§	1,689 (13.56%)	38 (19.69%)§	1,793 (13.43%)
Former smoker	247 (35.39%)§	3,639 (29.23%)	64 (33.16%)	3,950 (29.61%)
No smoking	385 (55.16%)	7,122 (57.21%)	91 (47.15%)§	7,598 (56.96%)
TSH (µU/mL) *	5.065 (4.43-6.26) §	1.48 (1.04-2.18)	0.28 (0.17-0.34) §	1.53 (1.04-2.32)
FT4 (ng/dl) *	1.10 (1.0-1.2)	1.145 (1.05-1.235)	1.20 (1.10-1.40) §	1.10 (1.00-1.24)

*BMI: body mass index; LDL: lipoprotein low density; TGC: triglycerides; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; Chagas disease: positive serology in the Chagatest – ELISA assay; TSH: thyroid-stimulating hormone; FT4: free thyroxine; * Median (Interquartile range); † Statistically significant difference ($p < 0.05$) without adjustment, compared to the euthyroidism; ‡$p < 0.05$ after adjustment by age; § $p < 0.05$ after adjustment by age and sex.*

Table 2 – Association between Heart Rate and Subclinical Thyroid Dysfunction, ELSA-Brasil, 2008-2010

	Subclinical Hypothyroidism			Euthyroidism		Subclinical Hyperthyroidism	
	Prevalence N (%)	OR (CI 95%)	"p"	Prevalence N (%)	Prevalence N (%)	OR (CI 95%)	"p"
Tachycardia > 100 bpm 413 (3.10%)	23 (3.76%)	1.04 (0.67-1.59)	0.874	385 (3.63%)	5 (2.89%)	0.79 (0.32-1.93)	0.604
> 110 bpm 344 (2.58%)	17 (2.81%)	0.91 (0.56-1.50)	0.715	323 (3.07%)	4 (2.33%)	0.75 (0.28-2.04)	0.576
Bradycardia < 60 bpm 1,964 (14.72%)	86 (12.74%)	0.80 (0.64-1.01)	0.062	1,858 (15.40%)	20 (10.64%)	0.65 (0.41-1.04)	0.074
< 50 bpm 211 (1.58%)	12 (2.00%)	1.07 (0.59-1.92)	0.830	195 (1.87%)	4 (2.33%)	1.25 (0.46-3.39)	0.667

Table 3 – Relationship between Heart Rate and TSH and FT4 Levels, ELSA-Brasil, 2008-2010

	TSH		FT4	
	Median (µU/ml)	p-value*	Median (ng/dl)	p-value*
Tachycardia (> 100 bpm)	1.63	0.004	1.20	0.021
Normal HR (60-100bpm)	1.52		1.10	
Bradycardia (< 60 bpm)	1.54	0.311	1.10	0.233

*TSH: thyroid-stimulating hormone; FT4: free thyroxine; HR: heart rate; *after adjustment.*

Table 4 – Association between Abnormalities on the ECGs and Subclinical Thyroid Dysfunction, ELSA-Brasil, 2008-2010

	Subclinical Hypothyroidism (615 ECGs)			Euthyroidism (11,003 ECGs)	Subclinical Hyperthyroidism (177 ECGs)		
	Prevalence N (%)	OR (CI 95%)	"p"	Prevalence N (%)	Prevalence N (%)	OR (CI 95%)	"p"
AF/Flutter 42 (0.36%)	2 (0.33%)	0.89 (0.22-3.70)	0.878	40 (0.36%)	0 (0%)	----------	0.422
Persistent supraventricular rhythm 89 (0.75%)	5 (0.81%)	1.08 (0.44-2.67)	0.870	83 (0.75%)	5 (1.69%)	0.75 (0.10-5.40)	0.773
Extrasystole 94 (0.80%)	4 (0.65%)	0.82 (0.30-2.25)	0.701	87 (0.79%)	3 (1.69%)	2.16 (0.68-6.90)	0.193
Long QT interval 334 (2.83%)	15 (2.15%)	0.85 (0.50-1.43)	0.532	315 (2.53%)	4 (2.07%)	0.82 (0.30-2.21)	0.688
LV QRS 166 (1.41%)	10 (1.63%)	1.16 (0.61-2.22)	0.644	154 (1.40%)	2 (1.13%)	0.81 (0.20-3.27)	0.762
Conduction disorders 2,067 (17.52%)	101 (16.42%)	0.92 (0.74-1.14)	0.437	1,942 (17.65%)	24 (13.56%)	0.73 (0.47-1.13)	0.158

AF: atrial fibrillation; LV QRS: Low QRS voltage; ECGs: electrocardiograms.

Discussion

This cross-sectional analysis of 13,341 individuals of this Brazilian cohort found no association of STD with HR, rhythm alterations, or conduction disorders, which suggests a limited influence of STD on cardiac rhythm and conduction. The only association found was an unexpected lower frequency of conduction disorders among the older participants with SCHypoTh compared to euthyroid participants, and it may be due to some unknown confounding factor not estimated or controlled for.

Of note, no population-based study has assessed the association between electrocardiographic abnormalities such as conduction disorders, low QRS complex voltage, prolonged QTi, and persistent supraventricular rhythms and the presence of STD, particularly SCHypoTh. Most of the studies on this subject are case reports or relate those abnormalities to clinical, rather than subclinical, hypothyroidism.

There is a paucity of studies on the prevalence of cardiac arrhythmias in the general population, without known heart disease or comorbidities, and most of those available address older individuals in developed countries. This prevalence varies according to the type of arrhythmia, age, sex, presence of structural heart disease or cardiovascular risk factors, and the diagnostic method employed.[29,30] AF was found in 0.35% of the participants in the present study, which is a similar result to those of population-based studies showing prevalence rates of 0.2% to 1.0%.[28,30-32] However, considering that the prevalence of AF can be as high as 10% in individuals aged 70 years or older,[32] the frequency of AF and flutter was low (1.32%) among older adults in this study.

Table 5 – Comparison between Previous Studies and ELSA-Brasil Results, 2008-2010

Study/Author	Population	Design/enrollment	TSH level (μU/mL)	Ascertainment of Events	Results
Consistent Findings					
Cross-Sectional Analysis:					
Cappola 2006 (Cardiovascular Health Study, USA)	3,233 elderly people (mean age 72.7 years)	Population-based prospective cohort study	0.45 – 4.5	ECG	No difference in AF prevalence between SCHyperTh and euthyroidism groups (8.5% vs. 5.2%. p > 0.05)
Longitudinal analysis:					
Nanchen 2012 (PROSPER Trial, Netherlands, Scotland and Ireland)	5,316 elderly people (mean age 75 years)	prospective cohort study; outpatients of centers study	0.45 - 4.5	ECG	No difference in AF incidence between SCHypoTh, SCHyperTh and euthyroidism groups in 3.5 years follow-up
DISCORDANT FINDINGS					
Cross-sectional analysis					
Auer 2001 (Austria)	23,838 patients (median 67.9 years old)	Cross-sectional Patients admitted in a hospital	0.4 – 4.0	ECG	Higher AF prevalence in SCHyperTh (12.7% vs. 2.3%. OR adjusted 2.8 CI95% 1.3-5.8)
Gammage 2007 (England)	5,860 elderly people (median 72 years old)	Cross-sectional; Primary care service	0.4 – 5.5	ECG	Higher AF prevalence in SCHyperTh (9.5% vs. 4.7%. OR adjusted 1.89 CI95% 1.01-3.57)
Vadiveloo 2011 (TEARS, Scotland)	2,004 cases (mean age 66.5 years) and 10,111 controls	Retrospective; Tayside health registry	0.4 - 4.0	ECG/ Holter	Higher arrhythmia frequency in SCHyperTh (2.7% vs. 1.4%. p < 0.001)

TSH: thyroid-stimulating hormone; ECG: electrocardiogram; SCHyperTh: subclinical hyperthyroidism; SCHypoTh: subclinical hypothyroidism; AF: atrial fibrillation.

Most longitudinal studies,[9,12,17,33-35] but not all,[36] have found AF to be associated with SCHyperTh. However, that association differs between cross-sectional studies. Interestingly, no participant with SCHyperTh in the present study manifested AF/atrial flutter. In line with this study, Cappola et al. showed no association between AF and STD at the baseline assessment of a community cohort of 2,639 older adults (mean age, 72.7 years).[9] In contrast, Auer et al. reviewed the data of 23,838 individuals admitted to a hospital in Austria and found a prevalence rate of 12.7% for AF among the 613 patients (mean age, 67.9 years) with SCHyperTh (adjusted OR, 2.8; 95% CI 1.3-5.8), but the tests were not performed at a single laboratory.[15] In a study by Gammage et al., the prevalence of AF was 9.5% among individuals with SCHyperTh in a cohort of 5,860 primary care patients with a median age of 72 years (adjusted OR, 1.89; 95% CI 1.01-3.57), however, the TSH levels adopted to define euthyroidism were higher (5.5 μU/mL).[16]

The prevalence of extrasystoles in the present study was also low (0.66% for SVES and 0.13% for VES), compared to the prevalence of VES in the HCHS/SOL study (0.98% in men and 0.53% in women).[29] In general, the prevalence rates of the other arrhythmias were similar to those found in the aforementioned studies. No association was noted between SVES or VES and STD, and no differences were detected in HR means between the groups in the present study. Vadiveloo et al. demonstrated in baseline data a greater prevalence of arrhythmias among the participants with SCHyperTh (2.7% vs. 1.4%, p < 0.001), although there was a higher frequency of preexisting cardiovascular disease in their cohort.[17]

In the present study, higher FT4 medians were identified in participants with tachycardia, albeit still within the normal range, which could be explained by the physiological effect of the thyroid hormone on cardiac chronotropism.[37] Gammage et al. found similar results, with a positive and direct correlation between FT4 levels and a tachyarrhythmia (AF) in their cross-sectional study.[16] Surprisingly, higher TSH medians were also associated with tachycardia after adjustment for potential confounding factors, but the probable mechanism for this association is unknown.

It can be speculated that STD may result in greater electrocardiographic repercussions only in specific populations with more severe comorbidities. In the ELSA population, a lower median age (51 years) and the smaller prevalence of comorbidities than in the populations recruited in cardiology or emergency services, can explain the discrepancies in relation to previous studies, which may also be due to the different TSH thresholds used to define SCHypoTh (4.5 to 5.5 μU/mL vs. 4.0 μU/mL).[9,12,16] The findings of the most relevant studies reporting concordant or discordant results with those of the present study are summarized in Table 5.

In line with previous studies,[1,2,13] SCHypoTh was more frequent than SCHyperTh in the current study (5.23% vs. 1.45%). As expected, SCHypoTh was more frequent with increasing age, female sex, higher BMI, and white skin color. In contrast, SCHypoTh was negatively associated with black skin color and current smoking.[1,2,6] SCHyperTh showed a positive and independent association with increasing age, female sex, and black skin color, which are also consistent with population-based studies.[3,6]

The strengths of the present study were the large multicenter samples, the methodological rigor in recruiting and data collection, and the centralized analysis of the laboratory tests and ECGs. The cohort was composed of volunteers, mostly middle-aged individuals, recruited outside of the hospital and evaluated in the absence of any acute illness, which most likely excluded non-thyroid diseases. The limitations of this study include the following: TSH was measured only once; FT4 concentrations were measured only for those participants with abnormal TSH levels, and a single ECG was used for the diagnosis of arrhythmias; and no other laboratory, clinical, or ecographic data were available to assess whether the laboratory test abnormalities indeed correspond to STD. This limitation should be kept in mind, especially considering the TSH medians that indicated mild STD. Not all of the ECGs were available for analysis, however the mean age of the participants whose ECGs were analyzed was greater than that of the total cohort sample, which might in fact overestimate the overall prevalence of arrhythmias e corroborates the lack of association with STD. Only 33 of the participants had TSH > 10 μU/mL (4.73% of SCHypoTh) while 35 showed TSH < 0.1 μU/mL (18.13% of SCHyperTh). Moreover, some ECG abnormalities were rather uncommon, as rhythm disorders, with a prevalence of less than 1%. Therefore, the statistical power to identify associations between those subgroups and rhythm and conduction alterations may have been insufficient. A longitudinal assessment is needed to determine the incidence of arrhythmias as well as their relative risk for each of the STD groups.

Conclusion

The present study provides contrary evidence to the association between electrocardiographic changes and STD in a seemingly healthy non-elderly population. Although, given the limitations inherent to a cross-sectional analysis, the lack of this association cannot be definitively excluded at this point, and a longitudinal assessment is needed.

Author contributions

Conception and design of the research: Ribeiro ALP, Rajão KMAB, Passos VMA, Benseñor IJM, Diniz MFHS; Acquisition of data: Ribeiro ALP, Passos VMA, Benseñor IJM, Vidigal PG; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Ribeiro ALP, Rajão KMAB, Passos VMA, Benseñor IJM, Vidigal PG, Camacho CP, Diniz MFHS; Statistical analysis and Writing of the manuscript: Rajão KMAB, Passos VMA, Camacho CP, Diniz MFHS; Obtaining financing: Passos VMA, Benseñor IJM,.

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 theFaculdade Federal de Minas Gerais under the protocol number ETIC 186/06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Subclinical Thyroid Dysfunction was not Associated with Cardiac Arrhythmias in the Cross-Sectional Analysis of the ELSA-Brasil Study

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Short Editorial related to the article: Subclinical Thyroid Dysfunction was not Associated with Cardiac Arrhythmias in a Cross-Sectional Analysis of the ELSA-Brasil Study

Brazil lacks large cohort studies with analyses of incidence and prevalence of diseases in all areas. In this context, the ELSA-Brasil study was an important milestone for the evaluation of cardiovascular diseases in the country. This study shows a very detailed means of exposing relevant facts to the occurrence or not of arrhythmogenic electrocardiographic manifestations in patients with subclinical thyroid hormone disorders. This issue is extremely relevant, has biological plausibility and generates several doubts regarding the patient.[1]

The study included a relevant sample of 13,341 patients in total, with a mean age of 51 years. The data collection, electrocardiographic specifications and laboratory tests were protocolized according to predetermined and uniform specifications in all patients. Moreover, they were comprehensively evaluated, from arrhythmias supposedly more frequent in thyroid disorders such as atrial fibrillation, plus basal heart rate, presence of extrasystoles and conduction intervals.[1]

On the other hand, there was a significant disparity between patients with alterations in hormonal levels when compared to those without alterations (6.68% vs. 93.32%), which in a way affects data analysis. Furthermore, the mean age of the patients involved in the study was the youngest of all previously performed studies with similar characteristics.[1]

Although it included elderly patients, the percentage was small, which may explain the small rate of cardiac arrhythmias in the studied sample. Finally, serum levels of free T4 were similar between the groups. Thus, with very similar levels of circulating hormones, it is to be speculated that the arrhythmogenic event rates were not different from each other.[1]

As mentioned in the article, the largest study published to date with similar characteristics included 23,838 patients and observed a higher incidence of atrial fibrillation in patients with subclinical hyperthyroidism. However, it was a cross-sectional study that included patients hospitalized for other comorbidities, a factor that interferes with the occurrence of events and that cannot be directly compared to studies with outpatient follow-up.[2]

Regarding the other studies, the only prospective studies showed results that were similar to those of the ELSA-Brasil study, performed in the outpatient setting, with a total of more than 8,500 included patients, and which did not show any differences regarding the incidence of atrial fibrillation between the groups.[3,4] It is noteworthy that the complete analysis of electrocardiographic data was unique in the ELSA-Brasil study, which makes it relevant in the area and with original information on the subject.[1]

A recent review published by Razvi et al.[5] highlighted the fact there is little evidence of the correlation between atrial fibrillation and subclinical hyperthyroidism and that there is no indication for treatment in patients under 65 years of age and TSH between 0.39 and 0.10 mIU/L related to concerns over cardiac arrhythmias.[5]

Similarly, in acute coronary syndromes, a recent study evaluated a sample of 505 patients in Brazil and found that higher TSH values (> 4 mIU/L) at the time of the clinical presentation showed a significant correlation with the occurrence of bleeding and cardiogenic shock. However, following the same trend as other studies, there was no correlation with the incidence of cardiac arrhythmias during hospitalization and TSH values.[6]

Thus, due to the significant discrepancies between different studies and populations regarding the occurrence of cardiac arrhythmias in subclinical forms of thyroid disorders, this study alone is not capable of suggesting changes in clinical behavior, but contributes significantly to the increase of evidence, reinforcing the negative side of interactions.

Keywords

Thyroid Diseases/complications; Pathologic Processes; Thyrotropin (TSH); Arrhytmias, Cardiac; Adult.

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Surgical Site Infection Prevention Bundle in Cardiac Surgery

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Abstract

Background: Surgical site infections (SSI) are among the most prevalent infections in healthcare institutions, attributing a risk of death which varies from 33% to 77% and a 2- to 11-fold increase in risk of death. Patients submitted to cardiac surgery are more susceptible to SSI, accounting for 3.5% to 21% of SSI. The mortality rate attributable to these causes is as high as 25%. Prevention of SSI in cardiac surgery is based on a bundle of preventive measures, which focus on modifiable risks.

Objective: The objective of this study was to identify SSI risk factors in clean cardiac surgery.

Methods: A retrospective cohort study analyzed 1,846 medical records from patients who underwent clean cardiac surgery. Fisher's exact test was used for bivariate comparison, and Poisson regression was used for independent analysis of SSI risk, considering a significance level of $p < 0.05$.

Results: The results of the study comprised a multivariate analysis. The variables that were associated with the diagnosis of SSI were: surgical risk index (OR: 2.575; CI: 1.224–5.416), obesity (OR: 2.068; CI: 1.457–2.936), diabetes mellitus (OR: 1,678; CI: 1.168–2.409), and blood glucose level (OR: 1.004; CI: 1.001–1.007).

Conclusions: This study evidenced that complete adherence to the bundle was not associated with a reduction in the risk of surgical infections. Diabetes mellitus, obesity, and surgical risk index assessment were, however, identified to increase association and consequently risk of SSI in cardiac surgery. (Arq Bras Cardiol. 2019; 112(6):769-774)

Keywords: Cardiac Surgical Procedures; Adult; Risk Factors/prevention and control; Patient Care Bundles; Anti-Infective Agents; Surgical Wound Infection; Cross Infection.

Introduction

Healthcare associated infections (HAI) are defined as any infection that occurs in a patient during the process of care in a health facility within 48 to 72 hours of initial contact with the healthcare system. Infection rates are higher in developing countries and in intensive care units.[1,2]

Surgical site infections (SSI) are among the most prevalent in health institutions. In the United States, in the year 2011, SSI affected an average of 157,500 patients. The risk of death attributable to this type of infection is high, varying from 33% to 77%, and SSI are associated with a 2- to 11-fold increase in risk of death.[3]

Patients who undergo cardiac surgery are particularly susceptible to hospital infections and SSI, which result in further interventions and additional costs for the health institution. SSI rates can vary from 3.5% to 21%, and the mortality rate due to these causes can reach 25%.[4,5]

Various risk factors are associated with SSI in cardiac surgery, including: age, nutritional status, diabetes mellitus, tobacco use, obesity, coexistence of infections in other sites, length of preoperative stay, skin preparation, mechanical ventilation, failure to comply with aseptic techniques, inadequate hand hygiene, distractions in the operating area, number of times doors are opened, and other environment-related factors.[6]

"Bundles" of preventive measures applied to surgical procedures have been effective in reducing infection rates. These measures include: delivering antibiotic prophylaxis within 1 hour before incision, discontinuing antibiotic use within 48 hours after cardiac surgery, performing hair removal during the immediate preoperative period, maintaining intraoperative normothermia of 35.5ºC or more, and blood glucose control during the immediate postoperative period, extended for 48 hours after the procedure.[7]

The objective of this study was to identify risk factors for SSI in major clean cardiac surgery procedures in a cardiology referral center.

Methods

This is a retrospective cohort study, conducted in the Instituto de Cardiologia (Cardiology Institute), a hospital with 250 beds for cardiology patients in the South of Brazil. The study evaluated patients who underwent major surgical procedures with and without the use of extracorporeal circulation during the period from January 2013 to December 2014. The study included all major surgeries in adults (age 18 or over). The following were excluded: pediatric patients, patients with incomplete medical records data, patients who died during immediate pre-, intra-, or postoperative, and patients who were hospitalized for less than 48 hours.

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The epidemiological diagnosis of infections followed the North American Center for Disease Control and Prevention (CDC) criteria. Infections were classified as superficial, deep, or organ/space. The institution has used a protocol for the prevention of SSI since 2003.

The bundle of preventive measures at the institution includes the following 6 items to be executed throughout the pre- and postoperative periods: preoperative bath with 2% chlorhexidine, 24 hours before the procedure; hair removal with electric clippers, within 2 hours prior to the start of surgery; maintenance of normothermia, at least 36ºC, during the immediate postoperative period; controlling blood glucose below 200 mg/dl, measured at 6:00 am on the first postoperative day; infusion of surgical antibiotic prophylaxis with anesthetic induction within 60 minutes prior to incision; and additional doses if the procedure lasts more than 4 hours, with a maximum use time of 24-48 hours.

The risks scores considered were the ASA classification developed by the American Society of Anesthesiologists and the National Nosocomial Infection Surveillance (NNIS) risk index. The NNIS risk index ranges from 0 to 3, taking the following items into account: contamination potential, procedure duration, and ASA classification. Each item is worth either 0 or 1 points in the score.[24]

Data collection made use of the Brazilian Hospital Infection Control Service (SCIH) information system. Additionally, patients' medical records were reviewed using the Brazilian Medical and Statistical Archive Service (SAME). The medical records were reviewed in the second semester of 2015.

Statistical analyses

Sample size calculation considered the rates of infection between 2003 and 2012. Considering a number of 900 procedures per year in the hospital and an average SSI rate of 3.23% for the period between 2003 and 2012 and that the complete application of the prevention bundle reduces the infection rate by 60%.[8] a sample of 1.846 medical records was calculated, with an alpha error of 5% and a beta error of 20%.

Fisher's exact test was used for bivariate comparison. Poisson regression was used for multivariate analysis which included variables with $p < 0.20$ from the bivariate analysis.[9] A significance level of $p < 0.05$ was considered.

The data collected were codified and inserted into a table using the program Microsoft Office Excel 2007, thus creating a databank. Complementary analyses were carried out using the program SPSS, version 18.0.

This study was approved by the research ethics committee of the Instituto de Cardiologia of the Fundação Universitária de Cardiologia, on September 17, 2014, under certificate number 4997/14, being accredited by the Brazilian National Commission of Ethics in Research (CONEP), with the Term of Confidentiality for Data Use attached.

Results

One thousand, eight hundred, and forty-six medical records of patients who underwent major surgical procedures were analyzed, 138 of which were excluded from the study for the following reasons: 23 pediatric patients, 85 deaths or hospitalizations lasting less than 48 hours, and 30 records with incomplete data which did not meet study inclusion criteria. The period studied, thus, included a total of 1,708 major cardiac surgery procedures in 1,708 patients.

One hundred and forty-two (8.3%) procedures developed SSI, of which 48.0% (n = 69) were thoracic site infections (13.3% superficial incisional; 24.5% deep incisional; 11.2% organ/space); 40.6% (n = 58) were saphenous vein infections; 7.7% (n = 9) were thoracic site and saphenous vein infections; and 3.0% (n = 4) were endocarditis. In heart transplant procedures, 1 in 4 became infected.

The demographic data of patients with and without the presence of SSI are shown in Table 1.

The following variables correlated with infection in bivariate analysis: arterial hypertension ($p = 0.01$), diabetes mellitus ($p = 0.001$), dyslipidemia ($p = 0.05$), obesity ($p = 0.001$), blood glucose level ≥ 200 mg/dl ($p = 0.03$), public or private hospitalization ($p = 0.008$), surgical risk index ($p = 0.001$). The following variables were associated with the diagnosis of SSI in multivariate analysis: surgical risk index, obesity, diabetes mellitus, and blood glucose level (Table 2).

Discussion

The SSI rate in our study was 8.3%. In developed countries, the SSI rate varies from 1.2% to 5.2%, whereas, in developing countries, it may be as high as 11.8%. Our rate was, therefore, higher than the general SSI rate in developed countries (1.2–5.2%), but lower than the rate in developing countries (11.8%).[3]

SSI rates following cardiac surgery in developing countries may vary from 3.5% to 21.0%.[4,5]

Diabetes mellitus, blood glucose level, obesity, and surgical risk index are factors associated with SSI, in accordance with the latest World Health Organization report (WHO, 2016), which underlines these factors in relation to risks that affect HAI.[3]

SSI risk factors are complex, and their prevention requires the integration of a range of measures, before, during, and after surgery. Prevention is the principal focus of the Institute for Healthcare Improvement (IHI) and the Surgical Care Improvement Project (SCIP) in the USA, both of which recommend a group of preventive measures to be taken.[10] These measures, called a "bundle," are carried out together to obtain better results than would be obtained by individual application. SSI prevention bundles in cardiac surgery involve the use of prophylactic antibiotics during the immediate pre-and postoperative period (up to 48 hours following incision); blood glucose level control during the first and second postoperative period; temperature and oxygenation control; decolonization of patients with intra-nasal mupirocin, and preoperative chlorhexidine bath.[3,7,10]

In our study, adherence to surgical prophylaxis protocol was not associated with a reduction in SSI rates. Studies in surgical procedures indicate that antimicrobial use within 60 minutes before the procedure has been associated with reduced infection rate.[3,11,12]

Table 1 – Sociodemographic data associated with SSI

	SSI (N/%)	No infection (N/%)	Total (N)
Male sex	92 (64.8%)	1,057 (67.9%)	1,149
Type of procedure			
– Myocardial revascularization	85 (8.4%)	923 (91.6%)	1,008
– Valve replacement	49 (34.5%)	545 (35.0%)	594
– Aortic dissection	8 (5.6%)	88 (5.7%)	96
Hypertension	133 (94.3%)	1,345 (87.2%)	1,478
Tobacco use	63 (44.7%)	620 (40.2%)	683
Diabetes mellitus	75 (53.2%)	484 (31.4%)	559
Dyslipidemia	58 (41.1%)	504 (32.7%)	562
Obesity	38 (27.1%)	169 (11.0%)	207
COPD	7 (5.0%)	70 (4.5%)	77
Renal insufficiency	9 (6.3%)	84 (5.4%)	93
Public healthcare	112 (78.9%)	1,061 (68.2%)	1,173
ASA class III	111 (78.2%)	1,282 (82.4%)	1,393
Adequate use of antibiotic bundle	33 (23.2%)	332 (21.4%)	365
Complete adherence to total bundle	6 (4.3%)	61 (3.9%)	67
Death	11 (7.7%)	165 (10.6%)	176

SSI: surgical site infection; COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists.

Table 2 – Multivariate Analysis. Poisson Regression

Risk Factor	Odds Ratio (OR)	Confidence Interval (IC)	p
Surgical risk index	2.575	1.224–5416	0.013
Public vs. private healthcare	1.473	0.974–2.229	0.067
Systemic arterial hypertension	1.770	0.877–3.573	0.111
Diabetes mellitus	1.678	1.168–2.409	0.005
Dyslipidemia	1.083	0.777–1.510	0.637
Obesity	2.068	1.457–2.936	< 0.001
Adequate glycemia (< 200 mg/dl)	1.077	0.724–1.601	0.715
Blood glucose level	1.004	1.001–1.007	0.007

In our study, 96% of patients used either a first or second-generation cephalosporin. Meta-analysis evidenced that the use of cefuroxime as a cardiac surgery prophylaxis demonstrated better protection against respiratory infections in the immediate preoperative period. Although our study did not evaluate this type of outcome, there was no difference in the comparison between cefazolin (institutional protocol effective before May 2014) and cefuroxime (institution recommendation as of June 2014) for SSI (data not shown).

The prevention bundle used at our research institution included six preventive measures. Complete adherence to the bundle was not associated with reduced risk of surgical infections. Regarding the CDC's bundle of measures, it establishes the following preventive measures with respect to the perioperative period: surgical antibiotic prophylaxis during the pre-, intra-, and postoperative periods; performing hair removal when necessary, without the use of razors; blood glucose level control during the pre- and postoperative periods; normothermia throughout the perioperative period; optimization of tissue oxygenation; skin preparation with alcoholic solutions; and finally the use of the Surgical Safety Checklist.[3]

Blood glucose level alone was associated with a reduced surgical infection risk. Nonetheless, dichotomized levels below 200 mg/dl were not associated with reduced infection rates. Various studies have associated blood glucose level with risk of infection in cardiac surgery. There is recent evidence that strict blood glucose control (levels below 180 mg/dl) can

reduce SSI rates in patients who undergo surgical procedures.[3] Furthermore, confirming the findings of our study, diagnosis of diabetes mellitus, regardless of blood glucose level, increases the risk of SSI in cardiac surgery. The SCIP, which was founded in 2003 as a national-level partnership of organizations committed to improving surgical care safety by reducing postoperative complications, developed a core measure to maintain blood glucose level at ≤ 180mg/dL during the perioperative and postoperative periods, based on evidence that this reduces SSI in cardiac surgery.[10,13,14] The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) also recommend blood glucose level goal of ≤ 180 mg/dL during the immediate postoperative period. According to a study conducted by the Society of Thoracic Surgeons, it has been demonstrated that maintaining blood glucose levels between 150 mg/dL and 180 mg/dL reduces the risk of SSI in cardiac surgery.[7,15] A randomized controlled study of 5,510 diabetic cardiac surgery patients, with an intravenous insulin protocol used to maintain blood glucose at ≤ 150 mg/dL, demonstrated that the use of this protocol is safe and that it led to a 77% reduction in SSI.[16]

Obesity is a risk factor for SSI in cardiac, colorectal, orthopedic, caesarean section, and general surgery, as the procedure becomes more complex and increases the duration of surgical stay, causing tissue hypoxia and hyperglycemia related to the obese patients' insulin resistance, thus, contributing to the risk of SSI. Obese patients have a higher risk of acquiring infections, especially when they are exposed to surgical procedures and hospitalization in intensive care units.[17-19] A study conducted in the USA demonstrated that risk of infection was 4.7 times higher in obese surgery patients and 6 times higher in surgery patients with morbid obesity, in comparison with normal-weight surgery patients.[19] Furthermore, a recent study followed up 33,936 patients after myocardial revascularization surgery, showing that the factors that determined high risk of surgical infection included female sex, obesity, unplanned reoperations, and longer hospital stays.[20] In our study, the risk of infection related to obesity was 1.8 times higher.

The surgical risk index is a good predictor of risk in surgeries. In one study, the use of NNIS risk index contributed to the stratification of SSI incidence rates in cardiac surgery. In this study, the incidence of mediastinitis was 0% when the patient's score was 0, 1.2% when it was 1, and 2.3% when it was 2.[21,22] Our study demonstrated that in clean surgeries, the component related to base pathologies, patient's physical state (ASA class), and procedure duration, as measured by NNIS risk index, was associated with a higher risk of infection.

Although obesity and diabetes mellitus are modifiable factors in most cases, these pathologies may signal greater risks. Healthcare professionals may then take greater care with the patient, for example, with strict attention to the surgical technique, dead space reduction, tissue circulation, and postoperative care.

There are some limitations to our study. It is a retrospective study of only one cardiology center. Although we assessed the patients' physical state and risk factors (ASA class) and procedural risks (length of surgical stay), the final analysis did not include some risk factors, such as patient skin antisepsis (preoperative); the surgical team's abilities and operating room assistants' behavior (intraoperative); surgical sterilization practices; the use of invasive procedures during the postoperative period, such as catheters, probes, or mechanical ventilation; and other risk factors related to infection.

Conclusion

Obesity, diabetes, and blood glucose level were independent factors associated with SSI in patients who underwent major cardiac surgery procedures. Surgical risk index was a good predictor score for SSI in cardiac surgery. Surgical antibiotic prophylaxis and adherence to the SSI prevention bundle for cardiac surgery were not associated with a decrease in SSI risk.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Andrade L, Siliprandi EMO, Pires R; Acquisition of data: Andrade L, Siliprandi EMO, Karsburg LL, Berlesi FP, Carvalho OLF, Rosa DS, Pires R; nalysis and interpretation of the data and Obtaining financing: Andrade L, Pires R; Statistical analysis: Andrade L, Karsburg LL, Berlesi FP, Pires R; Writing of the manuscript: Andrade L, Siliprandi EMO, Carvalho OLF, Rosa DS, Pires R.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Cardiologia - Fundação Universitária de Cardiologia - Unidade de Pesquisa under the protocol number 4997/14. 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

The Olympic Experimental Gymnasium Program and its Association with the Prevalence of Cardiovascular Risk Factors in Adolescents: A Cross-Sectional Study

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Abstract

Background: **Cardiovascular disease (CVD) is the leading cause of death worldwide. Physical activity (PA) and appropriate diet, if adopted in childhood and adolescence, may reduce the CVD burden in later life. The Olympic Experimental Gymnasium (OEG) project was implemented to increase the PA levels of students by means of regular physical exercise and healthy eating habits.**

Objectives: **To estimate and compare the prevalence of CVD risk factors in OEG schools versus regular schools (RSch) and to examine associations between the school environment and CVD risk factors.**

Methods: **In this cross-sectional study with a comparator group, adolescents aged 12-13 years attending three OEG schools (n = 719) and three RSch (n = 394) were evaluated after one year of the ongoing program to estimate the prevalence of overweight, pre-hypertension/hypertension, altered glycemia, and lipid profile. An α level of 0.05 was set for statistical analysis.**

Results: **RSch students had higher odds to have high blood pressure (OR 1.86, 1.36–2.54) and to be overweight (OR 1.49, 1.13–1.98) than OEG students. Glucose levels were not altered in most cases regardless of school type, and no differences were found in lipid profile. In the sensitivity analysis stratified by gender, girls from RSch were more likely to have high body mass index than boys.**

Conclusions: **Exposure of adolescents to the OEG policies was positively associated with an important reduction in CVD risk factors, including high blood pressure and overweight. (Arq Bras Cardiol. 2019; 112(6):775-781)**

Keywords: **Cardiovascular Diseases/mortality; Hypertension; Overweight; Dyslipidemias; Exercise; Life Style; Child; Adolescent; Diet.**

Introduction

The attributable fraction of deaths due to physical inactivity can reach values around five million persons in the world.[1] Among adolescents, the prevalence of a sedentary lifestyle is also high. The Study of Cardiovascular Risks in Adolescents (ERICA) found a frequency of 54% of physical inactivity, which was more prevalent in girls.[2] The same study, when considering approximately 37,000 subjects, found that higher physical activity (PA) levels were independently associated with cardiovascular risk and with sedentary time. Interestingly, PA levels do not appear to change the association between body mass index (BMI) and cardiovascular risk.[3]

Lifestyle patterns related to eating habits and PA practices established in the school environment can have potential consequences in adulthood. There is evidence that atherosclerosis begins in early life, progressing slowly into elderliness.[4] Scherr et al.[5] stated that it is important to consider the presence of cardiovascular risk factors in school children and that they may be related to lifestyle behaviors.

Given that young people spend most of their time in school, the role of school programs cannot be underestimated.[6] In this respect, the most common ways to increase PA through the school system have been based on engagement in physical education classes and extracurricular physical activities. However, those are often underused.[7]

School-based interventions to increase PA seem to be feasible as a strategy to reduce risk factors. Knox et al.[8] reported a decrease in cardiovascular risk factors among 115 participants aged 12 years-old after an 18-week intervention in a secondary school. Similarly, the ACORDA project found a reduction of obesity in adolescents after increasing PA levels with and without dietary advice after an 8-month interdisciplinary approach.[9]

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In 2012, Rio de Janeiro's city government initiated a project integrating academic and sports training: the Olympic Experimental Gymnasium (OEG).[10] Emphasis was given to sports practice (two hours a day, five times a week), and five healthy meals were provided to students every day. Conversely, in regular schools (RSch), PA practice is limited (once a week) and students have only one meal per day.

In this context, we aimed to examine potential associations between the school environment in OEG schools versus RSch and important cardiovascular disease (CVD) risk factors in adolescents. We hypothesized that the adolescents attending RSch would be more likely to have risk factors than those attending OEG schools.

Methods

This article was written according to the standards of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cross-sectional studies.[11]

Study design

A cross-sectional study with a comparator group was conducted at six public schools in Rio de Janeiro: three OEG schools and three RSch. Data collection was carried out in the schools from 2013 to 2015. Data were always collected in the mornings, on the same day of the week by the same trained investigator. To draw association inferences, we considered the school type (ER or OEG) as the exposure, and important CVD risk factors as the outcome, treated as categorical variables. A total of 1,113 students were included in a 2:1 allocation ratio to exposure (719 attending OEG schools) and non-exposure (394 attending RSch).

Eligibility criteria and participant selection

Eligible participants were all regularly enrolled sixth- to ninth-grade students attending the same school for at least one year. Students attending OEG schools needed to comply with the OEG policy of engaging in PA with energy expenditure > 5 metabolic equivalents (METs) five times a week. Attendance at PA sessions was self-reported by the students or their parents.

When selecting participants for the comparator group, efforts were made to match the students as closely as possible to avoid potential confounding factors. Thus, a match for chronological age, sex, and grade was made. In RSch, students spent about one hour weekly in PA.

At the time of data collection, four OEG schools were operating in Rio de Janeiro, but only three of them had been operating for at least one year. Therefore, all of the OEG schools were enrolled with no *a priori* sample size planning. RSch, selected by convenience sampling, were located in the same geographic region of the OEG schools, to avoid discrepancies especially due to socioeconomic status. Both OEG and RSch were public schools, attended by students from all regions of the city.

Data collection

Written informed consent was obtained from all students and their parents/guardians prior to inclusion in the study. The first school visit was then scheduled, and we performed the following procedures: capillary blood collection, medical interview, physical examination and blood pressure (BP) measurement. All data were collected following a circuit format, in which students passed by each station where the measurements were performed.

A trained medical staff interviewed the students and their parents/guardians using a structured questionnaire designed specifically for this study, in which data of sex and age, in addition to past medical history and current relevant health information were obtained. The medical staff also evaluated adolescents, including anthropometric assessment, measurement of BP and blood sample collection.

Capillary blood samples were collected after a 12-hour overnight fasting to determine glucose levels, total cholesterol, and triglycerides (Roche AccuTrend Plus Kits®). Altered glucose, total cholesterol and triglycerides levels were considered as results greater than 99 mg/dL, 170 mg/dL and 130 mg/dL, respectively. Height and weight were measured using a Filizola® scale, with maximum capacity of 150 kg, and a coupled vertical stadiometer of 220 cm. Based on BMI values, individuals were classified as eutrophic, overweight or obese, according to the percentiles of height and age for each individual subject. Office BP was measured three times in sitting position, using a calibrated aneroid sphygmomanometer in millimeters of mercury. Students with systolic and diastolic BP above the 95th percentile for their respective gender, age and height were considered hypertensive, while students with systolic and diastolic BP values between their 90th and 95th percentiles were classified as pre-hypertensive. All participants included in the analysis had participated in the PA program for at least one year. This was planned to minimize the risk of reverse causality. Reference values were based on the Brazilian Pediatric Society standards.[12]

Statistical analyses

A descriptive analysis was conducted, and data were expressed as mean and standard deviation for baseline characteristics and continuous variables, and as absolute frequencies and percentages for categorical variables. In the inferential analysis, the Shapiro-Wilk test was used to assess the normality of data distribution. Groups were then compared by an independent sample two-tailed Student's *t* test for continuous variables, and by the χ^2 test for categorical variables.

Association of school exposure with health status outcomes was assessed by a binomial logistic regression, and its diagnostic was performed to support the analysis. The health status outcomes regarding altered triglycerides, cholesterol, overweight/obesity (regarded as one variable), and pre-hypertension/hypertension were dichotomized into 'YES' and 'NO' according to the thresholds recommended by the Brazilian Pediatric Society.[12] Point estimates for the associations were expressed as odds ratio (OR) with their 95% confidence intervals (95% CI), and all analyses were adjusted for sex and age. An exploratory sensitivity analysis was planned in cases of disagreement between matching variables. 'OEG School' was chosen as the reference group for all analyses. No imputation for potential missing data was planned, and all available data for each analysis were used. All statistical analyses were conducted in the StataSE package v. 14.0. An α level of 0.05 was set for statistical inferences.

Results

A total of 1,113 students were screened, included, and evaluated. Of these, 719 were attending OEG schools and 394 were attending RSch. Table 1 shows comparative data between OEG and RSch students as well as the number of students analyzed for each category.

RSch students had a higher BMI than OEG students (21.4 ± 4.4 vs 20.5 ± 4.3 kg/m^2, p < 0.001), and overweight was also more prevalent in RSch students (33.8% vs 26.7%, p = 0.001). The prevalence of high BP was higher in RSch students than in OEG students (28.5% vs 16.3%, p = 0.013). RSch and OEG schools did not differ in the frequency of altered glycemia, total cholesterol or triglycerides.

Despite our efforts to match the groups for sex, the χ^2 test indicated differences between groups, with a higher proportion of girls in RSch than in OEG schools (64.0% vs 49.4%, p < 0.001). Due to this difference, we performed a sensitivity analysis stratified by sex and the results are shown in Table 2.

The difference observed in BMI between RSch and OEG students was limited to girls (21.9 ± 4.5 vs 20.6 ± 4.3 kg/m^2, p = 0.001), with no difference when only boys were compared (20.6 ± 3.9 vs 20.3 ± 4.2 kg/m^2, p = 0.564). There was a difference in the prevalence of overweight between RSch and OEG girls (35.7% vs 24.3%, p = 0.002), but not among boys (30.3% vs 29.0%, p = 0.777). There was no difference in any other parameter assessed.

To provide estimates based on associations, a binary logistic regression model was used for each health marker, adjusted for age and sex, and the results are shown in Table 3.

After adjusting for sex and age, RSch students were more likely to be overweight (OR 1.49, 1.13–1.98) and to have pre-hypertension and hypertension (OR 1.86, 1.36–2.34), while no differences were observed for altered total cholesterol or triglycerides.

After stratifying by sex, due to the previously found gender differences between schools, the girls attending RSch had higher odds to be overweight (OR 1.89, 1.30–2.75) and pre-hypertensive/hypertensive (OR 1.66, 1.10–2.51), with no association with altered total cholesterol and triglycerides. For boys, only the association between attending RSch and being pre-hypertensive/hypertensive was found to be significant (OR 2.20, 1.37–3.54).

Discussion

In this cohort study, we confirmed our primary hypothesis that students attending OEG schools had lower cardiovascular risk prevalence than students attending RSch. Our results are important because they highlight the association between a healthy school policy and reduction of CVD risk factors in adolescent students.

A proportion-difference test showed that overweight and pre-hypertension/hypertension were less frequent in OEG schools. The prevalence of overweight students in OEG schools was approximately 11% lower. The difference was even lower for pre-hypertension/hypertension (approximately 13%). Glucose levels were not altered in most cases. Although no differences were found between schools, the lipid profile was altered in almost half of the students.

The 2016 ERICA study, the largest cross-sectional study involving all regions of Brazil to assess the frequency of cardiovascular risk factors in students, also evaluated individuals of the same age as ours (12-14 years old) and of the same geographic region (southeast).[13,14] It should be noted that the ERICA study found a lower rate of pre-hypertension/hypertension (6.5%, 5.5–7.8%) and a lower overall prevalence of overweight (18.4%, 15.5–21.6%) in the subgroup of individuals of the same age range and residents of the same geographic region than those observed in our study. Conversely, Cureau et al.[14] reported a prevalence of 31.3% for high BP and 23.9% for overweight in a similar group. Several reasons may account for these differences, mostly regarding the criteria used to define pre-hypertension/hypertension and overweight, in addition to the use of different methodology, including the measurements obtained by aneroid and oscillometric devices.[15] As for the differences between OEG schools and RSch, Cureau et al.[14] provide useful findings to explain them, since the prevalence of physical inactivity in their cohort was estimated around 51%.

Considering the attributable risk fraction of physical inactivity to develop hypertension and obesity,[16-18] it seems

Table 1 – Comparison of demographic characteristics, anthropometric data and cardiovascular risk factors between students from regular schools (RSch) and Olympic Experimental Gymnasiums (OEG)

Variable	OEG	RSch	p value
Age (years)	12.6 ± 1.2 (n = 719)	13.3 ± 1.5 (n = 394)	
BMI (kg/m^2)	20.5 ± 4.3(n = 716)	21.4 ± 4.4 (n = 394)	0.001
Overweight	191/716 (26.7%)	133/394 (33.8%)	0.01
Altered glycemia	1/700 (0.1%)	0/393 (0.0%)	NA
Altered total cholesterol	270/714 (37.8%)	152/393 (38.7%)	0.78
Altered triglycerides	403/624 (64.6%)	253/387 (65.4%)	0.80
Pre-hypertension/hypertension	116/712 (16.3%)	112/393 (28.5%)	< 0.001

Data are reported as mean ± standard deviation or absolute number (percentage). BMI: body mass index; NA: not applicable; p-value obtained by chi-square test or Student's t test.

Table 2 – Comparison of demographic characteristics, anthropometric data and cardiovascular risk factors between students from RSch and OEG schools, stratified by sex

Variable	Girls			Boys		
	OEG	RSch	p value	OEG	RSch	p value
Students	354 (49.4%)	252 (64.0%)	< 0.001	362 (50.6%)	142 (36.0%)	< 0.001
Age (years)	12.6 ± 1.2 (n = 354)	13.4 ± 1.4 (n = 252)	< 0.001	12.6 ± 1.1 (n = 362)	13.2 ± 1.6 (n = 142)	< 0.001
BMI (kg/m^2)	20.6 ± 4.3 (n = 354)	21.9 ± 4.5 (n = 252)	0.001	20.3 ± 4.2 (n = 362)	20.6 ± 3.9 (n = 142)	0.56
Overweight	86/354 (24.3%)	90/252 (35.7%)	0.002	105/362 (29.0%)	43/142 (30.3%)	0.78
Altered glycemia	1/348 (0.3%)	0/252 (0.0%)	NA	0/352 (0.0%)	0/141 (0.0%)	NA
Altered total cholesterol	146/355 (41.1%)	107/252 (42.5%)	0.74	124/359 (34.5%)	45/141 (31.9%)	0.56
Altered triglycerides	226/321 (70.4%)	162/247 (65.6%)	0.22	177/303 (58.4%)	91/140 (65.0%)	0.19
Pre-hypertension/ hypertension	61/352 (17.3%)	67/251 (26.7%)	0.006	55/360 (15.3%)	45/142 (31.7%)	< 0.001

Data are reported as mean ± standard deviation or absolute number (percentage). OEG: Olympic Experimental Gymnasium project; RSch: regular schools; BMI: body mass index; NA: not applicable; p-value obtained by chi-square test or Student's t test.

Table 3 – Binary logistic regression models using cardiovascular risk factors as independent variables, adjusted for age and sex

	Overweight	Pre/Hyp	Altered TC	Altered TGL
Overall[a,b]	(n = 1010)	(n = 1105)	(n = 1104)	(n = 1010)
RSch	1.49 [1.13 – 1.98][§]	1.86 [1.36 – 2.54][§]	1.01 [0.77 – 1.31]	0.88 [0.66 – 1.16]
Girls[a]	(n = 606)	(n = 603)	(n = 606)	(n = 567)
RSch	1.89 [1.30 – 2.75][§]	1.66 [1.10 – 2.51][§]	1.03 [0.73 – 1.45]	0.69 [0.48 – 1.01]
Boys[a]	(n = 404)	(n = 502)	(n = 498)	(n = 443)
RSch	1.09 [0.71 – 1.69]	2.20 [1.37 – 3.54][§]	0.95 [0.62 – 1.46]	1.19 [0.78 – 1.82]

Data are reported as odds ratio and 95% confidence interval: OR [95%: lower – upper limit]. Pre/Hyp: pre-hypertensive/hypertensive; TC: total cholesterol; TGL: triglycerides; RSch: regular schools. [a]adjusted for age, [b]adjusted for sex, § = p < 0.05.

reasonable to hypothesize that the differences in health status between OEG and RSch students can result from the PA policy implemented in the OEG. The time course for weight changes and BP control by non-pharmacological intervention,[19] and the association between school PA policy and CVD risk factors[20,21] could support our hypothesis. As for lipid profile, the absence of differences was not a surprise, once PA is known to have only a slight effect on lipid content.[22] However, the high prevalence of dyslipidemia needs to be addressed.

In the whole sample, the prevalence of dyslipidemia was almost two times greater in RSch than OEG (38.1% vs 64.9%). In the ERICA study,[23] the frequency of hypercholesterolemia and hypertriglyceridemia was 20.1% and 7.8%, respectively, in a sample of 38,069 adolescents aged 12-17 years. A possible explanation for the discrepancy between our data and that of literature is that the age of 12-13 years corresponds to the pubertal spurt period in boys and girls, and hormonal and other biological interactions may influence biological markers, making it difficult to correctly quantify them.[24]

It is also important to point out the association between obesity and hypertension. Bloch et al.[12] reported a higher prevalence of hypertension in obese adolescents (28.4%) than in overweight (15.4%) and eutrophic (6.3%) adolescents. The fraction of hypertension attributable to obesity was 17.8%, which raises the hypothesis that about one-fifth of hypertensive patients would not have high BP if they were not obese. This seems important and could serve as a basis for decision-makers of the potential benefits of increasing school-based PA interventions, including intermediate outcomes as control of hypertension, a major cause of cardiovascular mortality in later life.[25]

Interestingly, while both boys and girls attending RSch were less physically active and had a higher frequency of pre-hypertension/hypertension, only girls appeared to benefit more from attending OEG schools when the goal was control of body weight. A possible explanation for this finding is that boys are usually more active than girls and more frequently engaged in non-scheduled PA.[26]

Regarding our exploratory binomial logistic regression analysis, after adjusting for age and sex, RSch students had higher odds to be overweight and to have pre-hypertension/hypertension than OEG students, supporting the rationale and results described above.[19] Actually, no differences were found for altered glycemia or lipid profile. The results of the International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE), a large multicenter cross-sectional study, demonstrated a positive association between sedentary behavior and obesity, even in the cluster analysis of 6,000 students from 12 countries[27] and in the evaluation of those meeting the recommendations for 24-hour movement guidelines.[28]

Regarding our sensitivity analysis in the logistic regression model, it is important to note that the magnitude of association between the school policy and being overweight increased for girls (OR: from 1.49 [1.13–1.98] to 1.89 [1.13–2.75]) and decreased for boys (OR: from 1.49 [1.13–1.98] to 1.09 [0.71-1.69]), when compared to that of the fully adjusted model. With respect to the association between the school policy and pre-hypertension/hypertension, the magnitude of association slightly decreased for girls (OR: from 1.86 [1.36–2.54] to 1.66 [1.10–2.51]) and increased for boys (OR: from 1.86 [1.36–2.54] to 2.20 [1.37–3.54]), with no difference in lipid profile.[29]

Despite the imbalance between the sexes, which motivated the sensitivity analysis, there may be a rationale to explain the changes in the magnitude of the point-estimation. Previous findings support that, overall, girls are more likely to be overweight than boys – perhaps because boys are more physically active and less sedentary.[30] Nevertheless, data from NHANES revealed that the prevalence of risk factors for CVD and metabolic syndrome was higher in boys than in girls,[31] which is in line with he statement that boys are more likely to be pre-hypertensive/hypertensive than girls.[32] This apparently counterintuitive fact could be supported by the present experiment. Among girls, 606 were overweight, and 603 were diagnosed with pre- or hypertension. Among boys, 404 were overweight and 502 were pre-hypertensive or hypertensive. These numbers indicate that other risk factors, such as family history, may be associated with elevated BP – since at least 98 boys had this condition despite the absence of overweight. Therefore, the interactions between school environment and sex are not sufficient to explain the differences in both overweight and pre-hypertension/hypertension observed in the fully adjusted model and in the model stratified by sex. However, this analysis supports the fact that sex may explain the prevalence of overweight and pre-hypertension/hypertension in adolescents regardless of PA status.

Limitations and future directions

The results of this study need to be interpreted in light of some limitations. First, because of the cross-sectional design, we cannot establish a causal relationship between school environment (i.e., school PA policy) and the development of CVD risk factors. Second, we did not measure the level of PA of the participants to verify whether they met the PA recommendations of the school policy – this is why we chose school, instead of PA level, as the exposure. Third, no adjustment was made for socioeconomic status, parental influence, or dietary intake, which might have some influence on the development of CVD risk factors. Finally, the categorization of some continuous variables for analysis cannot be disregarded as a limitation, even though we used thresholds commonly reported in the literature.

On the other hand, the hypothesis raised by our study needs to be addressed in intervention-based studies, like multicenter, cluster randomized controlled trials. We addressed, with a valuable sample size, the prevalence of some CVD risk factors in the school environment of a middle-income country in a chronological age-homogeneous sample. The use of higher PA doses, like that of the OEG policy, need to be tested and confirmed in future experiments.

Conclusion

The prevalence of pre-hypertension/hypertension and overweight differed between schools, and students attending OEG had lower proportion and odds of developing CVD risk factors.

Author contributions

Conception and design of the research and Acquisition of data: Scheer C, Belém LJ, Fabiano LCC, Pinheiro LT; Analysis and interpretation of the data: Scheer C, Helal L, Belém LJ, Fabiano LCC, Pinheiro LT, Stein R; Statistical analysis: Scheer C, Helal L, Belém LJ, Fabiano LCC, Pinheiro LT; Obtaining financing: Scheer C, Stein R; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Scheer C, Ferrari F, Helal L, Stein R.

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 Instituto Brasileiro de Cardiologia under the protocol number CAAE 14549513.1.0000.5272. 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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Physical Activity and Healthy Eating Patterns in Public Schools in Brazil: A Strategy to Avert Risk Factors in Adulthood

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Short Editorial related to the article: The Olympic Experimental Gymnasium Program and its Association with the Prevalence of Cardiovascular Risk Factors in Adolescents: A Cross-Sectional Study

Cardiovascular disease (CVD) remains the leading cause of death globally, however, 80% of premature heart disease, stroke and diabetes can be prevented.[1] Atherosclerotic cardiovascular disease (ASCVD) can begin in youth, exacerbated by exposure to factors associated with increased cardiovascular risk.[2] There are interventions to prevent risk factors onset (primordial prevention), to identify and treat risk factors in childhood and adolescence (primary prevention) and to address the risk of additional events in those who already have ASCVD or other CVDs (secondary prevention) at a young age.[3] Adolescence presents a prime opportunity to assess risk factors for CVD and to intervene to prevent its development.

The manuscript by Scherr et al.[4] highlights the importance of a school-based program including physical activity (PA) and healthy eating patterns in adolescence for the prevention of cardiovascular risk factors.

The Olympic Experimental Gymnasium (OEG) is a project initiated by Rio de Janeiro's city government integrating academic and sports training. The schools participating in the OEG project provide sports practice (two hours a day, five times a week), and five healthy meals to students every day. In this article, the authors evaluate the influence of sports practice and healthy eating habits in OEG schools compared with PA once a week and one meal per day, in regular schools (RSch). The students had to be exposed to the interventions for one year prior to data collection. The authors aimed to examine potential associations between the school environment in OEG schools versus RSch and important CVD risk factors in adolescents. They hypothesized that the adolescents attending RSch would be more likely to have risk factors than those attending OEG schools.

In this cross-sectional study, a total of 1,113 students, from the same geographic region were included in a 2:1 allocation ratio to exposure (719 attending OEG schools) and non-exposure (394 attending RSch).

Although the study was cross-sectional, the students were included if they had participated in the OEG or RSch program for at least one year. Association between exposure and health status was addressed by a binomial logistic regression. The results of this program showed that the prevalence of prehypertension/hypertension and overweight differed among schools and that students attending OEG schools had lower proportion and odds of developing CVD risk factors. Higher body mass index, prehypertension/hypertension and overweight were more prevalent among RSch students. However, when analyzed by gender, girls had higher BMI and prevalence of overweight. After adjusting for sex and age, RSch students were more likely to have overweight (OR 1.49; 95%CI 1.13-1.98) or to be pre-hypertensive/hypertensive (OR 1.86; 95% CI 1.36-2.34). No differences were found for total cholesterol, glycemia or triglycerides, according to school exposure.

As this study was cross-sectional, causality could not be inferred. Evaluation of exposure, but not the level of PA, baseline status of participants, and not only the effects of exposure are limitations of this study. Prospective studies, with cluster randomization of interventions, should be done to assess lifestyle modification in adolescence and the association with risk factors.

Recently, the American Heart Association issued a statement to guide cardiovascular risk reduction in high-risk pediatric patients.[3] Although there are recommendations for high, moderate and at-risk categories, general strategies for lifestyle improvement are recommended for blood pressure, lipids (LDL-cholesterol and triglycerides), blood glucose, PA, diet, weight, and smoking in those who yet did not present these risk factors.

The major modifiable risk factors for CVD (smoking, hypertension, hypercholesterolemia, diabetes, and obesity) often begin in early life.[5] Several studies have found that the number of CVD risk factors present in individuals correlates with the severity of atherosclerosis in both children and young adults.[6-8] Initiatives to promote a better lifestyle must be encouraged in schools and adopted by policymakers, educators and stakeholders. In addition, in those at risk, an adequate risk stratification[9] should be performed to avert the onset of cardiovascular risk factors.

Keywords

Adolescent; Exercise; Healthy Diet; Risk Factors/prevention and control.

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Heart Failure with Mid-Range Ejection Fraction – State of the Art

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Abstract

In 2016, the European Society of Cardiology (ESC) recognized heart failure (HF) with ejection fraction between 40 and 49% as a new HF phenotype, HF with mid-range ejection fraction (HFmrEF), with the main purpose of encouraging studies on this new category. In 2018, the Brazilian Society of Cardiology adhered to this classification and introduced HFmrEF in Brazil. This paper presents a narrative review of what the literature has described about HFmrEF. The prevalence of patients with HFmrEF ranged from 13 to 24% of patients with HF. Analyzing the clinical characteristics, HFmrEF shows intermediate characteristics or is either similar to HF with preserved ejection fraction (HFpEF) or to HF with reduced fraction (HFrEF). Regarding the prognosis, HFmrEF's all-cause mortality is similar to HFpEF's and lower than HFrEF's. Studies that analyzed cardiac mortality concluded that there was no significant difference between HFmrEF and HFrEF, both of which were lower than HFpEF. Despite the significant increase of publications on HFmrEF, there is a great scarcity of prospective studies and clinical trials that allow delineating specific therapies for this new phenotype. To better treat HFmrEF patients, it is fundamental that cardiologists and internists understand the differences and similarities of this new phenotype.

Introduction

The classification and characterization of heart failure (HF) by phenotypes has an important relevance in clinical practice, since these phenotypes are currently based on left ventricular ejection fraction (LVEF) and have different characteristics in relation to prognosis and treatment.[1]

Classically, two main HF phenotypes have been described; the HF with reduced ejection fraction (HFrEF) with LVEF < 40% and the HF with preserved ejection fraction (HFpEF), with LVEF ≥ 50%.[2-4] Different guidelines have proposed a new phenotype in the current decade, the HF with mid-range ejection fraction (HFmrEF).

The American College of Cardiology/American Heart Association published a new HF guideline in 2013, in which patients with LVEF between 41% and 50% were classified as "borderline" HFpEF.[2] In 2016, the ESC recognized HF with LVEF between 40% and 49% as a distinct phenotype; the HFmrEF, mainly intended to stimulate studies that address epidemiology, etiology, characteristics, and prognostics of this new category.[3] Finally, the Brazilian Society of Cardiology (BSC) introduced HFmrEF as a new clinical phenotype in its 2018 guideline of acute and chronic HF.[5]

With the introduction of this new classification, HFmrEF has received great attention and, consequently, has been better studied and characterized. The present review study aims to describe what is currently known about HFmrEF and discuss future perspectives that will contribute to a better approach for this group of patients.

Keywords

Heart Failure/physiopathology; Stroke Volume; Natriuretics Peptides; Diagnostic Imaging; Electrocardiography; Ecocardiography; Magnetic Resonance Imaging.

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Epidemiology

Prevalence

In the United States, it is estimated that more than 6.5 million people have HF,[6] and the percentage of individuals with HFmrEF is between 13% and 24%.[7,8] The prevalence of HFmrEF in studies performed with hospitalized patients ranged from 13% to 26%,[7,9-12] while the prevalence of HFmrEF in outpatients varied from 9% to 21%.[8,13-17]

The last census of Brazilian Institute for Geography and Statistics (IBGE) in 2010 census showed an increase in the elderly population in Brazil, and therefore a great potential for the increase of at-risk HF patients. In the DIGITALIS study performed in the city of Niterói, state of Rio de Janeiro, Brazil, a prevalence of 9.3% of HF was identified in patients from the family physician program (59 individuals among 633 volunteers),[18] in which 64.2% of these patients were characterized as having HFpEF and 35% as HFrEF.[18] Recently, according to unpublished data based on the DIGITALIS study database, the prevalence of HFmrEF patients in Niterói was 22%, HFrEF was 19% and HFpEF was 59%.

Diagnosis

According to the latest acute HF guideline of BSC,[5] the diagnosis of HF is based on the combination on medical history findings, physical examination, electrocardiogram and chest x-ray results, as detailed in figure 1. An echocardiogram should be performed for diagnostic confirmation if there is clinical suspicion of HF. In low suspicion cases or if there are diagnostic doubts, the measurement of brain natriuretic peptides (BNP and/or NT-proBNP) and an echocardiogram should be performed, if available. A normal echocardiogram and/or plasma BNP levels < 35 pg/mL and/or NT-proBNP < 125 pg/mL make the HF diagnosis improbable. In the presence of BNP levels > 35 pg/mL and/or NT-proBNP > 125 pg/mL and/or altered echocardiogram results, the HF diagnosis becomes probable. The LVEF echocardiography evaluation contributes

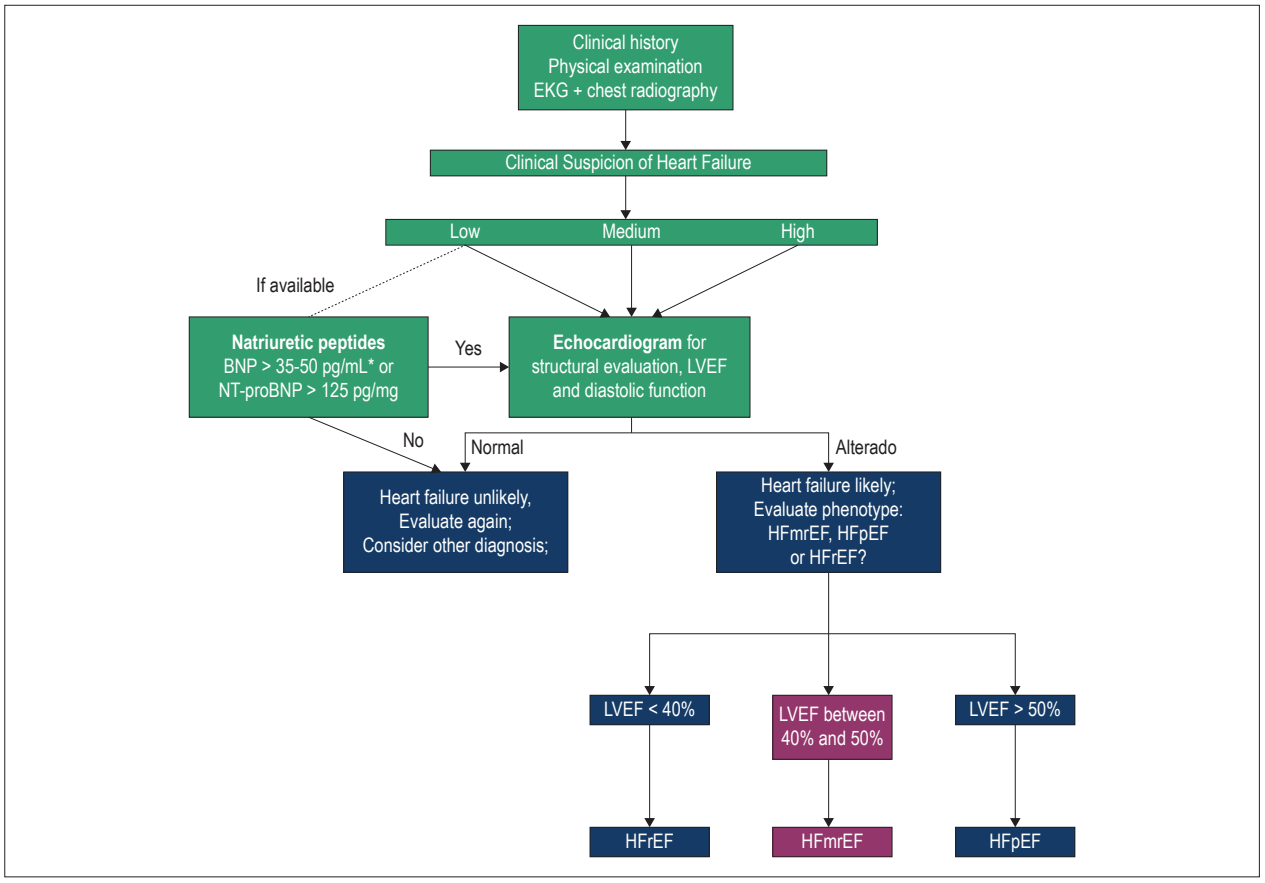

Figure 1 – *Diagnostic algorithm in the clinical suspicion of heart failure. Adapted from: Brazilian Guideline for Chronic and Acute Heart Failure of 2018;[5] HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; EKG: electrocardiogram; BNP: brain natriuretic peptide; NT-proBNP: amino-terminal fragment of pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction.*

to establishing the HF clinical phenotype, since the clinical signs and patients' symptoms with HFrEF, HFmrEF and HFpEF are similar.[3]

A relevant aspect regarding the HFmrEF diagnosis involves methodological aspects related to the cardiac imaging techniques. The LVEF evaluation by echocardiography has been the standard method used to categorize patients with HF; however, it is common that the values obtained are different in relation to other methods, such as cardiac magnetic resonance imaging, radioisotope ventriculography and angiocardiography.[19,20] In addition, the ejection fraction evaluation by echocardiography shows considerable intra and inter-observer variability over time, as well as under therapeutic intervention effect.[19,20]

Clinical-epidemiological characteristics

Previous studies have shown that patients with HFmrEF had clinical characteristics that, although intermediate between the HFrEF and HFpEF groups, were more similar to those of HFpEF.[8,9,13,21] Nevertheless, in relation to the presence of ischemic disease, different studies have found that HFmrEF resembles HFrEF, showing a higher prevalence.[7,22-24]

In the study by Kapoor et al.,[7] based on the GWTG-HF (Get With The Guidelines - Heart Failure) registry, patients with HFmrEF were older (mean age of seventy-seven years) and showed a higher percentage of females (48%) when compared to patients with HFrEF, being more similar to HFpEF. Moreover, HFmrEF showed a high prevalence of comorbidities such as DM (50%), atrial fibrillation (AF) (42%), chronic obstructive pulmonary disease (COPD) (36%), anemia (27%) and renal failure (26%), "also similar to HFpEF to HFpEF. However, there was a higher prevalence of ischemic heart disease in up to two thirds of the patients, similar to what as observed with HFrEF.

However, in the meta-analysis published by Lauritsen et al.,[25] patients with HFmrEF had entirely intermediate characteristics, and there were significant differences between patients with HFmrEF and HFrEF and between patients with HFmrEF and HFpEF. Patients with HFmrEF were older than those with HFrEF ($p < 0.001$) but were younger than those with HFpEF ($p < 0.001$). The proportion of men and the prevalence of ischemic heart disease in patients with HFmrEF were lower than in those with HFpEF ($p < 0.001$ and $p < 0.034$, respectively), but higher than in those with HFpEF ($p < 0.001$ and $p < 0.034$ respectively). Hypertension was more frequent in patients with

HFmrEF than in those with HFrEF ($p < 0.001$), but less frequent than in patients with HFpEF ($p < 0.001$). Diabetes mellitus (DM) was significantly less frequent in patients with HFmrEF and HFrEF ($p = 0.17$) than in those with HFpEF ($p = 0.021$). AF was more frequent among patients with HFmrEF than among those with HFrEF ($p < 0.001$), but less frequent than in patients with HFpEF ($p < 0.001$). The prevalence of COPD was lower in individuals with HFmrEF than in HFpEF ($p < 0.001$), but higher when compared to patients with HFrEF ($p = 0.001$). Patients with HFmrEF had significantly better renal function than patients with HFpEF ($p < 0.001$) but worse than patients with HFrEF ($p = 0.001$).

In the RICA[26] registry, patients with HFmrEF showed mixed characteristics in relation to the other groups. Patients with HFmrEF were similar to patients with HFrEF regarding hypertension rates, and chronic kidney disease (CKD) history, as well as in relation to the presence of higher systolic pressure, higher blood pressure, lower frequency of New York Association (NYHA) classes III-IV, higher prevalence of AF and previous HF.

The study by Bhambhani et al.,[22] which analyzed 28,829 without HF participants for an average of 12 years, found that 48% of the patients who developed HFmrEF were females. In addition, participants with HFmrEF shared some similarities with the HFrEF group, including lower body mass index (BMI) in relation to patients with HFpEF, with a lower obesity prevalence, a higher coronary artery disease (CAD) prevalence and lower levels of high density lipoproteins (HDL). Other clinical characteristics of participants with HFmrEF were intermediate between those with HFpEF and HFrEF.

The CHARM[27] study found that patients with HFmrEF were similar to HFpEF for most of the characteristics, including age, systolic blood pressure, percentage of women, previous myocardial infarction and AF. HFmrEF was intermediate between HFrEF and HFpEF regarding the history of hypertension, NYHA and BMI class distribution. Some characteristics, such as DM, were simultaneously prevalent in all three categories.[27,28]

In addition, the study by Wang et al.[23] showed no significant differences in gender between HFmrEF, HFpEF and HFrEF. The HFmrEF group was intermediate compared to the other groups regarding characteristics such as age, smoking history, DM and CKD. In contrast, the HFmrEF group was similar to HFpEF regarding the history of ischemic heart disease, with both groups showing significantly higher rates than HFpEF.

In the Swedish Heart Failure[24] registry, HFmrEF was intermediate in terms of age, gender, hypertension, AF, valvular and renal disease. However, the presence of ischemic disease was more common in HFrEF and HFmrEF when compared to HFpEF, and the prevalence of DM did not differ between the three groups. The BMI was lower and fewer patients had anemia in HFmrEF.

A summary of the clinical-epidemiological HFmrEF characteristics is shown in figure 2.

Biomarkers

Regarding biomarkers, HFmrEF has an intermediate profile, with inflammatory biomarkers being more common in HFpEF and heart distension biomarkers in HFrEF.[13] In the study by Bhambhani et al.[22] was found that the predictors of HFmrEF were similar to the predictors of other types of HF. However, a higher BMI was a predictor of HFpEF, but not of HFmrEF, and natriuretic peptides were more robust predictors of HFpEF than of HFmrEF.

The Swedish Heart Failure registry[24] concluded the median value of NT-pro BNP in HFmrEF was 1,540 pg / mL with an interquartile range of 652-3,317. This value was minimally and not significantly higher than in HFpEF but was significantly higher than in HFrEF ($p < 0.001$). The study by Moliner et al.[29] also concluded that NT-ProBNP levels in HFmrEF were significantly lower than in HFrEF ($p = 0.02$), but similar to

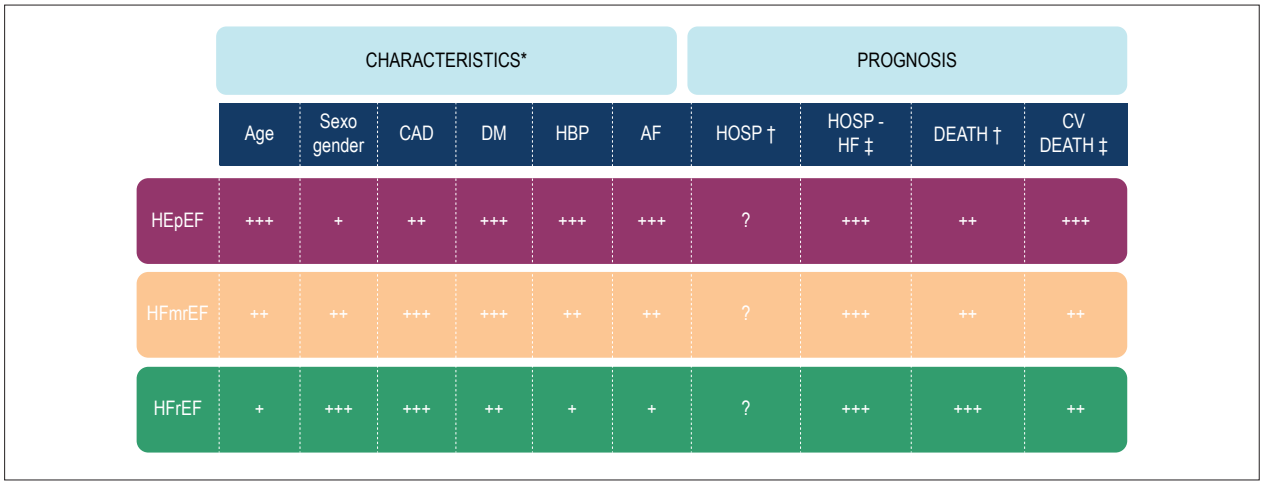

Figure 2 – *Comparisons of the clinical characteristics among the different phenotypes of HF; ? : presence of conflict between studies; CAD: coronary artery disease; DM: diabetes mellitus; HBP: high blood pressure (hypertension); AF: atrial fibrillation; HOSP: hospitalization; HOSP-HF: hospitalization for HF; DEATH: death from all causes; CV-DEATH: cardiovascular death; * Data for constructing the characteristics were taken from references;[7,22-27,32] † Data taken from references;[27,32] ‡ Data taken from reference.[32]*

HFpEF levels (p = 0.88). All other biomarkers were similar between HFrEF and HFmrEF. Cystatin-C and ST2 were significantly lower in HFmrEF than in HFpEF (p = 0.01 and p = 0.02, respectively) Galectin-3 and soluble transferrin receptor were relatively lower in HFmrEF when compared to HFpEF, but the difference was not statistically significant.

Pathophysiology

In the 2016 guideline, the ESC suggested that HFmrEF may have both a mild systolic dysfunction and a diastolic dysfunction contribution.[3] A recent study published by Rastogi et al.,[30] observed that HFmrEF consists of a heterogeneous group of patients, and consists of at least 3 subgroups based on LVEF, such as: patients with previous LVEF < 40% (recovered HFmrEF), patients with previous LVEF > 50% (impaired HFmrEF) and patients with previous LVEF between 40-50% (unchanged HFmrEF).[30] Most patients in this study were classified as having recovered HFmrEF (73%), while 17% of patients were classified as impaired HFmrEF and only 10% were categorized as unchanged HFmrEF.[30]

Also, in this study, the subgroup with recovered HFmrEF had a higher prevalence of male patients and a higher prevalence of patients with CAD, compatible with the characteristics of patients with HFrEF. In contrast, the subgroup with impaired HFmrEF consisted mostly of women with a history of hypertension and AF or flutter, as well as patients with HFpEF. In contrast, the subgroup with impaired HFmrEF consisted mostly of women with a history of hypertension and AF or flutter, as well as patients with HFpEF. Another important observation, in the impaired HFmrEF subgroup, patients had significantly more advanced diastolic dysfunction at the echocardiogram assessment when compared to patients with recovered HFmrEF.[30] A common finding in different cohorts[13,14,31] was that HFmrEF resembled HFrEF in relation to the high prevalence of CAD and a higher risk of new CAD events. In the Swedish Heart Failure register, no difference was observed between the prevalence of CAD between HFmrEF (61%) and HFrEF (60%), while HFpEF was associated with a lower prevalence of the disease (52%).[14] Chioncel et al.[31] based on the long-term HF record of the ESC, found that ischemic etiology was present in 48.6% of patients with HFrEF, 41.8% of patients with HFmrEF, but only in 23.7% % of patients with HFrEF. In the TIME-CHF study,[24] post-hoc analysis, the ischemic etiology was 58.2%, 56.5% and 31.3% for HFrEF, HFmrEF and HFpEF, respectively. Therefore, regarding the etiology, patients with HFmrEF are more similar to those with HFrEF than to the ones with HFpEF.

Prognosis

Both the CHARM study and the prognosis meta-analysis performed by Altaie et al.[32] concluded that all-cause mortality in HFmrEF patients is significantly lower than in patients with HFrEF (p < 0.001 and RR 0.9; 95% CI 0.85–0.94; p < 0.001, respectively) and statistically similar to patients with (HR 0.98; CI 95% 0.82 – 1.19; p = 0.88 and RR 0.98; 95% CI 0.86–1.12; p = 0.82, respectively).[27,32]

Regarding the cardiac mortality, the meta-analysis of Altaie et al.[32] concluded there was no significant difference between HFrEF and HFmrEF (RR 0.89, 95% CI, 0.69-1.15, p = 0.38) while HFpEF showed significantly higher cardiac mortality (RR 1.09, 95% CI, 1.02-1.16, p = 0.001).

In the analysis of the prognosis by separating subgroups of HFmrEF, in the study by Rastogi et al.,[30] the patient cohort with recovered HFmrEF showed significantly better clinical outcomes compared to patients with HFrEF, after adjusting for age and gender. In contrast, the clinical endpoints of the subgroup with impaired HFmrEF were not significantly different from those with HFpEF after adjusted for the same factors.[30] By observing time to death / transplantation / cardiac hospitalization between the subgroups, the recovered HFmrEF had a significantly better prognosis compared to impaired HFmrEF (p = 0.011), whereas there was no significant difference between the two groups and unchanged HFmrEF.[30]

Hospitalization

The studies differed regarding hospitalization rates. The meta-analysis of Altaie et al.,[32] demonstrated that there was no significant difference in all-cause hospitalization for both HFrEF and HFmrEF, and between HFpEF and HFmrEF (RR 0.91, 95% CI, 0.18-4.59, p = 0.9, and RR 0.95, 95% CI, 0.84-1.07; p = 0.38, respectively). Regarding the HF hospitalization, the meta-analysis also did not show any significant differences between HFrEF and HFmrEF or between HFpEF and HFmrEF (RR 0.92, 95% CI, 0.84-1.01, p = 0.08, and RR 1.05, 95% CI, 0.83-1.33; p = 0.69, respectively.) However, in the CHARM study, all-cause hospitalization was significantly lower in patients with HFmrEF than in the HFpEF phenotype (HR 8.89; 95% CI, 0.81-0.98; p = 0.02).[27] When comparing the different HFmrEF in the Rastogi et al.,[30] cohort subgroups, the recovered HFmrEF had a better prognosis compared to HFmrEF (p = 0.029) when observing the time until the first hospitalization for a cardiac event. However, there was no significant difference in relation to the subgroup of unchanged HFmrEF when compared to the other two.

Pharmacological treatment and comorbidity management

In the TOPCAT study, spironolactone did not present in the primary endpoint (consisting of cardiovascular death, cardiac arrest or HF hospitalization), however, there was a reduction in HF hospitalizations in the treatment group with the greatest benefit observed in patients with LVEF from 45% to 55%.[33]

On the other hand, the study by Yan-guo Xin et al.,[34] which evaluated spironolactone use in 229 patients with HFmrEF, showed that the drug use reduced the incidence of primiparous death from all causes (21.3% vs. 34.5%, p = 0.014), as well as improving quality of life. However, there was no difference between the groups receiving different doses of medication (21.8 vs 20.7%, p = 0.861.50 mg vs. 25 mg, respectively).

The OPTIMIZE-HF study, when evaluating the use of ACE inhibitors and ARBs, showed there was no associated benefit in patients with HFmrEF.[21] Patients with LVEF <40% were compared with those with LVEF ≥ 40%, for long-term outcomes in relation to the use of beta-blockers.[21] In patients with LVEF of 40-50%, as in all patients with LVEF ≥ 40%, there was no significant influence of drug use on the outcomes.[35]

However, the CHARM study showed that the candesartan use improved outcomes for HFmrEF to a degree comparable to improvement for HFrEF. For the HFmrEF group, the incidence rates for the primary outcome (cardiovascular death or HF hospitalization) of candesartan vs. placebo were 7.4 vs. 9.7 per 100 patients per year (HR 0.76, 95% CI, 0.61-0.96, p = 0.02), and the incidence rate of recurrent hospitalization for HF was 0.48 (95 % CI, 0.33-0.70, p <0.001).[27,36]

The study by Cleland JGF et al.,[37] which included 18,637 patients, found that for patients with HF with sinus rhythm and LVEF between 40% and 49%, beta-blockers showed a reduction in cardiovascular death when compared to placebo (HR 0.048, 95% CI, 0.24-0, 97, p = 0.04) and improvement in LV systolic function.[37]

In the study by Gwag et al.,[38] maintenance therapy with β-blocker was seen to be associated with LVEF improvement in patients with HFmrEF (HR 2.021; 95% HF 1.033-3.033; p = 0.04). In addition, maintenance therapy with renin-angiotensin system blockers or aldosterone antagonists were significantly associated with improved survival (HR 0,309; CI 95% 0,162–0,588; p < 0,001; and HR 0,240; CI 95% 0,085 – 0,673; p = 0,01, respectively).

Digoxin use was evaluated in the study by Abdul-Rahim AH et al.,[39] which included 7788 patients, with 1995 patients being classified as HFmrEF. Digoxin reduced cardiovascular death or HF hospitalization (HR: 0.83; 95% CI, 0.66-1.05).[39]

The study Chang et al.[9] showed the comorbidities observed in patients with HFmrEF were more similar to the ones observed in patients with HFpEF, and CAD was associated with greater declines in LVEF in patients with HFpEF.[40] Therefore, the management of CAD can help prevent LV systolic dysfunction progression in individuals with HFmrEF.[21]

Non-cardiac comorbidities, such as hypertension, DM and COPD, are highly prevalent in the HF population and contribute to the general morbidity of these patients.[41] In patients with HFmrEF, uncontrolled hypertension was the main precipitant factor of hospitalization for HF compared to the other HF groups.[7] In patients with HFmrEF and hypertension, therapy with angiotensin II receptor blockers (ARB) or aldosterone antagonists has shown a reduction in hospitalizations, which suggests that such drugs can be used to control hypertension and reduce the risk of LVEF decline in patients with HFmrEF.[7] Regarding the patients with HF undergoing treatment for DM sodium-glucose cotransporter-2 (SGLT2) inhibitors use in patients at high cardiovascular risk showed improvements in the primary outcome, consisting of death from cardiovascular causes, infarction and non-fatal stroke. (HR 0.86; 95% CI, 0.74-0.99; p < 0.001 for noninferiority and p = 0.04 for superiority). In addition, empagliflozin use showed a reduction in cardiovascular death and death from all causes (HR 0.62, 95% CI 0.49-0.77, p < 0.001 and HR 0.68, 95% CI, 0.57-0.82, p < 0.001, respectively), in addition to the reduction in hospitalization for HF (HR 0.65, 95% CI, 0.50-0.85, p = 0.002).[42]

The current BSC HF guideline[5] proposes that initially, the specific treatment of the etiology and comorbidities should be addressed, when possible. Patients with a history of HFrEF who show an improvement of LVEF, which reclassifies them as HFmrEF patients, should be treated by maintaining the therapeutic optimization for HFrEF. For patients with previous HFpEF who show worsening of LVEF and also those with persistent HFmrEF, the use of beta-blocker and angiotensin-convertingenzyme inhibitor (ACEi) or ARB (if ACEi is not tolerated) is recommended. The treatment scheme proposed by the SBC is shown in figure 3.

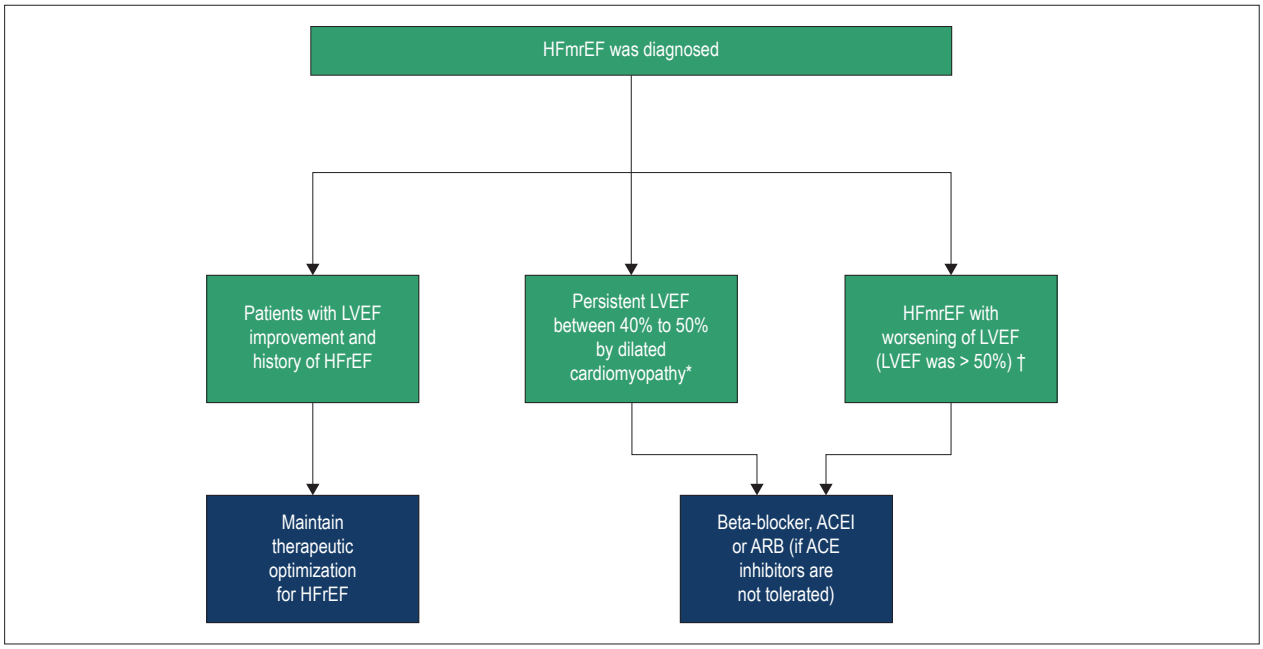

Figure 3 – *Algorithm for treatment of HFmrEF according to the Brazilian Guideline for Chronic and Acute Heart Failure of 2018;[5] ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blockers; * In the absence of deposit cardiomyopathies, hypertrophic, inflammatory or infectious diseases; † Particularly for coronary heart disease and/or acute myocardial infarction.*

Future perspectives

The precision medicine use in the cardiovascular area has advanced, and the identification of HF phenotypes is important for the development of new therapeutic alternatives that offer a better prognosis for the patient with HF.

Although some studies have demonstrated the efficacy of certain therapies in patients with HFmrEF, most publications are retrospective studies that perform a new analysis of previous databases. Therefore, prospective studies and randomized clinical trials including patients with HFmrEF are essential for the creation of therapies with solid evidence-based recommendations.

Conclusion

After the establishment of HFmrEF as a new HF category by national and international guidelines, there was a considerable increase in publications on this type of patients, which allowed a better understanding of their clinical profile, pathophysiological and clinical outcome. However, there is still a great shortage of prospective studies and randomized double-blind clinical trials that allow the specific therapy delineation for this new category of HF. The knowledge of HFmrEF peculiarities by cardiologists and internists is fundamental for the best diagnosis and management of these patients, in addition to the identification of areas of uncertainty regarding the development of basic and clinical researches.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Mesquita ET, Barbetta LMS, Correia ETO; Acquisition of data: Barbetta LMS, Correia ETO.

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The Diuretic Effect of Sacubitril/Valsartan Might Be Clinically Relevant

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Recently, patients with heart failure have been prescribed a novel and innovative drug. Sacubitril/valsartan is a new drug modality that brings a 16% reduction in total mortality, a 20% reduction in cardiovascular mortality and 21% reduction in hospital admissions due to heart failure. The benefit is undoubtedly clinically relevant and the clinical trial which have shown such benefit have achieved an unprecedented statistical significance.[1]

The mechanism of action of sacubitril/valsartan combines the well-known vasodilatory effect of valsartan associated with the neutral endopeptidase (NEP) inhibition effect of sacubitril, which will ultimately result in increased serum levels of natriuretic peptides, increased action of endogenous natriuretic peptides in target tissues by prolonging its tissue half-life, and consequently increased vasodilatory, anti-proliferative and natriuretic effects.[1]

Although the current approach of replacing enalapril with sacubitril/valsartan might sound as a switch of vasodilators in patients with heart failure, the addition of natriuretic effect provided by sacubitril may in fact be the driving force of the clinical benefits. In favor of this concept we can make a few comments:

a. Hypotension, more frequently seen in sacubitril/valsartan than in the enalapril group, could possibly be associated with hypovolemia caused by the natriuretic effect of sacubitril;

b. Patients who received valsartan (160 mg twice daily) in the Val-HEFT trial[2] did not show the same benefit on mortality or on hypotensive adverse events as those demonstrated in the PARADIGM-HF trial (sacubitril/valsartan 97/103 mg twice daily).

c. A post hoc analysis of data from the PARADIGM-HF study revealed that the increase in the mean dose of furosemide was smaller in the sacubitril/valsartan group compared with the enalapril group, and that the median dose of furosemide increased in the enalapril group, but not in the sacubitril/valsartan group.[3]

It is well known from observational studies and meta-analyses that increased doses of diuretics have been linked to worse prognosis in patients with heart failure. Despite inherent biases associated with observational studies, it is biologically plausible that diuretics are potentially harmful due to heir hyperreninemic, vasoconstrictive and hypokalemic effects. One of the few clinical trials conducted on diuretics in patients with heart failure, the DOSE trial, have shown greater kidney toxicity associated with higher doses of furosemide. Diuretic dose reduction associated with sacubitril/valsartan therapy might be a desired secondary effect of this compound in patients with heart failure.[4,5]

In that sense, studies on diuretic withdrawal are mostly needed. The REBIC (REde Brasileira de Insuficiência Cardíaca – Heart Failure Brazilian Network) trial is under way and is intended to be the largest clinical trial ever conducted designed to assess the effects of diuretic withdrawal in ambulatory patients with heart failure.[6] A subgroup of patients on sacubitril-valsartan will be compared with those on angiotensin-converting enzyme inhibitors/angiotensin receptor blocker for tolerance of diuretic withdrawal.

While no other data are available, it is reasonable to recommend closer attention to patients' volume status and exercise a low threshold to decrease or even discontinue diuretics in heart failure patients on sacubitril/valsartan.

Author contributions

Conception and design of the research and Writing of the manuscript:: Beck-da-Silva L; Critical revision of the manuscript for intellectual content: Beck-da-Silva L, Rohde LE.

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Keywords

Heart Failure; Valsartan/therapeutic use; Aminobutyrates/pharmacology; Angiotensin Receptor Antagonists/pharmacology; Natriuretic Peptides/physiology; Tetrazoles/farmacologia.

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Case 3/2019 – Young Male with Intense Dyspnea, Pulmonary Infiltrate, Normal Cardiac Area and Obliteration of the Apical Portion of the Left Ventricle

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A 25-year-old male patient was hospitalized for severe dyspnea, even at rest, and with productive cough. The patient had been seen a week before with a complaint of back pain that irradiated to the precordial region triggered by exertion, such as climbing stairs and walking a block, which had started two weeks before.

The patient was a smoker (8-pack-years) and reported having hypothyroidism after treatment with radioactive iodine. Previous examinations were carried out for him to be cleared for exercise practice.

The electrocardiogram (ECG) (November 24, 2010) showed left atrial overload and a left ventricular strain pattern. There was an accentuation of ST-depression in the stress test.

At admission (October 14, 2011), heart rate was 100 bpm, blood pressure was 100/70 mmHg, and the physical examination was normal.

The ECG (October 14, 2011) revealed sinus tachycardia (101 bpm), PR interval of 144 ms, QRS duration 103 ms, QTc of 451 ms, left chamber overload and secondary alterations in ventricular repolarization (Figure 1). The chest X-ray (October 14, 2011) was normal. (Figure 2)

The laboratory tests (October 14, 2011) showed: red blood cells, 4,600,000/mm^3; hemoglobin; 14 g/dL, hematocrit; 39%, MCV 85 fL, RDW-CV 12.9%; leukocytes, 11,110/mm^3 (72% neutrophils, 7% eosinophils, 17% lymphocytes and 4% monocytes); platelets, 185,000 / mm^3; sodium, 138 mEq/L; potassium, 4.5 mEq/L; PT, (INR) 1; APTT (rel), 0.93; D-dimer, 485 ng/mL; CK-MB, 0.94 ng/mL; troponin I, 0.535 ng/mL; urea, 35 mg/dL; and creatinine, 0.94 mg/dL. On the following day, CK-MB was 0.71 ng/mL; troponin I, 0.511 ng/mL; total cholesterol, 219 mg/dL, HDL-c, 25 mg/dL; LDL-c, 171 mg/dL; triglycerides, 116 mg/dL; glucose, 92 mg/dL.

The echocardiogram (October 17, 2011) disclosed diameters of the aorta 27 mm, of the left atrium 43 mm, septum thickness of 11 mm, posterior wall of 10 mm, normal right ventricular diameter, and left ventricular diameters (diastole/systole) of 54/34 mm, ejection fraction of 65%; marked hypertrophy in the mid-apical region, pseudonormal filling pattern. There was no left ventricular outflow tract obstruction or valve alterations.

The coronary angiotomography (October 18, 2011) did not disclose coronary calcifications or lesions. However, left atrial dilation and obliteration of the apical portion of the left ventricle were observed.

Diagnoses of hypertrophic cardiomyopathy and hypercholesterolemia were made. He was prescribed 50 mg of atenolol, 100 μg of levothyroxine and 20 mg of omeprazole and was referred for outpatient follow-up (October 18, 2011).

Four days after hospital discharge (October 22, 2011), the patient sought emergency medical care for severe dyspnea, even at rest and in decubitus, in addition to productive cough.

The physical examination (October 22, 2011) disclosed a heart rate of 101 bpm, blood pressure of 112/70 mmHg, pulmonary auscultation showing diffuse crackling rales, cardiac auscultation and abdomen without alterations, and mild edema of legs and feet, without any suggestive signs of deep venous thrombosis.

The ECG (October 22, 2011) was similar to the previous one, with sinus tachycardia, left chamber overload and ST-segment depression with a superior concavity and accentuation of T-wave negativity in leads V_3 to V_6. (Figure 3).

A bilateral diffuse alveolar infiltrate was observed on the chest X-ray (October 23, 2011). (Figure 4)

The laboratory tests (October 22, 2011) showed: erythrocytes, 3700000/mm^3; hemoglobin, 11.6 g/dL; hematocrit, 31%; MCV, 84 fL; RDW-CV 13.2%; leukocytes, 4100/mm^3 (18% band cells; 67% segmented; 2% eosinophils; 11% lymphocytes; and 2% monocytes), platelets, 207000/mm^3; creatinine, 1.06 mg/dL; urea, 35 mg/dL; BNP, 1296 pg/mL; potassium, 4 mEq/L; sodium, 132 mEq / L; arterial lactate, 7 mg/dL; urine type I: density 1.009, ph = 5.5, proteins 0.5 g/L, leukocytes 2000/mL, erythrocytes 79000/mL and presence of severe hemoglobinuria.

The pulmonary angiotomography (October 24, 2012) showed no alterations in vascular and mediastinal structures or signs of pulmonary thromboembolism; there was a confluent, diffuse, centrolobular micronodular infiltrate, in some areas with a tree-in-bud pattern, with a predominantly bronchocentric distribution, associated with areas of ground-glass opacity attenuation, more evident in the apices and posterior basal segments. These findings were considered compatible with an inflammatory or infectious process. There was bilateral pleural effusion, moderate to the right and small to left. (Figure 5)

The high-resolution chest tomography (November 1, 2011) disclosed lymphadenomegaly of para-aortic (2.7 x 1.3 cm)

Keywords

Young Adult; Heart Failure/physiopatology; Hypothyroidism; Cardiomyopathy, Hypertrophic Tobacco and Disorder; Hypercholesterolemia; Diagnostic Imaging; Inflammation; Pneumonia.

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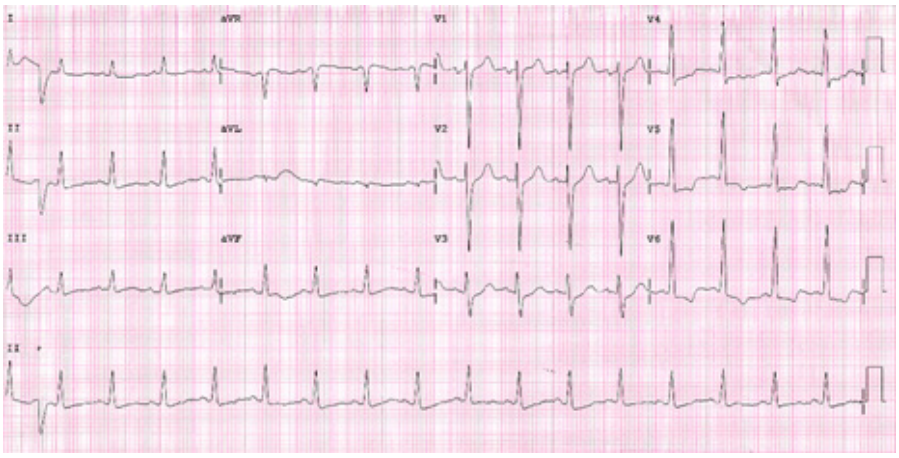

Figure 1 – *ECG: Sinus tachycardia, left chamber overload, intraventricular conduction disturbance of the stimulus, ventricular repolarization secondary alterations.*

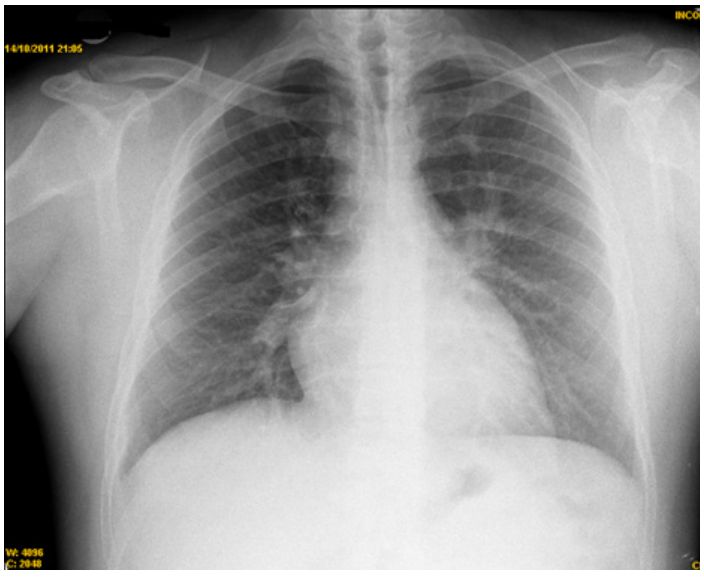

Figure 2 – *PA Chest X-ray: normal*

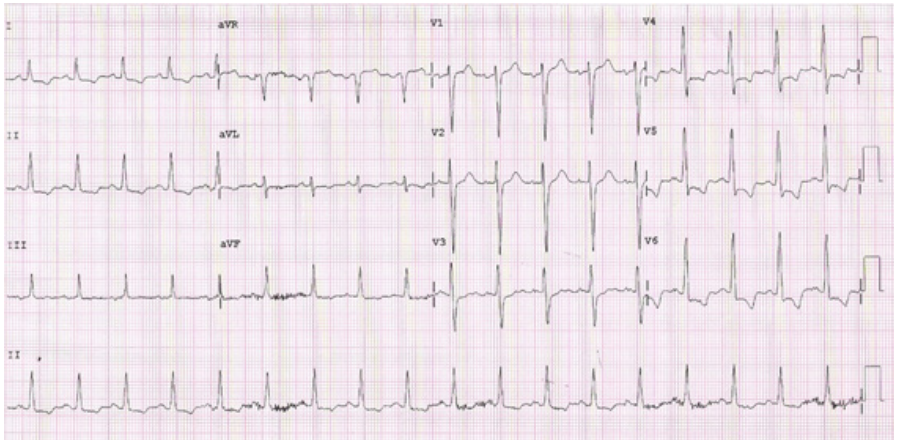

Figure 3 – *ECG: sinus tachycardia, left chamber overload, and ST-segment depression with superior concavity from V_3 to V_6.*

Anatomopathological Correlation

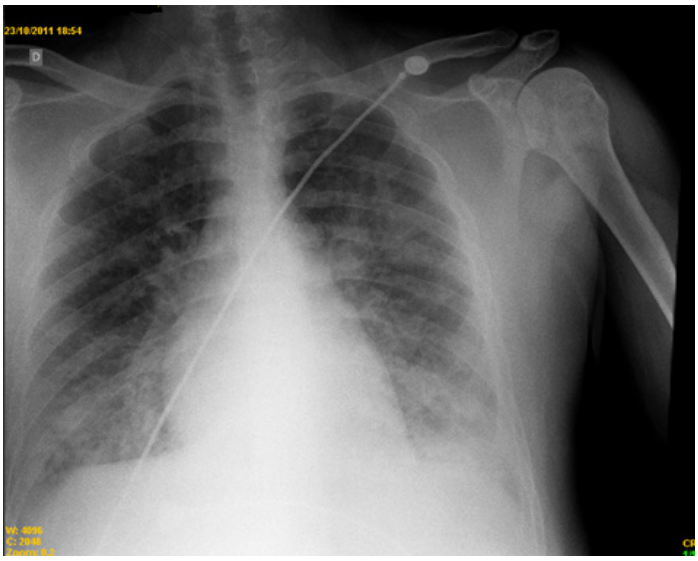

Figure 4 – *PA Chest X-ray PA: bilateral alveolar infiltrate.*

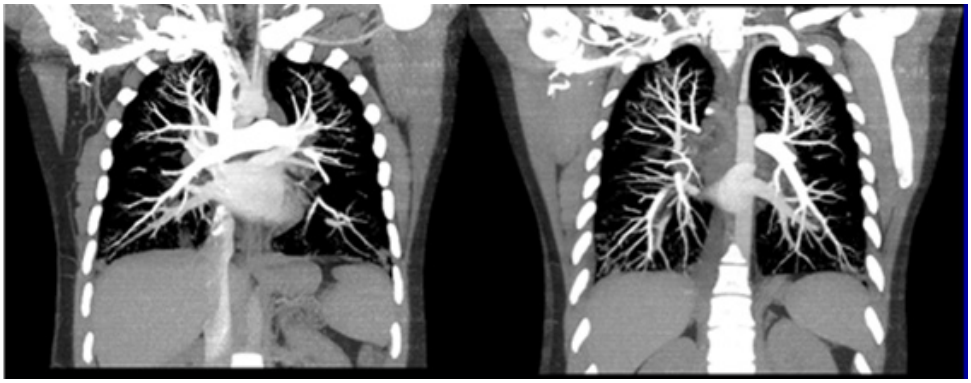

Figure 5 – *Pulmonary angiotomography showing no signs of thromboembolism.*

and right subcarinal (1.9 x 1.5 cm) chains; there were no tracheal and bronchial alterations; there was a predominantly centrolobular diffuse interstitial and alveolar infiltrate, at times confluent with interlobular thickening, more evident at the bases. There was also bilateral pleural effusion, moderate to the right. (Figure 6)

The echocardiogram (November 03, 2011) showed left atrial dilation and left ventricular mid-apical hypertrophy (18 mm), with intense trabeculation and obliteration of its tip, suggestive of endocardial fibrosis (Figure 7), and moderate mitral regurgitation, with signs of papillary muscle fibrosis and hypertrophy, with a left intraventricular gradient of 30 mmHg.

A new echocardiogram (November 11, 2011) disclosed left ventricular mid-apical hypertrophy, with intense trabeculation and obliteration of its tip, suggestive of endocardial fibrosis; ejection fraction subjectively estimated at 50% due to discrete apical hypokinesia. Mitral regurgitation was quantified as minimal in this echocardiogram and in subsequent ones (November 16 and 23, 2011).

The bronchial lavage (November 11, 2011) did not disclose the presence, by PCR, of *Pneumocystis carinii*, *Mycobacterium tuberculosis*, *Legionella sp.*, Adenovirus, Herpes simplex or Cytomegalovirus. The cytology showed 115 cells/mm^3 (leukocytes 9% - 87% polymorphonuclear, 10% lymphocytes, 3% monocytes, 29% macrophages, 62% epithelial cells (7% flat, 21% cylindrical goblet, 72% cylindrical ciliated cells), and absence of bacteria and fungi.

The transesophageal echocardiography (November 23, 2011) did not disclose any new alterations (Table 1).

A new echocardiogram (December 07, 2011) disclosed a left ventricle with moderate to severe systolic function impairment (Table 1), and a hyperrefringent image was observed in the left ventricle, probably corresponding to the apical hypertrophy of the ventricular septum.

Due to lowering of consciousness level, a lumbar puncture was performed (June 29, 2004); the CSF analysis showed ADA (adenosine deaminase) of 2.5 U/L. Tests for Adenovirus, Cytomegalovirus, Herpes simplex, *Cryptococcus sp*,

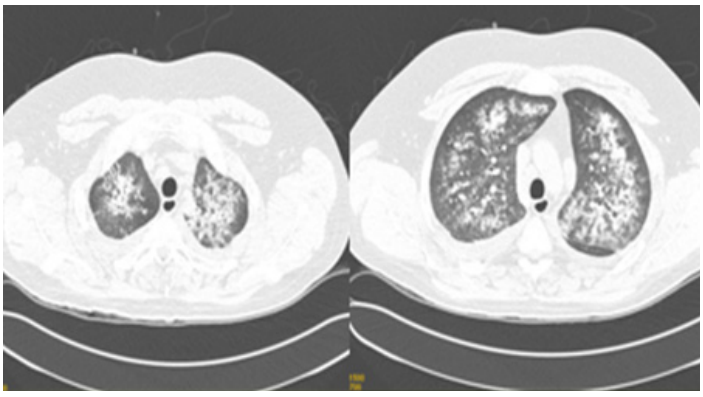

Figure 6 – *Chest CT: diffuse interstitial and alveolar infiltrate.*

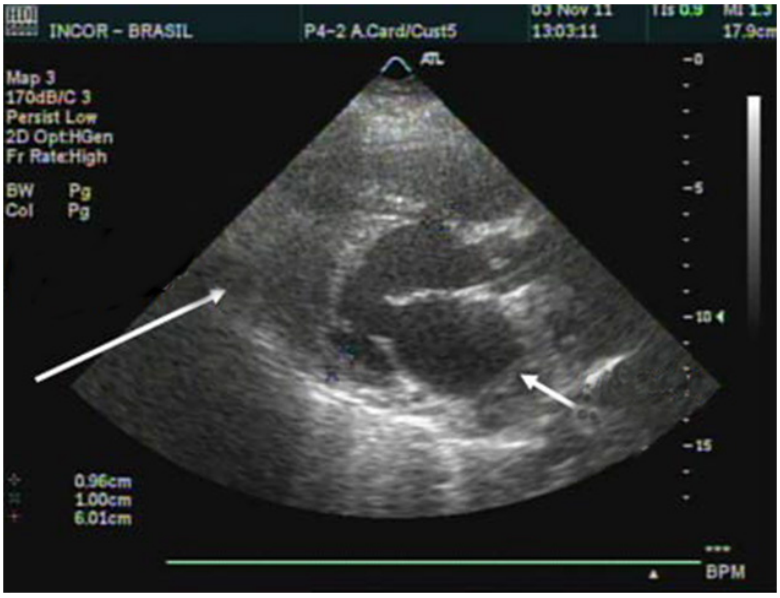

Figure 7 – *Parasternal, long-axis transthoracic echocardiogram: left atrium (short arrow) dilation and amputation of the left ventricular apex (long arrow).*

Table 1 – Echocardiograms at the last hospitalization

	Nov 3, 2011	Nov 11, 2011	Nov 23 (TE)	Dec 7, 2011
Aorta (mm)	25	-	32	
Left atrium (mm)	48	-	47	
Right ventricle (mm)	24	-	-	
Septum (mm)	10	-	12	
Posterior wall (mm)	10	-	10	
LV diastolic diameter (mm)	60	-	60	
LV systolic diameter (mm)	40	-	42	
LV ejection fraction VE (%)	61	50	55	35%
Pulmonary artery systolic pressure (mmHg)	-	30	40	

LV: left ventricle; TE: Transesophageal.

Anatomopathological Correlation

Table 2 – Laboratory evolution

	30 Oct	15 Nov	30 Nov	6 Dec
Red blood cells (millions/mm³)	4.3	2.8	2.2	3.1
Hemoglobin (g/dL)	12	7.9	6.4	9.3
Hematocrit (%)	37%	26	22	29
Leukocytes/mm³	26,210	9,650	9,210	26,970
Neutrophils (%)	91	97	87	78
Eosinophils (%)	0	0	0	0
Lymphocytes (%)	6	2	11	20
Monocytes (%)	3	1	2	2
Platelets/mm³	276,000	69,000	101,000	83,000
Creatinine (mg/dL)	1.36	2.98	4.94	2.64
Urea (mg/dL0	68	189	256	120
Sodium (mEq/L)	135	146	155	139
Potassium (mEq/L)	4.2	4.4	5.1	4.8
Lactate (mg/dL)	23	37	11	35
PT (INR)	1.2	1.1	1.3	1.2
APTT (rel)	0.86	0.85	1.04	0.98
CRP (mg/L)	15.90		124	109
AST (U/L)		90	37	
ALT (U/L)		211	359	

PT: prothrombin time; APPT: partially activated thromboplastin time; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: Alanine aminotransferase.

Toxoplasma sp and resistant acid-fast bacilli were negative and there was no growth of bacteria or fungi in the cultures. The cell count was 11 cells /mm³ - 31% lymphocytes, 66% monocytes and 3% macrophages; protein level was 475 mg/dL; glycorrhachia was 105 mg/dL.

Skull (November 29, 2011) and abdomen CT (November 30, 2011) showed normal results.

A new high-resolution chest tomography (November 30, 2011) disclosed persistence of the diffuse and symmetrical interstitial-alveolar infiltrate, characterized by diffuse ground-glass parenchymal attenuation and multiple nodular and micronodular opacities, predominantly centrilobular, sometimes confluent and delineating a tree-in-bud pattern, with a predominant distribution in the pulmonary medulla, compatible with alveolar filling. Further findings suggestive of inflammatory or infectious processes associated with edema or alveolar hemorrhage were described. There was no pleural effusion.

Blood culture was positive for *Staphylococcus haemolyticus*, sensitive to vancomycin and teicoplanin, and urine culture was positive for *Pseudomonas aeruginosa*, sensitive to piperacillin /tazobactam. A subsequent culture of urine disclosed growth of *Candida* non-albicans.

He was initially treated with vancomycin and piperacillin/tazobactam and, subsequently, imipenem and meropenem, teicoplanin, amphotericin, fluconazole, caspofungin, and acyclovir.

Due to the presence of signs suggestive of pulmonary alveolar hemorrhage and hematuria, there was a diagnostic suspicion of Goodpasture Syndrome and the investigation was initiated.

The search for neoplastic markers (July 10, 2004) disclosed - alpha-fetoprotein = 1.9 ng/mL, CA-125 = 401.4 U/mL, CA-15.3 = 14.9 U/mL, CA-19.9 = 20.1, carcinoembryonic antigen (CEA) = 2.7 ng/mL. The search for antinuclear and antimitochondrial antibodies, and antineutrophil cytoplasmic antigen (ANCA) was negative. The C3 fraction of the complement was 18 mg/dL, and the C4 fraction was 10 mg/dL. The evolutive results of the laboratory tests are shown in table 2.

The patient developed worsening of the pulmonary and hemodynamic picture, anemia (received packed red blood cell transfusion), thrombocytopenia and renal failure (was submitted to dialysis) and underwent a cardiorespiratory arrest with pulseless electrical activity; initially, he was successfully resuscitated, but had a recurrence and died (December 7, 2011).

Clinical aspects

This is the case of a young, male patient, smoker, who had hypothyroidism post-treatment with radioactive iodine, who sought medical care due to symptoms of dyspnea and cough for a week; these complaints had been preceded by chest pain at exertion two weeks before. The medical evaluation at the first consultation was notable for the presence of tachycardia and mild leukocytosis in the whole blood count.

The chest X-ray was normal despite the presence of dyspnea at rest. Interestingly, the ECG performed during a routine medical evaluation 11 months before symptom onset showed signs suggestive of heart disease, with left chamber overload.

If we evaluate the present case based on the analysis of the possible diagnostic hypotheses at the time of the first consultation, we can observe that the main clinical elements on this occasion are: chest pain and dyspnea. There are several causes of chest pain and dyspnea in young individuals, which include diseases of the cardiovascular system, as well as of other organs and systems such as the digestive and musculoskeletal systems.

In the present case, the following can be considered: as non-cardiac causes, spontaneous pneumothorax, pneumonia and pulmonary embolism. The clinical and radiological presentation was not compatible with the first two hypotheses, whereas pulmonary embolism is a hypothesis compatible with the initial clinical presentation, especially if we take into account the discrepancy between symptom intensity and the radiological findings and the presence of persistent tachycardia; in spite of the fact that pulmonary embolism is a rare event in young patients,[1] in this case ,there were risk factors such as history of smoking, as well as the presence of possible cardiopathy (as suggested by the ECG performed 11 months before symptom onset).

A complementary investigation was performed for the presence of pulmonary embolism through D-dimer measurement, and pulmonary artery angiotomography. However, after obtaining a D-dimer value < 500 in association with absence of suggestive radiological findings at the angiotomography made the diagnosis of pulmonary embolism very unlikely.[2] If we consider cardiac causes for chest pain and dyspnea in young individuals, myocarditis and non-atherosclerotic coronary disease should be seen as noteworthy. In spite of the fact that myocarditis is able to result in a clinical picture compatible with that of the patient's presentation, pre-existing electrocardiographic findings did not support these possibilities.

We can evaluate the present case based not only on the analysis of the symptoms that led the patient to the hospital, but also taking into consideration the interesting electrocardiographic findings recorded 11 months before symptom onset; thus, we are led to consider the case from the perspective of the diagnostic possibilities of asymptomatic cardiopathy in a young individual, and which may have left chamber overload as its electrocardiographic manifestation. We can presume the possibility of diseases with primary myocardial involvement (cardiomyopathies), as well as diseases that determine secondary myocardial involvement, such as arterial hypertension and valvular diseases. However, the blood pressure measurement on arrival, as well as the cardiac semiology, did not indicate these possibilities. Regarding the cardiomyopathies, those of familial origin should be considered mainly in this context and may include both hypertrophy (hypertrophic cardiomyopathy) and dilation (dilated cardiomyopathy) or restriction (restrictive cardiomyopathy) as the myocardial phenotypic expression.

In this respect, the morphological and functional findings provided by the echocardiogram are of interest. In the present case, the findings of October 17, 2011 indicate a slight increase in the interventricular septal thickness, with hypertrophy of the mid-apical portions of the left ventricle, determining LV filling impairment, but without determining ventricular dilatation or systolic function impairment. These findings might be compatible with the presence of hypertrophic cardiomyopathy, a genetic disease that affects young male and female patients; it is usually asymptomatic during the first decades of life and is commonly diagnosed during routine physical examinations.[3] Chest pain at exertion and dyspnea are common symptoms. Genetic studies indicate that the hypertrophy is caused by dominant mutations in more than 11 genes encoding sarcomere or adjacent Z-disk protein components. Of the patients who were successfully genotyped, approximately 70% had mutations in two genes: the myosin heavy chain (MYH7) gene and the myosin-binding protein C (MYBPC3) gene; more than 1,400 mutations have been described, most of them restricted to family groups. In patients with hypertrophic cardiomyopathy, the left ventricular wall thickness may vary in intensity, ranging from mild (13-15 mm) to very intense (> 50 mm).[4] Asymmetric patterns of left ventricular hypertrophy, including noncontiguous areas of hypertrophy, can occur. Although diffuse thickening of the left ventricular wall is evident in approximately 50% of patients, a minority (10-20%) may present hypertrophy confined to small portions of the left ventricle.[5] Moreover, patients with hypertrophic cardiomyopathy may have unusual patterns of hypertrophy (e.g., apical hypertrophy), which is associated with giant T-wave inversion on the ECG and is typically caused by sarcomeric mutations.[6]

Another possibility to be considered – especially if we take into account the mild ventricular overload in the ECG, the presence of apical obliteration, the absence of hypertrophy greater than 14mm at the echocardiogram and the presence of atrial dilatation – is that of endomyocardial fibrosis. This is a cardiac disease of uncertain etiology. Its distinctive morphological characteristic is the obliteration of the ventricular apices, ventricular filling impairment and great dilation of the atria. However, its clinical presentation is usually that of a chronic disease, with signs of predominantly right heart failure and large dilation of the atria, often with intracavitary thrombi, findings that were absent in the present case. Although its etiology is still unknown, it is suggested to be associated with three basic conditions: eosinophilia and parasitic diseases, nutritional patterns (excess of vitamin D, toxic agents found in contaminated foods and magnesium deficiency have been reported) and genetic susceptibility.[7] In cases where there is an association with pulmonary cycle parasitic agents, there may be involvement of the lungs, with non-cardiogenic pulmonary edema, pneumonitis, and alveolar infiltrate.[8] A hallmark of this condition is hypereosinophilia in the peripheral blood, a manifestation that was absent in the present case. Cardiac involvement has also been described in other hypereosinophilic syndromes, such as Churg-Strauss Syndrome (characterized by asthma or allergic rhinitis and necrotizing vasculitis).[9] In the present case, the possibility of Goodpasture syndrome, a specific autoimmune disease of the lungs and kidneys, was considered and is characterized by the occurrence of antibodies against the basement membrane of these organs. Cardiac involvement has not been yet described in this disease.[10]

Anatomopathological Correlation

Despite the initial diagnostic and therapeutic approach, the patient's symptoms intensified, and he once again sought medical care due to dyspnea worsening and the appearance of productive cough. On physical examination, tachycardia persisted and pulmonary crepitations with discreet edema of the legs and feet appeared.

The chest X-ray, as well as the first chest tomography, suggested the presence of alveolar infiltrate. The laboratory evaluation is notable for the decrease in hemoglobin and sodium, and BNP elevation. Taken together, the clinical findings indicate that the patient had started a picture of heart failure (presence of lower limb edema, anemia – possibly dilutional – hyponatremia, elevation of BNP and distribution of infiltrate at the apices and posterior portions of the lungs, in association with right pleural effusion). Moreover, the finding of young leukocyte forms in peripheral blood, of leukocyturia, hematuria and hemoglobinuria indicate the existence of an inflammatory and/or infectious process.

The presence of the association of heart failure with inflammatory signs in a patient with underlying heart disease led us to consider the possibility of infective endocarditis. The diagnosis of endocarditis is based on the presence of predisposing heart disease (more commonly a valvulopathy), findings of an inflammatory process and persistent bacteremia; from the clinical-morphological viewpoint, the characteristic lesion is of vegetation detected by the echocardiogram. Despite the findings of underlying heart disease and progressive inflammatory/infectious process, there was no finding of vegetation by the echocardiography; additionally, the finding of *Staphylococcus haemolyticus in* blood culture only has diagnostic value when recovered in multiple cultures collected at different times, because it is a skin-colonizing agent.[11] Finally, it should be noted that the use of multiple antibiotic agents may reduce the chance of recovery of infectious agents in blood cultures.[12]

From a clinical and epidemiological point of view, one of the main causes of infection and septicemia in patients with heart disease is pneumonia, of which clinical and radiological characteristics are compatible with the clinical evolution of the present case. As there was recent hospital admission, it is possible to consider the possibility of acquired pneumonia caused by nosocomial bacterial flora. In this regard, a study of necropsies performed in patients with heart disease found pneumonia as the most commonly found infectious diagnosis.[13] Moreover, in a study of 1,989 patients hospitalized for heart failure, the presence of pneumonia was a factor related to a worse prognosis, as was the intensity of the inflammatory process measured by the Protein C level in peripheral blood.[14] **(Dr. Victor Sarli Issa)**

Diagnostic hypotheses: Restrictive cardiomyopathy, smoking, hypothyroidism, acute decompensated heart failure, pneumonia, multiple organ dysfunction. **(Dr. Victor Sarli Issa)**

Necropsy

The heart weighed 516 g. The cross-section of the ventricles showed marked concentric myocardial hypertrophy and fibrous obliteration of the left ventricular cavity apex (Figure 8). The hypertrophic process predominated in the apical portion, with extensive organized and organizing thrombosis, which impaired both the left ventricular inflow (Figure 9) and outflow tracts (Figure 3), leading to marked reduction in the cavity volume. There was no subaortic obstructive septal hypertrophy. In the basal portion of the inflow tract, the left ventricular free wall measured 2.0-cm thick and the ventricular septum, 2.5 cm. In the mid-apical portion the left ventricular free wall measured 2.5 cm. The mitral valve showed cusps and chordae tendineae of normal aspect, but its papillary muscles were surrounded by the ventricular cavity thrombosis (Figures 9 and 10). The histological analysis of the myocardium showed focal areas of cardiomyocyte disarray and thick-walled arterioles in the left ventricle (Figure 11). There was irregular fibrous thickening of the tip of the endocardium

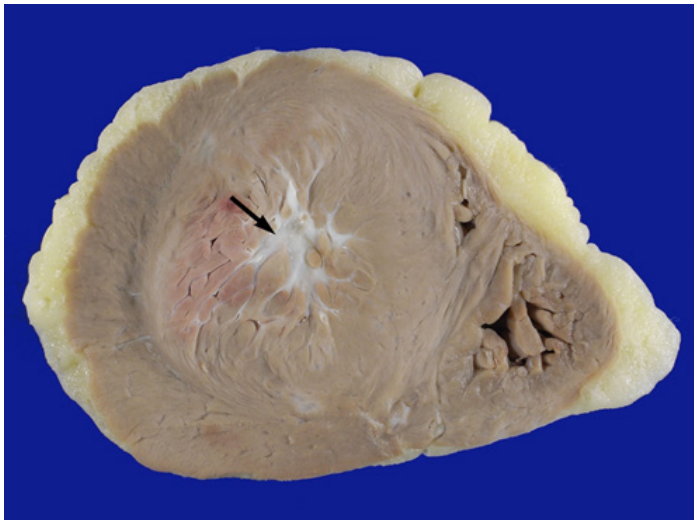

Figure 8 – *Cross section of the ventricles, showing the evident left ventricular concentric hypertrophy and the fibrous obliteration of the cavity apex (arrow).*

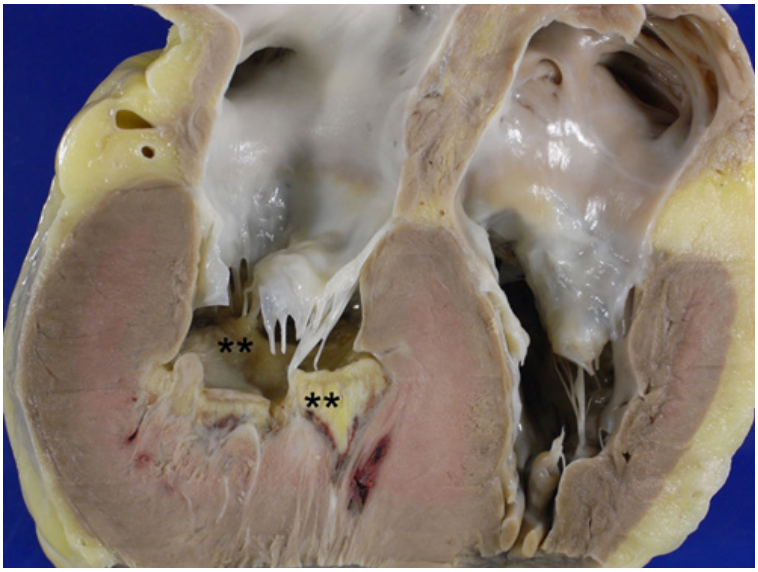

Figure 9 – *Longitudinal section of the heart, disclosing the ventricular inflow tract. The left cavity has decreased volume due to extensive organizing thrombosis, which surrounds the papillary muscles (asterisks).*

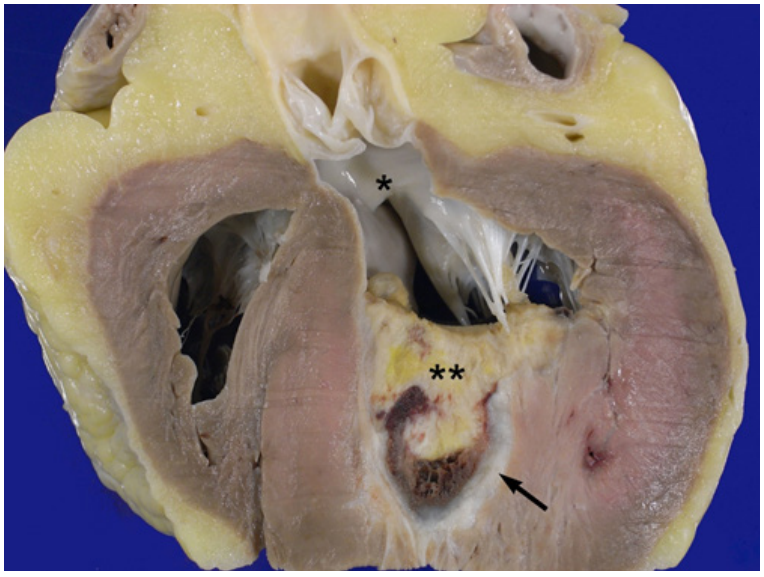

Figure 10 – *Extensive thrombosis in the left ventricular cavity (double asterisk) extending to the outflow tract. Note the whitish, fibrous thickening of the endocardium (arrow) and absence of hypertrophic obstruction of the subaortic region (asterisk).*

and mid-apical left ventricular region, with underlying myocardial penetration, as well as an extensive organized and organizing thrombosis (Figure 12). The endocardium close to the myocardium consisted of looser collagen, with neovascularization foci, hemosiderin deposition, and discrete mononuclear inflammatory infiltrate. Eosinophils were not detected. The lungs weighed 1,134 g together and showed marked chronic passive congestion, with septal thickening and hemosiderin deposition, as well as foci of fibrin extravasation into the alveolar spaces, rare fibrin thrombi in the parenchymal arterioles and extensive recent bilateral alveolar hemorrhage. There was no vasculitis. The kidneys showed acute tubular necrosis, with no glomerular lesions, thrombi or vasculitis. The thyroid weighed 8g, showing extensive atrophy with fibrous replacement of the parenchyma; the remaining follicles showed variable sizes and there were rare foci of lymphohistiocytic inflammatory infiltrate. Other necropsy findings were steatonecrosis of abdominal fat and centrilobular hepatic necrosis with cholestasis. **(Dr. Luiz Alberto Benvenuti)**

Anatomopathological diagnoses: Hypertrophic cardiomyopathy/endomyocardial fibrosis; chronic passive congestion of the lungs; thyroid fibrosis and atrophy; alterations secondary to cardiogenic hemodynamic shock (cause of death). **(Dr. Luiz Alberto Benvenuti)**

Anatomopathological Correlation

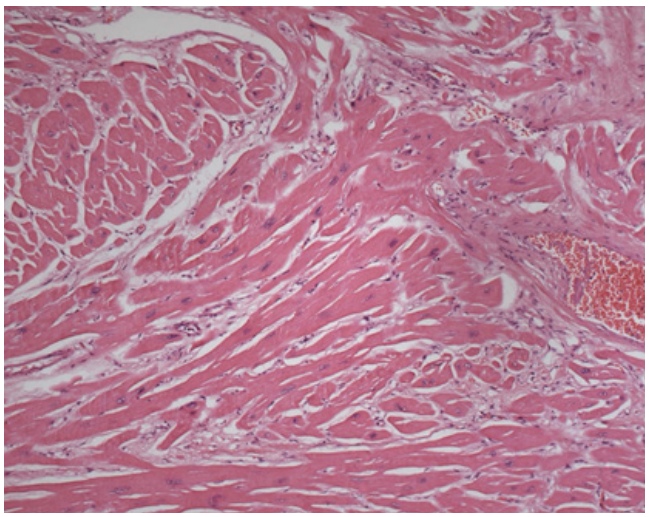

Figure 11 – *Left ventricular cardiomyocyte disarray. Hematoxylin-eosin, X100.*

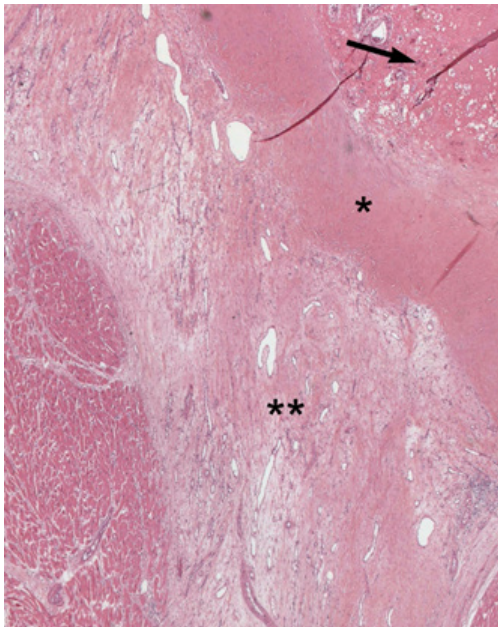

Figure 12 – *Histological constitution of the affected endocardium, compatible with endomyocardial fibrosis. There is luminal thrombosis (arrow), superficial area of dense fibrosis (asterisk) and underlying area of loose fibrosis with neoformed vessels and foci of discrete inflammatory infiltrate (double asterisk). Hematoxylin-eosin, X 25*

Comments

This is an interesting case of a 25-year-old male patient with a history of hypothyroidism after treatment with radioactive iodine at an unspecified date, who developed congestive heart failure and died after a year of clinical follow-up. Imaging tests disclosed significant hypertrophy of the left ventricular mid-apical region, with obliteration of the tip of the cavity, and the hypotheses of hypertrophic cardiomyopathy and endocardial fibrosis were suggested. The presence of suggestive signs of pulmonary hemorrhage and hematuria raised the suspicion of Goodpasture syndrome, but the complementary exams were not suggestive of this entity.

The necropsy showed it was a case of cardiomyopathy of unusual pattern, characterized by the superposition of findings of hypertrophic cardiomyopathy and endomyocardial fibrosis. On the other hand, the findings were not typical of any of these diseases alone. Although there was marked left ventricular wall concentric hypertrophy, with apical and mid-mural predominance related to the hypertrophic cardiomyopathy, the areas of cardiomyocyte disarray, which constitute the most significant finding of the disease, did not occur in extensive areas, as usual.[15] Regarding the endomyocardial fibrosis, there was fibrous obliteration of the left ventricular apex, the typical histopathological constitution of the affected endocardium, and

cavity thrombosis at different development stages, both the left ventricular inflow and outflow tracts were affected, which is not described in endomyocardial fibrosis and typically affects only the ventricular apex and inflow tract.[16] It is noteworthy that we have previously reported the simultaneous occurrence of both cardiomyopathies, with typical findings, in a patient who underwent surgical resection of endomyocardial fibrosis and subsequently died.[17] The present case illustrates the difficulty to classify the cardiomyopathy into one of the four traditional basic types, namely: dilated, hypertrophic, restrictive, and arrhythmogenic,[18] and there is a current trend towards a purely descriptive classification, i.e., the MOGE(S) classification.[19]

Regarding the suspected Goodpasture syndrome, the necropsy did not show lesions in the renal glomeruli or evidence of vasculitis in the lungs or other organs, and the alveolar pulmonary hemorrhage can be explained by the heart failure and terminal cardiogenic shock, which is the cause of death. Therefore, there are no anatomopathological elements to allow the diagnosis of Goodpasture syndrome, which is in line with the results of the performed complementary tests. The thyroid atrophy corresponds to the sequela of the radioactive iodine treatment of the patient's hyperthyroidism. **(Dr. Luiz Alberto Benvenuti)**

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Extensive Anterior Myocardial Infarction ... and Something Else?

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Case report

A 64-year-old Caucasian female, with a one-week history of stress angina. She was admitted to the hospital 2 hours after the onset of oppressive retrosternal pain at rest.

Risk factors: hypertension, smoker, dyslipidemia and diabetes.

Figure 1 shows electrocardiography/vectorcardiography (ECG/VCG) at admission.

Echo: Ventricular and atrial chambers of normal size (left atrial (LA) size: 30 mm); mild to moderate reduction of left ventricular ejection fraction = 41% by anterior akinesia.

The percutaneous coronary intervention was indicated, and two drug-eluting stents were implanted.

Introduction

Atrial infarction (AI) is rarely diagnosed before death because of its characteristically subtle and nonspecific ECG findings. AI occurs in 0.7 to 52% of ST-elevation myocardial infarctions. Its incidence in autopsy has been widely variable, from 0.7 to 42%, with a large series of 182 patients demonstrating an incidence of 17%.[1] Ischemic damage to the atrial myocardium is usually associated with infarction of cardiac ventricles, but isolated AI can occur.[2]

AI ECG patterns

The ECG patterns of AI are generally subtle because of the thinner atrial walls and their inability to generate enough voltage to be appreciated on the ECG. This atrial voltage is also often eclipsed by the depolarization of the larger ventricles. Although several AI ECG patterns have been described, none have been validated by prospective studies. The first description of "infarctus auricularis" was made 93 years ago by Cler.[3] Twenty-two years later, Langendorf reported one case of AI found at autopsy that in retrospect could have been recognized antemortem from ECG changes.[4] Hellerstein reported the first case with the correct antemortem diagnosis of AI confirmed by necropsy.[5]

There are other potential causes for P wave morphologic abnormalities and PR-segment displacements besides AI. Sympathetic overstimulation, pericarditis, atrial enlargement, and interatrial blocks have been described.[6] Pronounced sympathetic activity produces a descending PR-segment, depressed J point and ascending ST segment with the PR and ST segments having concordant deviations. Pericarditis can cause ECG changes if the inflammation involves the epicardium or the visceral pericardium as the parietal pericardium is electrically inert.

Accepted ECG criteria of AI are those proposed by Liu et. Al.:[7]

a) Major:

- PR-segment elevation > 0.5 mm in leads V_3 and V_6 with reciprocal depression in leads V_1 and V_2 of small amplitude;
- PR-segment elevation > 0.5 mm in lead I with reciprocal depressions in II-III;
- PR segment depression of >1.5 mm in precordial leads with 1.2 mm depressions in I, II and II, associated with atrial arrhythmia.

b) Minor:

- P wave with M-shaped, W-shaped, or notched; depression of the PR segment of small amplitude without elevation of this segment in other leads cannot be regarded by itself as positive evidence of AI.
- Patients having an acute myocardial infarction with any form of supraventricular arrhythmias, such as atrial fibrillation, atrial flutter, atrial tachycardia, wandering atrial pacemaker and atrioventricular blocks.[8]

Regarding the location of AI, the literature evidence is limited and often conflicting. The right atrium (RA) is involved five times as often as the LA.[1]

Main complications of AI are: supraventricular arrhythmias, atrial rupture, cardiogenic shock and thromboembolic phenomena in the brain or lungs. Diagnosis currently is made in an appropriate clinical setting with characteristic P-wave shape, eventually the Bayés´s syndrome (complete interatrial block in the Bachman region associated with supraventricular arrhythmias).[9] Theoretically, PR-segment displacements should correlate to the location of the AI in the same manner as ST-segment displacements in ventricular infarction. Thus, involvement of the laterobasal (formerly dorsal) wall, which corresponds to the LA, will result in PR-segment elevation in leads II and III with reciprocal depression in lead I.[5] Likewise, involvement of the anterior

Keywords

Myocardial Infarction/physiopathology; P Wave; Diagnosis Imaging; Arrhythmias, Cardiac; Risk Factors; Percutaneous Coronary Intervention; Drug-Eluting Stents

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or anterolateral wall, which corresponds to the LA, will produce PR-segment elevation in lead I with reciprocal depression in leads II, III and the anterior precordial leads V2-V4.[7] However, there are no universally accepted criteria.

Discussion

Detailed ECG analysis revealed PR-segment displacement in several leads. With the aim to clarify this doubt, we isolated the P loop by VCG and enhanced its size 32-fold. We found that the P loop in VCG fulfilled criteria for biatrial enlargement ("Erlenmeyer-like" shape) (Figure 2) with notches in the central portion of the loop; this confirmed the suspicion of associated AI. The apparent contradiction of an atrial abnormality in VCG in conjunction with apparently normal atria on echocardiography could be explained by the fact that the echocardiogram is not an optimal method to evaluate the size of the RA and ventricle, particularly in the absence of concomitant right ventricular enlargement; therefore, enlargement of the RA could go unnoticed. On the other hand, LA dilatation is not unexpected in an extensive anterior infarction with increase in the end-diastolic pressures. However, in the initial stages post-MI, the atrial chamber size can still be normal, although VCG shows a clearly abnormal P loop. In Figure 2, the comparison with the normal P loop is shown in the 3 planes in this case (AI with biatrial enlargement).

The role of atrial coronary perfusion is incompletely understood. One of the main limitations of our current understanding is that the origin of posterior LA coronary irrigation is unknown.[10]

Currently, three coronary branches supplying blood to the atria are known:

1. The right anterior atrial artery or sinus node artery, and other small branches arising from the right coronary artery, such as the right intermediate atrial artery.
2. The "ramutis ostii cavae superioris" or left anterior atrial artery which arises from the left main coronary artery, the proximal portion of the left circumflex (LCX), obtuse

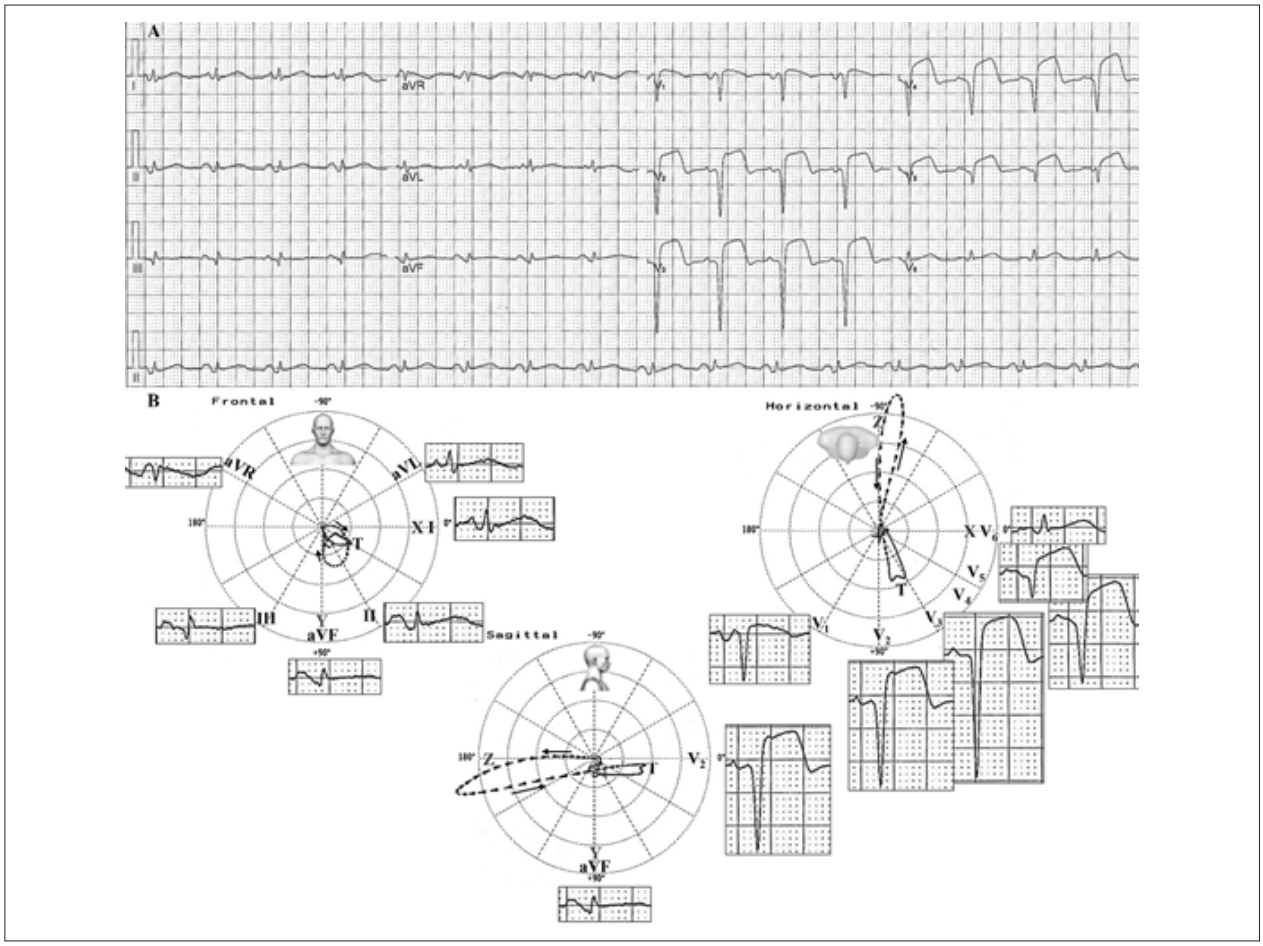

Figure 1 – *ECG/VCG correlation. A) ECG diagnosis: Left atrial enlargement (positive Morris index), PR-segment depression in I, II, III and aVF, low QRS voltage in the limb leads (the amplitude of all the QRS complexes in these leads is < 5 mm). QS Pattern from V_1 to V_5, and low r voltage wave in lead V_6. ST-segment elevation convex upward. B) VCG diagnosis: combination of anteroseptal anterior and anterolateral infarction: QRS loop directed to the back and minimally to the left near the orthogonal Z lead. The T-loop directed to the front with broad QRS/T angle (≈+170°). Conclusion Acute extensive anterior myocardial infarction. Possible association with atrial infarction.*

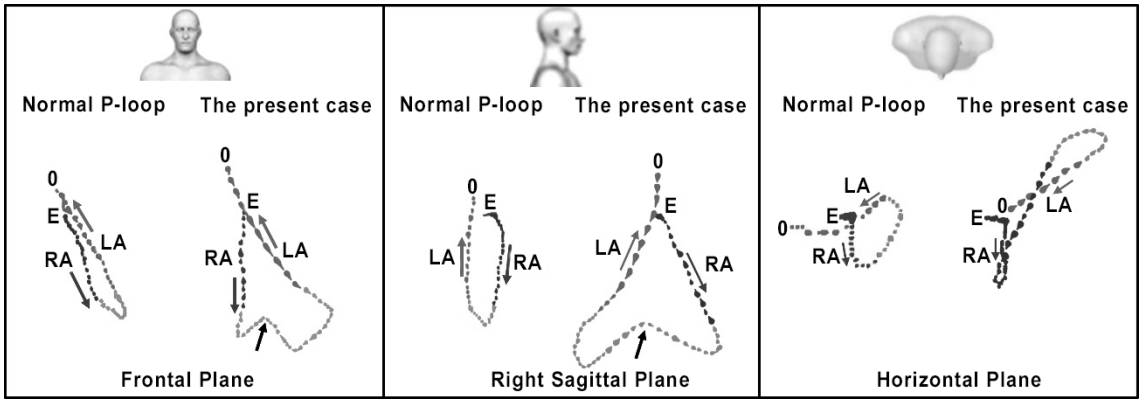

Figure 2 – *Comparison between normal P loops and the present case. Frontal plane: In the present case, the maximal vector voltage is > 0.2 mV, and the morphology is broad with a notch in the middle portion (arrows). Right sagittal plane: The maximal anterior forces are ≥ 0.06 mV and maximal posterior forces are > 0.04 mV: biatrial enlargement. Horizontal plane: the normal P loop maximal vector location is located between +50° and -45°, maximal vector voltage is < 0.1 mV, maximal anterior forces are up to 0.06 mV and maximal posterior forces are up to 0.04 mV. In the present case, anterior and posterior forces exceed these values. Conclusion: biatrial enlargement and suspicion of AI by notched P loop in the frontal and right sagittal plane. RA: right atrium; LA: left atrium.*

marginal, or diagonal coronary arteries.[11] In the present case, the coronary obstruction occurred in the proximal portion of the LAD, consequently also the diagonals that can irrigate the LA causing AI in this structure.

3. The branches of LCX. These branches provide irrigation for the LA.[12]

Conclusion

Though AI was first reported 89 years ago, its recognition remains elusive. AI should be suspected in any patient who presents with typical chest pain, elevated cardiac biomarkers and ECG changes consistent with AI: PR-segment deviations (elevation and depression), the presence of abnormal P-wave shape (M-shaped, W-shaped, irregular or notched) and/or presence of supraventricular tachyarrhythmias. P loop VCG analysis appears to be a valuable diagnostic tool.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Riera ARP, Barros RB, Silva e Sousa Neto AF, Raimundo RD, Abreu LC, Nikus K; Analysis and interpretation of the data: Riera ARP, Nikus K.

Potential Conflict of Interest

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Sleep Disorders Impair Attaining Ideal Cardiovascular Health

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In the recent article "Ideal Cardiovascular Health and Job Strain: A Cross-Sectional Study from the Amazon Basin", by Muniz et al.,[1] the authors proposed that cardiovascular health (CV) is influenced by the workplace conditions. The study involved 478 employees, which had wide access to health information, from a University in the Amazon Basin, Brazil. Researchers used a validated version of the Job Demand Control Model (JDC model)[2] questionnaire to assess work stress. The study is an innovative one, since it is the first one to explore this hypothesis in the Amazon Basin. The authors found a high prevalence of poor CV, which was mainly associated with a poor diet and obesity,[1] suggesting that participants with high job strain are more likely to have eating disorders, resulting in weight gain.

Weight gain and hormonal alterations have been observed in patients with sleep disturbances, such as obstructive sleep apnea. Obstructive sleep apnea is a very prevalent sleep disorder that leads to the development of metabolic syndrome, cardiovascular outcomes and contributes to systemic inflammation.[3]

According to Genta et al.,[4] sleep disorders, in association with obesity, also cause cognitive deficit, difficulty in concentration and irritability. It is important to highlight that the effects of sleep disorders are not restricted to the nocturnal period, but may extend throughout the day and, consequently, decrease the quality of life of the affected individuals.

Muniz et al.[1] proposed to fight obesity, thereby reducing poor CV outcomes, through strategies to develop healthy behaviors such as physical activity projects, educational campaigns and making a low-fat diet available in the campus restaurants. We would like to highlight the fact that the inclusion of sleep awareness campaigns could also bring benefits to the employee's health. Sleep hygiene habits are critical to maintaining a healthy lifestyle. One of the most important elements of these habits is sleep duration, which should be adequate without excess or deprivation. The National Sleep Foundation[5] proposes that simple changes be made and applied regarding the daily sleep hygiene routine. In addition, the investigation of sleep disorders by health professionals can have a great impact on life expectancy and on improving cardiovascular health.

Keywords

Sleep/physiopathology; Sleep Wake Disorders/physiopathology; Cardiovascular Diseases; Ocupational Stress

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Reply

We appreciate the interest in our study. We agree with our readers that sleeping disorders may play a role in the association between job strain and cardiovascular health. Sleep apnea has a prevalence of 35% among those with overweight.[1] In our sample, more than 65% had BMI > 25 kg/m^2, suggesting a high prevalence of sleep apnea and probably a high influence in job stress. Although sleep apnea screening using questionnaires or polysomnography was not performed in our study, we asked the participants whether they had sleeping disturbances in the previous weeks due to any concerns at the workplace. We found that those with high job strain were more likely to answer "yes" to this question than other participants (40% vs 21%, $p < 0.001$), suggesting that a low sleep quality was more prevalent among those with high job strain. Therefore, future studies should evaluate whether sleep disturbances can explain the association between job strain and cardiovascular health. In accordance with our readers, we propose a strategy to promote a healthy lifestyle that would encompass a sleep awareness campaign, including promotion of sleep hygiene and also questionnaires to screen for sleep apnea. In addition, programs to control obesity would help to improve sleep quality, because it has been proved to reduce the apnea-hypopnea index in subjects with sleep apnea.[2] In conclusion, strategies that include sleep awareness may help improve the impact on cardiovascular health.

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Miguel Morita Fernandes-Silva
Odilson Marcos Silvestre

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Vascular Ultrasound Statement from the Department of Cardiovascular Imaging of the Brazilian Society of Cardiology – 2019

Development: Department of Cardiovascular Imaging (Departamento de Imagem Cardiovascular – DIC) of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC)

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Note: These Guidelines 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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If the last three years the author/developer of the Statement:

Names Members of the Statement	Participated in clinical studies and/or experimental trials supported by pharmaceutical or equipment related to the guideline in question	Has spoken at events or activities sponsored by industry related to the guideline in question	It was (is) advisory board member or director of a pharmaceutical or equipment	Committees participated in completion of research sponsored by industry	Personal or institutional aid received from industry	Produced scientific papers in journals sponsored by industry	It shares the industry
Cláudia Maria Vilas Freire	No	No	No	No	No	No	No
José Aldo Ribeiro Teodoro	No	No	No	No	No	No	No
Carmen Lucia Lascasas Porto	No	No	No	No	No	No	No
Orlando Veloso	No	No	No	No	No	No	No
Ana Cláudia Gomes Pereira Petisco	No	No	No	No	No	No	No
Fanilda Souto Barros	No	No	No	No	No	No	No
Márcio Vinícius Lins Barros	No	No	No	No	No	No	No
Mohamed Hassan Saleh	No	No	No	No	No	No	No
Marcelo Luiz Campos Vieira	No	No	No	No	No	No	No
Simone Nascimento dos Santos	No	No	No	No	No	No	No
Monica Luiza de Alcantara	No	No	No	No	No	No	No
Salomon Israel do Amaral	No	No	No	No	No	No	No
Ana Cristina Lopes Albricker	No	No	No	No	No	No	No
Armando Luis Cantisano	No	No	No	No	No	No	No

Statement

Content

1. Introduction and Equipment

1.1. Introduction

The use of ultrasound (US) in Medicine started in the decade of 1940 and, since then, it has played a significant role in the diagnosis of cardiovascular diseases (CVD). It is a diverse technology that follows the physical principles of propagation of US waves in different media. Due to its broad applicability, relatively low-cost, and reproducibility, US has a secure place in diagnostic aid. Members of the Department of Cardiovascular Imaging (DCI) – experts in vascular ultrasound (VUS) – prepared this guideline to indicate the best use of this technique, according to recommendations from the current medical literature. We included the main aspects related to equipment components, software, transducers, and their evolution since the last guideline, and addressed the most relevant topics in the field of diagnosis of vascular diseases. The foundation behind using VUS to diagnose important pathologies, such as carotid atherosclerotic disease, diseases in vertebral arteries, abdominal aorta and its branches, was

based on recommendations from the DCI panel of experts in 2015 and 2016.[1,2]

This guideline does not aim to compare VUS with other imaging examination methods or expound on the use of VUS in the follow-up of vascular diseases after the initial diagnosis. For this content, the reader should consult more extensive and specific publications on the subject.

Our goal is to disseminate the best practices in VUS to various services in the country, standardize the interpretation of examinations, and contribute to the proper use of this non-invasive, widely available, and low-cost tool.

1.2. Equipment

In a country with continental dimensions and different economic realities like Brazil, it is difficult to determine what ideal equipment is. We cannot demand from a small laboratory in the interior of the country to work with equipment that has the same technological resources needed for a laboratory that assists a large number of patients. This standardization intends to suggest the appropriate minimum resources of equipment and the ideal way to perform, with safety and accuracy, the examinations whose protocols will be described below, always remembering that this area is in constant evolution.

1.2.1. Machine

The equipment must be capable of delivering the following types of image and Doppler: (a) two-dimensional image; (b) color flow imaging (CFI); (c) pulsed wave Doppler; (d) continuous wave Doppler (for some types of transducers, but not required for vascular examinations); (e) power Doppler, also known as power angio and Doppler energy – way of mapping the flow without indicating the direction, based on the amplitude of the signal (ideal resource, but not essential to the examination).

More advanced tools, such as second-harmonic imaging, B-Flow, inversion recovery pulse sequences – for the use of microbubble contrast –, and even transducers capable of producing three-dimensional images, are useful in complex examinations, but not yet part of our daily practice. They will also be covered for information purposes as a way to encourage the technological progress that brings additional benefits to patients.

1.2.2. Applications (Software)

Among the application options, the equipment must have specific presets to each type of study to expedite and facilitate the task of the examiner.

1.2.3. Multi-frequency or Broadband Transducers

• **Linear transducer**: ideal frequency between 5 and 10 MHz (in some cases, frequencies of 4 or 12 MHz can be useful); for studies of superficial structures, since transducers of higher frequency have better axial image resolution, but their use is limited due to the large sound damping when traveling through tissues.

• **Convex transducer**: ideal frequency between 2 and 5 MHz; used in studies of deeper structures, such as abdominal ones, with the advantage of covering a larger area compared to sector transducers of similar frequencies.

• **Low-frequency sector transducer**: 2 to 4 MHz; useful when the examiner needs continuous Doppler in studies of abdominal arteries.

• **High-frequency sector transducer**: 4 to 10 MHz; useful when the acoustic window is limited by bone structures.

• **Micro-convex transducer**: frequency between 4 and 8 MHz; adaptable to sites with limited window, such as bone structures, dressings, wounds, or other situations in which the contact surface available for the probe is reduced, without loss of lateral resolution in distal fields, as presented by sector transducers.

1.2.3.1. Image Orientation

In longitudinal images, most vascular imaging guides recommend displaying cranial structures on the left side of the screen, and caudal structures on the right. In transverse planes, structures on the left side of the screen must correspond to the marking on the upper left corner of the monitor. That way, transverse planes will display right lateral structures, as well as left medial structures on the left side of the monitor screen.[3,4]

2. Carotid and Vertebral Arteries

According to the World Health Organization (WHO), CVDs are the main causes of morbidity and mortality worldwide. In 2012, 17.5 million people died from CVDs, the equivalent to 31% of all deaths occurred in the period, with estimates that 7.4 million resulted from coronary artery disease (CAD) and 6.7 million from cerebrovascular accident (CVA).[5]

Ultrasound of carotid arteries is valuable and widely used in cardiovascular risk assessment, as it measures the intima-media thickness (IMT), detects atherosclerotic plaques, and can evaluate the morphology of plaques and degree of stenosis, characteristics associated with cerebrovascular events.

2.1. Intima-media Thickness and Detection of Carotid Artery Plaques for Cardiovascular Risk Assessment

With the publication of the Brazilian Guidelines for Dyslipidemia and Atherosclerosis Prevention in 2007 and 2013,[1,6-8] the Mannheim consensus documents of 2004-2011,[9] and the American Society of Echocardiography consensus,[10] Brazilian experts in the VUS field joined forces to disseminate the correct way to measure IMT and detect atherosclerotic plaques in carotid arteries. In the latest update of the Brazilian guideline in 2017,[8] IMT measurement was not included separately in the stratification of cardiovascular risk, but in the characterization of atherosclerotic plaque as IMT > 1.5 mm. Another aspect that shows the importance of correctly measuring IMT is its use in several research protocols. Since the American and European expert consensuses use IMT as an aggravating factor for cardiovascular risk, we decided to include the measurement technique in this guideline. This section aims to standardize the technique to measure IMT and detect carotid plaques.

2.2. Ultrasound Definition of Intima-media Thickness and Carotid Plaque

In two-dimensional images, IMT is characterized by a double line with defined intima-lumen and media-adventitia interfaces. IMT is the distance between the two acoustic interfaces. The atheromatous carotid plaque (CP) can be defined as a focal structure that spreads at least 0.5 mm into the arterial lumen, and/or measures more than 50% of the surrounding IMT value, and/or has an IMT > 1.5 mm.[9] Figure 1 schematically illustrates the IMT measurement and the three ways to define CP.

2.2.1. Indications

The European and American consensuses[9,10] recommend measuring IMT in specific groups (Table 1). In these groups of individuals, IMT is considered increased when above the 75 percentile for their age, gender, and ethnicity, according to one of the normative tables, assisting in the discussion of clinical treatment and change in lifestyle. If a CP is found, regardless of the obstruction degree, IMT measurement does not need to be reported, except for exams explicitly requested for this purpose. In these cases, if the CP is located in the IMT measurement, it should be included in the value.

2.2.2. Measurement Protocol

The recommended protocol is similar to the one described by the ELSA-Brasil study[13] (Table 2).

After collecting numerical IMT data, the average values will be compared with existing reference numbers, according to normative tables of the studies ELSA Brasil,[13] CAPS,[14] or MESA.[15] The decision about which table to use will depend on the gender, age, and ethnicity of the individual.

Although the manual point-to-point measurement is less reproducible – considering the differences in ultrasound equipment used in our country –, the consensus was that it could be used if the equipment does not automatically measure IMT, strictly respecting the technical recommendations. The examiner should pay special attention when placing the cursor in the intima-lumen and media-adventitia interfaces and be very cautious not to overestimate the values. In this case, measure each side at least five times to obtain the mean value (mean IMT).[16]

2.2.3. Interpretation of Results

Mean IMT [mean of measurements in the right or left common carotid artery (RCCA and LCCA, respectively)]: most types of equipment provide this measurement automatically or semi-automatically (in the latter case, the examiner can make small adjustments based on the automatic one). After calculating the mean IMT values from each side, compare them to the table to find the equivalent percentile. The individual under study is classified in the highest percentile.

To determine the percentile of IMT measurement, consult tables 3 to 5, according to the age group of the individual under study.

2.2.4. How to Prepare a Report

Describe the mean IMT on each side, in mm, in the body of the report. Also, include in conclusion if the value is

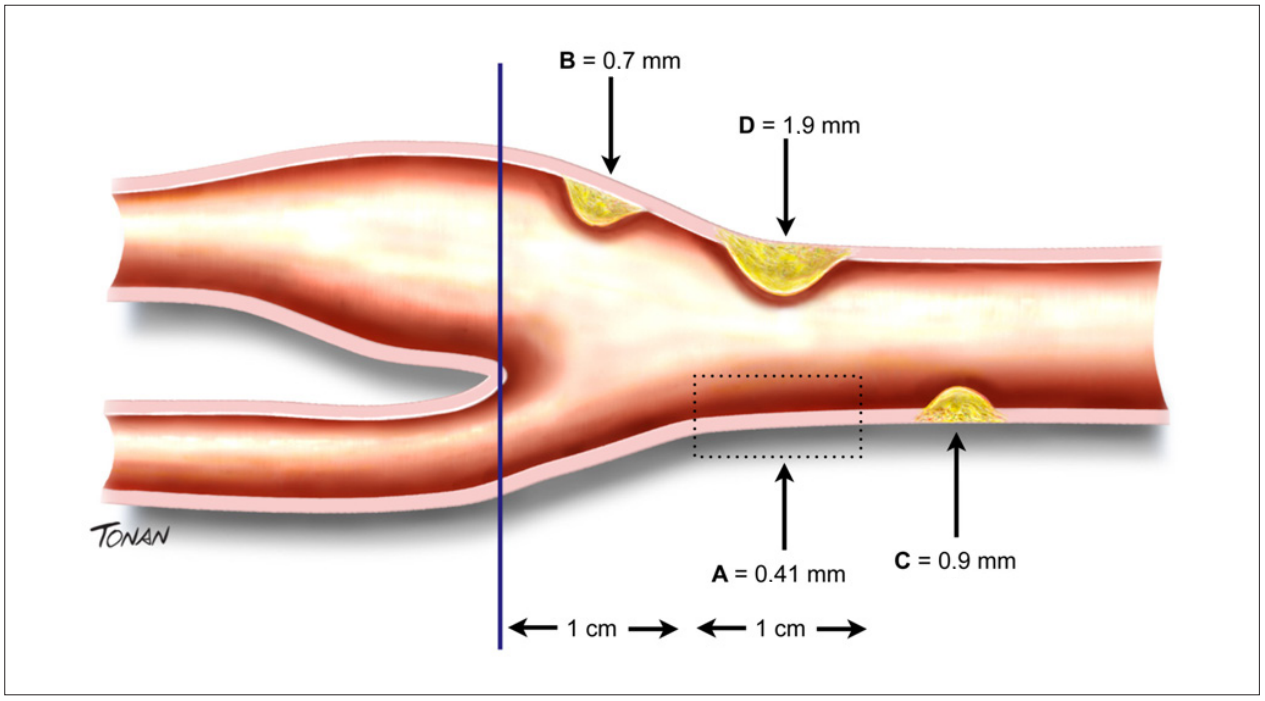


Figure 1 – *Schematic illustration showing examples of IMT and plaque measurements. IMT measurement (A). Different measurements of 3 carotid plaques: encroaching ≥ 0.5 mm on the arterial lumen (B); measurement > 50% of the surrounding IMT value (C); large plaque (D).*

Table 1 – When to measure the intima-media thickness

1. Intermediate cardiovascular risk: use the IMT measurement as an aggravating factor for high risk reclassification[10]
2. Patients known to have a higher cardiovascular risk and hard clinical classification:
• Patients with familial hypercholesterolemia[11]
• Patients with autoimmune diseases or who use immunosuppressants, corticosteroids, antiretroviral drugs, or other medicines that induce elevation of cholesterol[12]
• History of early cardiovascular disease in first-degree relatives[10]
• Individuals < 60 years with a severe abnormality in a risk factor[10]
• Women < 60 years with at least two risk factors[10]

IMT: intima-media thickness.

Table 2 – Protocol to measure intima-media thickness

• Two-dimensional fundamental imaging
• Do not zoom
• Transducer with frequency > 7 MHz
• Proper gain adjustment; depth between 3.0 and 4.0 cm
• Longitudinal plane of the common carotid and carotid bifurcation
• Capture images in the anterior and posterior accesses or the sternocleidomastoid muscle, with the most rectilinear image possible and with a well-defined double-line pattern, and choose the best one
• Measure it in the posterior wall of the common carotids on the right and left sides, 1 cm from the bifurcation, in automatic/semi-automatic mode

above or below the 75 percentile and the table used, with its bibliographic reference.

Inform the presence of carotid plaques, with their specific characteristics and quantification, according to the criteria recommended by the recent Brazilian consensus.[1]

2.3. Morphological Evaluation of Carotid Atherosclerotic Plaques

CP morphology plays an essential role in the incidence of cerebrovascular events and can also be an important predictor of events.[17,18]

Recognizing the ultrasound characteristics of the plaque can help to identify unstable ones. Describe the following properties: location, extension, echogenicity, texture, surface, presence of movable components, and anechoic areas next to the fibrotic capsule. Report these characteristics for the most important plaques, particularly those with more than 50% stenosis.

• **Location:** we recommend subdividing the carotids into distal and proximal common carotid, bifurcation, external branch, and proximal and medial internal branch (Figure 2).

• **Extension**: must be measured, as it can be correlated with events and affects the choice of surgical and endovascular treatment.[19]

• **Echogenicity**: defined by comparing the plaque echogenicity to that of adjacent structures (blood, muscle, adventitia of the vessel, and bone), and classified into:[20]

- Hypoechoic or echolucent: darker, that is, echogenicity similar to that of blood and less echogenic than the sternocleidomastoid muscle.

- Isoechoic: echogenicity close to that of muscle.

- Hyperechoic: lighter than the adjacent muscle.

- Calcified: very echogenic, creating acoustic shadowing due to calcium deposition. Echogenicity is comparable to that of the bone.

• **Echotexture**: Reilly et al.[21] classified the texture of the plaque as homogeneous or heterogeneous.

- Homogeneous: uniform in both low and high echo levels.

- Heterogeneous: a mixture of high, medium, and low echo levels.

• **Surface**: lumen surface is categorized into three classes:[20,22]

- Smooth: irregularities of less than 0.4 mm depth.

- Irregular: from 0.4 to 2 mm depth.

- Ulcerated: crater greater than 2.0 mm depth.

2.4. Quantification of Carotid Artery Stenosis

Several institutions published evaluation criteria for carotid stenosis, with some differences in interpretation.[3,23-25] However, in 2003, a consensus document was published in the USA to make recommendations on the performance of VUS of carotid arteries. The United Kingdom followed them in 2009, and the DCI of the Brazilian Society of Cardiology (BSC) in 2015.[1,3,4]

Table 3 – ELSA Brasil:[13] individuals of both genders, aged 40 to 65 years, of white, multiracial, or black ethnicity

Mean IMT LCCA (mm)

	Ethnicity	Percentile	40y	45y	50y	55y	60y	65y
Man	White	P 25	0.47	0.49	0.52	0.54	0.57	0.60
		P 50	0.53	0.57	0.60	0.64	0.67	0.71
		P 75	0.60	0.65	0.69	0.73	0.77	0.81
		P 90	0.70	0.75	0.80	0.85	0.90	0.95
	Multiracial	P 25	0.48	0.50	0.53	0.56	0.58	0.61
		P 50	0.53	0.57	0.61	0.65	0.69	0.73
		P 75	0.60	0.65	0.70	0.75	0.80	0.85
		P 90	0.69	0.75	0.80	0.86	0.92	0.97
	Black	P 25	0.49	0.52	0.55	0.58	0.62	0.65
		P 50	0.56	0.59	0.63	0.67	0.71	0.75
		P 75	0.64	0.68	0.72	0.77	0.81	0.86
		P 90	0.71	0.78	0.84	0.91	0.97	1.03

	Etnia	Percentile	40y	45y	50y	55y	60y	65y
Woman	White	P 25	0.44	0.47	0.50	0.53	0.56	0.59
		P 50	0.49	0.52	0.56	0.59	0.63	0.66
		P 75	0.54	0.58	0.63	0.67	0.71	0.75
		P 90	0.61	0.66	0.71	0.76	0.81	0.86
	Multiracial	P 25	0.45	0.48	0.51	0.54	0.57	0.60
		P 50	0.50	0.53	0.57	0.60	0.64	0.67
		P 75	0.56	0.60	0.64	0.68	0.72	0.77
		P 90	0.63	0.68	0.73	0.78	0.83	0.88
	Black	P 25	0.46	0.49	0.52	0.55	0.58	0.61
		P 50	0.51	0.55	0.59	0.63	0.67	0.70
		P 75	0.57	0.62	0.66	0.70	0.75	0.79
		P 90	0.64	0.70	0.76	0.82	0.88	0.94

Mean IMT RCCA (mm)

	Ethnicity	Percentile	40y	45y	50y	55y	60y	65y
Man	White	P 25	0.45	0.48	0.51	0.53	0.56	0.59
		P 50	0.51	0.54	0.58	0.61	0.65	0.69
		P 75	0.59	0.63	0.67	0.71	0.75	0.79
		P 90	0.66	0.71	0.76	0.81	0.85	0.90
	Multiracial	P 25	0.44	0.47	0.50	0.53	0.56	0.60
		P 50	0.50	0.54	0.58	0.62	0.66	0.69
		P 75	0.58	0.63	0.68	0.73	0.77	0.82
		P 90	0.69	0.74	0.79	0.84	0.89	0.94
	Black	P 25	0.46	0.50	0.53	0.57	0.60	0.64
		P 50	0.54	0.58	0.62	0.66	0.70	0.74
		P 75	0.61	0.67	0.73	0.78	0.84	0.90
		P 90	0.70	0.77	0.83	0.89	0.95	1.02

	Etnia	Percentile	40y	45y	50y	55y	60y	65y
Woman	White	P 25	0.44	0.47	0.50	0.53	0.55	0.58
		P 50	0.48	0.52	0.56	0.59	0.63	0.66
		P 75	0.53	0.58	0.62	0.66	0.70	0.75
		P 90	0.59	0.64	0.69	0.74	0.79	0.84
	Multiracial	P 25	0.44	0.47	0.50	0.53	0.56	0.59
		P 50	0.49	0.52	0.56	0.60	0.64	0.68
		P 75	0.55	0.59	0.63	0.68	0.72	0.76
		P 90	0.62	0.67	0.72	0.77	0.82	0.87
	Black	P 25	0.46	0.49	0.53	0.56	0.59	0.63
		P 50	0.51	0.55	0.59	0.63	0.67	0.71
		P 75	0.58	0.62	0.67	0.71	0.76	0.80
		P 90	0.64	0.71	0.77	0.83	0.90	0.96

RCCA: right common carotid artery; LCCA: left common carotid artery; IMT: intima-media thickness.

Table 4 – CAPS table:[14] individuals of both genders, aged 25 to 45 years. There is no ethnic classification

	Percentile	Age						
		25	35	45	55	65	75	85
Man	%25	0.515	0.585	0.634	0.68	0.745	0.814	0.83
	%50	0.567	0.633	0.686	0.746	0.83	0.914	0.937
	%75	0.633	0.682	0.756	0.837	0.921	1.028	1.208

	Percentile	Age						
		25	35	45	55	65	75	85
Woman	%25	0.524	0.575	0.619	0.665	0.718	0.771	0.807
	%50	0.567	0.615	0.665	0.719	0.778	0.837	0.880
	%75	0.612	0.66	0.713	0.776	0.852	0.921	0.935

2.4.1. Measurement Techniques to Quantify Stenosis

The assessment of carotid stenosis with VUS is based on measurements of flow velocity and their relationships using spectral Doppler, associated with the evaluation of two-dimensional and color Doppler imaging. With the patient in the supine position, use transverse and longitudinal ultrasound planes that allow the visualization of the right and left carotid system.

Figure 3 shows the recommendation from DCI-BSC for the sequence of evaluation of carotid stenosis.

2.4.1.1. Quantification of Carotid Stenosis with Hemodynamic Parameters

Arterial flow velocity measured by Doppler is presented as flow velocity waveforms (spectrum) for each site examined.

Table 5 – MESA table:[15] individuals of both genders, aged 65 to 84 years, of white, black, Chinese, or Hispanic ethnicity

Mean IMT RCCA																
Percentile	White man				White woman				Black man				Black woman			
	Age				Age				Age				Age			
	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84
%25	0.52	0.57	0.65	0.72	0.51	0.55	0.65	0.72	0.58	0.61	0.71	0.74	0.55	0.60	0.65	0.71
%50	0.62	0.68	0.77	0.83	0.58	0.65	0.75	0.83	0.67	0.74	0.85	0.85	0.64	0.71	0.76	0.83
%75	0.71	0.81	0.92	0.97	0.67	0.76	0.87	0.93	0.80	0.92	0.99	1,02	0.74	0.81	0.92	0.96
Percentile	Chinese man				Chinese woman				Hispanic man				Hispanic woman			
	Age				Age				Age				Age			
	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84
%25	0.54	0.56	0.62	0.66	0.55	0.54	0.59	0.67	0.53	0.60	0.65	0.71	0.51	0.57	0.65	0.63
%50	0.64	0.70	0.73	0.79	0.60	0.63	0.71	0.77	0.62	0.67	0.78	0.81	0.58	0.69	0.76	0.78
%75	0.73	0.83	0.92	0.98	0.70	0.77	0.84	0.96	0.73	0.82	0.90	0.92	0.67	0.77	0.87	0.92
Mean IMT LCCA																
Percentile	White man				White woman				Black man				Black woman			
	Age				Age				Age				Age			
	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84
%25	0.54	0.57	0.67	0.71	0.50	0.55	0.63	0.70	0.56	0.63	0.69	0.72	0.54	0.59	0.63	0.68
%50	0.63	0.69	0.81	0.85	0.58	0.64	0.73	0.80	0.69	0.75	0.82	0.85	0.63	0.67	0.76	0.78
%75	0.78	0.82	0.95	1,00	0.67	0.75	0.85	0.94	0.81	0.92	0.99	1,02	0.73	0.80	0.90	0.91
Percentil	Chinese man				Chinese woman				Hispanic man				Hispanic woman			
	Age				Age				Age				Age			
	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84	45-54	55-64	65-74	75-84
%25	0.55	0.57	0.62	0.69	0.49	0.52	0.58	0.64	0.55	0.61	0.68	0.72	0.51	0.58	0.62	0.68
%50	0.63	0.70	0.72	0.84	0.58	0.63	0.71	0.76	0.64	0.72	0.80	0.86	0.58	0.68	0.72	0.77
%75	0.73	0.84	0.86	0.97	0.67	0.72	0.87	0.94	0.75	0.85	0.98	0.97	0.68	0.79	0.86	0.91

RCCA: right common carotid artery; LCCA: left common carotid artery; IMT: intima-media thickness.

Wave characteristics depend on the type of local flow, as well as changes in blood velocity resulting from conditions proximal and distal to the measurement site. In the internal carotid artery (ICA), the resistance of flow velocity waveforms is usually of low. In the external carotid artery (ECA), the resistance of velocity waveform is high, while in the common carotid artery (CCA), it is intermediate between ICA and ECA[13] (Figure 4).

Measure the velocities in the proximal and distal segments of CCA. To evaluate the velocity ratio in the quantification of ICA stenosis, assess CCA at approximately 2 cm from the bifurcation, preferably in a rectilinear segment, without plaques.[4] Analyze ICA in the proximal and middle segments, since atherosclerotic lesions usually affect the proximal 2 cm. The cursor must be parallel to the vessel wall, with a volume sample smaller than the lumen, and positioned in its center and toward the flow, so the insonation angle is $\leq 60^{o}$ (Figure 5).[1,26]

After identifying the stenosis with B-scan and/or color Doppler, document the spectral tracing in this point, and pre-stenotic and post-stenotic regions. The velocity evaluation given by the spectral tracing must include the peak systolic velocity (PSV) and end-diastolic velocity (EDV) in CCA and ICA. Systolic and diastolic velocities provide the following relationships (ratios): PSV ICA/PSV CCA, PSV ICA/EDV CCA, and EDV ICA/EDV CCA.

Subocclusions are diagnosed based on the narrowing of the vessel lumen using color/power Doppler, with thin flow (string sign or trickle flow); however, it might be associated with high, low, or undetectable velocities, which occasionally hinders the diagnosis.[1]

In turn, carotid occlusions can be diagnosed with ultrasound as the absence of patent lumen in grayscale and undetected flow with color/power Doppler and/or spectral Doppler, in addition to the presence of high-resistance flow

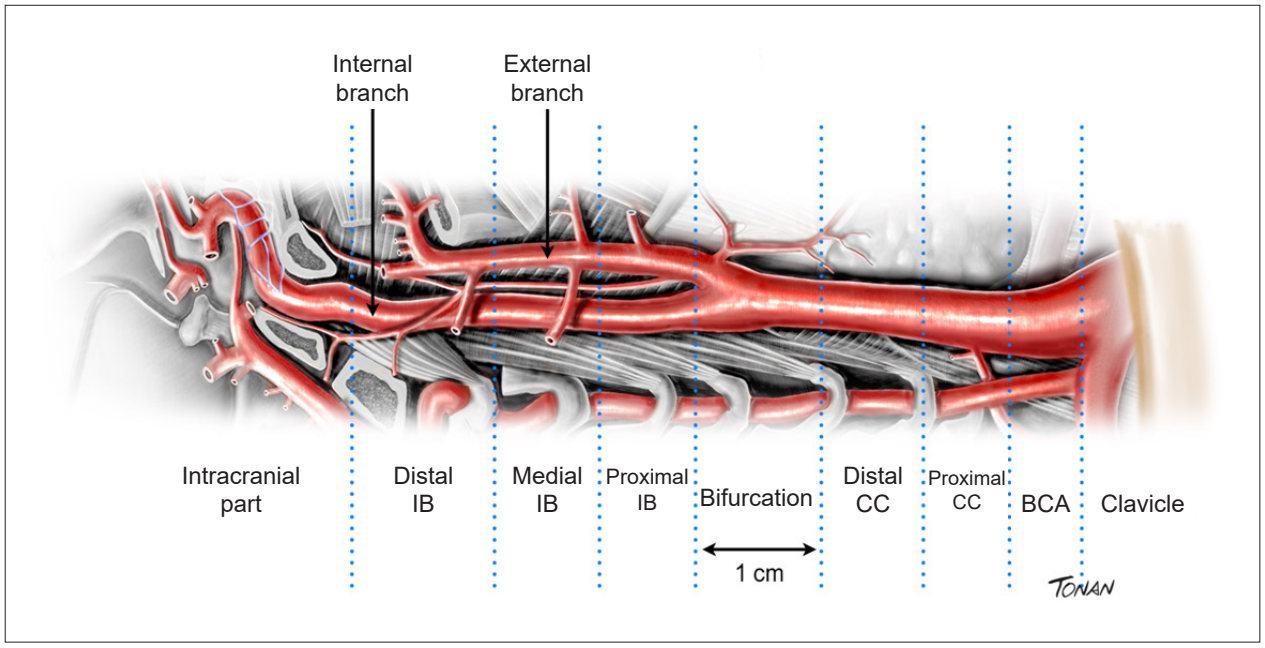


Figure 2 – *Right carotid and its anatomical subdivisions recommended by the group (adapted from the Mannheim study).9 CC: common carotid; IB: internal branch; BCA: brachiocephalic artery.*

in CCA and staccato flow – flow with minimal velocity and very high-resistance at the occlusion or pre-occlusion site.[1]

The study group from DCI-BSC suggests the use of table 6 to quantify ICA stenosis.[1]

2.4.1.2. Quantification of Carotid Stenosis with Anatomic Parameters

The anatomical criterion (Figure 6) is based on the assessment of lumen reduction and should be used to characterize, in particular, stenosis below 50% (without hemodynamic repercussion); however, it is also a great contributor in stenosis greater than 50%, in which the hemodynamic criterion can fail to quantify stenosis accurately (e.g., severe aortic stenosis, significant contralateral carotid stenosis, among others). Lumen reduction is preferentially measured by diameter, and the result of the carotid stenosis range should be reported in intervals of 10%. It is recommended not to measure plaques smaller than 20% to avoid possible differences in the measurement of diameter reduction when the thickened intima is included or stopped being included.[1]

2.4.2. Circumstances that Can Change the Measurement of Flow Velocities and Anatomic Evaluation

Velocity evaluation can be compromised in some situations that affect measurements of spectral analysis. They can be located in the carotid bifurcation – distal or proximal – or even, in the contralateral carotid. Among the conditions proximal to the bifurcation, we underline aortic valve diseases (stenosis or insufficiency), atherosclerotic stenosis, or arteritis with involvement of the aortic arch, branches, and common carotid[1] (Table 7).

Anatomic evaluation can be affected in circumstances such as arterial calcification with acoustic shadowing, improper adjustment of equipment, among others.

2.4.3. Report Description

Relevant information for the report:

- Specify the type of transducer used.
- Inform the technical quality of the examination (report situations that can lower its quality – e.g., presence of catheters).
- Describe the presence of atherosclerotic plaques, their location, extension, morphological characteristics, and degree of stenosis – quantified in deciles according to the DCI-BSC recommendation.[1]
- Report other findings of or related to carotid arteries (e.g., tortuosities, dissections, tumors, arteritis).

2.5. Ultrasound Assessment After Carotid Intervention

Treatment of symptomatic and asymptomatic carotid atherosclerotic disease has been the subject of multidisciplinary debate. Interventional treatment can be done by carotid endarterectomy or carotid stenting.

Ultrasound is the examination of choice for the follow-up after carotid intervention, and its protocol has the same sequence of the examination of carotid arteries without intervention, with some peculiarities in the intervention site. For more information about what to report on the vascular intervention site, the basic protocol of ultrasound follow-up, and velocity parameter tables, we suggest consulting the DCI recommendations recently published.[1]

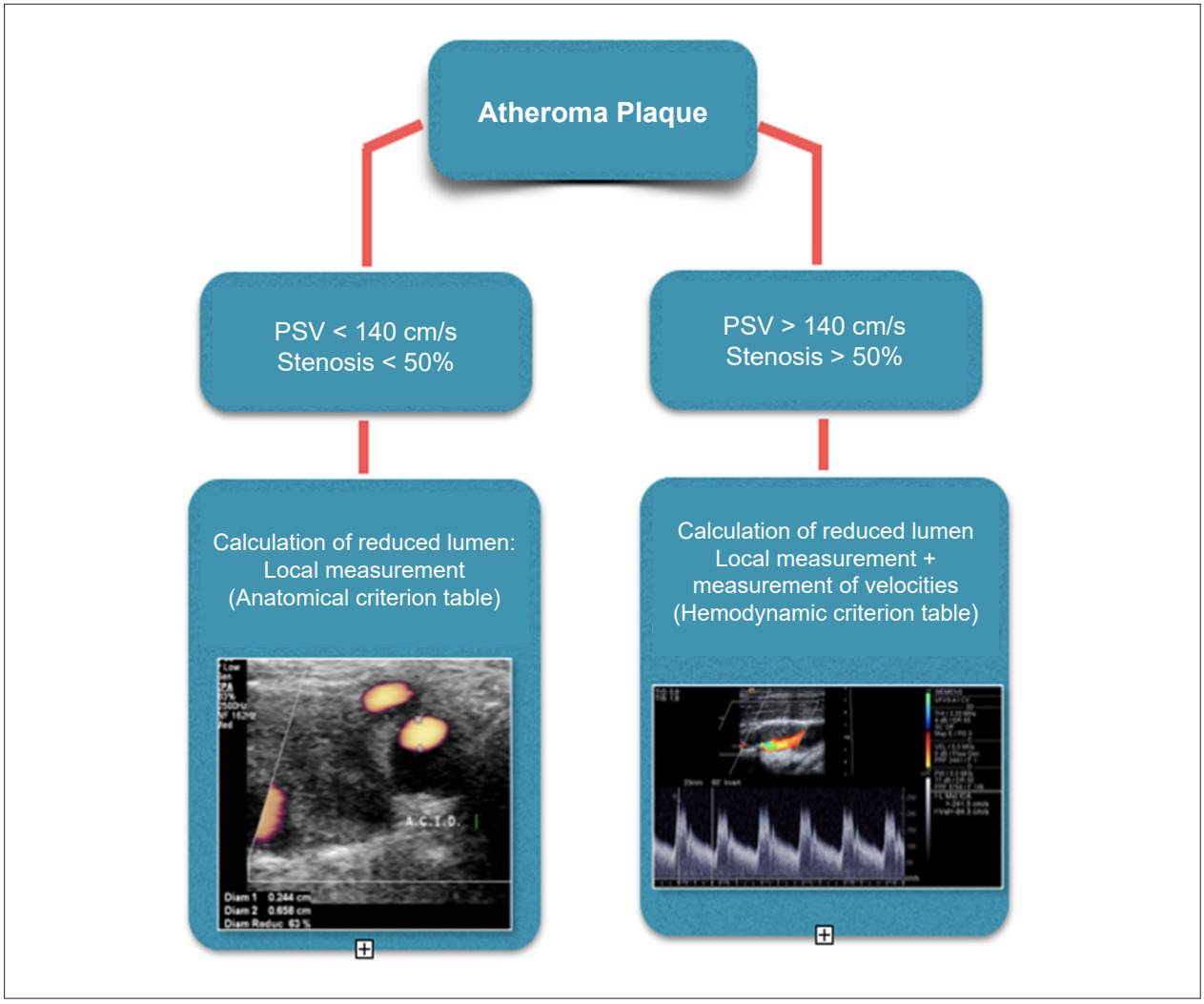


Figure 3 – *Recommendation from the Department of Cardiovascular Imaging of the Brazilian Society of Cardiology for the sequence of evaluation of carotid stenosis. PSV: peak systolic velocity.*

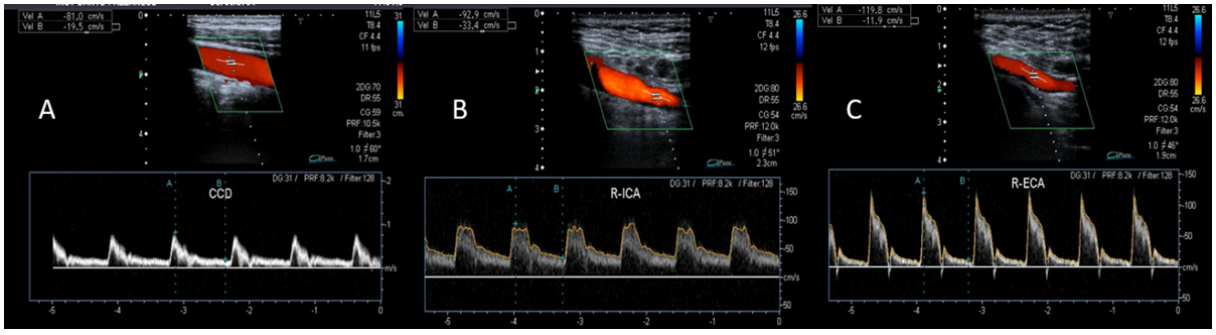


Figure 4 – *Normal flow patterns of carotid arteries. (A) Common carotid artery. (B) Internal carotid artery. (C) External carotid artery.*

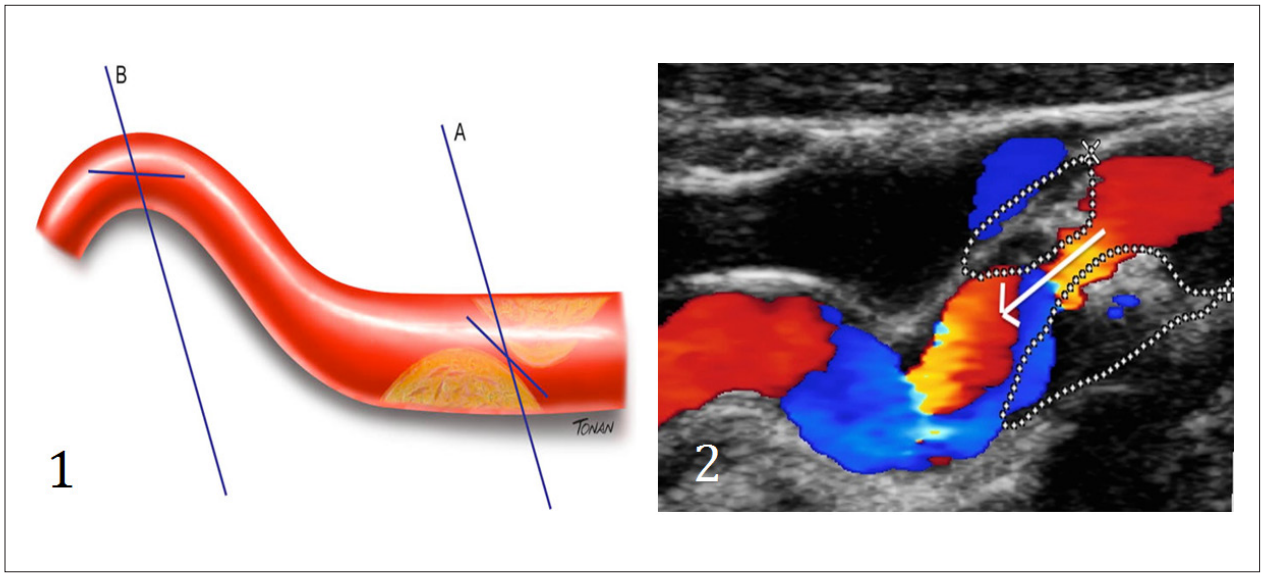


Figure 5 – *(1) Diagram illustrating the placement of the cursor and the insonation angle. (A) Parallel to the jet in case of stenosis. (B) Parallel to the vessel. (2) Cursor and insonation angle toward the flow jet in case of stenosis (arrow).*

Table 6 – Quantification of internal carotid artery stenosis (Department of Cardiovascular Imaging of the Brazilian Society of Cardiology)

% Anat Dist St (Nascet)	PSV cm/s	EDV cm/s	PSV IC/ PSV CC	PSV IC / EDV CC	EDV IC / EDV CC
< 50%	< 140	< 40	< 2.0	< 8	< 2.6
50 to 59%	140 to 230	40 to 69	2.0 to 3.1	8 to 10	2.6 to 5.5
60 to 69%	–	70 to 100	3.2 to 4.0	11 to 13	–
70 to 79%	> 230	> 100	> 4.0	14 to 21	–
80 to 89%	–	> 140	–	22 to 29	> 5.5
> 90%	> 400	–	> 5.0	> 30	
Subocclusion	Variable – thin flow	Variable – thin flow	Variable – thin flow	Variable – thin flow	Variable – thin flow
Occlusion	Lack of flow	Lack of flow	Not applicable	Not applicable	Not applicable

The colors represent, from left to right, the most relevant criteria according to the literature. CC: common carotid; IC: internal carotid; EDV: end-diastolic velocity; PSV: peak systolic velocity.

2.6. Ultrasound Evaluation of Vertebral Arteries

The VUS evaluation of extracranial vertebral arteries contributes to the carotid study. It is divided into four segments: three extracranial and one intracranial (Figure 7).[27,28]

2.6.1. Methodology to Perform the Examination

The patient's position is the same as that adopted for the carotid study.

To evaluate the extracranial part of vertebral arteries, start the examination by the V2 segment. At this point, with the aid of color Doppler and small angulation movements, try to identify the artery (as well as its vein) and record the spectral curves, adapting the scale and insonation angle of the vessel. Past this point, the artery is displayed toward its origin. The V3 segment of the vertebral artery lies below the mastoid process of the temporal bone (anatomic mark for the study). This region presents the vessel end of the transverse foramen and its course around the mastoid process (also called "atlas loop" due to its anatomical relationship with this vertebral body).[3] The typical parameters expected are:

Diameter: ranges from 2 to 4 mm. Caliber asymmetry among vertebral arteries is common (73% of cases), and the left one has a more dilated caliber in 50% of cases.[28,29] The normal standard with pulsed wave Doppler is waveforms with laminar antegrade flow of low-resistance, PSV between 20 and 60 cm/s in the V2 segment, and that can range from 30 to 100 cm/s in the origin of the vertebral artery. Due to the frequent diameter asymmetry, there is a considerable difference in PSV and resistance index (RI) among the normal vertebral arteries of an individual.[27]

Vertebral artery hypoplasia is defined as a vessel diameter equal to or lower than 2.0 mm (or caliber asymmetry among vertebral arteries with ratio > 1:1.7).[28]

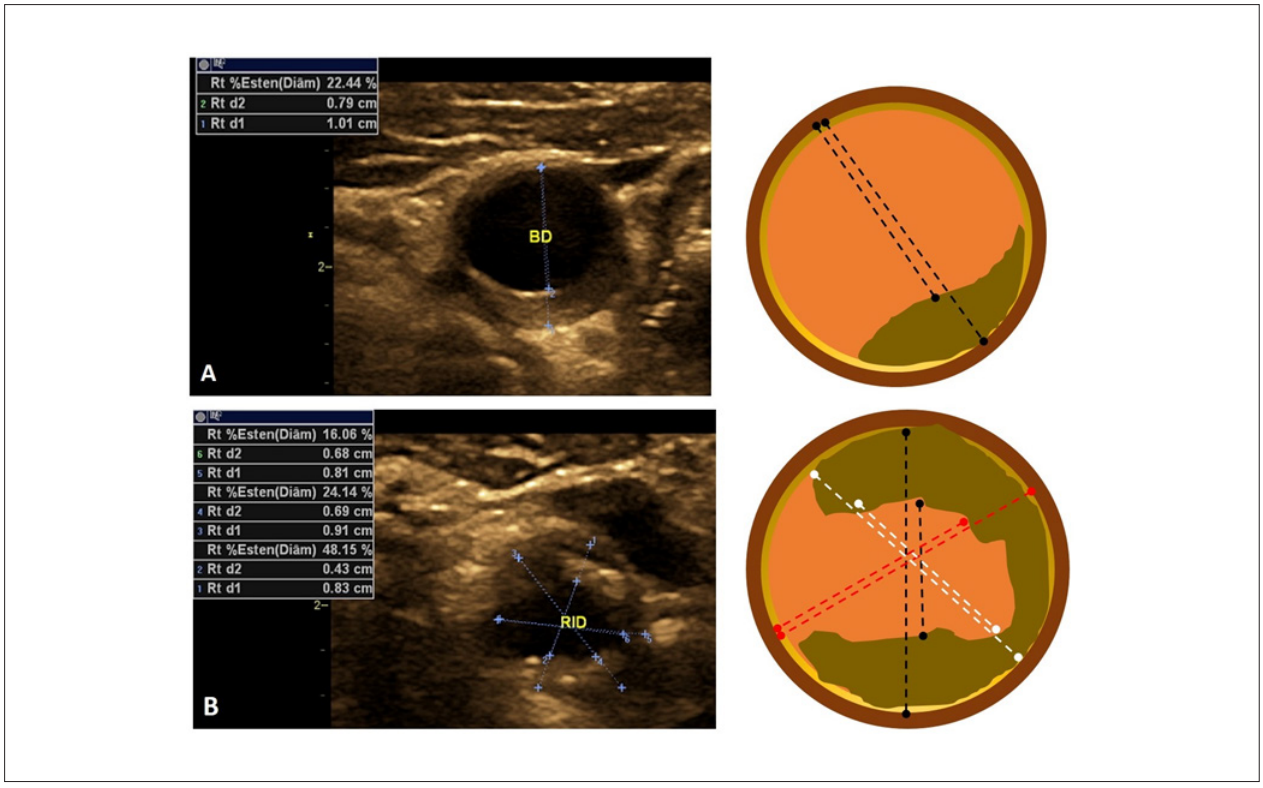


Figure 6 – *Measurement of lumen reduction. (A) Smooth atheromatous plaque in the lumen. (B) Irregular atheromatous plaque in the lumen.*

Table 7 – Circumstances that can change the measurement of flow velocities

Pathology	Abnormalities in VUS	Assessment alternatives
Stenosis proximal to the common carotid artery or brachiocephalic artery	Reduced absolute flow velocities (PSV and EDV)	Using the velocity ratio and evaluation by the anatomical criterion
Significant stenosis or contralateral carotid occlusion	Compensatory increase in flow velocities	Using the velocity ratio and evaluation by the anatomical criterion
Arrhythmias (atrial fibrillation)	Variable velocity peaks	Waiting for the most regular period, or using an average of five beats and anatomical criterion
Aortic valve stenosis	Reduced absolute flow velocities (PSV and EDV)	Using the velocity ratio and evaluation by the anatomical criterion
Aortic valve insufficiency	Increase in PSV flow, with the possibility of retrograde diastolic flow	Using anatomical criterion or velocity ratio that does not involve EDV

VUS: Vascular Ultrasound; EDV: end-diastolic velocity; PSV: peak systolic velocity.

2.6.2. Quantification of Stenosis

Proximal stenosis (V0-V1) diagnosis results from the increase in flow velocities at the lesion site. The DCI-BSC standardization[3] suggests the values presented in table 8, adapted from the study by Hua et al.[30] Evaluate stenosis in the remaining segments with VUS based on multi-parameter analysis, such as turbulent flow with color Doppler, local increase in flow velocities, increase in velocity rates, and distal flow damping, since there are no tables of quantification of stenosis for these segments.

3. Abdominal Aorta and Branches

3.1. Abdominal Aortic Aneurysm

3.1.1. General Considerations

Aneurysms are defined as a local dilation equal to or greater than 50% of the proximal or normal arterial diameter, necessarily involving all vessel layers. Even though the diameter of the abdominal aorta changes with age, gender, and biotype,

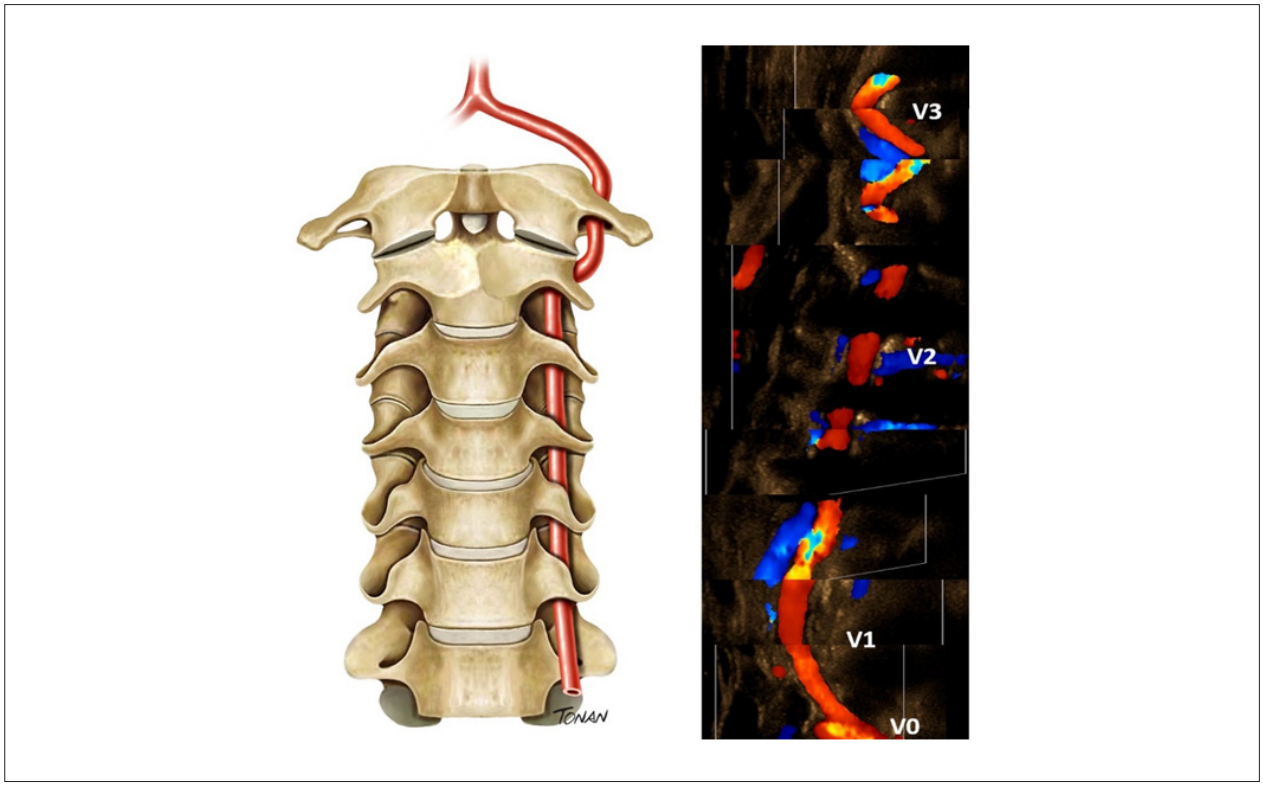


Figure 7 – *Extracranial segments of the vertebral artery (V0-V3).*

Table 8 – Cut-off velocity values for proximal vertebral artery stenosis

Stenosis	< 50%	50 to 69%	70 to 99%
V_{max}	≥ 85 cm/s	≥ 140 cm/s	≥ 210 cm/s
VVR	≥ 1.3	≥ 2.1	≥ 4
EDV	≥ 27 cm/s	≥ 35 cm/s	≥ 55 cm/s

VVR: maximum velocity rate at the stenosis site and the V2 segment; EDV: end-diastolic velocity.

the mean diameter of the infrarenal aorta is approximately 2.0 cm, with upper normal limit < 3.0 cm. Thus, abdominal aortic aneurysm (AAA) is defined as an aorta that measures > 3.0 cm. AAAs are located between the diaphragm and the aortic bifurcation and can be classified as suprarenal, juxtarenal, and infrarenal. Approximately 85% of AAAs are infrarenal, and 5% involve the suprarenal aorta.[31] About 25% of patients with AAA have associated iliac artery aneurysm.[2]

Aneurysms can be fusiform, saccular, or with eccentric shapes. The type of asymmetry can significantly influence the risk of rupture and, as aneurysms grow, they can form laminated thrombi that preserve the arterial lumen.[2]

VUS is the most used examination to screen and diagnose asymptomatic patients in emergency units without a prior diagnosis and symptomatic ones. Computed tomography angiography (CTA) is the examination of choice for pre- and postoperative assessment; however, VUS does not lose its value for being more accessible, costing less, and not using nephrotoxic contrast. The current availability of microbubble contrast makes VUS quite attractive, particularly in postoperative assessments.[32]

3.1.2. Clinical Indications[2]

- Screening (Table 9).
- Follow-up: monitor the growth and determine the appropriate time for surgery.[33]
- Evaluation of pulsating abdominal mass, signs of rupture, or growth.
- Preoperative AAA examination: report data on the access route, abnormalities in iliac arteries, fixation site of the endoprosthesis, aspect and measurements of the aneurysmal sac, and presence of parietal thrombi.
- Postoperative AAA examination.

3.1.3. Examination Instructions and Protocols (Table 10)

3.1.4. Examination Protocol for Abdominal Aortic Aneurysm According to Recommendations from the Department of Cardiovascular Imaging[2]

The examination must be conducted from the subxiphoid region to the aortic bifurcation, followed by the study of

Table 9 – Recommendation from the Department of Cardiovascular Imaging for screening and follow-up of abdominal aortic aneurysm

Screening
• Men aged 65 to 75 years
• Men aged 55 to 75 years with a family history of AAA and/or who smokes
• Women aged 55 to 75 years with a family history of AAA and/or who smokes
Follow-up interval
• 2.6 to 2.9 cm – reevaluate in 5 years (sub-aneurysmal dilation)
• 3.0 to 3.9 cm – 24 months
• 4.0 to 4.5 cm – 12 months
• 4.6 to 5.0 cm – 6 months
• > 5.0 cm – 3 months
Indication for intervention
• ≥ 5.5 cm
• AAA-related symptoms
• Growth rate > 1.0 cm per year

AAA: abdominal aortic aneurysm.

right and left common iliac arteries and their external and internal branches.

The evaluation uses B-scan, with transverse, coronal, and longitudinal planes to detect atheroma plaques and measure the diameters, especially if dilations are found. Take the anteroposterior (AP) measurement of the aneurysm during the peak systolic expansion, reporting if it was made from outer wall to outer wall (OTO) or inner wall to inner wall (ITI).

• **Screening**: use the B-scan during the subxiphoid part of the echocardiogram or in routine abdominal ultrasound.

• **Diagnosis and follow-up**: screen the aorta from the subxiphoid region to its bifurcation, followed by the study of iliac arteries and branches.

• **Preoperative assessment**: descriptions, necessary measurements, and relevant data are described in figure 8.

• **Postoperative assessment**: inform the surgical techniques used. They are described in detail in the DCI recommendations.[2]

Essential information to include in the medical report (Figure 8):

Table 10 – Examination instructions and protocols for the study of abdominal aorta and branches

Examination instructions	Abdominal aorta	Aortoiliac segment	Mesenteric arteries and celiac trunk	Renal arteries
Low-frequency convex or sector transducers (2 to 5 MHz)	x	x	x	x
Preferentially in the morning with 6- to 8-h fasting	x	x	x	x
The patient should not smoke, chew gums, or consume carbonated beverages	x	x	x	x
Optional antiflatulent	x	x	x	x
Supine position with head raised at 30°	x	x	x	x
Lateral position	x	x	–	x
Transverse, coronal, and longitudinal planes	x	x	x	x
What to evaluate:				
B-scan:				
Dimensions	x	x	x	x
Anatomic changes	x	x	x	x
Morphology of walls and plaques	x	x	x	x
Presence of thrombi	x	x	–	–
Color Doppler:				
Aliasing	x	x	x	x
Lack of flow (occlusion)	x	x	x	x
Spectral Doppler:				
PSV	–	x	x	x
PSV ratio (V2/V1)	–	x	–	–
EDV	–	–	x	x
Renal aortic ratio	–	–	–	x

EDV: end-diastolic velocity; PSV: peak systolic velocity.

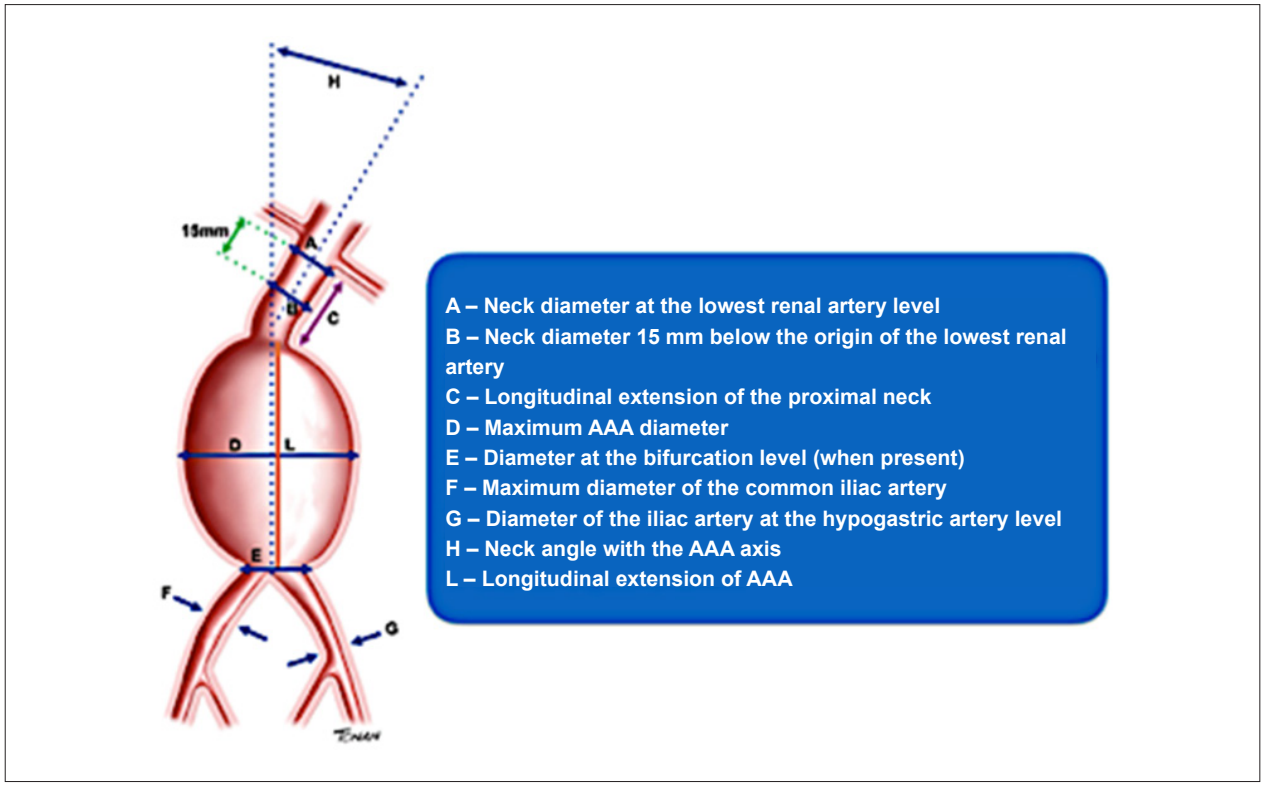


Figure 8 – *Preoperative assessment of abdominal aortic aneurysm (AAA).*

• Diagnostic examination:

- Report technical difficulties.

- Measure the largest diameter of the aorta.

- Inform the presence of tortuosities or enlargement of the aorta.

- Define the location of the aneurysm: supra-, juxta-, or infrarenal.

- Describe the anatomical shape of the aneurysm: saccular, fusiform, or other.

- Inform the presence or absence of wall thrombi, the intraluminal diameter, and signs of rupture.

• Additional information for the preoperative examination:

- Diameters:
  - ○ Neck in the lowest renal artery plane.
  - ○ Neck 15 mm below the origin of the lowest renal artery.
  - ○ Maximum AAA – AP transverse plane (ITI or OTO).
  - ○ Bifurcation plane (when present).
  - ○ Both common iliac arteries.
  - ○ Iliac artery bifurcation.
- Longitudinal extension of the proximal neck.
- Neck angle with aneurysm axis.
- Longitudinal extension of AAA.

3.2. Aortoiliac Atherosclerotic Disease

VUS allows the identification, localization, and anatomic extension of atherosclerotic lesions, and evaluates the aortic wall to register not only the presence of atherosclerotic lesion but of ulceration, calcification, thrombus, dissection, and dilation. When performed by trained and experienced professionals, this technique has good diagnostic accuracy for aortoiliac atherosclerotic disease, with 86% sensitivity and 97% specificity for lesions > 50% stenosis.[34]

3.2.1. Clinical Indications for Venous Ultrasound in Cases of Aortoiliac Atherosclerotic Disease

• Symptoms of acute ischemia (distal embolism) and intermittent claudication with decreased or absent femoral pulse, gluteal claudication, erectile dysfunction, and pain at rest.

• Clinical signs such as abdominal bruit and reduced ankle-brachial index.

• Prior VUS showing abnormalities in the velocity curve pattern of femoral arteries.

• Follow-up of grafts and endoprostheses for the treatment of aortoiliac obstruction.

• Suspected diagnosis of aortic dissection.

• Suspected diagnosis of arteritis.

3.2.2. Examination Protocol for Aortoiliac Atherosclerotic Disease According to DCI Recommendations (Table 10)

3.2.2.1. Diagnostic Criteria

• **Stenosis**: measure PSV at the lesion site (V2) and 1 to 2 cm proximal to the lesion (V1) and calculate the velocity ratio (V2/V1). Determine the spectral curve with an angle ≤ 60º parallel to the turbulent flow axis (Figure 9). The degree of stenosis should be classified according to table 11.

• **Occlusion**: lack of flow in any aortoiliac segment, even with scan parameters that detect low-velocity flows. Presence of typical preocclusive waveform (high peripheral resistance, low peak systolic velocity, and lack of diastolic flow). Collateral vessels can be found in occluded pre- and post-segment (re-entry point). The post-occlusive spectrum is characterized by monophasic waveform, with reduced PSV and prolonged acceleration time - *parvus/tardus* (Figure 9). Hypoechoic image with a concave interface in colored flow and spectrum in preocclusive *staccato* pattern suggests thromboembolic occlusion.

• Essential information to include in the medical report:

- Diagnostic examination:

○ Report if there were technical difficulties during the examination.

○ In case of dilations, inform the largest diameter of the aorta and/or iliac arteries.

- Additional information for the preoperative examination:

• Inform the presence, aspect, and location of atherosclerotic plaques, as well as the degree of stenosis of lesions. Table 12 lists the general limitations of VUS examination.

3.3. Mesenteric Arteries

3.3.1. General Considerations

Mesenteric vessels are represented by the celiac trunk (CT) and superior and inferior mesenteric arteries (SMA and IMA, respectively). Anatomically, CT starts just below the aortic hiatus of the diaphragm and originates the splenic and hepatic arteries.

SMA and IMA begin approximately 0.5 to 2 cm below CT and 4 to 5 cm above the aortic bifurcation, respectively (Figure 10).[35]

Table 11 – Classification of the degree of stenosis with pulsed wave Doppler

Classification	Systolic velocity ratio
Stenosis < 50%	V2/V1 < 2.0
Stenosis ≥ 50%	V2/V1 ≥ 2.0
Stenosis ≥ 70%	V2/V1 ≥ 4.0
Occlusion	Lack of flow

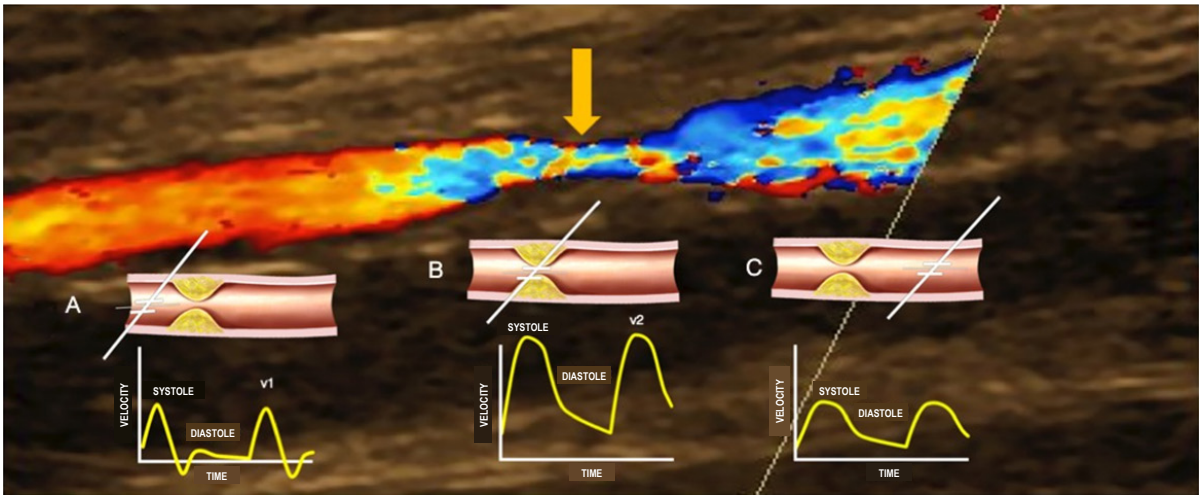


Figure 9 – *Color flow imaging showing the flow proximal to the lesion in red and the turbulent flow at the lesion site (arrow). The diagrams A and C demonstrate the velocity spectrum with Doppler. (A) Cursor proximal to the lesion to measure V1. (B) Cursor at the lesion site to measure V2. (C) Cursor distal to the lesion with damped waveform.*

*This document will not cover the VUS assessment in the postoperative follow-up of aortoiliac obstructions, in case of suspected diagnosis of aortic dissection and arteritis. We suggest the recent publication of DCI recommendations as additional reading.[2]

Table 12 – General limitations of vascular ultrasound in the evaluation of abdominal aorta and branches

Aorta and iliacs	Mesenteric arteries/Celiac trunk	Renal arteries
• Hostile abdomen	• Hostile abdomen	• Hostile abdomen
• Obesity	• Obesity	• Obesity
• Intestinal meteorism	• Intestinal meteorism	• Intestinal meteorism
• Examiner-dependent	• Patient with severe abdominal pain – in acute ischemia	• Anatomic changes
• Low-quality equipment	• Examiner-dependent	• Examiner-dependent
	• Low-quality equipment	• Low-quality equipment

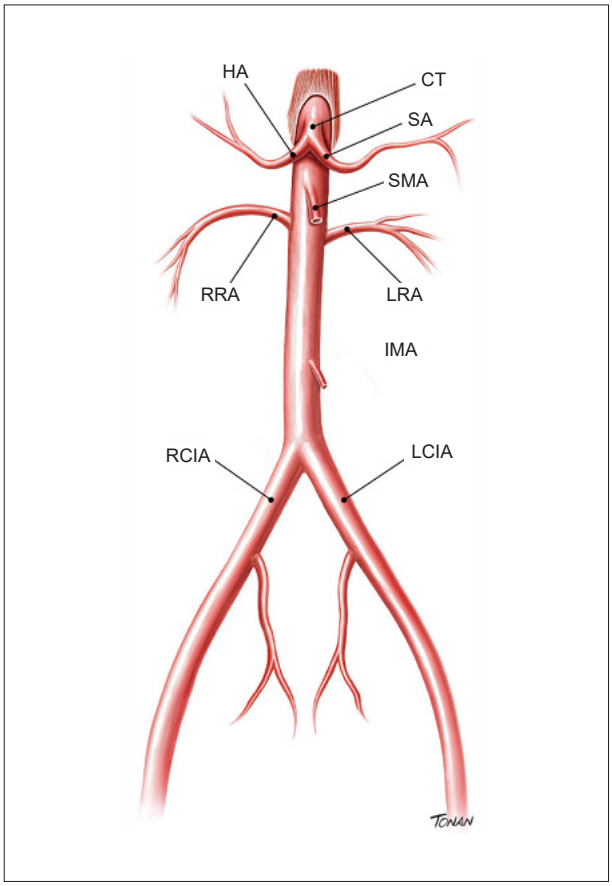


Figure 10 – *Abdominal aorta and branches. SA: splenic artery; HA: hepatic artery; RCIA: right common iliac artery; LCIA: left common iliac artery; IMA: inferior mesenteric artery; RRA: right renal artery; LRA: left renal artery; SMA: superior mesenteric artery; CT: celiac trunk.*

Mesenteric artery obstructive disease progresses chronically and asymptomatically. The clinical manifestation represented by postprandial abdominal pain (mesenteric angina) and/or progressive weight loss occurs when two or more mesenteric vessels are involved. Older men are more frequently affected. Atherosclerosis is responsible for more than 90% of diseases that strike mesenteric arteries and is usually dissemination of the atheromatous process that involves the entire aorta.[36]

Arteriography is the standard diagnostic method; however, VUS is the first examination indicated for the study of symptomatic chronic intestinal ischemia for being non-invasive and risk-free.[37]

The objective of VUS is to determine the presence, location, extension, and severity of the stenotic lesion. The study must include the SMA, CT, and IMA, with the evaluation of SMA and CT being more important.[38]

3.3.2. Clinical Indications

• Recurrent postprandial abdominal pain (mesenteric angina).

• Weight loss without a known cause.

• Abdominal bruit.

The DCI recommendations describe in detail the protocols of follow-up after surgical or endovascular treatment and assessment of compression syndromes.[2]

3.3.3. Examination Preparation and General Protocol (Table 10)

• **Specific examination protocol:**[39,40]

- Place the transducer in the epigastric region; using the transverse plane, identify the SMA anteriorly, the aorta posteriorly, and the right renal vein between these two vessels (Figure 11A). In this same location, using the longitudinal plane of the aorta, find the CT and SMA (Figure 11B).

- B-scan: evaluates the presence of atherosclerotic or aneurysmal disease.

- Color flow imaging: assesses vessel patency and indicates flow turbulence, suggesting the probable stenosis site.

- Spectral analysis: used to analyze PSV and EDV. Measure these velocities in the origin of the vessel and/or in places with suspicion of stenosis. Position the insonation angle toward the blood flow.

- Velocities of mesenteric vessels are influenced by respiration; therefore, patients should hold their breath during the measurement.

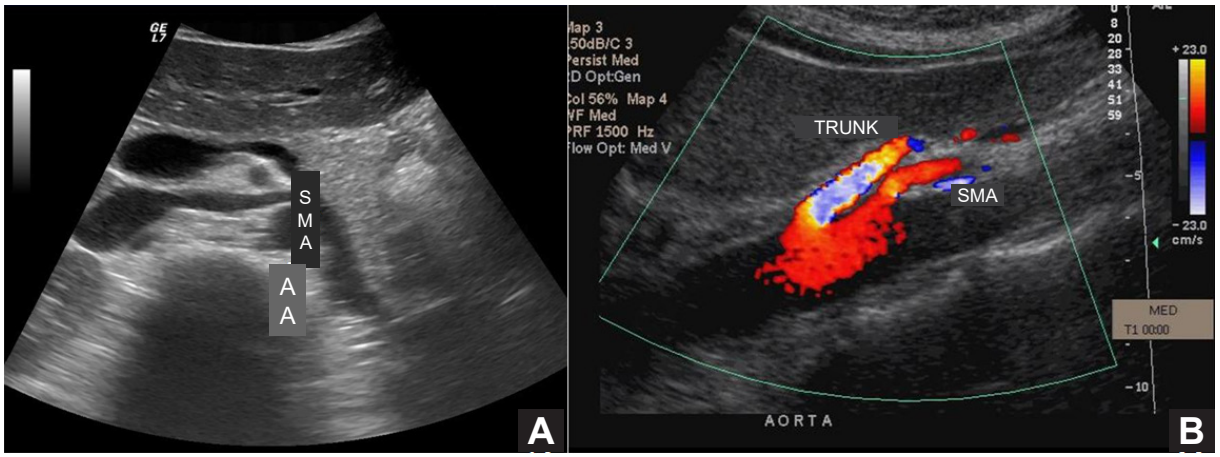


Figure 11 – *Mesenteric vessels and abdominal aorta. (A) Transverse plane with B-scan showing the superior mesenteric artery (SMA) anteriorly and the abdominal aorta (AA) posteriorly. (B) Longitudinal plane of the abdominal aorta and emergence of the celiac trunk and SMA.*

• Table 13 presents the ultrasonographic criteria to assess flow in CT and SMA.[2,41-43]

3.3.4. Essential Information to Include in the Medical Report

• Report if there were technical difficulties during the examination.

• Presence or absence of atherosclerotic disease.

• Lesion site.

• Measurement of stenosis.

• Measurement of PSV and EDV.

3.3.5. Examination Limitations

Table 12 lists the examination limitations.

3.4. Renal Arteries

3.4.1. General Considerations

Prevalence of renal artery stenosis (RAS) changes according to the population studied. RAS is the most common cause of secondary hypertension among the general population of hypertensive patients, representing approximately 1 to 6% of cases.[44,45]

The most frequent cause of RAS is atherosclerosis (85% to 90% of cases), which often strikes the origin of and/or the segment proximal to the renal artery and can be unilateral or bilateral. Its prevalence increases with age, diabetes, and atherosclerosis in other arterial sites. It is considered an independent predictor of adverse events such as acute myocardial infarction, CVA, and death due to cardiovascular causes.[45,46]

Fibromuscular dysplasia – a non-inflammatory disease – is responsible for 10% of RAS cases. Its frequency among the general population is unknown, but it is more usually reported in young women. Renal artery involvement occurs in its mid-distal segment and is often bilateral.[47]

With the quality improvement of imaging methods, RAS diagnosis became feasible and of great interest, aiming to identify patients who would benefit not only from drug therapy but also from renal revascularization procedures. Among the imaging examinations, VUS is the initial method

Table 13 – Ultrasonographic criteria to assess the native celiac trunk and superior mesenteric artery

Artery	Normal Doppler	Stenosis ≥ 50%	Stenosis ≥ 70%	Occlusion
CT	Low-resistance	PSV > 240 cm/s EDV > 40 cm/s	PSV > 320 cm/s EDV > 100 cm/s	Lack of flow Retrograde CHA flow
SMA Fasting	High-resistance	PSV > 295 cm/s EDV > 45 cm/s	PSV > 400 cm/s EDV > 70 cm/s	Lack of flow
SMA Postprandial	Low-resistance	PSV > 295 cm/s EDV > 45 cm/s	PSV > 400 cm/s EDV > 70 cm/s	Lack of flow

CHA: common hepatic artery; SMA: superior mesenteric artery; CT: celiac trunk; EDV: end-diastolic velocity; PSV: peak systolic velocity.

of choice to investigate RAS due to its advantages, such as being non-invasive, low-cost, having no risk of radiation, and, mainly, the lack of contraindications related to the use of nephrotoxic contrast. Ultrasound evaluation of renal arteries has high specificity in competent laboratories, demonstrating that, when the vessels are correctly assessed, its results rarely differ from those obtained by arteriography.[45,48-50]

Table 14 shows the main indications to investigate RAS, according to the principal American guidelines.[51,52]

The principal objectives of the study of renal arteries are:

• Identify the main renal arteries and, if possible, the accessory ones.

• Locate and grade stenotic lesions resulting from atherosclerotic disease or not.

• Monitor the progression of RAS.

• Follow-up after renal artery revascularization.

3.4.2. Examination Protocol (Table 10)

• Patient's position: Supine, using transverse and longitudinal ultrasound planes to analyze the abdominal aorta and origin of renal arteries.

• Lateral, using the coronal plane to assess all middle and distal segments of renal arteries. Use this plane to measure the longitudinal diameter of the kidney and analyze the intrarenal flow in segmental or interlobular arteries.[2]

• B-scan: used to identify atheroma plaques in the renal artery and evaluate the echogenicity and size of the kidney.

• Color flow imaging and/or power Doppler: evaluate artery patency. Power Doppler indicates possible stenosis sites through flow turbulence or reduction in the vessel lumen.

• Spectral analysis: Essential to measure systolic and diastolic velocities (PSV and EDV). Use the transverse or coronal plane, keeping the cursor directed at the flow jet, with an insonation angle < 60° in the renal artery and 0° in intraparenchymatous arteries.[53]

• Measure PSV and EDV at the origin of the renal artery or in any segment with suspicion of stenosis.

• Use the longitudinal plane of the aorta, near the origin of the SMA, to measure its PSV and calculate the renal aortic ratio (RAR).

3.4.3. Diagnostic Criteria for Renal Artery Stenosis

Diagnostic criteria for RAS are classified as direct and indirect. The first consists of evaluating the renal artery from its origin in the aorta and, if possible, in all its extension. The second analyzes the hemodynamic repercussion of the proximal lesion of the renal artery on intraparenchymatous arteries.

The direct criterion comprises renal artery PSV and EDV and aortic PSV to calculate RAR (renal artery PSV/aortic PSV). The low-resistance waveform is considered normal for the renal artery. PSV is the most accurate parameter to grade RAS, with values that range between 180 and 250 m/s from study to study. EDV and RAR are used to aid the RAS evaluation. According to several studies, RAR ranges from 3.2 to 3.7 to estimate hemodynamically significant stenosis. Situations such as aortic coarctation, severe left ventricular dysfunction, aortic dissection or aneurysm, and systolic aortic velocities > 100 cm/s or < 40 cm/s can change the velocities in renal arteries and their relationships.[2]

Indirect criteria, represented by the measurement of the kidney size and analysis of intraparenchymatous artery flow, should be combined with direct criteria to optimize the results. A difference of 1.5 cm in kidney size can result from hemodynamically significant stenosis or even renal artery occlusion. Regarding the analysis of intraparenchymatous artery flow, initially, there is a reduction in the first systolic peak (FSP), prolonged acceleration time (AT) with decreased acceleration rate (AR), and flattening of the systolic wave until the *parvus/tardus* pattern is found. AT > 70 ms is associated with 60% RAS, while the *parvus/tardus* flow is present in more severe stenosis (80%).[2]

Table 14 – Clinical indications to investigate renal artery stenosis

● Onset of hypertension in patients aged ≤ 30 years
● Onset of severe hypertension in patients aged ≥ 55 years
● Patients with accelerated hypertension (sudden or persistent worsening of previously controlled hypertension)
● Patients with resistant hypertension (treatment failure with full doses of three antihypertensive drug classes, including diuretics)
● Patients with malignant hypertension (with target-organ damage: acute renal failure, acute congestive heart failure, new visual or neurological disorder, and/or advanced retinopathy)
● Patients with worsening of renal function after administration of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker
● Patients with unexplained renal atrophy or discrepancy > 1.5 cm from kidney sizes
● Patients with sudden and unexplained pulmonary edema (flash pulmonary edema)
● Patients with renal failure or unexplained congestive heart failure
● Patients with refractory angina
● Patients with multiple vessel coronary artery disease
● Patients with abdominal aortic aneurysm

Table 15 summarizes the criteria recommended by DCI-BSC for hemodynamically significant RAS (> 60%). All references to these criteria are detailed in the guideline.[2]

Renal artery occlusion might be suggested if the vessel flow is not seen during color flow imaging and/or power Doppler, and not detected with pulsed wave Doppler, associated with a longitudinal diameter of the ipsilateral kidney < 8.5 cm.

Follow-up after renal revascularization is not part of the scope of this publication and can be found in the DCI guidelines.[2]

3.4.4. Limitations of the Renal Artery Study

Listed on table 12.

3.4.5. Essential Information to Include in the Medical Report

- Report if there were technical difficulties during the examination.
- Inform the presence or absence of atherosclerotic disease or signs of fibromuscular dysplasia.
- Lesion site.
- Measurement of stenosis.
- Measurement of renal artery PSV and EDV.
- Measurement of aortic PSV.
- Measurement of pulsatility index (PI) and RI in intraparenchymatous arteries (preferably the segmental artery).
- Measurement of kidney size.

4. Lower-Limb Arteries

VUS can evaluate peripheral arterial diseases (PADs) with high accuracy, enabling the anatomical and functional assessment of arterial lesions, in addition to identifying the location, extension, and hemodynamic repercussion of stenosis or occlusion.[54,55]

4.1. Clinical Indications

- Anatomic diagnosis of stenosis or occlusion in the stenotic PAD in symptomatic patients considered for revascularization.[56-59]
- Follow-up of the progression of stenotic disease previously diagnosed.
- Surgical therapeutic planning for patients diagnosed with PAD.[60,61]
- Diagnosis and follow-up of peripheral arterial aneurysms.[62]
- Diagnosis, follow-up, and treatment of pseudoaneurysms.[63,64]
- Evaluation of autogenous or synthetic vascular grafts, with follow-up and diagnosis of complications.[65-67]
- Monitoring of arterial sites submitted to percutaneous intervention, such as angioplasty, thrombolysis, thrombectomy, atherectomy, and stenting.[68-71]
- Confirmation of significant arterial abnormalities detected by another imaging method.
- Evaluation of vascular and perivascular abnormalities, such as masses, aneurysms, pseudoaneurysms, dissections, thrombosis, embolism, vascular malformation, and arteriovenous fistula (AVF).
- Evaluation of arterial integrity in trauma.
- Evaluation of artery compression syndromes, such as popliteal artery entrapment.

4.2. Examination Protocol (Table 16)

4.3. Diagnostic Criteria

Stenosis: measure PSV at the lesion site (V2) and 1 to 4 cm proximal to the lesion (V1) and calculate the velocity ratio (V2/V1). Obtain the spectral curve with an angle ≤ 60° parallel to the turbulent flow axis (Figure 9). The degree of stenosis should be classified according to table 17.[60,61] Other criteria that can assist in grading stenosis are: prolonged AT in distal arteries, which could indicate hemodynamically significant lesions in proximal segments.

Occlusion: lack of flow in any lower-limb arterial segment, even with scan parameters that detect low-velocity flows. Presence of typical preocclusive waveform (high peripheral resistance, low peak systolic velocity, and lack of diastolic flow). Collateral vessels can be found in occluded pre- and post-segment (refilling point). The post-occlusive spectrum is characterized by monophasic waveform, with reduced PSV and prolonged AT (*parvus/tardus* pattern). Hypoechoic image with concave interface in colored flow and spectrum in standard pre-occlusive staccato suggests thromboembolism (Table 18).

Table 15 – Velocity criteria to quantify renal artery stenosis both native and after stenting

Degree of stenosis	Renal artery PSV	Renal aortic ratio	Renal artery EDV	Intrarenal flow	Renal artery PSV after stenting	Renal aortic ratio after stenting
Normal	< 200 cm/s	< 3.5	< 150 cm/s	AT < 70 ms	< 390 cm/s	< 5
< 60%	≥ 200 cm/s	< 3.5	< 150 cm/s	AT < 70 ms	< 390 cm/s	< 5
≥ 60%	≥ 200 cm/s	≥ 3.5	< 150 cm/s	AT < or ≥ 70ms	> 390 cm/s	≥ 5
≥ 80%	≥ 200 cm/s	≥ 3.5	≥ 150 cm/s	AT ≥ 70 ms *tardus/parvus* flow	≥ 390 cm/s	≥ 5
Occlusion	-	-	-	Might have *tardus/parvus* flow	-	-

AT: acceleration time; EDV: end-diastolic velocity; PSV: peak systolic velocity.

Table 16 – Protocol for diagnostic examination and preoperative mapping

Artery	B-scan		Pulsed Wave Doppler		Color Imaging
	Normal	Abnormal	Normal	Abnormal	
CFA Proximal SFA Mid SFA Distal SFA PA PTA ATA FA TFT	Transverse: evaluate the diameter and aspect of the wall Longitudinal: evaluate the aspect of the wall and intraluminal diameter	Transverse: measure the dilations and, if possible, the intraluminal stenosis Longitudinal: measure the lesion extent	Longitudinal: use an angle ≤ 60 degrees, laminar flow, and multiphase curve (triphase)	Longitudinal: evaluate the flow in the stenosis, and proximal and distal to the stenosis Use the peak systolic velocity in the site of highest velocity (V2), with angle ≤ 60 degrees, and 1 to 4 cm proximal to the lesion (V1) to calculate the velocity ratio (V2/V1) Flow in the post-stenotic segment: velocity turbulence or decrease Post-stenotic velocity curve of the parvus/tardus type indicates hemodynamic repercussion	Assess vessel patency with intraluminal color filling Occlusion: lack of color filling Shows flow turbulence – mosaic aspect (aliasing) Guide the volume scan of the sample to detect the point of highest velocity

FA: fibular artery; CFA: common femoral artery; DFA: deep femoral artery; SFA: superficial femoral artery; PA: popliteal artery; ATA: anterior tibial artery; PTA: posterior tibial artery; TFT: tibial-fibular trunk.

Table 17 – Classification of the degree of stenosis in native arteries with pulsed wave Doppler

Classification	Systolic velocity ratio
Stenosis < 50%	V2/V1 < 2.0
Stenosis ≥ 50%	V2/V1 ≥ 2.0
Stenosis ≥ 70%	V2/V1 ≥ 4.0
Occlusion	Lack of flow

Aneurysm: report the identification and location of the aneurysm. Measure the largest diameter including the adventitial layer (out-out) with two-dimensional image in transverse plane. Investigate and document the presence of intraluminal thrombus with color flow imaging.

Pseudoaneurysm: characterized by dilation that does not compromise all arterial layers and having a connecting channel with the arterial lumen. Evaluate all of these structures with two-dimensional image and color imaging, measuring the calibers. Use spectral Doppler in the connecting channel, where the typical "to-and-fro" flow can be found (Table 18). Therapeutic interventions should use color imaging and pulsed wave Doppler as a guide, evaluating blood flow in the native artery, aiding in the puncture – in cases of thrombin treatment –, and verifying the thrombosis of the pseudoaneurysm in all treatment modalities.[63]

Table 18 presents the different patterns of arterial flow, with their names, clinical meanings, and main occurrence situations.

4.4. Essential Information to Include in the Medical Report

- Report if there were technical difficulties during the examination.
- Wall aspect and diameter of all arteries studied, when necessary.
- Presence, aspect, location, and degree of stenosis of atherosclerotic plaques.
- Stenosis velocity and characteristics of velocity curves in the post-stenotic segment.
- Signs of segmental or complete arterial occlusion.

4.5. General Limitations of the Peripheral Artery Ultrasound

- Examiner-dependent.
- Equipment of low technical quality.
- Lower-limb edema.
- Unhealed ulcer.

5. Arteriovenous Fistulas for Hemodialysis

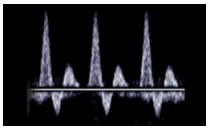
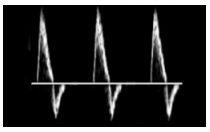
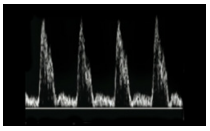
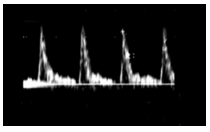
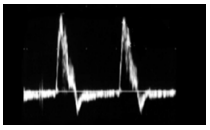
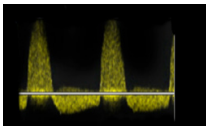
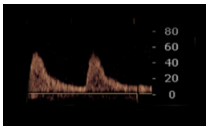
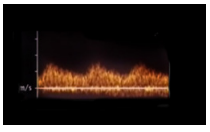
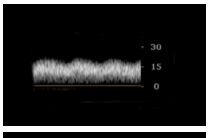
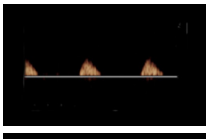
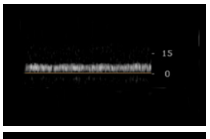
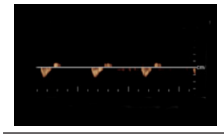
5.1. Introduction

AVFs can be congenital, traumatic, or specifically created for hemodialysis. This guideline will cover only the technical aspects of VUS evaluation of AVF for hemodialysis (AVFH), which can be of two types:

1. Autogenous – radiocephalic or brachiocephalic (Brescia-Cimino) fistula. Figure 12 shows the latero-lateral connection between artery and vein in A; the terminal connection between the artery and lateral of the vein in B; the terminal connection between the vein and lateral of the artery in C; and the termino-terminal connection between artery and vein in D.[72]

2. Polytetrafluorethylene (PTFE) grafts. Figure 13 shows an example of a straight PTFE graft between the basilic vein and

Table 18 – Arterial flow patterns in various situations

	Name	Clinical meaning	Occurrence situation
	Triphasic	Found in young and normal individuals	Normal
	Triphasic without the elastic component	Found in old adults with reduced vessel elasticity	• Normal old adults • Bad US beam alignment
	Biphasic hyperemic	Without retrograde component, but reaches the baseline. Increased velocities	• Inflammatory process • Normal reactive vasodilation
	Biphasic post-obstructive	Without retrograde component, but reaches the baseline. Low velocities	After moderate obstructions
	Biphasic with retrograde pandiastolic component	Retrograde pandiastolic component. Usually with normal velocities	Vessels that provide collateral to other stenotic arteries. In most cases, vessels without proximal lesions
	Biphasic "to-and-fro"	Pronounced retrograde pandiastolic component	• Pseudoaneurysm • Type II endoleak
	Acute monophasic	Low velocity, with little increase in acceleration time	Moderate and moderate to severe post-stenosis, WITH vasodilation reserve
	Damped monophasic	Low velocity, with increased acceleration time	Severe post-stenosis or post-occlusion, WITH vasodilation reserve
	Extremely damped monophasic	Very low velocity, with high increase in acceleration time	Post-occlusion, WITH vasodilation reserve
	Monophasic without diastole	Extremely low velocity, with increased acceleration time, without diastole flow	Post-occlusion, WITHOUT vasodilation reserve. Severe multisegmental lesions
	Continuous	Extremely low velocity, with acceleration time so increased that it is not possible to differentiate PSV from EDV	Post-occlusion, WITH vasodilation reserve. Severe multisegmental lesions
	Retrograde	Low velocity, can be damped or not, and can even have a retrograde component	Retrograde filling of a vessel with proximal occlusion

EDV: end-diastolic velocity; PSV: peak systolic velocity.

radial artery in A; a loop PTFE graft between the basilic vein and radial artery in B; a curved PTFE graft between the artery and brachial vein in C; and a loop PTFE graft between the great saphenous vein and femoral artery in the lower limb in D.[73]

The most common AVFH types are the radiocephalic and brachiocephalic;[73] however, as an alternative, they can be created between other vessels, such as the ulnar artery and basilic vein, or the brachial artery and basilic vein, but they must be superficialized.

5.2. Examination Indications

The main indications for VUS in cases of AVFH are:

• Preoperative vascular mapping, with planning for the procedure, including evaluation of central vessels.[74,75]

• Maturation assessment, especially in obese patients. Maturation occurs when AVFH can withstand repeated venous punctures with large-caliber needles. This process can fail in up to 60% of cases.[74,76,77]

• Functional follow-up of AVFH to detect complications early.

• Recommendation: perform an examination before the procedure for planning and two after to reduce its failure rate.[74,78]

• Contraindications for the procedure: Paget-Schroetter syndrome and deep venous thrombosis (DVT).

5.3. Technique[79]

• High-tech equipment – with high-frequency and/or variable frequency linear probe.

• Patient at rest in a room at ambient temperature, with the upper limb extended parallel to the body.

• Measure the anteroposterior diameters of vessels in transverse planes.

• Possible sites to measure flow volume: afferent – in the artery, 1 to 2 cm before the anastomosis; and efferent – in the vein, 1 to 2 cm after the anastomosis.

• Observe the abnormalities in two-dimensional planes and analyze turbulent flows with color flow imaging

• The Doppler angulation should be parallel to the blood flow (closer to 60°).[79]

• Spectral Doppler characteristics: artery – low-resistance flow; vein – arterialized flow pattern.

5.4. Diagnostic Criteria

5.4.1. Protocol to Create Arteriovenous Fistulas for Hemodialysis

• Choose the non-dominant member, if possible.

• Follow the order: 1st option – wrist; 2nd option – elbow; 3rd option – prosthesis.

• Measure the arterial and venous diameter (a tourniquet can be used in the member to evaluate venous distensibility).[80,81]

- Ideal venous or arterial diameter: elbow – 4 mm; wrist – 3 mm.

- Minimum functional diameter: elbow – 2 mm; wrist – 1.8 mm.[72]

• Measure the depth between vessels and skin surface; the ideal for puncture is < 5 mm. [79]

• Measure the distance between artery and vein to be used (Figure 14).

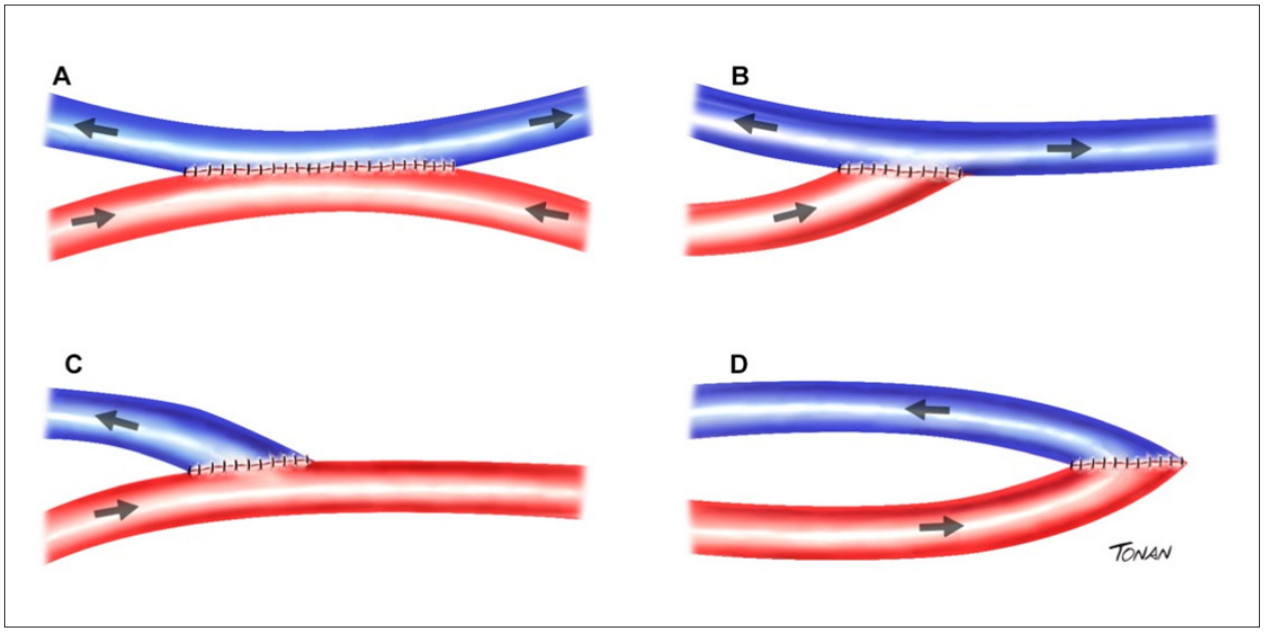


Figure 12 – *Types of brachiocephalic fistulas (Brescia-Cimino). (A) Latero-lateral between artery and vein. (B) Terminal artery – lateral vein. (C) Terminal vein – lateral artery. (D) Termino-terminal between artery and vein.*

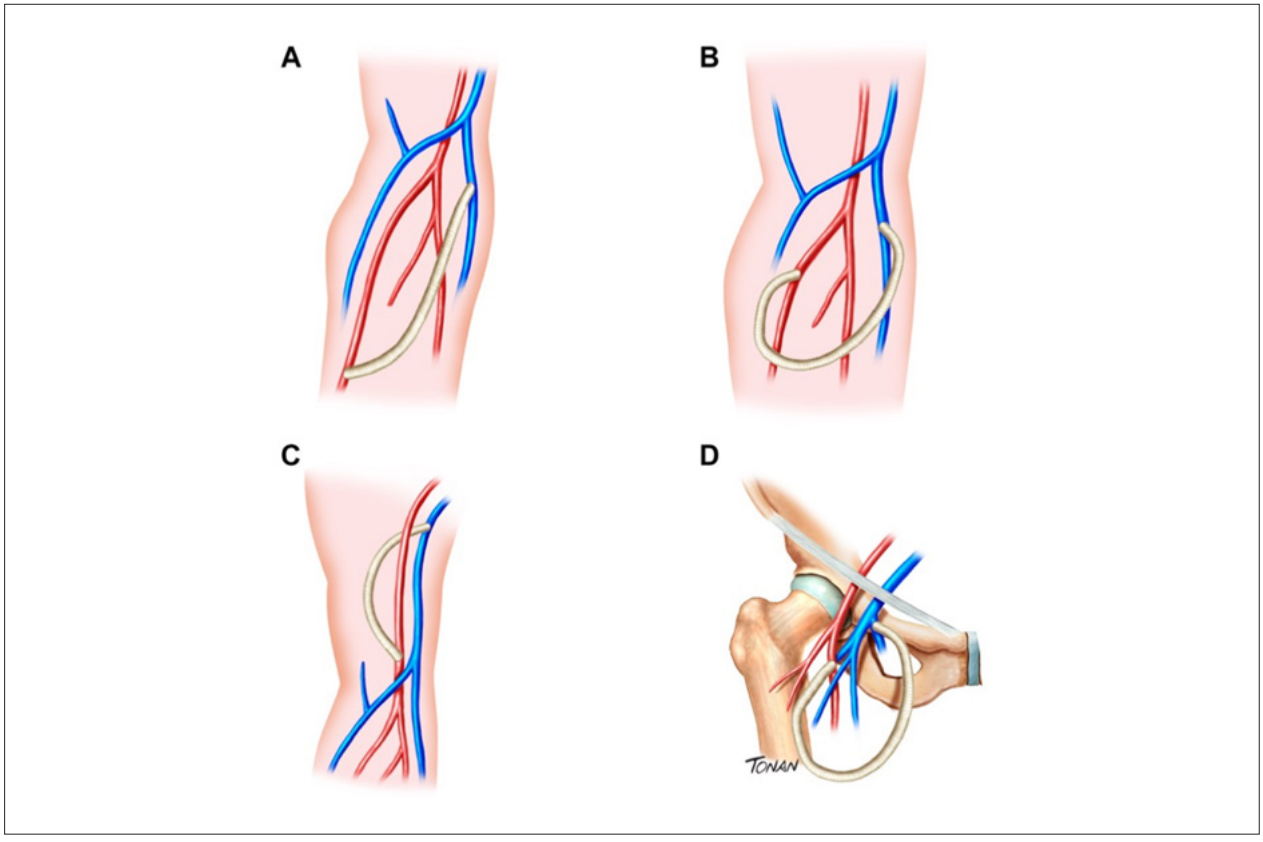


Figure 13 – *Types of polytetrafluoroethylene (PTFE) grafts. (A) Straight PTFE graft between the basilic vein and radial artery. (B) Loop PTFE graft between the basilic vein and radial artery. (C) Curved PTFE graft between the brachial artery and vein. (D) Loop PTFE graft between the great saphenous vein and femoral artery.*

5.4.2. Protocol after Procedure[77,79,81]

• Measurements of artery, vein, and anastomosis;

- Ideal venous or arterial diameter: elbow – 4 mm; wrist – 3 mm

- Minimum functional diameter: 2 mm

• Flow volume: to obtain the effective flow volume through an AVFH, measure the diameter of the drainage vein by its inner edges (in cm), preferably with a transverse plane, to calculate its radius (R) and, consequently, its area (in cm^2). Take this measurement farther from the anastomosis site of the fistula, where the color flow imaging shows no flow turbulence, usually 2 to 5 cm from the anastomosis. Find the flow in the same place of the vein where the diameter was assessed with pulsed wave Doppler. Locate the sample volume in the center of the vessel and correct the Doppler flow angle to up to 60°. Determine the mean flow velocity (V_{MEAN}) in cm/s with pulsed wave Doppler. Calculate the mean of 3 to 5 cardiac cycles. Apply the following formula:

$$\text{Mean flow (ml/min)} = V_{MEAN}\ (\text{cm/s}) \times R^2\ (\text{cm}^2) \times \pi \times 60\ (\text{s})$$

The values below are used for normal flow volume of homologous and heterologous AVFH:

• Brescia-Cimino fistula (radiocephalic) = 614 ± 242 ml/min.

• PTFE = 464 ± 199 ml/min.

• Mean normal value = 514 ml/min.

Fistulas with flow volume < 450 ml/min have a high risk of thrombosis in 2 to 6 weeks.

The minimum functional flow volume for AVFH in the elbow is ≥ 200 ml/min, and in the wrist is ≥ 150 ml/min.

Hyperflow is considered when the flow volume is > 3,000 ml/min.

• Maturation protocol:[73,74,77] AVFH maturation consists of an increase in caliber and flow of the vessels used.

Assess vessel diameter and structure (≥ 6 mm), flow volume (≥ 600 ml/min), and the distance between the vein and skin surface ≤ 6 mm.

Wait at least 14 days; the ideal scenario is individualization with follow-up for each patient and interval superior to 30 days. If possible, wait 60 or even 90 days before the first canalization.

Table 19 summarizes the main objectives of VUS findings.

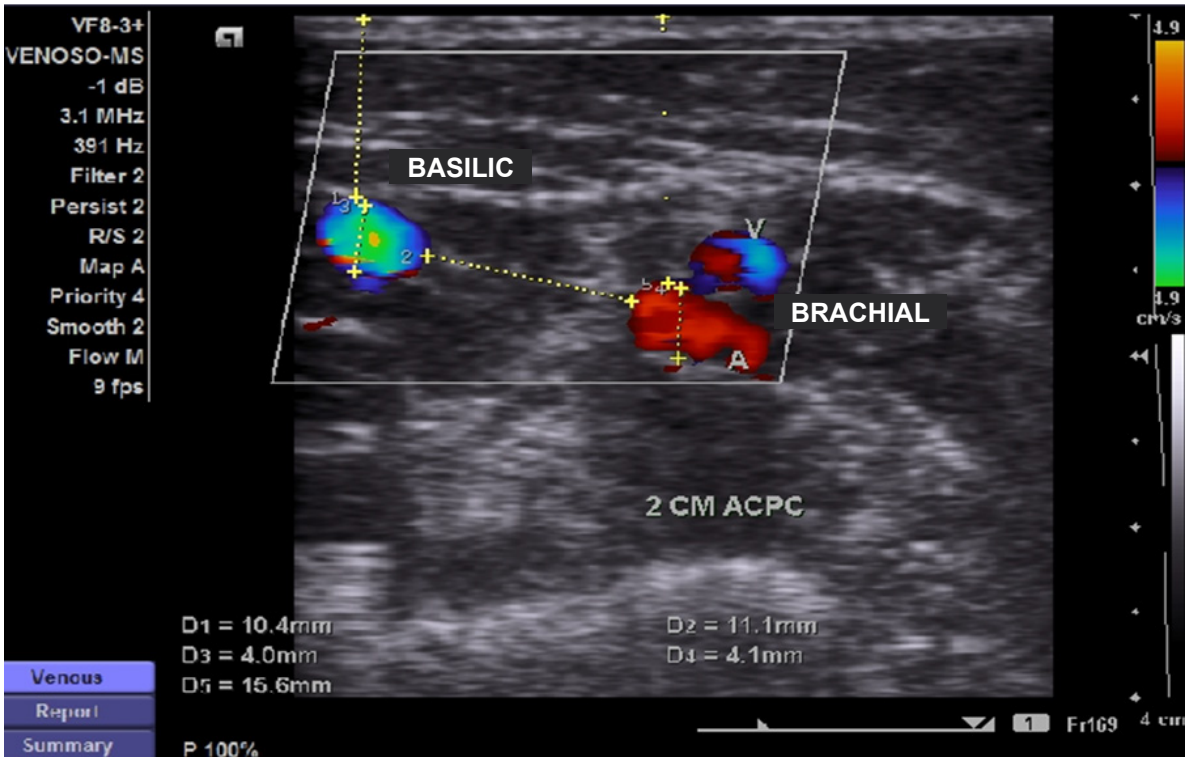


Figure 14 – *Measurement of the distance between the brachial artery and basilic vein before the creation of alternative arteriovenous fistulas.*

Table 19 – Objectives of arteriovenous fistulas for proper hemodialysis (95%)[77]

• Vascular diameter: > 4 mm
• Flow volume: > 500 ml/min
• Maturation time: > 30 days
• Diameters < 3mm and flow volume < 400 ml/min = high probability of failure
• Vessel diameter should increase with time

5.4.3. Causes and Types of Failures (Autogenous and Prosthetic)[74,76,79,82]

- Arterial: diabetes mellitus and significant atheromatosis.
- Venous: fibrosis.
- Anastomosis site: turbulence and intimal hyperplasia.
- Significant escape through tributary veins.
- Steal phenomenon, in which retrograde flow is found in the radial artery distal to AVFH (Figure 15).
- Pronounced tortuosities.
- Intimal hyperplasia (valves).
- Thrombosis (dissection by puncture).
- Idiopathic: puncture and surgical technique.
- Significant stenosis with V2/V1 ≥ 4 (if ≥ 2 indicates stenosis > 50%; angioplasty is recommended in case of clinical and/or hemodynamic abnormalities associated).
- Occlusion.
- Aneurysm, dilation due to prosthesis degeneration and pseudoaneurysm.
- Infection.
- Hematoma, seroma, and lymphocele.

5.4.4. Examination Limitations

Inexistent, with rare exceptions in highly significant edemas, fibrotic scars, and presence of orthopedic devices.

5.4.5. Suggestions to Elaborate the Report and Conclusion

1. Examination before the procedure (Table 20):

- Report deep and superficial venous thrombosis; abnormalities in the arterial system; and anomalous anatomic changes, such as the number of vessels, paths, and forearm vessels that continue in the arm
- Inform the measurements of calibers and proper flows.

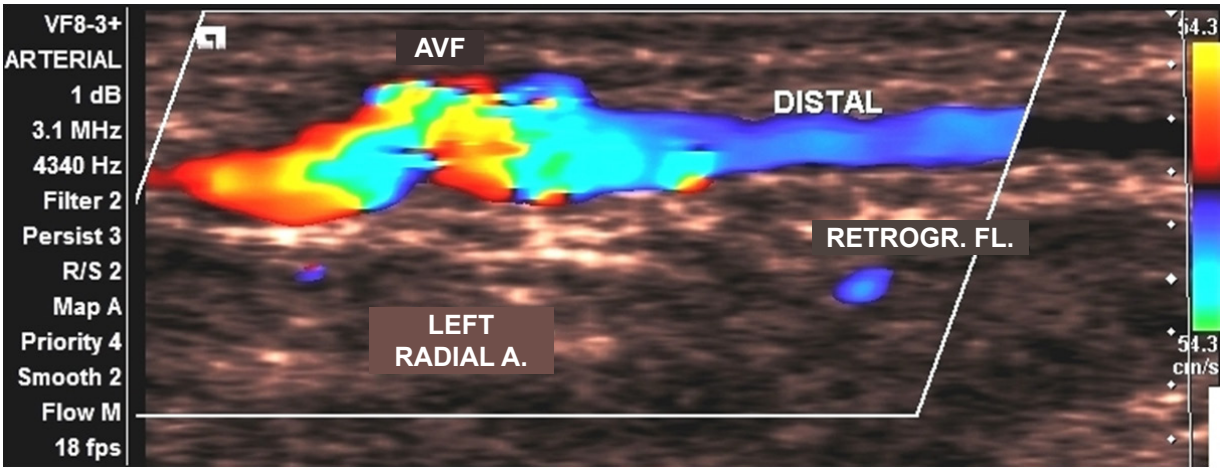


Figure 15 – *Steal phenomenon with retrograde flow in the radial artery (in blue), in the segment distal to the anastomosis of arteriovenous fistulas for hemodialysis.*

Table 20 – Mapping of arteriovenous fistulas for hemodialysis before the procedure

	Arterial diameter – mm			Venous diameter – mm				
Axillary	**Brachial**	**Radial**	**Ulnar**	**Brachial**	**Radial**	**Ulnar**	**Cephalic**	**Basilic**
Proximal arm/forearm								
Mid arm/forearm								
Distal arm/forearm								
Elbow/wrist								
Skin-vessel depth								
Distance A-V								

2. Examination after the procedure (Table 21):

• Describe the type of AVFH and its location; inform if it is functional, dysfunctional, or non-functional, mentioning the cause, location, and extension of the involvement

• Report the afferent and efferent volumes (ml/min).

6. Deep Venous Thrombosis

6.1. Introduction

DVT and pulmonary embolism (PE) are part of the same disease spectrum: venous thromboembolism (VTE). DVT

Table 21 – Mapping of arteriovenous fistulas for hemodialysis after the procedure

Anastomosis:	Arterial diameter – mm			Venous diameter – mm				
Axillary:	**Brachial**	**Radial**	**Ulnar**	**Brachial**	**Radial**	**Ulnar**	**Cephalic**	**Basilic**
Proximal arm/forearm								
Mid arm/forearm								
Distal arm/forearm								
Elbow/wrist								
Skin-vessel depth								

represents approximately two-thirds of the cases and PE, one-third. Between 85% and 90% of DVT cases occur in the lower limbs.[83]

VTE is a severe, preventable, and high-incidence disease – the third most common CVD, after acute myocardial infarction and CVA. Therefore, VTE is a serious and potentially lethal condition that can affect both inpatients and outpatients. After the first VTE episode, the chance of recurrence is high.[84,85]

The venous thrombus often begins at the venous cuspid level (Figure 16) – either superficial or deep veins – and extends proximally in 13% of cases, retrogradely in 4%, and in both directions in 10%.[86-88] It can be partial – when occupying part of the lumen of the vein involved – or total. Thrombus located in the superficial system indicates superficial venous thrombosis, while DVT involves the deep venous system, and can strike one or more veins.[89] DVT in lower limbs is considered proximal if it affects the popliteal vein and/or proximal veins, with or without the involvement of other leg veins, and distal if it affects deep infrapatellar veins.[87,90]

The objective examination is crucial as the clinical diagnosis alone is not reliable. The consequences of diagnostic error are severe. At an early stage, it can result in death and, at a later stage, depending on the pathophysiology (obstruction, reflux, or both), it can cause chronic venous hypertension, leading to debilitating conditions, such as post-thrombotic syndrome (PTS) and, in case of pulmonary involvement, pulmonary hypertension.[83,85,91] Furthermore, although effective, the unnecessary use of anticoagulant therapy results in higher costs and risk of hemorrhage.[92]

6.2. Post-Thrombotic Syndrome

PTS is defined as a combination of symptoms and objective findings in patients with DVT in lower or upper limbs. PTS is a debilitating disease and the most common and less known consequence of DVT.[93,94] One to five years after the DVT episode, approximately 30% to 50% of patients develop PTS, with 5% to 10% of them being severe cases, even when treated correctly.[94,95]

PTS is a combination of venous hypertension secondary to flow obstruction or valvular incompetence and microcirculation and lymphatic abnormalities.

6.2.1. Deep Venous Thrombosis Diagnosis

As the accuracy of the clinical diagnosis of DVT is low (< 50%), few patients with suspicion of DVT effectively have the disease (12% to 31%). Therefore, the recommendation is to perform an accurate and objective examination that can confirm or rule out DVT.[87,92,96] The current gold standard examination to diagnose DVT is compression VUS.[92,97]

Three categories of examinations are used to determine the probability of DVT:[92,98]

1. Clinical probability based on anamnesis and clinical examination

2. D-dimer levels

3. Imaging studies – the most commonly used is venous VUS, and the less used are venography, CTA, and venous magnetic resonance angiography. This guideline will cover only VUS.

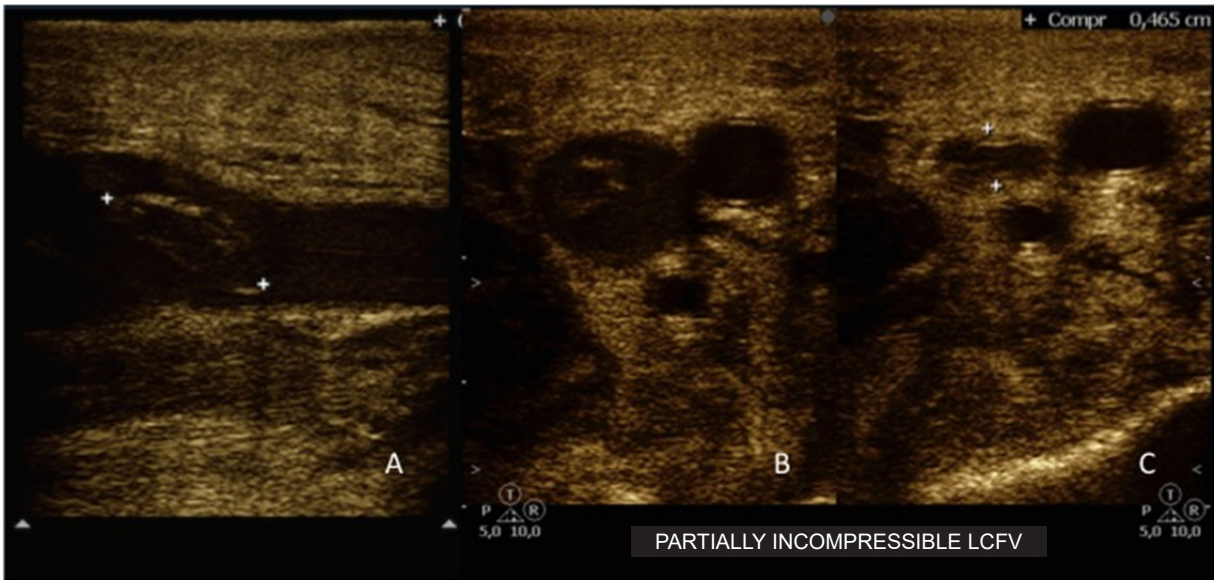


Figure 16 – *Two-dimensional image of a recent partial thrombus (acute) located in the valve sinus of the common femoral vein, shown through longitudinal (A) and transverse (B) planes. There is no complete collapse of the vein during compression (C).*

6.2.2. Vascular Ultrasound

VUS is considered the current gold standard examination to diagnose acute DVT.[99] The PIOPED II study showed 95.5% agreement between CTA and ultrasound in diagnosing or ruling out DVT. In addition, we must remember that VUS is useful not only in diagnosing DVT in symptomatic or asymptomatic (with a high risk of DVT) patients but also in identifying other conditions that cause signs and symptoms indistinguishable from DVT.

Knowledge about vascular anatomy and its variations is crucial since the frequency of variability in the number of veins is high, with the possibility of only one of them being involved, in addition to the different levels of confluences and paths.

To diagnose thrombosis, we adopt several criteria, listed below.

1. Venous compression: the normal vein has thin, smooth, and regular walls, and is completely collapsible with transducer compression (Figure 17).

Incompressibility is the main criterion for DVT diagnosis (Figure 16).

A few conditions might hinder this compressibility, and sometimes special maneuvers are necessary. They are:

• Presence of a strong muscle group in the path to be compressed; for instance, the adductor canal requires compression in the external side of the thigh.

• Neurogenic bladder needs draining through urinary catheterization.

• Proximity to bone structures; for example, compression is limited in infrapatellar veins due to the size of the transducer.

2. Vein caliber: usually the vein has twice the caliber of the adjacent artery. Acute venous thrombosis presents great distension of the vessel wall, with an increase in vein caliber and loss of this relationship. Over time, with the process of recanalization, the vein caliber decreases disorderly in some segments, losing the uniformity usually observed along the vessels. In the most chronic stage, a complete vein retraction might occur, with calibers becoming smaller than those of arteries, at times, hindering their recognition during the examination.

3. Characteristics of the venous wall: parietal irregularities or diffuse parietal thickening, intraluminal trabeculations or synechia, structural valve abnormalities, loss of anatomical relationship with adjacent structures, even if tenuous, which can mean a previous DVT already recanalized.

Intraluminal echoes indicate presence of thrombus and its echogenicity can characterize or not its age.

4. Color imaging: color flow imaging is an important tool for venous thrombosis.

While color flow filling all lumen in longitudinal and transverse planes indicates normality, the lack of color or flaws in filling the vessel can point to partial or complete thrombosis, particularly in recent partial thrombi with low echogenicity.

Flow around the vessel strongly suggests acute DVT. Flow permeating the thrombus indicates recanalization and chronicity of the process.

Take precautions regarding the scale and gain of the equipment, and the proper performance of maneuvers that increase venous flow, generating a color signal.

5. Spectral analysis: the normal venous flow with spectral Doppler is spontaneous and phasic with respiration, increases with distal compression maneuvers, and ceases with Valsalva maneuvers (proximal veins) or proximal compression.[85] The spontaneity of the flow might not be observed in distal veins of patients in the supine position, and distal compression maneuvers and/or mobilization of the limb to displace the blood column become necessary. Loss of phasicity, with continuous flow pattern, is an indirect sign of occlusion or proximal compression. Damped response to distal

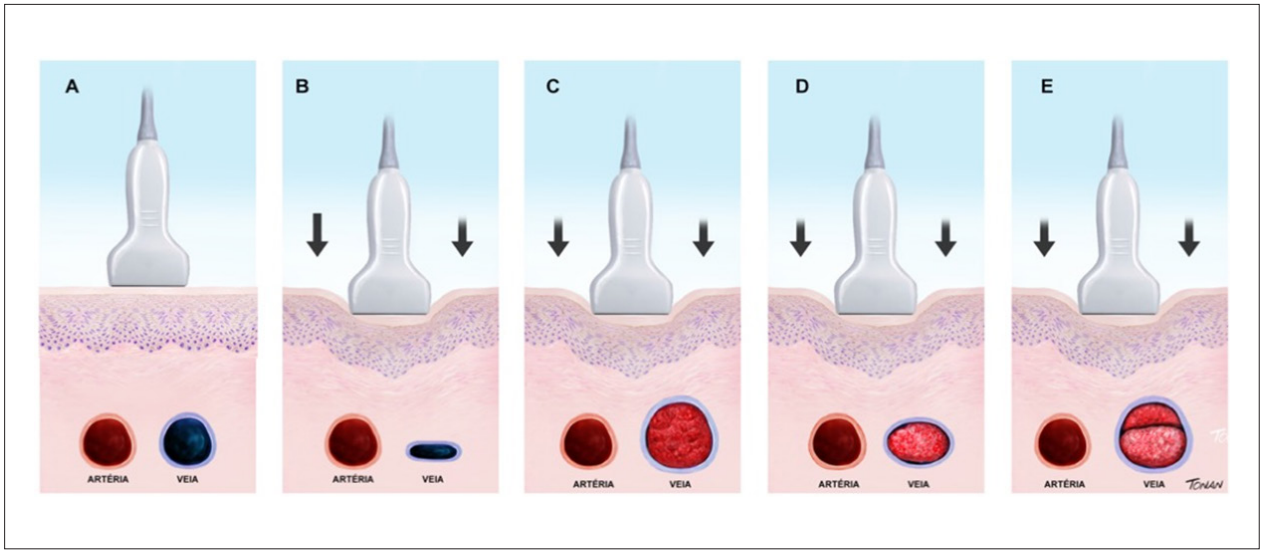


Figure 17 – *Venous compression maneuver. (A) Artery and vein without compression. (B) Normal vein with total compression. (C) Dilated and incompressible vein, with recent thrombus. (D) Incompressible vein, with old thrombus (chronic). (E) Rethrombosis.*

compression indicates obstruction between the compression site and the location of the sample flow.

Retrograde flow occurs when there is valve damage. Thus, valve regurgitation is a pathological sign, which can warn to the presence of previous thrombosis, and valve agenesia or venous reflux secondary to hyperflow should be ruled out.

Table 22 describes VUS characteristics that assist in the identification of stages of venous thrombosis.

Valsalva and inspiration and expiration maneuvers help and add information (Table 23).

6.3. Rethrombosis

High risk of recurrent venous thromboembolic disease persists after DVT treatment, with a cumulative incidence of these complications close to 30% in eight years of follow-up; among them, mortality reaches 30%, mainly due to malignant diseases.[100,101] Relevant predictive factors for risk of recurrence are male gender, thrombus location, and D-dimer.[102] Other less known risk factors are residual thrombus occupying 50% of the vessel lumen diameter after treatment and failure in normalization of compression with VUS.[101]

As the non-invasive diagnosis of recurrence is difficult, some ultrasound criteria can be used, such as:

- Measurement of the residual thrombus mass.
- Abnormalities in the thrombus extension.
- Ultrasound characteristics of the thrombus – low echogenicity, slight compressibility, presence of tail, adhesion to the wall, and increase in venous diameter (≥ 2 times the contralateral vein, or compared to the diameter of the adjacent artery).[100,101,103]

6.4. Examination Technique

Some protocols assess only the proximal segment (femoropopliteal) or the compression VUS of two points (common femoral vein and popliteal vein). These protocols, known as point of care, facilitate the examination by emergency physicians and are proving to be an alternative in the emergency room.[106] However, evaluating the entire venous system is important for a proper DVT diagnosis, better assessment in case of recurrence, and to assist in the differential diagnosis with other pathologies. This guideline recommends always performing a full examination.[107,108]

In lower limbs, the patient should be in a comfortable supine position with the torso and head elevated up to 30°, close to the edge of the bed, on the same side of the examiner, with a slight lateral rotation of the hip and slight knee flexion.

In upper limbs, the patient should be in the supine position, with the limb stretched alongside and slightly away from the body.

Examine the deep venous system starting with the inguinal fold, gently compressing the veins with the transducer, using transverse planes.[85,104,105] The goal is to confirm the absence

Table 23 – Venous flow variation according to the phase of the respiratory cycle

Flow	Inspiration	Expiration
Lower limbs	↓	↑
Upper limbs	↑	↓
Subclavians	↑	↓

Table 22 – Characteristics of different stages of deep venous thrombosis observed in vascular ultrasound

Stage	Acute	Intermediate (subacute)	Chronic
Event time	Up to 14 days	14 to 28 days	> 28 days
Vessel caliber	Dilated	Still dilated, normal, or slightly reduced	Usually reduced
Incompressibility	Total or partial	Total or partial	Partial or absent
Thrombus aspect	Hypoechoic	Isoechoic	Hyperechoic Parietal irregularities Fibrotic residues Residual thrombus: caliber > 2 mm after maximum compression in 6 months or > 3 mm in two consecutive examinations
Flow	Absent or partial	Flow channels permeating the thrombotic mass Can have microfistula	Multiple flow channels permeating the thrombus Complete lumen filling Presence of collaterals Continuous flow or reduced amplitude spectrum Can have orthostatic reflux

or presence of recent or residual thrombi, every 5 cm, throughout the venous trunk in the femoropopliteal segment by the medial thigh, the infrapatellar segment for the popliteal and trifurcation, the posteromedial leg for calf muscle veins (gastrocnemius, soleus, intergemellar), posterior tibial and fibular veins up to the ankle, as well as superficial veins (great and small saphenous veins along its entire extension).

The fibular and soleus veins can be seen in the lateral leg, using the fibula as an anatomical reference. In this case, fibular veins are more superficial in relation to the transducer and posterior tibial veins, deeper. To that end, the patient should change positions, flexing the knee and placing the foot on the bed. Do not neglect this maneuver even in hospitalized patients due to the high prevalence of DVT in segments proximal to fibular veins in this group of individuals.

Anterior tibial and foot veins are rarely studied unless there is a sign of local involvement.

Investigate iliac veins when the patient has DVT in common femoral veins, and it is not possible to identify the end of the thrombus, or when the flow detected in these veins is continuous or has low amplitude.

Alternate between transverse and longitudinal images using color imaging to evaluate flow and, when necessary, spectral Doppler.

Save all stages of the examination (videos and still images) digitally. Currently, clinical research protocols of international multicenter studies recommend recording the maneuver of compressing the vein – with and without compression – in the same picture (dual image). In case of thrombus, measure the venous diameter, in determined sites, to evaluate the residual thrombotic mass.[107]

Follow the same evaluation protocol for deep and superficial venous systems in upper limbs, middle and distal segments of subclavian veins, and jugular veins.

During the follow-up of patients with DVT and recanalization, they preferably should stay in the orthostatic position or, when not possible, sitting for the study of venous reflux.

Do not forget that the temperature in the room can significantly influence the performance of these examinations. Cold induces vasoconstriction and should be avoided. The ideal temperature is 22 to 25°C.

6.4.1. Transducers

In general, high-frequency (5 to 12 MHz) linear transducers are used for normal-weight and thin patients. In overweight/obese patients, the study of the adductor canal and even of leg veins in individuals with moderate/severe edema can use transducers of greater depth range, such as convex abdominal ones, whose frequency varies from 3 to 5 MHz.[108]

6.4.2. Information for the Report

• Presence or lack of signs of deep and/or superficial venous thrombosis.

• Information about the characteristics of the thrombus.

• Extension of thrombosis: essential and, if possible, with approximate measurements of anatomical reference points, such as the anterior-superior iliac spine, inguinal fold, knee, malleolar or plantar region, axillary fold, elbow fold, and wrist fold.

• In case of chronic thrombosis:

- Measurements of residual thrombotic masses can be included in the report and/or images, with their locations so that they can be compared later.

- Presence of orthostatic reflux.

7. Transcranial Doppler

The main purpose of the study called transcranial Doppler (TCD) is to gather hemodynamic information from intracranial trunk arteries non-invasively, using flow insonation with pulsed wave Doppler.[109,110] The skull has always represented a barrier to reach the vessels since US does not penetrate the calcium in bone tissue and there are limited areas (transorbital and transtemporal windows, and foramen magnum) for examination. Also, arteries are located in deeper parts of the brain, making it difficult to obtain proper images and safely collect a sample capable of providing the spectral curves needed to interpret the hemodynamic status registered at a given moment. These unfavorable characteristics determine that a transducer capable of insonating flow in all trunk arteries of anterior and posterior circulations needs to be small and have a low frequency (2.0 MHz or less). CFI safely identifies vessels and analyzes flows.

7.1. Types of Transcranial Doppler

• ***"Blind" TCD***: only uses transducer with pulsed wave Doppler, without B-scan image (Table 24).

• ***TCD with color Doppler***: transducer with image from B-scan, pulsed wave Doppler, and CFI associated.

• ***TCD with microbubble contrast***: color TCD associated with intravenous infusion of microbubble contrast.

• ***TCD with macrobubbles***: color TCD associated with peripheral intravenous infusion of saline or glucose solution mixed with ambient air and shaken (macrobubbles).

7.2. Examination Technique and Protocol

The main focus of any TCD examination must be identifying all trunk arteries safely and recording the spectral flow curve of each vessel. Therefore, the usefulness of CFI is indisputable. Currently, using devices exclusively dedicated to "blind" Doppler is warranted in the monitoring of continuous flow during surgeries and in neurointensive units.

The basic TCD protocol should include the use of all possible windows to transmit US to intracranial arteries:[109] a) *transorbital (right and left)*, to insonate carotid siphons and ophthalmic arteries; b) *transtemporal (right and left)*, to visualize distal internal carotids, anterior cerebral (A1 and A2 segments), middle cerebral (throughout M1 segments and at the beginning of M2), top basilar, and posterior cerebral arteries (throughout P1 and P2 segments); c) *transforaminal,* to study V4 segments of vertebral and basilar arteries (proximal and middle segments), with the possibility of insonating posterior-inferior cerebellar branches of vertebral arteries.

The patient can be in a supine position or sitting. The head should be turned according to the window used at the time. The examiner can follow any sequence and must record images of spectral flow curves of each vessel examined – with identification –, according to the international standard. Including pictures or videos done with CFI ensures safety in confirming identification and possible anatomical variants (very common) or technical difficulties during the examination.

Visualizing brain structures with B-scan determines the ability of the US in penetrating the bone wall in the window chosen and its usability for the examination. CFI will show (or not) flow in lumens of regional arteries, guiding the sample volume of pulsed wave Doppler with precision up to the lumen segment to be insonated to obtain the spectral flow curve. In addition to flow waveform morphology of each vessel, the routine of integral measurement of velocities has to be followed to ensure the collection of essential data to the hemodynamic analysis required in various pathologies with suspicion of DTC: PSV, EDV, mean velocity, RI, and PI (make sure that the equipment preset includes these calculations).

Table 25 lists the clinical indications for TCD.

*According to the **Brazilian Guidelines for the Application of Transcranial Ultrasound as a Diagnostic Test for the Confirmation of Brain Death** (defined by a group of experts from the Department of Neurosonology of the Brazilian Academy of Neurology in 2012), the criteria[122] are:

• A single TCD is enough to confirm brain death.

• TCD should be performed only in patients with previously established clinical diagnosis, in accordance with the current Brazilian regulations; moreover, the patient needs to have stable hemodynamic conditions (with or without the use of drugs), and minimum systemic systolic blood pressure of 90 mmHg (below this value, the examination will not have diagnostic validity).

• A full standard TCD study is mandatory, with images in B-scan and color flow imaging (if available), and spectral flow curves of all intracranial trunk arteries.

• Characteristic TCD findings in *cerebral circulatory arrest*: spectral flow curves with low-amplitude systolic wave (velocity < 50 cm/s) or curves with an *alternating flow* pattern (waves with antegrade systolic component followed by retrograde diastolic component).

• Lack of flow in intracranial trunk arteries is not a criterion for brain death, except in cases in which a prior TCD was performed during the same hospitalization, with a record of flow in the arteries analyzed.

• Anterior circulation: in case of inadequate transtemporal windows, reporting criteria for "vascular collapse" in both carotid siphons becomes mandatory to diagnose brain death.

• Posterior circulation: if it is not possible to detect flow in the basilar artery, findings of "vascular collapse" in both intracranial vertebral arteries are crucial to diagnosing brain death; on the other hand, findings related to basilar "vascular collapse" in the presence of residual blood flow in at least one vertebral artery will invalidate the conclusive diagnosis of the examination as an indication of brain death in this region.

• Residual blood flow can be detected in almost 20% of patients, especially in intracranial carotid arteries and in patients who underwent craniotomy (but this finding tends to disappear in a few hours).

• The examination report must have a detailed account of the findings in each anterior and posterior circulation artery and be conclusive regarding the presence or lack of criteria for *cerebral circulatory arrest* that corroborate the clinical diagnosis of brain death.

*****Spencer scale**

The number of embolic spikes shown in the device screen is also useful information since the greater the number of macrobubbles, more significant the size of the shunt(s) through the foramen ovale (Spencer scale): *grade 0* – lack of HITS; *grade 1* – 1 to 10 HITS; *grade 2* – 11 to 30 HITS; *grade 3* – 31 to 100 HITS; *grade 4* – 101 to 300; *grade 5* – > 300 HITS ("curtain effect"). Above grade 2, the right-left cardiac shunt is significant. In case of countless spikes ("curtain effect"), consider the possibility of pulmonary AVF.

Examination protocol: peripheral intravenous infusion of solution with "macrobubbles" (8 ml of saline or glucose solution mixed with 2 ml of ambient air and shaken until it becomes homogeneous), followed immediately by vigorous Valsalva maneuver performed by the patient for 5 seconds and simultaneous insonation of spectral flow curves (pulsed wave Doppler) in cerebral and basilar arteries. The examination must be conducted in basal conditions (flow record with Valsalva maneuver in the right and left middle cerebral arteries and

Table 24 – Identification of intracranial trunk arteries with "blind" transcranial Doppler[114]

Artery	Depth	Flow Vm	Flow direction in relation to the transducer
Carotid siphon	55 to 70 mm	40 to 50 cm/s	Positive or negative
Ophthalmic	40 to 60 mm	20 cm/s	Positive
Distal internal carotid	55 to 70 mm	45 cm/s	Positive
Anterior cerebral	60 to 70 mm	60 cm/s	Negative
Middle cerebral	35 to 60 mm	70 cm/s	Positive
Posterior cerebral	55 to 70 mm	40 cm/s	Positive (P1), negative (P2)
Vertebral	55 to 70 mm	40 cm/s	Negative
Basilar	70 to 120 mm	45 cm/s	Negative

Table 25 – Clinical indications for transcranial Doppler[115,116]

Pathology	Objective	Observation	Findings
Brain death*	Additional examination judicially valid to confirm cerebral circulatory arrest	Standard study of anterior and posterior circulation arteries is mandatory. In case of residual blood flow, repeat after 12 hours	Spectral curve with short peak systolic (< 50 cm/s) pattern and lack of diastolic flow; or "alternating" pattern (antegrade systolic and retrograde diastolic flow)
Intracranial hypertension[111]	Adjuvant indirect monitoring, including after decompressive craniectomy	Qualitative analysis of the curve pattern, which can vary dynamically (inversion of the diastolic component delimits the irreversible stage)	Progressive reduction of the diastolic component of the spectral flow curve according to the severity of hypertension
Ischemic CVA (acute phase)[112,113]	Monitoring of vessel reperfusion in case of thrombolysis (up to 4.5 hours after the start of the event), which lasts approximately 40 minutes (but can take more than 1 hour)	Monitoring can be intermittent (conventional equipment) or continuous (transducer with "blind" Doppler fixed to a helmet adjustable to the patient's head)	Reappearance of gradual flow according to the degree of reperfusion (TIBI scale of spectral curve pattern)
Subarachnoid hemorrhage** [114] (Table 26)	Diagnosis, assessment of severity, and monitoring of vasospasm, recommending early intervention	Perform the examination at hospital admission and repeat it daily in case of vasospasm (critical period: 4 to 14 days after the event). Insonate all arteries at each examination	Increase in mean flow velocity, according to the severity. Lindegaard ratio (velocity ratio between the middle cerebral artery and ipsilateral internal carotid) differentiates true spasm from hyperemia
Patent foramen ovale*** [115]	Shunt study in patients with ischemic CVA (transient or permanent)	Intravenous infusion of shaken saline solution ("macrobubbles") associated with the Valsalva maneuver	HITS (gaseous emboli) recorded in spectral curves are counted and classified according to the Spencer scale
Sickle cell disease**** [116-118] (Table 27)	Diagnosis and grading of intraluminal stenosis to stratify the risk of ischemic CVA and define the therapeutic approach. Monitoring of therapeutic response	Mandatory in patients aged 2 to 16 years	Mean flow velocity defines the periodicity of follow-up and approach (blood exchange)
Migraine[119]	Support for clinical diagnosis and differentiation from other headaches	It can be performed in the intercritical period or during a painful crisis (different results)	Measurement of pulsatility index and mean flow velocity in all vessels
Transoperative monitoring[120,121]	Preoperative assessment of CVA risk (monitoring of spontaneous microemboli; study of cerebral flow reserve) and peroperative monitoring of emboli and cerebral flow reduction during neurological and cardiovascular surgeries	Continuous flow monitoring of middle cerebral arteries using two transducers with "blind" Doppler fixed to a helmet adjustable to the patient's head. Monitoring should continue in the postoperative (due to microemboli during this period)	Report of emboli rate (solid and/or gaseous) and reduction in mean flow velocity compared to the baseline value (> 15%) determine the risk of ischemic CVA in the immediate postoperative period*****

CVA: cerebrovascular accident; HITS: high-intensity transient signals; TIBI: thrombolysis in brain ischemia (scale). Information followed by asterisks (*) have additional data, presented in the text below.

basilar arteries) and after the infusion of macrobubbles (that is, six times in total). In the event of a record with "curtain" pattern, stop the study (which will be considered positive).

*****Microembolic signals are detected in up to 70% of cases during the first hour after endarterectomy. A rate of 50 "microembolic signals"/hour occurs in up to 10% of cases and is predictive of ipsilateral focal ischemia.[121]

7.3. Limitations of Transcranial Color Doppler

Limitations of TCD basically result from the barrier the cranial bone represents to US. The use of contrast agents ("microbubbles") greatly reduced the cases of inconclusive examinations due to a "lack of adequate windows." The inexperience of the examining physician is also a crucial limiting factor; the learning curve is relatively long and requires dedication.

7.3.1. Essential Information to Include in Transcranial Doppler Reports

The basic structure of any additional examination must have:

• Patient's identification (full name and age).

• Clinical indication (the purpose of the examination will determine the type of TCD needed).

• Technical quality of the examination (reporting possible issues that interfere in obtaining the necessary images for the study).

• Record of all ultrasound windows used, and vessels examined (justifying the cases that were impossible to study).

• Description of specific characteristics found in each technical resource used:

- Color flow imaging – lumen patency or occlusion, laminar or turbulent ("mosaic") pattern, direction (antegrade or retrograde).

***Table 26 – Vasospasm classification**

Artery: MCA	MFV (cm/s)	Lindegaard ratio
Mild	120 to 130	3 to 6
Moderate	130 to 200	3 to 6
Severe	> 200	> 6
Artery: ACA	> 50% of MFV in 24h	–
Artery: PCA	> 110	–
Artery: VA	> 80	–
Artery: basilar		Soustiel ratio
Mild	80 to 95	2 to 2.49
Moderate	> 85	2.5 to 2.99
Severe	> 115	> 3

MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery; VA: vertebral artery. Note: Lindegaard ratio is the ratio between the highest mean flow velocity (MFV) in the middle cerebral artery (M1) and MFV in the ipsilateral extracranial internal carotid. Soustiel ratio is the ratio between vertebral MFV and basilar MFV.

- Pulsed wave Doppler – laminar or turbulent pattern, direction (antegrade or retrograde), velocities of spectral flow curves (peak systolic, end-diastolic, and mean), and PI and resistance according to the clinical indication of the examination (e.g., sickle cell disease requires mean velocity).

- Contrast solution with "macrobubbles" – record and count of HITS in the study of patent foramen ovale and paradoxical embolism.

- Use of contrast agent with "microbubbles" (SonoVue®).

- In the intraoperative monitoring, report the occurrence and count of HITS/hour and variations in flow velocities with potential risk for ischemic CVA in the postoperative period.

Conclusion: avoid etiological diagnosis (TCD is a study of cerebral hemodynamics and findings should be correlated to the clinical indication of examination: for instance, the presence or lack of criteria for vasospasm, with grade classification and time reference to the onset of symptoms of subarachnoid hemorrhage).

Note: in cases of sickle cell disease, it is mandatory to specify, after the conclusion, the recommended date to repeat the reassessment examination (following the Brazilian Guidelines for Transcranial Doppler in Children and Adolescents with Sickle Cell Disease, 2010).[123] In other pathologies, this suggestion is prohibited due to professional ethics.

8. Contrast in Vascular Ultrasound

The introduction of contrast agents in ultrasound examinations considerably expanded the clinical value of this method. B-scan ultrasound is an excellent method to demonstrate the anatomical and morphological characteristics of parenchymal tissue but does not provide any information about the viability and integrity of microcirculation. Color Doppler ultrasound (CDUS) added data about blood flow velocity but is not able to quantify the volume and show with enough sensitivity the blood flow in microcirculation,[124-126] where velocity is too low to be detected without artifacts created by tissue and transducer maneuvers. Also, the spatial resolution of CDUS is limited, the representation of velocity is angle-dependent, and numerous artifacts can influence the diagnostic interpretation of images. Contrast-enhanced Doppler ultrasound substantially increased the sensitivity of CDUS and reduced some limitations.

The technical innovation was the introduction of specific image components for contrast in US equipment, allowing direct visualization of signals emitted by microbubble contrast agents, regardless of their velocities. Due to typical characteristics of microbubble signals (which are fundamentally different from those originating in tissues), "specific microbubble" images (contrast only) are created, which can show volume and perfusion of the parenchymal tissue with extremely high sensitivity and spatial resolution.[124]

******Table 27 – Recommendations of the Brazilian Guidelines for Transcranial Doppler in Children and adolescents with Sickle Cell Disease (2010)[123]**

Mean flow velocity	CVA risk group	Approach
Inadequate ultrasonic windows	Inconclusive	Use another imaging method to assess cerebrovascular events
Difficult execution: uncooperative patient	Inconclusive	Repeat in 3 months, with a different examiner if possible
< 70 cm/s	Low flow	Repeat the examination in 30 days
< 170 cm/s	Normal	Repeat the examination in 12 months
170 to 184 cm/s	"Low conditional"	Repeat the examination in 3 months: if < 170 cm/s, repeat in 12 months
184 to 199 cm/s	"High conditional"	Repeat the examination in 30 days: if < 170 cm/s, repeat TCD every 3 months; if two consecutive examinations are abnormal, consider long-term blood exchange
200 to 220 cm/s	Abnormal	Repeat the examination in 30 days: if > 200 cm/s, blood exchange; if "high conditional", repeat TCD in 3 months; if "low conditional", repeat it in 6 months
> 220 cm/s	Abnormal	Imminent risk of CVA, consider long-term blood exchange

CVA: cerebrovascular accident; TCD: transcranial Doppler.

The creation of each "specific microbubble" signal requires proper interaction between signals of the microbubble contrast agent and the insonated US beam.

8.1. Properties of Ultrasound Contrast Agents

Unlike contrasts for magnetic resonance imaging (MRI) and computed tomography, which use physical and chemical characteristics of cells to generate their effect, microbubble contrast uses the physical attributes of US, that is, the higher the density difference between media, the greater the reflection of energy emitted and larger the amplitude of US signal. Unquestionably, the gaseous medium provides the greatest difference, corresponding to a signal increase of approximately 30 decibels.

US contrast agents are microbubbles of gas inside capsules with flexible and stable phospholipid membranes and a defined size. The SonoVue®[127] agent (produced by Bracco Imaging S.p.A., Milan, Italy), sold in Europe, the United States, parts of Asia, and South America, is the only product currently authorized in Brazil by the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária* – Anvisa) and members of the National Regulatory Agency for Private Health Insurance and Plans (*Agência Nacional de Saúde Suplementar* – ANS). SonoVue® consists of encapsulated microspheres of sulfur hexafluoride gas. Microbubbles have an average diameter of 2.3 μm (a size that prevents them from crossing blood vessel walls and reaching the interstitial space). As a lipophilic gas, its solubility in blood is low, and it does not spread outside the capsule. This protein shell composed of a single layer of phospholipids acts as a surfactant, giving it stability and flexibility along its path in the blood macro- and microcirculation. Therefore, SonoVue® is considered an integral agent of the blood pool and a marker of blood circulation (property that distinguishes it from contrasts used in MRI and computed tomography, which can cross into the extracellular space).

After the microbubble bursts, the gas is almost entirely exhaled through the lungs during respiration, without undergoing liver metabolism or renal excretion.[124] Thus, there is no contraindication to its use in patients with renal failure.

8.2. Technical Aspects that Influence the Acquisition of Contrast Images

Currently, most US manufacturers have exclusive software for studies with contrast, which can be included in the original configuration of the machine or purchased separately. However, even equipment without a specific image component for contrast has some parameters the operator can configure. The following concepts and adjustments of the equipment must be known to get the best result during the contrast study:

8.2.1. Mechanical Index

A unique characteristic of contrast agents for US (non-existent in those used for MRI and computed tomography) is that they are modified by the waves used to detect them. When exposed to US, microbubble behavior changes according to the US power emitted, that is, the amplitude of the acoustic wave [called mechanical index (MI) in the equipment]. In non-contrast studies, MI ranges from 1.6 to 1.9; under this acoustic power, the microbubble always oscillates vigorously and bursts, causing two unwanted effects: a sudden increase in signal intensity with an excessive blurring of the image, and a significant reduction in contrast concentration, consequently shortening the examination time. This image mode, called "image by acoustic stimulation," does not require equipment with contrast technology (but, on the other hand, it does not use the full potential of the contrast agent, limiting it to its echo-enhancer function).

After reducing MI to $\leq$ 0.1, we can not only keep the integrity of microbubbles but also make them oscillate non-linearly (initial compression followed by expansion) and resonate, emitting different frequencies (known as "harmonic frequencies") from the fundamental one emitted by the transducer. Equipment with this technology can filter signals emitted specifically by microbubbles, leading to a more lasting study that highlights microbubble over tissue signal (virtually nulled in the image, appearing as a dark background).

This type of study, also called "contrast study with low MI", allows the examiner to evaluate the contrast wash-in continuously in the local studied, the enhancement period, and the concentration of microbubbles in the target structure [essential for situations such as the study of vessels of vessels (*vasa vasorum*), carotid plaques, renal capillary (perfusion) distribution, and masses].[124]

An undesired effect of the contrast study with low MI is the depth limitation of the pulse wave, which undergoes greater attenuation as it moves through tissues. Some ways to minimize this effect are: adopting alternative acoustic windows that allow closer proximity with the structure of interest, using broadband transducers with lower frequencies, and, as a last resort, increasing the MI and consequently destroying more bubbles in the proximal field.[128]

8.2.2. Image Gain

A noteworthy equipment control in the contrast study is the image gain, which amplifies the signal received during the post-processing in the equipment. High gain produces a bright image and widespread increase in background noise, obscuring the contrast signal (once the saturation level of the equipment has been reached, there will be no margin to amplify the signal caused by contrast). Therefore, during the contrast study, the equipment gain should be reduced until the image is virtually black, except for highly echogenic structures. Some manufacturers have gain adjustment controls for contrast studies that can easily be turned on and off during the examination.

When performing a manual adjustment, make sure to have the least amount of acoustic signals before contrast injection and understand if this signal results from an increase in MI (when specific structures are seen in the image) or gain (which causes a widespread rise in noise across the image).[6]

8.2.3. Contrast Level

A last technical aspect worth mentioning is the dose of contrast injected. High doses initially blur (saturation) the

signal and attenuate (acoustic shadowing) structures in the distal field until contrast concentrations drop to a proper level. In addition, distinguishing small enhancing differences between structures is not possible, given that the upper limit of dynamic range (grayscale) of the equipment has been exceeded.[128] One way of highlighting different enhancing levels caused by contrast in a structure is to adjust the dose of contrast to allow adequate opacification, without blurring or attenuation, and increase the dynamic range of the equipment. In turn, low doses will not reach the opacification level desired.

8.3. Indications for Contrast in Vascular Ultrasound

Table 28 lists the main indications for microbubble contrast agents in US studies of different vascular systems (consensus of the European Federation of Societies for Ultrasound in Medicine and Biology, published in 2011).[129] The levels of evidence, based on multicenter and/or single-center studies, were classified as A (good), B (moderate), and C (recommended by expert consensus).

8.4. Preparation, Application, and Dose of Microbubble Contrast

SonoVue® is a kit that includes: a vial with 25 mg of lyophilized powder in an atmosphere of sulfur hexafluoride; a syringe filled with 5 ml of sodium chloride 9 mg/ml (0.9%) solution; a transfer system. The contrast is easy to prepare at the bedside, following the manufacturer's instructions. After transferring the content of the syringe to the vial with powder, shake it for 20 seconds to create microbubbles and transform the saline solution into a milky suspension (indicating homogeneous microbubble distribution). In this state, the suspension can be stored for up to 6 hours. If microbubbles accumulate on the surface during rest, shake the solution again, so the microbubbles regain homogeneous distribution before use.

The usual route of administration is by intravenous bolus injection in a vessel with caliber suitable for puncture with a needle of 20G in diameter (preferably in the antecubital fossa). Administer a small initial volume, followed by a flush of 5 ml of saline solution at 0.9% to push the contrast agent into the central vein (which happens in seconds).

In most publications, the recommended dose for a single injection in VUS studies is 2.4 ml, ranging from 1 to 4.8 ml, according to the organ studied, the probe used, and the sensitivity of the equipment available (always remembering that probes with higher frequencies need higher doses, in this case, 4.8 ml).[7] The first 10 to 40 seconds after bolus injection correspond to the contrast enhancement curve (wash-in and wash-out) and should be continuously recorded for later analysis. In some specific situations, such as the study of late endoleaks, the period of evaluation can reach 5 minutes; in these cases, shorter videos can be recorded. Bear in mind that the higher the MI, the greater the destruction of bubbles, and shorter the duration of contrast. After the bubbles burst, the lungs quickly (2 minutes) and fully eliminate the sulfur hexafluoride (Anvisa).

SonoVue® is a safe agent, with a low complication rate. Reports of anaphylactic reaction correspond to < 0.002% of cases.

Table 28 – Indications for contrast agents in vascular ultrasound

System	Application	Level of evidence	Probe
Carotids	Occlusion or subocclusion	B	Linear
	In-stent stenosis	B	
	Dissection	C	
	Plaque neovascularization	B	
Aorta	Dissection, extension of the flap to branches, false lumen patency, re-entry points, and perfusion level of branches that originate from false lumen	C	Convex abdominal or sector cardiac
	Differentiation between an inflammatory aneurysm and contained rupture	B	
	Endoleak	A	
Intracerebral vessels	Signal increase in unsatisfactory basal study	A	Sector cardiac
	Perfusion in ischemic CVA	C	
Complications in vascular accesses	Arteriovenous fistulas	C	Linear or convex abdominal or sector cardiac
	Pseudoaneurysms, hematomas	C	
Kidney	Signal increase in the renal artery	C	Convex abdominal or sector cardiac
	Renal perfusion	C	
Lower limbs	Obstructive atherosclerotic disease (assessment of collateral circulation and microcirculation)	C	Linear or convex abdominal
	Deep venous thrombosis (signal improvement and inflammatory reaction in perithrombus)	C	

CVA: cerebrovascular accident.

8.5. Basic Protocol for Vascular Ultrasound with Microbubble Contrast

After defining the indication for microbubble contrast in VUS examination, follow the mandatory basic routine:

• Repeat and record the standard CDUS examination of the organ of interest

• Secure venous access for injection of contrast solution with microbubbles (peripheral vein puncture or deep vein already in use)

• Prepare the contrast solution with microbubbles (SonoVue®) following the manufacturer's instructions

• Activate the specific image component for contrast in US equipment; if there is no specific software, adjust MI (< 0.6 and the closest possible to 0.1), image gain (darken the background), and choose the appropriate windows to reduce the depth of the target-organ under study

• Administer the contrast solution, make adjustments to reduce excessive enhancement, and record digital images (videos) for 10 to 40 seconds after the initial bolus injection; in specific longer examinations, record the necessary videos during the procedure (which can reach 5 to 8 minutes) for later analysis.

Note: analysis of examination with microbubble contrast is fundamentally dynamic and the duration of the study is short due to the fast destruction of microbubbles by US waves, even when using very low MI. Thus, recording it in digital media is essential for later processing and careful review of images, ensuring a safe diagnosis and permanent storage of results.

8.6. Limitations of the Use of Contrast in Vascular Ultrasound

• Inexperience of the examiner (proper training in ultrasound with contrast is crucial for an effective and safe diagnosis).

• Equipment without a specific software for image with contrast makes it difficult (but not impossible) to conduct a conclusive examination.

• Access to microbubble contrast in units of the Brazilian public health system.

• Complete lack of "window" that allows US transmission to the organ of interest (rare).

• Hypersensitivity to microbubble contrast (rare).

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Statement