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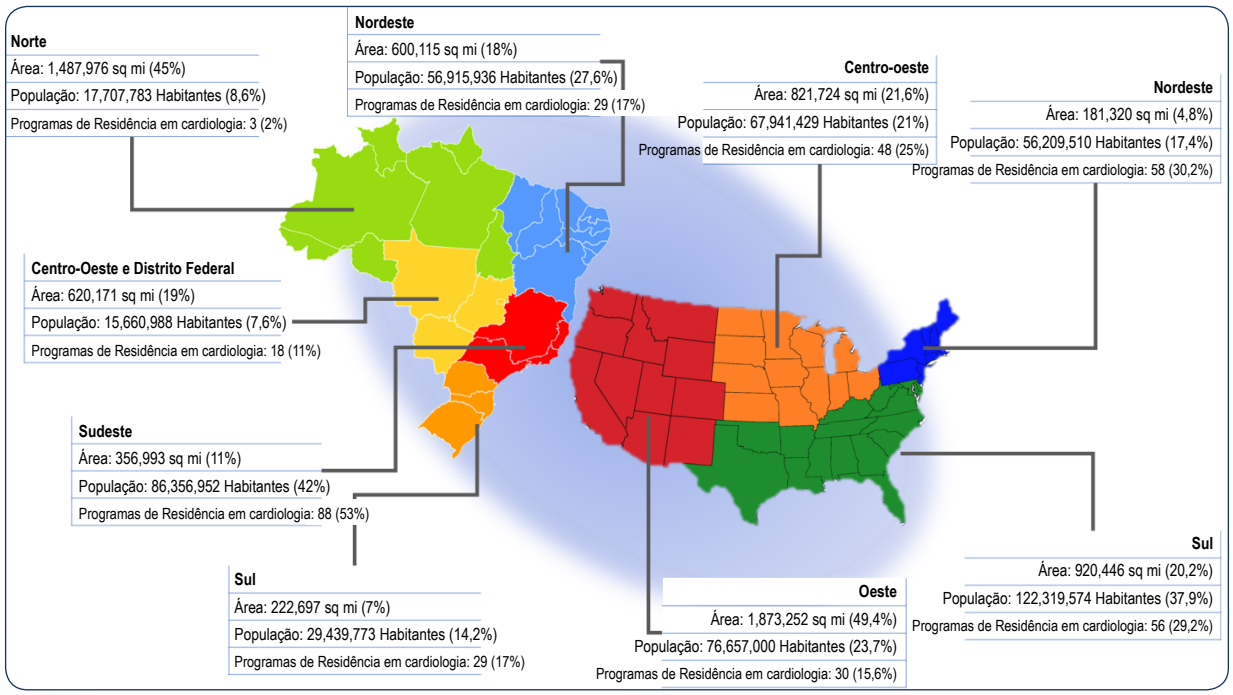

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Behavioral Economics and Innovation Uptake: Building New Capabilities to Overcome Barriers to Technology-Enabled Care

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Introduction

The Federal Medical Council (CFM) has recently published a new resolution on telemedicine in Brazil. The 2227/2018 resolution, establishing the criteria for the use of telemedicine, was published in *Diario Oficial da União* (DOU, the official journal of the federal government of Brazil) on February 6, 2019.[1] This new policy, aimed at defining telemedicine as a way of providing medical services by means of technology, is much more aggressive than the previous one published in 2002, which limited the use of telemedicine to medical consultations made by telephone or internet, and implied the presence of a health professional at both ends of the communication channel. The current resolution expanded the concept of telemedicine in providing technological solutions for remote patient monitoring and treatment (drug prescription and surgical interventions), and analysis of laboratory results. However, soon after its release, the new document caused an intense public debate on the theme dividing stakeholders for and against the incorporation of telemedicine into practice nationwide. The debate was so intense that the Federal Medical Council revoked the resolution, as published in the DOU on March 6, 2019.[2]

The revocation of the policy after intense societal debate indicates the significant challenges regarding the implementation of technology-enabled care in Brazil. Such debate should not be the end, but rather, the beginning of a social mobilization to reframe the use of connected technology in healthcare in the country. To tackle the barriers to the uptake of technology-enabled care in Brazil, one should better understand the stakeholder positions, and consider the political and cultural environment, the ethical and legal apparatus and the available technology infrastructure.[3]

A more comprehensive understanding of the contemporary scenario where technology-enabled care may fit into Brazilians' needs is critical to suggest approaches that might lead to societal benefit while being acceptable by physicians and other stakeholders.

Keywords

Telemedicine/economics; Telemedicine/legislation and jurisprudence; Telemedicine/trends; National Health Science, Technology and Innovation Policy; Telemedicine/methods

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Objectives

This is an exploratory paper, aiming to provide a personal overview of potential barriers to the incorporation and dissemination of telemedicine in Brazil. It is also an objective to discuss potential approaches to overcome these barriers.

A) Analysis of the stakeholders

A.1) The State and Telemedicine - The Government as a stakeholder

From the political point of view, government initiatives concerning telemedicine have been led primarily by the Brazilian Ministry of Health and were designed to promote the use of telemedicine in the expansion and improvement of health services. The dimensions involved, however, are beyond the limits established by the Ministry of Health. An effective inter-ministerial action would be required to foster the economy (innovation and economic efficiency) and the social dimension (interest of the population and equality) to leverage telemedicine towards the expansion and improvement of healthcare.

A.2) Challenging the "status quo" - Providers as stakeholders: institutions, physicians and other practitioners

Culture is another limiting factor in the dissemination of telemedicine from the perspective of institutions, physicians and other practitioners. From the need for adjusting to the new working process, to the challenging relationship between power structure and professional structure, the adoption of the latest technology may generate significant resistance. The resistance to change is strengthened by the risk aversion[4] and uncertainties that are commonly related to the introduction of a "new way of doing things". On the one hand, technology-enabled care may help overcome the obstacle of access posed by the distance (especially in a continental-dimension country like Brazil) with expected gains with the information and communication technologies, *i.e.*, by increasing access and reducing costs. However, the interdependence between telemedicine and health services organization in guiding new investments may cause a shift in the arena of power. These complexities and uncertainties pose a substantial barrier to the dissemination of the new technologies.

Likewise, telemedicine faces resistances from practitioners.[2] Telemedicine involves multidisciplinary players, encompassing health practitioners of diverse disciplines, information and communication technology experts, managers and policy makers. The adoption of this technology requires the redesigning of work processes in their multiple aspects that generate tensions and conflicts.

Physicians, in general, are not trained to be part of a "real team" and tend to behave more like a chairperson, which can increase the tension among team members. Moreover, telemedicine changes the typical doctor-patient relationship, requiring a process of acceptance, by all, of the technological mediation. Beyond that, physicians believe that these technologies may constitute an unsafe medical practice, in part due to the infeasibility in performing a remote physical examination. Overcoming institutional and professional cultural barriers is an essential step in the process of telemedicine dissemination and consolidation. Finally, reimbursement is another issue; physicians feel they will be pressured to care for more patients, dedicating less time to each patient, with lower reimbursement rates.

A.3) Patients: what do they want? Are they willing to trade off? Consumers as stakeholders

From the patient perspective, although telemedicine may add distinct value to their needs and cheaper access to healthcare, as a health consumer, they may fail to buy the "innovative product" because it may require them to change their behavior.[5] Although it may be cheaper in financial terms, there are psychological costs associated with behavior changes: people irrationally overvalue benefits they currently possess relative to those they do not.[6]

B) Behavioral economics and innovation uptake

The understanding of the psychology of gains and loss, and more deeply, the concepts of loss aversion, *status quo* bias, and the endowment effect,[4,6] associated with why the adoption of innovation fails[5] may help propose specific solutions where telemedicine may be acceptable by providers and wanted by patients.[7] Examples of approaches regarding telemedicine that might lead to societal benefit while being fair to physicians are described below:

B.1) To make behaviorally compatible products: the development and incorporation of mobile health sensors may offer a sense of safety that is missing to remote physicians. If one can rely on such type of device for feedback of a "remote" physical examination, physicians would feel more secure in guiding and discussing about a patient's condition using technology mediation. This may minimize physicians' resistance to telemedicine.

B.2) Seek out the deprived individuals (the ones with no access to healthcare): telemedicine has the potential of solving significant current health challenges. In addition to the Brazilian territorial extension, there are thousands of isolated, difficult-to-access locations where healthcare services are extremely scarce, and physicians are lacking. Some physicians are mandated to serve in remote areas (military physicians). Fostering the development of the required infrastructure for the establishment of telemedicine in remote areas will open the doors for communities to have access not only to healthcare but also to other resources (like education). This will promote secondary gains as enhancing local and regional economic progress and may attract physicians and their families to places that otherwise would not be the first choice to live.

B.3) Find believers (Millennials): According to Ripton,[8] millennial generation has been changing healthcare by forcing a greater emphasis on technology solutions for healthcare delivery. The development of technology-enabled solutions targeting this population may speed up and sustain the adoption of telemedicine not only in Brazil but also in other countries. The millennials' demand will force physicians to adapt (and incorporate) to technology-enabled care, to be competitive in the market.

B.4) Strive for 10x improvements[5]: telemedicine benefits should be so great that it would overcome physicians and patients' overweighing of potential losses. Besides adding efficiency and reducing costs, telemedicine has the potential to expand the actions of health practitioners, integrating them into healthcare services and systems. Also, one can explore the potential savings and share them with practitioners in a new type of employment relationship and reimbursement model that may improve acceptance of telemedicine among physicians while promoting societal benefits.

C) Other considerations

C.1) Ethics and legal issues in the digital age: is technology changing faster than expected?

Besides what has been discussed above, there is also a lack of synchronization between the vast potential of these technologies and the prevailing ethical and legal apparatus. Contrary to a comprehensive national policy, there is a general scenario of fragmentation, characterized by different norms and standards issued by various bodies and with distinct focuses.[3] Even though a single instrument would hardly reach these goals, the fragmentation is one more hurdle to overcome to achieve the potential of telemedicine.

C.2) Infrastructure – Are humans slower than expected?

Also, mention should be made of the scarcity of resources and technical expertise, as well as infrastructure issues. Brazil has unequal geographic distribution concerning broadband availability.[3] This means the infrastructure of the broadband data network is one of the most limiting factors to the expansion of telemedicine, particularly, in the countryside of Brazil.

C.3) Health services in Brazil

Finally, it should be mentioned the precariousness of health services in Brazil, including primary care facilities, outpatient clinics, and even specialized hospital services. Scarce resources, management problems, lack of practitioners, inadequate compensation, outdated facilities, lack of equipment and consumables, among many other aspects, are repeatedly mentioned as the leading causes of such precariousness, witnessed by health professionals and users. This is even worse

in remote and peripheral areas and is a significant barrier to the dissemination and consolidation of telemedicine in Brazil.[3] Therefore, even with the implementation of all technological infrastructure required for telemedicine, which is typically an interdisciplinary activity, it would not guarantee an improved and more expanded access to healthcare.

Conclusion

The primary characteristic of telemedicine is its ability to make access to health services democratic. To accomplish that, legislative initiatives (economic and social) that support and encourage the use of this technology, a regulatory apparatus, mobilization of a core group of companies, and development of scientific capability are required. From the healthcare perspective, telemedicine is capable of promoting higher integration of the healthcare system, overcoming the still existing and deleterious fragmentation that prevents the access to full healthcare rights. Investments in infrastructure are mandatory to widespread adoption of telemedicine. Beyond that, other challenges that limit its development are most related to the stakeholder's conflicts, interdependence, and demands. In this regard, understanding some of the concepts related to behavioral economy and innovation uptake failure may increase or create opportunities and approaches where the use of technology-enabled care might lead to societal benefit while being acceptable to physicians and other stakeholders.

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Evaluation of Serum Levels of Inflammation, Fibrinolysis and Oxidative Stress Markers in Coronary Artery Disease Prediction: A Cross-Sectional Study

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Abstract

Background: **Coronary Artery Disease (CAD) has long been recognized as a global health issue. Inflammation, Fibrinolysis and Oxidative Stress play an important role in the disruption of plaques leading to CAD. Markers that reflect this pathophysiologic mechanism may have prognostic value.**

Objective: **To estimate the serum concentrations of high-sensitivity C-reactive protein (hs-CRP), sialic acid (SA), vitronectin (VN), plasminogen activator inhibitor-1 (PAI-1), oxidized low density lipoprotein (OX-LDL) and malondialdehyde (MDA) with significant prognostic value in patients with CAD.**

Methods: **The markers included, hs-CRP, SA, VN, PAI-1, OX-LDL and MDA, were compared between 160 angiographically diagnosed CAD patients and 20 age- and sex-matched healthy individuals. The subjects were divided into 4 groups according to angiography results, and association between all risk factors of CAD was studied. Serum levels of SA, VN, PAI-1, and OX-LDL were measured by enzyme-linked immunosorbent assay (ELISA); MDA was measured based on reaction with thiobarbituric acid (TBA); and hs-CRP level was estimated by immunoturbidimetry using a commercial kit. The diagnostic value of these variables was further assessed by ROC curve analysis. Multiple logistic regression was used to evaluate the diagnostic power of the combination. Furthermore, $p < 0.05$ was considered as significant.**

Results: **Serum levels of hs-CRP, SA, VN, PAI-1, and OX-LDL were significantly higher in patient groups compared to control group ($p < 0.001$). Using both normal and CAD patients as subjects, ROC analysis was performed. The cutoff for OX-LDL, MDA, PAI-1, VN, hs-CRP and SA was 2.67 (ug/mL), 5.49 (mmol/mL), 67 (ng/mL), 254 (ng/mL), 3.4 (mg/dL), 7/89 (mg/dL), respectively. Eventually, the complete diagnostic efficacy was classified as: SA, hs-CRP, PAI-1, OX-LDL, MDA and VN.**

Conclusion: **Serum levels SA, hs-CRP, VN, PAI-1, OX-LDL and MDA may be predictive of adverse cardiovascular outcomes. Interestingly, these analyses can help as diagnostic and monitoring markers in CAD patients. (Arq Bras Cardiol. 2019; 113(4):667-674)**

Keywords: **Coronary Artery Disease; Biomarkers; Inflammation Fibrinolysis; Oxidative Stress; Sialic Acids; Vitronectin.**

Introduction

Atherosclerotic coronary artery disease (CAD) remains one of the world's major health problems, accounting for 12.7% of global mortality.[1] As we know, atherosclerosis is known as a chronic inflammatory process that is initiated with the dysfunction or activation of the arterial endothelium. Moreover, endothelial damage and reactive oxygen species (and other free radicals) have emerged as main factors in practically all pathways that lead to the development of atherosclerosis.[2] Risk factors identified recently that are related to pro-atherogenic cardiovascular disease include those associated with impaired coagulation or fibrinolysis, cardiovascular remodeling and inflammation.[3] Notably, increase in plasma levels of risk markers for atherosclerotic cardiovascular disease have been recognized to play an important role in both the onset and the progression of atherosclerotic plaque. These prognostic markers may assist in therapy to match the intensity of the patient's disease.[4-8]

Remarkably, Vitronectin (VN) is present in plasma, extracellular matrix, and granules of blood platelets. It consists of adhesive glycoproteins, which play a key role in the regulation of processes such as platelet adhesion, aggregation and clotting, via binding to integrin, plasminogen activator inhibitor (PAI-1), urokinase plasminogen activator receptor (UPAR), and heparin.[9,10] In spite of that fact, plasma VN levels were significantly increased in patients with CAD, also showing a positive correlation with severity of the disease.[11] Notably, PAI-1 has been recognized as

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a central molecule linked to pathogenesis and progression of thrombotic vascular events, including stroke. In addition, elevated plasma PAI-1 levels are associated with vascular thrombosis.[12] A previous study suggested that high levels of PAI-1 in CAD are associated with the risk of endothelial dysfunction and premature atherosclerosis.[13] Sialic acid (SA) is derivative of neuraminic acid, and comprises the terminal sugar part of the oligosaccharide chain in glycolipids and glycoproteins, acting as a cofactor in several cell surface receptors, such as LDL receptor. Its intake of LDL occurs prominently in smooth muscle cells of blood vessels and is increased in several pathological and inflammatory states, such as in atherosclerosis.[5,14,15] Therefore, following an inflammatory reaction or injury, desquamating or secretion from damaged cells can lead to an elevated concentration of SA.[16] Oxidative stress and inflammation also play vital roles in the pathogenesis and progression of CAD.[6] Oxidized low density lipoprotein (OX-LDL) and correlated composites are also observed in lesion formation at the later stages of atherosclerosis. Hence, OX-LDL could play a major role in both atherogenesis and plaque complications.[17,18] Additionally, malonaldehyde (MDA) results from lipid peroxidation, and its measurement is an undependable marker of oxidative damage, making MDA a suitable indicator and marker for identification and further evaluation of patients with CAD.[17] Among several markers of inflammation, highly sensitive C-reactive protein (hs-CRP) has been established as significant in people with CAD. Several studies demonstrated that hs-CRP is associated with increased CAD risk.[19] Previous findings reported elevated VN, MDA, OX-LDL, PAI-1, hs-CRP and SA levels, which were positively correlated with CAD. Although the pathological aspects of these risk factors have been studied, their role has not been recognized in the early and accurate diagnosis of atherosclerosis in patients with CAD. This study aimed to determine concentrations of the prognostic value of serum levels of hs-CRP, SA, VN, PAI-1, OX-LDL and MDA in patients with CAD, all of which can manifest in CAD, in an effort to examine the importance of combining these biomarkers with the diagnosis of CAD.

Methods

Subjects

The sample size was 180 subjects, based on a convenience sample. The subjects were divided into 4 groups according to angiography results. The control group was a no Stenosis group which included 40 subjects with non-significant disease that had no clogged vessels but suffered from chest pain such as angina pectoris; 40 with single occluded vessel disease (1VD); 40 with double occluded vessel disease (2VD); and 40 individuals with triple occluded vessel disease (3VD). In addition, the control group was composed of healthy individuals without any presentation of CAD (n = 20). Peripheral blood sampling was obtained after one night of fasting in the Shahid Madani hospital, located in East Azerbaijan, Iran.

Ethics

Before the beginning of the study, the protocol was presented to the independent ethics committee of the Medical Faculty of the Tabriz University of Medical Sciences (ethics number 91/2-3/5). An informed consent was obtained from all of participants. All patients with the renal disease, lung disorders, liver dysfunction, autoimmune disease, infectious diseases and cancer were excluded from the study.

Laboratory methods

All blood samples were obtained from a peripheral vein after 12 hours of overnight fasting. Subsequent plasma and serum were separated within 30 minutes, and samples were stored at –70°C until the tests were performed.

Measurement of parameters

Enzyme-linked immunosorbent assay (ELISA) procedures were used to determine serum levels of OX-LDL (Glory Science co. Ltd, Cat. No: 93614), PAI-1 (Boster Science co. Ltd, Cat. No: EK0859) and VN (Glory Science co. Ltd, Cat. No: 11668). SA was also measured by ELISA, using a commercial kit (Crystal Day, China). Serum MDA was measured based on reaction with Thiobarbituric Acid (TBA); extraction accompanied with normal butanol; absorption measured by spectrophotometer and value calculated according to a standard curve. Serum levels of hs-CRP were estimated by high-sensitivity turbidimetry method using Biosystems kit (Barcelona, Spain, COD 31927); the assay was evaluated on semi-autoanalyser (Alcyon 300, made in USA) in the Biochemistry lab.

Analytical methods

All statistical analyses were carried out using SPSS software, version 20.0 (SPSS Inc., Illinois, USA). All quantitative variables were expressed as mean ± standard deviation or median and interquartile range. The qualitative variables were expressed in numbers and percentage. The normality of the data was evaluated by the normal curve (skewness and standard deviation of skewness) of Kolmogorov-Smirnov test. Differences for multiple groups were analyzed using independent t-test, and one-way analysis of variance (ANOVA). Also, the chi-square test was used for categorical variables. The Kruskal-Wallis test was used for the quantitative variables if the normality assumption of the residuals was not met. Moreover, ROC curve analysis was used to evaluate the diagnostic effect of VN, MDA, OX-LDL, PAI-1, hs-CRP and SA by logistic regression model. A statistical analysis was defined when $p < 0.05$.

Results

The prognostic indicators were used in the current study. Table 1 lists the general characteristics of the study groups. Differences between patient and control groups based on age and sex distribution were subject to an independent-samples t-test. The results showed that there were no significant differences between the groups ($p < 0.3$). However, smoking, hypertension and diabetes showed significant difference between the patient and control groups (p value: 0.004, 0.01, and 0.02, respectively). Table 2 represents group mean parameter values obtained from a one-way ANOVA analysis; the mean serum levels of parameters that have been compared among subgroups were categorized based on number of occluded vessels of study population. Significant differences in all cardiovascular risk factors measured

Table 1 – General characteristics of the study groups

Characteristic	Control	No Stenosis	1VD	2VD	3VD	p value
Sample size	20	40	40	40	40	-
Age(mean(SD))	57.5(3.2)	58.80(7.5)	58.9(7.9)	61.0(11.8)	60.5(10.5)	0.37*
Sex(male/female)	17/3	21/19	31/9	30/10	25/15	0.30**
Smoking (N (%))	0(0%)	13(32.5)	19(47.5)	16(40)	24(60)	0.004**
Hypertension (N (%))	0(0%)	25(62.5)	26(65)	12(30)	19(47.5)	0.01**
Diabetes (N (%))	0(0%)	7(17.5%)	11(27.5%)	12(30%)	15(37.5%)	0.02**

** One-way analysis of variance; ** Chi square test.*

Table 2 – Comparison of the mean serum levels of cardiovascular risk factors among subgroups categorized based on number of occluded vessels of CAD patients

p Value	3VD	2VD	1VD	No Stenosis	Control	Variable
0.001*	3.13 ± 0.42	2.76 ± 0.38	2.62 ± 0.27	2.28 ± 0.32	1.41 ± 0.22	OX-LDL (ug/mL)[1]
0.001*	7.12 ± 1.21	6.39 ± 0.66	5.25 ± 0.98	5.20 ± 0.44	4.32 ± 0.86	MDA (mmol/mL)[1]
0.001*	86.8 ± 6.8	76.9 ± 4.7	75 ± 14.2	51.5 ± 10.8	41.7 ± 11.9	PAI-1 (ng/mL)[1]
0.001**	361 (95.75)	264 (100.75)	304 (184.25)	208 (61.75)	200 (26)	VT (ng/mL)[2]
0.001**	5.23 (1.05)	7.53 (0.86)	5.21 (0.39)	1.52 (1.03)	2.54 (0.78)	hs-CRP (mg/dL)[2]
0.001*	169.9 ± 15.3	138.3 ± 12.3	108.6 ± 9.2	60 ± 11.6	51.0 ± 5.0	SA (mg/dL)[1]

*OX-LDL: oxidation of low-density lipoprotein; MDA: Malondialdehyde; PAI-1: Plasminogen Activator Inhibitor; VT: Vitronectin; hs-CRP: high-sensitivity C-reactive protein; SA: sialic acid; 1VD: Stenosis in one of vessels; 2VD: Stenosis in two of vessels; 3VD: Stenosis in three of vessel. [1] Mean ± standard deviation; [2] Median (inter quartile range). * Performed by ANOVA test. ** Performed by Kruskal-Wallis test.*

were found in all subgroups compared to controls ($p < 0.001$ for all of them). Moreover, there were significant differences among subgroups that were not mentioned (previously reported in other references).[11,20,21] The critical values of VN, MDA, OX-LDL, PAI-1, hs-CRP and SA levels were determined by ROC curve analysis. Both specificity and sensitivity of these six parameters in CAD were compared. A combined assay was then performed, using six indexes. In addition, using both healthy individuals and CAD patients as subjects, ROC analysis was performed, which showed the areas under the curve for OX-LDL, MDA, PAI, VN, hs-CRP and SA (0.870, 0.804, 0.951, 0.799, 0.962 and 0.971, respectively). All risk factors had satisfactory diagnostic efficacy for CAD. The overall rank of efficacy was (from lower to higher): VN, MDA, OX-LDL, PAI-1, SA and hs-CRP. PAI-1, SA and hs-CRP had particularly high validity in the diagnosis of CAD (Figure 1 and Table 3). Notably, the criteria of variables were specified with reference to appearance levels in both healthy individuals and CAD patients, Cutoff for OX-LDL, MDA, PAI1-, VN, hs-CRP and SA were 2.67 (ug/mL), 5.49 (mmol/mL), 67 (ng/mL), 254 (ng/mL), 3.4 (mg/dL), 7/89 (mg/dL), respectively. The sensitivity and specificity were 70% and 75%, 74% and 77 %, 92% and 90%, 70% and 83%, 94% and 93%, 94% and 96%, respectively. PAI1-, SA and hs-CRP had the highest sensitivity and specificity in the test, compared to OX-LDL, MDA and VN (Table 4). The efficacy of the combined assay was then compared using six parameters (OX-LDL, MDA, VN, PAI1-, SA and hs-CRP). Such combined assay increased the predictive value of sensitivity and specificity to 99% and 99%, respectively (Table 5). The area under ROC curve was 0.99 (95% CI: 0.975∼1.005, Figure 2).

Discussion

Commonly, major risk factors causing atherosclerotic lesions in human coronary arteries comprise genetic factors, hyperlipidemia, diabetes, infections, hypertension or oxidative stress, with little correlation with patients' age and environmental factors.[22] It is noteworthy that this pathological process includes macrophages and smooth muscle cells (SMCs), with addition and deposition of lipids and extracellular matrix proteins, especially glycoprotein.[22,23] Previous studies confirmed that serum levels of VN, PAI-1, OX-LDL, MDA, hs-CRP and SA are significantly higher in CAD patients compared with healthy controls and positive correlation with severe diseases. A climb in these analyses in patients with CAD when compared to controls is already well distinguished in recent studies.[11,20,21,24] The present study considerably assessed the prognostic value of glycoprotein, fibrinolysis, oxidative stress and inflammatory biomarkers including VN, PAI-1, and OX-LDL, MDA, hs-CRP and SA in patients with CAD.

Remarkably, VN is a multifunctional plasma glycoprotein with a multiple binding domain, which regulates processes such as platelet adhesion, aggregation and clotting. Besides, VN can be expressed and produced in the vessel wall, predominantly in atherosclerotic lesions.[25] Later studies showed that PAI-1 stimulates VN expression in SMCs by binding LDL receptor-related protein-1 (LRP1), and controls vascular VN expression in vivo. Therefore, autocrine regulation of vascular VN expression by PAI-1 may play important roles in vascular homeostasis and pathologic vascular remodeling.[26]

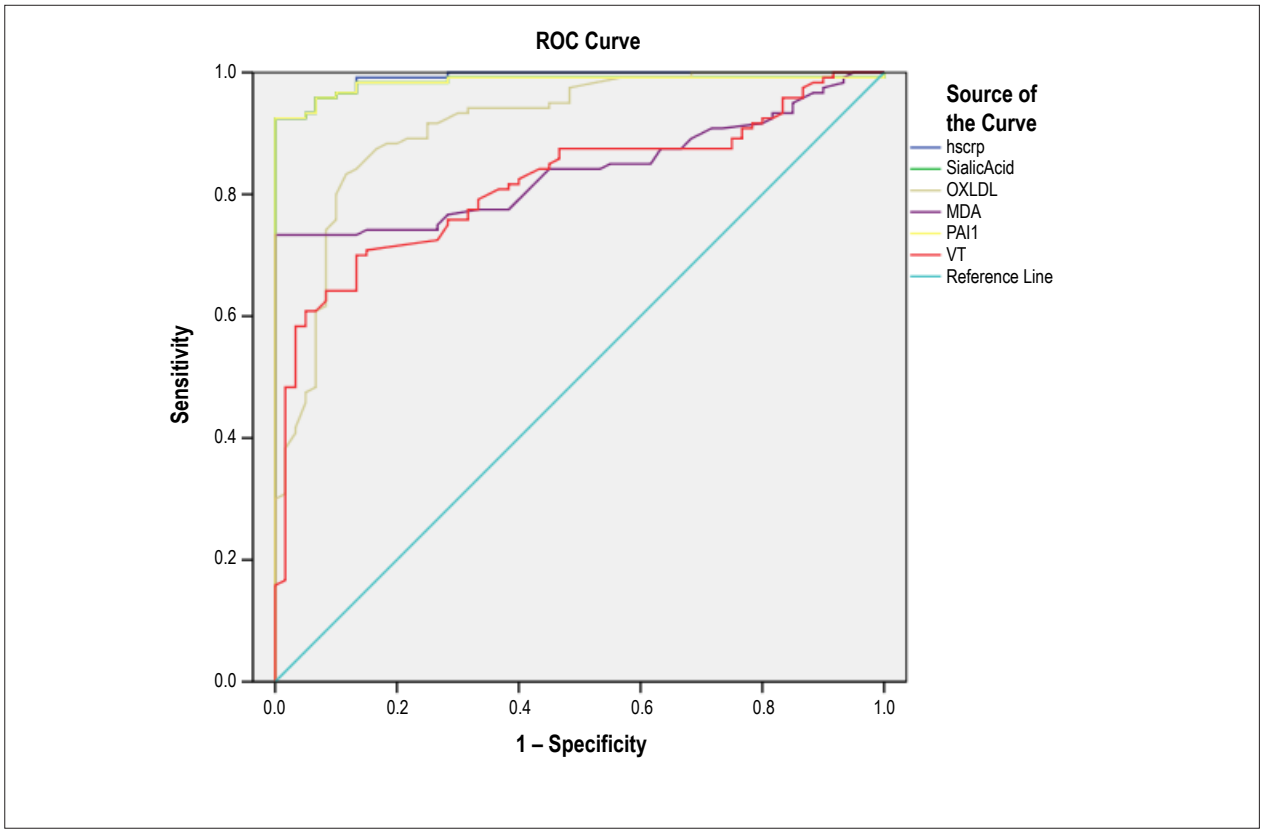

Figure 1 – *ROC analysis of VN, MDA, OX-LDL, PAI-1, hs-CRP and SA. VN: vitronectin; MDA: malondialdehyde; OX-LDL: oxidized low density lipoprotein; PAI-1: plasminogen activator inhibitor-1; hs-CRP: high-sensitivity C-reactive protein; SA: sialic acid.*

Several studies have found a regulatory function for VN in the hemostatic response to vascular injury.[9] Also, VN binds PAI-1 and adjusts its action by stabilizing the active PAI-1 conformation, and potentially controls PAI-1 clearance.[27] Serum levels of VN were found to be increased patients with CAD when compared with controls.[9,11] Derer et al.[26] suggested that VN is a clinically useful biomarker for unfavorable cardiovascular outcomes in patients following acute stenting undergoing coronary interventions.[26] Therefore, VN may serve as a marker for CAD, and elevated levels may indicate its role in the diagnosis and/or progression of CAD. Notably, there is suggestion that high plasma PAI-1 concentrations are related with the progression of coronary syndromes and the development of myocardial infarction.[26,28] Clinical and experimental studies demonstrated that PAI-1 deficiency in humans is accompanied by abnormal bleeding, whereas elevated PAI-1 plasma levels are associated with vascular thrombosis, indicating the crucial role of PAI-1 in hemostatic clot stabilization.[13] Moreover, previous studies have shown that PAI-1 is significantly elevated in CAD patients in comparison to controls, and it has also a significant relationship with severity of the disease.[20,29] In addition, it was reported that PAI-1 is an independent predictor of coronary microvascular dysfunction in hypertension.[30] Our results suggested that prominent levels of PAI-1 concentrations may predict and be a diagnosis marker for CAD.

Furthermore, oxidative stress has an important role in the beginning and progression of atherosclerosis. OX-LDL is more atherogenic than the native LDL, and has been recognized to accumulate in atherosclerotic lesions in the aorta and coronary arteries of patients with CAD.[2,8,17] Additionally, MDA is produced from breakdown of lipids during peroxidation processes, and serum MDA is a reliable marker of oxidative damages. Previous findings also have confirmed the involvement of lipid peroxidation in CAD by referring to the plasma levels of MDA observed in CAD patients compared with healthy controls. More recent cross-sectional studies demonstrated a positive relationship between elevated levels of OX-LDL and MDA with severity of acute coronary syndromes.[20,31] Ehara et al.[32] reported that the plasma OX-LDL level in patients with CAD increases by approximately 3.5 fold than in control subjects.[32] Remarkably, the findings in this study indicated that both oxidative stress parameters can be used as diagnosis markers of CAD, and the impact of this oxidative stress may progress to an atherosclerotic event. Impressively, in arterial injury accompanied by inflammatory response, inflammation plays a key role in the pathogenesis of CAD and its impediments. Hence, SA and hs-CRP have gained importance as inflammatory markers and as indicators and predictors of the process of acute coronary syndromes.[19,33] Increased production

Table 3 – Area under curve of ROC

Test Variable	Area	SD[a]	p value[b]	Asymptotic 95% Confidence Interval	
				Lower bound	Upper bound
OX-LDL	0.870	0.032	.000	0.806	0.934
MDA	0.804	0.034	.000	0.738	0.869
PAI-1	0.951	0.010	.000	0.921	0.992
VT	0.799	0.036	.000	0.729	0.869
SA	0.962	0.021	.000	0.921	0.998
hs-CRP	0.971	0.032	.000	0.953	0.995

Note: [a]. Under the nonparametric assumption, [b]. Null hypothesis: true area = 0. OX-LDL: oxidation of low-density lipoprotein; MDA: Malondialdehyde; PAI-1: Plasminogen Activator Inhibitor; VT: Vitronectin; SA: sialic acid; hs-CRP: high-sensitivity C-reactive protein.

Table 4 – Diagnostic efficacy of parameters

index	Positive criteria	Sensitivity/%	Specificity/%	False negative /%	False positive/%
SA	≥ 89.7 (mg/dL)	94	96	6	4
hs-CRP	≥ 3.4 (mg/dL)	94	93	6	7
PAI-1	≥ 67 (ng/mL)	92	90	8	10
VT	≥ 254 (ng/mL)	70	83	30	17
OX-LDL	≥ 2.67 (ug/mL)	70	75	30	25
MDA	≥ 5.49 (mmol/mL)	74	77	26	23

OX-LDL: oxidation of low-density lipoprotein; MDA: Malondialdehyde; PAI-1: Plasminogen Activator Inhibitor; VT: Vitronectin; SA: sialic acid; hs-CRP: high-sensitivity C-reactive protein.

Table 5 – Combined assay of PAI-1, VT, OX-LDL, MDA, SA and hs-CRP

Index	Sensitivity/%	Specificity/%
OX-LDL, MDA, PAI-1, SA, hs-CRP	97	95
OX-LDL, MDA, SA, hs-CRP, VN	98	97
OX-LDL, VT, PAI-1, SA, hs-CRP	98	97
VT, MDA, PAI-1, SA, hs-CRP	97	97
OX-LDL, MDA, PAI-1, VT, SA, hs-CRP	99	99

OX-LDL: oxidation of low-density lipoprotein; MDA: Malondialdehyde; PAI-1: Plasminogen Activator Inhibitor; VT: Vitronectin; SA: sialic acid; hs-CRP: high-sensitivity C-reactive protein.

of isolated acute phase reactants increases the SA levels. SA is associated with atherosclerosis independently of other cardiovascular risk factors.[15] Previous studies have reported total serum levels of SA that were high in patients with acute coronary syndrome when compared to healthy controls.[34] Specifically, Govindarajan et al.[14] showed that the total plasma SA level was significantly higher in patients with myocardial infarction than in those with unstable and stable angina. In a recent 17-year follow-up study, elevated serum levels of SA were found to be predictive of cardiovascular events in apparently healthy individuals.[35] In addition, several studies suggested a positive relation between hs-CRP and CAD among healthy individuals.[36,37] Mahajan et al.[38] found a relation between inflammatory markers and coronary artery involvement on diabetic patients suffering from early onset CAD.[38] In addition, many evidences have indicated that hs-CRP is a cautiously sensitive systemic marker for diagnosis of inflammation and a useful and potent predictive marker of cardiovascular events.[11,39] This study has shown that serum hs-CRP and SA levels may be used as predictive or diagnosis biomarkers in patients with CAD.

The findings in this study showed significant elevated serum levels of OX-LDL, MDA, PAI1-, VN, hs-CRP and SA in patients with CAD, when compared to healthy individuals. hs-CRP, SA and PAI-1 had the best sensitivity and specificity, suggesting the value of these biomarkers in patients with CAD diagnosis. ROC curve analysis showed satisfactory diagnostic power of all these six indexes, from highest to lowest: SA, hs-CRP, PAI-1, OX-LDL, MDA, and VN.

This study also considered the diagnostic value of combined assay for all indexes for the best confirmative diagnosis value, including hs-CRP, SA, PAI-1, OX-LDL, MDA, and VN, resulting in elevated sensitivity and specificity values, without significant decrease of negative predictive value. These results supported the complementary role of combined assay in diagnosis of CAD.

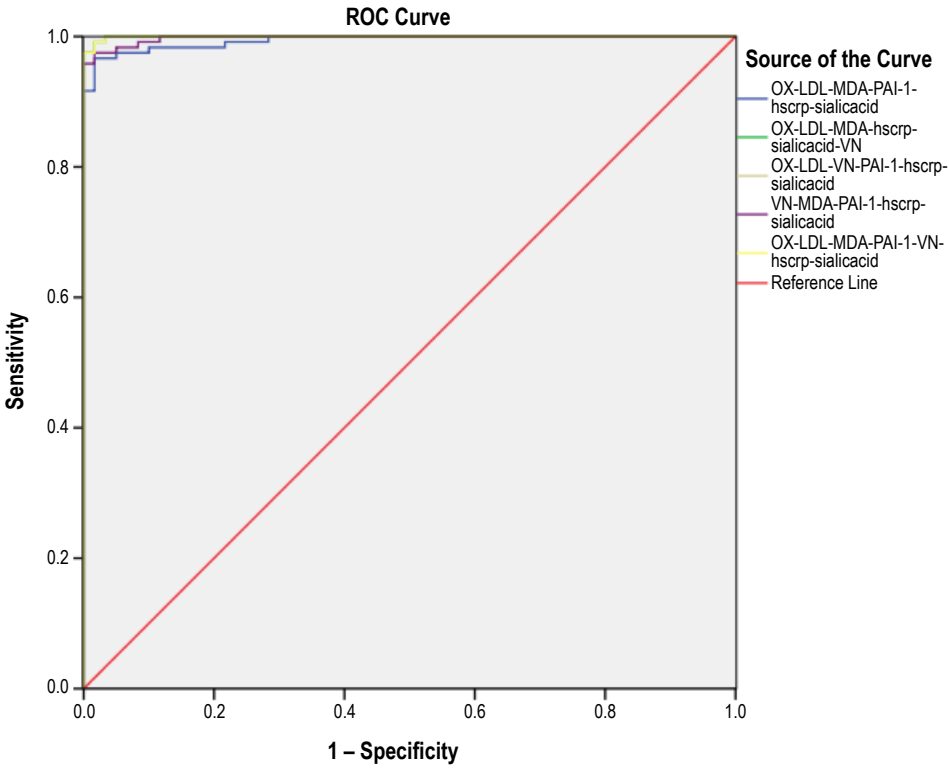

Figure 2 – *ROC curve of combined assay. VN: vitronectin; MDA: malondialdehyde; OX-LDL: oxidized low density lipoprotein; PAI-1: plasminogen activator inhibitor-1; hs-CRP: high-sensitivity C-reactive protein; SA: sialic acid.*

One of limitations of this study is the probability of a non-representative sample, in an attempt to select a random sample, since the hospital is a referral hospital and the patients approached this hospital in special days, which may lead to selection bias.

Also, this study is only cross-sectional, which might not show temporal relationships, and thus the observed associations may not necessarily be causal.

Conclusions

In the present study, high serum concentrations of SA (≥7/89 mg/dL), hs-CRP (≥3.4 mg/dL), PAI-1 (≥67 ng/mL) and increase in OX-LDL, MDA, and VN were found to be independent significant predictors of CAD in patients. In addition, the results suggested that using serum levels of hs-CRP, SA, PAI-1, OX-LDL, MDA, and VN may be helpful in clinical monitoring. The combined assay of serum PAI-1, OX-LDL, MDA, and VN can improve the sensitivity and specificity for diagnosing CAD, and can be used for population screening and for monitoring patients with CAD. Therefore, while we suggest the use of these biomarkers as a diagnostic apparatus for CAD patients, they need to be further explored to confirm this suggestion.

Author contributions

Conception and design of the research and Obtaining financing: Abolhasani S; Acquisition of data: Mahmoodi N; Analysis and interpretation of the data: Shahbazloo SV; Statistical analysis: Saadati HM; Writing of the manuscript: Abolhasani S, Khanbabaei N; Critical revision of the manuscript for intellectual content: Khanbabaei N.

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 Medical Faculty of the Tabriz University of Medical Sciences under the protocol number 91/2-3/5. 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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Evaluation of Serum Levels of Inflammation, Fibrinolysis and Oxidative Stress Markers in Coronary Artery Disease Prediction: A Cross-Sectional Study

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Short Editorial related to the article: Evaluation of Serum Levels of Inflammation, Fibrinolysis and Oxidative Stress Markers in Coronary Artery Disease Prediction: A Cross-Sectional Study

When assessing patients with coronary artery disease (CAD) traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking, stress, physical inactivity, obesity, and family history are not found in 20% of the patients,[1] and up to 40% of patients have only 1 risk factor.[2] Considering the high prevalence of CAD and the fact that despite the numerous efforts made in primary prevention, the disease still has a high incidence, identifying markers that can predict at-risk patients is a goal that should always be pursued.

However, when evaluating a possible marker of disease, it must meet certain criteria. It should identify individuals at risk (accuracy), its results should be the same when repeated in other patients (reliability) and, especially, it should allow early intervention aiming at reducing the incidence of the problem (therapeutic impact).[3]

The discovery and validation model of a biomarker first comprises its detection, followed by its evaluation in patients with and without the disease. Afterwards, retrospective studies are analyzed to determine whether there is a threshold that differentiates cases and controls to detect the test positivity threshold. Subsequently, screening tests are prospectively applied to large cohorts. Finally, the biomarker is validated in a randomized clinical trial.[4]

The present study,[5] using a cross-sectional design, evaluated serum levels of inflammation, fibrinolysis and oxidative stress markers in 4 groups of patients with suspected CAD (3 of them with different degrees of CAD and 1 group without lesions) and 1 control group. The analysis showed that serum levels of high sensitivity C-reactive protein (hs-CRP), sialic acid, vitronectin, plasminogen-1 activator inhibitor, and oxidized low-density lipoprotein (Ox-LDL) were significantly higher in the CAD groups than in the control group. As expected, smoking, hypertension, and diabetes were more prevalent in the CAD group than in the control group, showing that traditional risk factors are likely to be associated with increased inflammatory, fibrinolysis, and oxidative stress levels. The evaluation of the levels of CAD markers was not studied prospectively, and it is impossible to assess whether the reduction in serum levels would be related to a better prognosis.

To date, the only marker that meets all the aforementioned criteria, i.e., accuracy, reliability and therapeutic impact, seems to be the hs-CRP. Primary prevention studies using statins showed a decrease in outcomes and markers after intervention in an apparently healthy group.[6] Secondary prevention studies using monoclonal antibodies (canakinumab) that reduce inflammatory activity have also reduced events, irrespective of LDL levels,[7] raising the possibility that in the near future the much desired reduction in the so-called residual risk may be an attainable target.

Keywords

Coronary Artery Diseases/physiopathology; Biomarkers; Inflammation; Oxidative Stress; Fibrinolysis.

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Strain Analysis of Left Ventricular Function in the Association of Hypertrophic Cardiomyopathy and Systemic Arterial Hypertension

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Abstract

Background: **Hypertrophic cardiomyopathy (HCM) is the most common heart disease of genetic origin in the world population, with a prevalence of at least 1/500. The association with systemic arterial hypertension (SAH) is not uncommon, as it affects approximately 25% of the world population. Most studies aim at the differential diagnosis between these diseases, but little is known about the magnitude of this association.**

Objective: **To compare left ventricular global longitudinal strain (GLS) in HCM patients with and without associated SAH.**

Methods: **Retrospective cross-sectional study that included 45 patients with HCM and preserved ejection fraction, with diagnosis confirmed by magnetic resonance imaging, including 14 hypertensive patients. Transthoracic echocardiography was performed, with emphasis on left ventricular myocardial strain analysis using GLS. In this study, $p < 0.05$ was considered statistically significant.**

Results: **Left ventricular strain was significantly lower in hypertensive individuals compared to normotensive individuals (–10.29 ± 2.46 vs. –12.35% ± 3.55%, $p = 0.0303$), indicating greater impairment of ventricular function in that group. Mean age was also significantly higher in hypertensive patients (56.1 ± 13.9 vs. 40.2 ± 12.7 years, $p = 0.0001$). Diastolic dysfunction was better characterized in hypertensive patients ($p = 0.0242$).**

Conclusion: **Myocardial strain was significantly lower in the group of patients with HCM and SAH, suggesting greater impairment of ventricular function. This finding may be related to a worse prognosis with early evolution to heart failure. Prospective studies are required to confirm this hypothesis. (Arq Bras Cardiol. 2019; 113(4):677-684)**

Keywords: **Ventricular Function, Left; Cardiomyopathy, Hypertrophic; Hypertension; Strain; Heart Failure.**

Introduction

The first cases of hypertrophic cardiomyopathy (HCM) were published in the 1860s, in France, related to left ventricular outflow tract obstruction.[1] In 1957, Brock authored the first report based on hemodynamic, surgical and necropsy findings, describing the disease as subvalvar aortic stenosis with functional left ventricular obstruction, which may be related to systemic arterial hypertension (SAH).[2] In 1958, Teare published the first histopathological description of obstructive HCM.[3] The nonobstructive form was described by Braunwauld et al. in 1963, and confirmed by subsequent studies.[4,5]

HCM is currently defined as the primary myocardial disease of genetic origin with the highest prevalence in the world population (at least 1/500), regardless of ethnicity, sex or age, being the leading cause of sudden death in young people.[5,6] It results from the mutation of one or more sarcomere genes, presenting significant diversity in phenotypic expression and clinical course. It is characterized by an increase in ventricular wall thickness that cannot be explained by an overload condition alone. The non-obstructive form of the disease is more frequent.[5,7]

SAH affects approximately 25% of the world population. Data from VIGITEL (2006-2014) and the World Health Organization confirm this prevalence in the Brazilian population.[8,9] Due to the high prevalence of SAH, the association of SAH and HCM is not uncommon.

Differential diagnosis between HCM and hypertensive heart disease has been a challenge in many situations where the phenotypic expression of these diseases is similar.[10] In this context, echocardiography has become an important tool, especially with the advent of new technologies, such as myocardial strain analysis, which assists differential diagnosis. Besides, global longitudinal strain (GLS) analysis detects early abnormalities in ventricular function before impairment of ejection fraction.[11,12] The purpose of this study was to compare left ventricular GLS in HCM patients with and without SAH, and to assess the impact of this association on ventricular function.

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Methods

Study participants

A retrospective cross-sectional study was conducted between September 2014 and April 2016 in patients followed up at the cardiology outpatient clinic of Hospital Universitário Pedro Ernesto – UERJ – diagnosed with HCM. This study was approved by the Research Ethics Committee with Certificate of Presentation for Ethics Appreciation (CAAE) number 23561113.2.0000.5259, and it is according to the Helsinki Declaration of 1975 updated in 2013. All patients who accepted to participate in the study have read and signed an informed consent form.

Inclusion criteria were: diagnosis of HCM confirmed by magnetic resonance imaging (MRI), age over 18 years, preserved left ventricular ejection fraction (EF) (>55%), no interventions for septal reduction and no pacemaker or defibrillator. Patients with atrial fibrillation and known coronary artery disease were excluded.

Diagnostic confirmation by MRI with gadolinium was based on the distribution of hypertrophy and late enhancement pattern.[13] The convenience sample included 45 patients, including 22 (48.9%) males with mean age of 45.1 ± 13.9 years. In this group, 14 (31.1%) had hypertension previously diagnosed according to the Brazilian guidelines for SAH.[8] The flowchart with the selection of patients is shown in Figure 1.

Echocardiographic analysis

Transthoracic echocardiographic test was performed by an experienced echocardiographer on a Philips® iE33 Matrix equipment using 3-1 MHz matrix transducer. One-dimensional, two-dimensional and Doppler echocardiography analysis was performed following the recommendations of the American Society of Echocardiography.[14]

The echocardiographic classification of Maron et al.,[15] which divides hypertrophy into types I, II, III, and IV (Figure 2) was used to define the type of left ventricular hypertrophy. The obstructive pattern was considered for left ventricular outflow tract gradients greater than 30 mmHg, measured by continuous Doppler, at rest and after Valsalva maneuver.[5] The approach of diastolic function and ventricular filling pressures followed the recommendations of the American Society of Echocardiography for patients with HCM.[16]

In the myocardial strain analysis, we used speckle tracking. Strain is calculated for each left ventricular segment as the relative mean strain between two speckles. As a measure of strain, it is expressed in negative percentages (-%); the closer to 0, the lower the strain. Values lower than -18% were considered normal strain. Only GLS was analyzed because it is more widely used and considered a robust index for clinical studies. Also, GLS is the first to be impaired in most heart diseases, including HCM, when ejection fraction is still preserved.[12]

Echocardiographic protocol for GLS included 4-chamber, 3-chamber and 2-chamber apical views. GLS analysis was processed offline using the software Philips® QLab 9.0. These results were translated into curves, one for each ventricular segment, and the overview, with the quantification of velocities, was expressed on a bull's eye map, exemplified in Figure 3.

Echocardiographic scans were stored and the images revised. Examiner and reviewer are the authors of the study. Strain analysis was repeated by the reviewer on all scans. Intraobserver and interobserver variability was evaluated using the coefficient of variation (CV = 100 (s/x) (%)). We obtained good agreement and the coefficients were considered low (<10%).

Statistical analysis

The collected data were entered in a Microsoft Excel™ spreadsheet, and later analyzed in R Studio, version 1.0.143. Continuous variable distributions were expressed using mean and standard deviation as measures of central tendency and dispersion for each of the groups analyzed. To assess whether there was a difference between the groups, unpaired Student's *t*-test was used after Levene's test for equality of variances. For categorical variables, the nonparametric approach was chosen, where the difference between proportions was evaluated by the X^2 test (with Yates correction) and Fisher's exact test. In cases where there were more than two categories, the Kruskal-Wallis test was used. In this study, $p < 0.05$ was considered statistically significant.

Results

Of 55 initially eligible patients, 10 were excluded: 6 by atrial fibrillation, which impairs GLS analysis, 2 by known coronary artery disease, which also interferes with strain analysis, and 2 whose HCM diagnosis had not been confirmed by MRI. The patients' general characteristics are shown in Table 1. Figure 4 shows a set of charts with the main results. Mean age was higher in the hypertensive group, and body mass index (BMI) and mean systolic and diastolic pressures were higher in this group. No significant differences were observed regarding gender and functional class between the groups.

Regarding the echocardiographic findings, there was less strain in hypertensive patients (–10.29% ± 2.46) than in normotensive patients (–12.35% ± 3.55), indicating greater impairment of ventricular function in this group ($p = 0.0303$). Although all patients had preserved EF, mean left ventricular systolic diameter (LVSD) was higher in hypertensive patients, but still within normal limits.

Diastolic dysfunction was more evident in hypertensive patients ($p = 0.0242$), with a lower number of undetermined cases. In hypertensive patients, longer isovolumetric relaxation time (IVRT), lower E/A ratio in mitral flow, as well as a lower septal E/e' ratio were observed on mitral annulus tissue Doppler. Mean left atrial volume was increased in both groups, but without any significant difference between them (Table 2).

In the hypertrophy type analysis, in the general sample, type III was the most frequent one (40%), followed by type II (31%), I (15.7%) and IV (13.3%), but no significant difference was observed between the groups regarding the type of hypertrophy. In this sample, there were no cases of concentric hypertrophy. Also, there was no significant difference between the groups regarding left ventricular outflow tract obstruction, with a higher percentage of the nonobstructive form in the overall sample (66.7%).

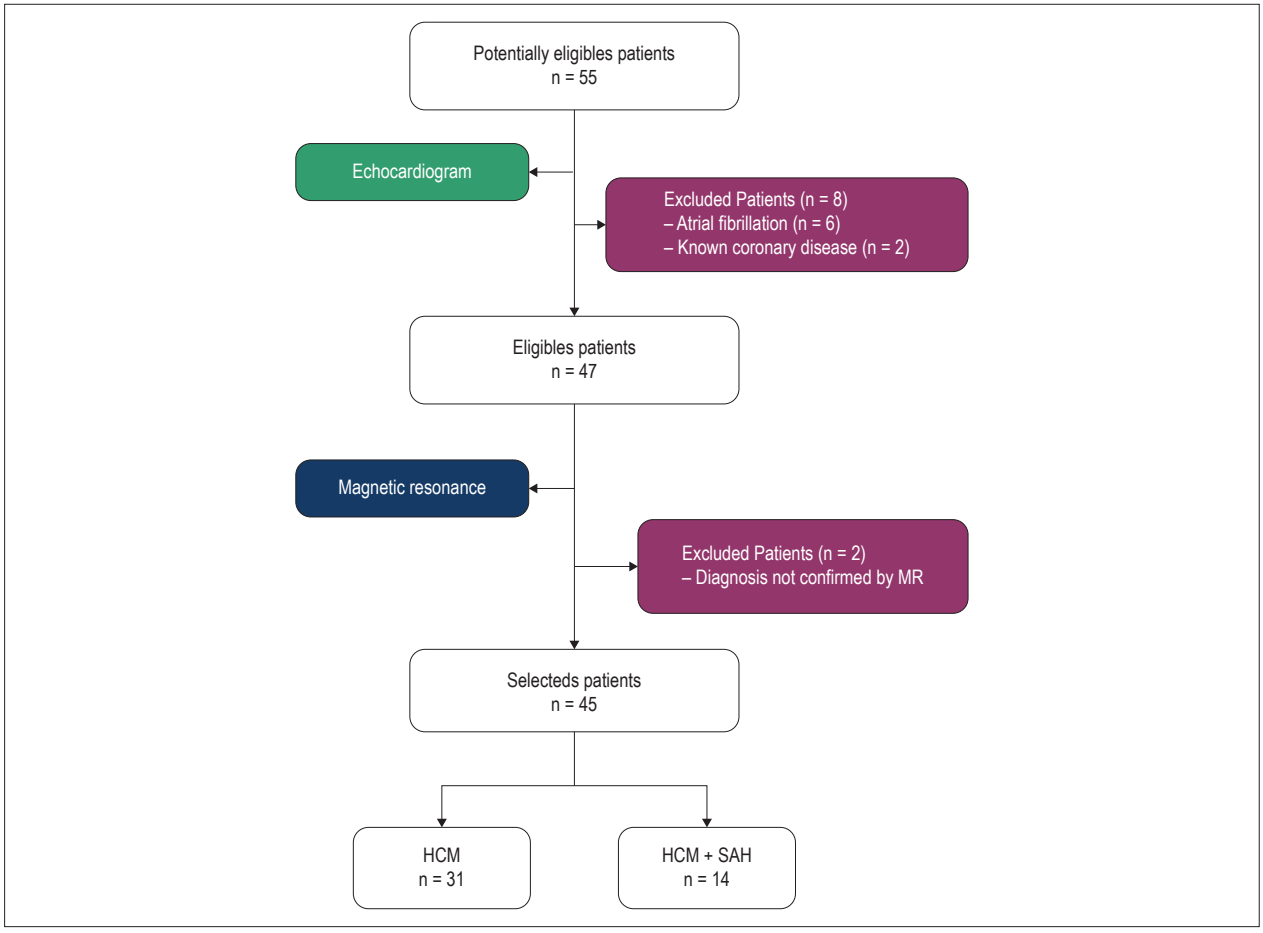

Figure 1 – *Flowchart of patient selection. MR: magnetic resonance; HCM: hypertrophic cardiomyopathy; SAH: systemic arterial hypertension.*

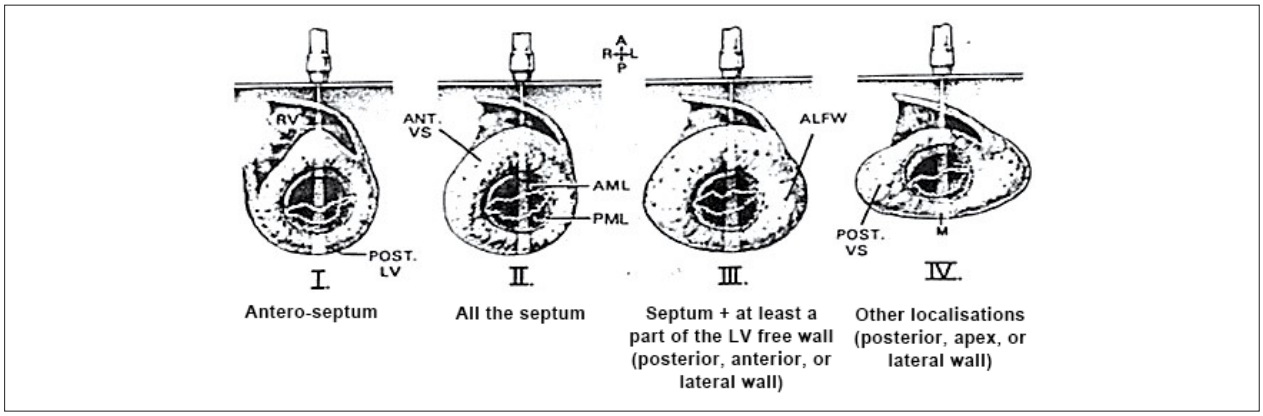

Figure 2 – *Phenotypic classification originally described by Maron. Type I: hypertrophy involving the basal septum; Type II: hypertrophy involving the entire septum; Type III: hypertrophy involving the septum and at least part of the left ventricular free wall (posterior, anterior or lateral); Type IV: other isolated locations (posterior, apical or lateral). Maron BJ. et al.*[15]

Mean blood pressure was higher in the hypertensive group. In this group, nine patients (64%) had increased blood pressure before the test, with 144x92 mmHg maximum. In the group without hypertension, six patients (19%) had a slight blood pressure increase with 135x84 mmHg maximum.

Regarding the medications used, more medications were used by the group of hypertensive patients, especially angiotensin receptor blockers, calcium antagonists and diuretics. No patient was taking cardiotoxic drugs or any drugs interfering with ventricular function.

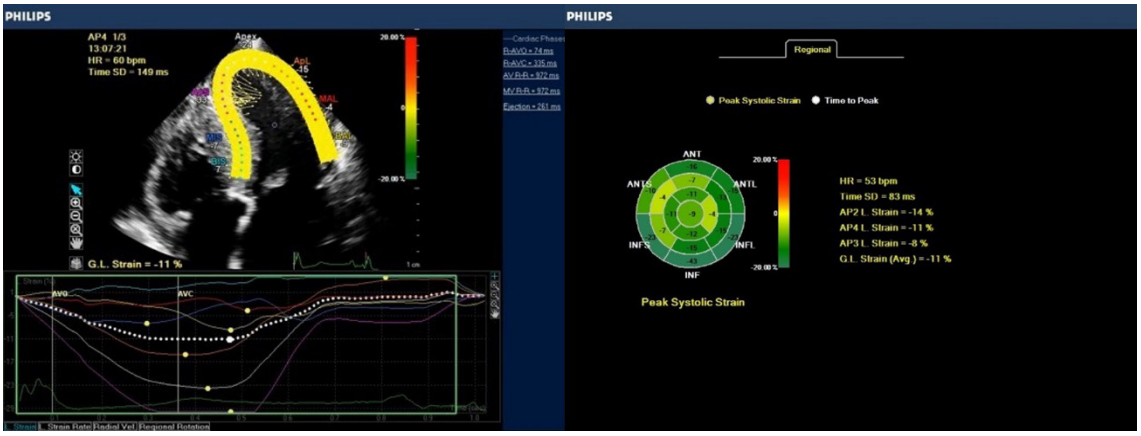

Figure 3 – *Global longitudinal strain systolic peak curves in the four-chamber apical section (left) and the parametric image of the left ventricle in the bulls-eye (right) in a patient with HCM and hypertension.*

Table 1 – Characteristics of HCM patients in the different groups

Variables	Normotensive patients (n = 31)	Hypertensive patients (n = 14)	p
Age (years)	40.16 ± 12.73	56.14 ± 13.87	0.0001
Male sex	15 (48%)	7 (50%)	0.9323
BMI (kg/m^2)	25.6 ± 3.97	29.2 ± 2.93	0.0045
SBP (mmHg)	113 ± 12	128 ± 12	0.0004
DBP (mmHg)	71 ± 9	81 ± 9	0.0027
Functional Class (NYHA)			**0.1110**
I	12 (38.7%)	2 (14.3%)	
II	19 (61.29%)	11 (78.57%)	
III	0 (0%)	1 (7.14%)	
Hypertrophy type			**0.1492**
I	5 (16.1%)	2 (14.3%)	
II	12 (38.7%)	2 (14.3%)	
III	12 (38.7%)	6 (42.9%)	
IV	2 (6.5%)	4 (28.5%)	
LVOT obstruction	9 (29%)	6 (43%)	0.5133
Medications			
Beta-blocker	22 (70%)	12 (86%)	0.4578
ACEI	2 (6.45%)	4 (28.57%)	0.0651
ARB	1 (3.23%)	11 (78.57%)	< 0.0001
Calcium antagonist	2 (6.45%)	5 (35.71%)	0.0226
Nitrate	1 (3.23%)	1 (7.14%)	0.0503
Hydralazine	0 (0%)	1 (7.14%)	0.3111
Diuretics	0 (0%)	8 (57.14%)	< 0.0001

Values expressed as mean±standard deviation or proportion, as indicated. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker.

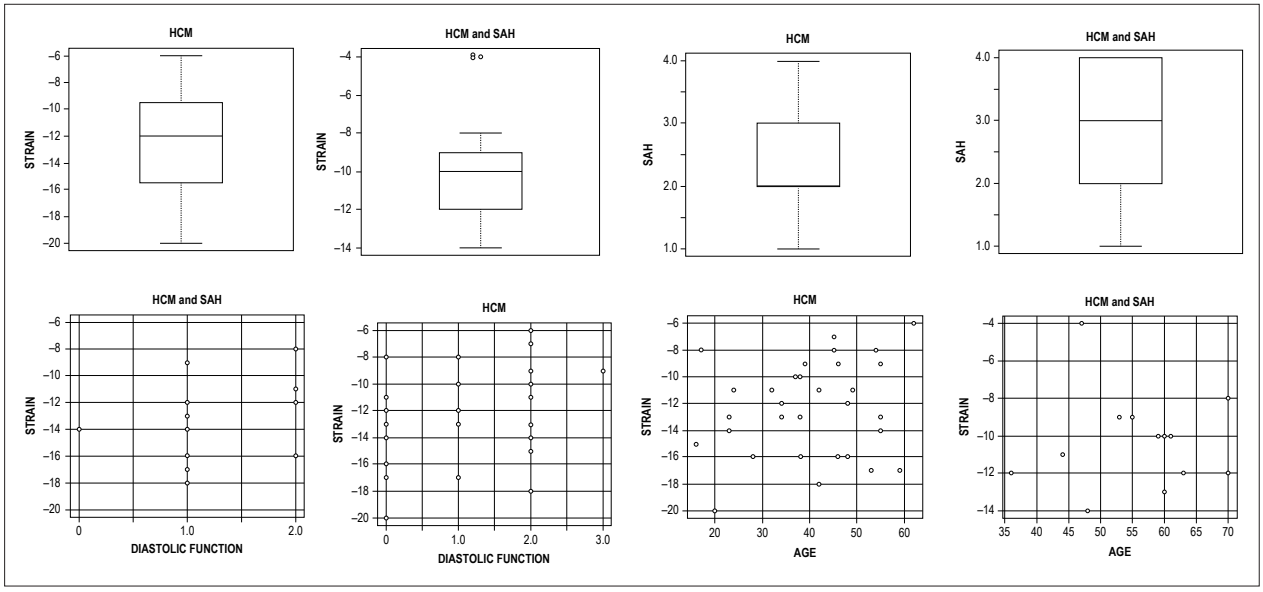

Figure 4 – *Graphs showing the main results of patients with hypertrophic cardiomyopathy (HCM) with and without associated systemic arterial hypertension (SAH). The analyzed STRAIN is the global longitudinal strain. LVH refers to the types of left ventricular hypertrophy (I, II, III, and IV) and diastolic function refers to types I, II, and III.*

Table 2 – Demographic data

Variables	Normotensive patients (n = 31)	Hypertensive patients (n = 14)	p
Measures			
LVDD (mm)	4.56 ± 0.66	4.76 ± 0.60	0.3485
LVSD (cm)	2.42 ± 0.49	3.45 ± 0.46	0.0008
S/PW	2.03 ± 0.65	1.63 ± 0.44	0.0425
LA volume (ml/m^2)	37.76 ± 17.14	38.97 ± 16.79	0.8245
RV (cm)	1.70 ± 0.43	1.71 ± 0.31	0.9757
EF% (Teichholz)	80.18 ± 5.76	74.01 ± 9.90	0.0116
E (cm/s)	78.23 ± 16.30	76.13 ± 26.83	0.7465
A (cm/s)	50.92 ± 16.92	80.70 ± 22.71	< 0.001
E/A	1.57 ± 0.56	0.96 ± 0.25	0.0003
EDT (ms)	241.90 ± 79.15	261.00 ± 66.23	0.4363
IVRT (ms)	119.94 ± 24.90	141.50 ± 35.08	0.0228
septal e' (cm/s)	5.75 ± 1.30	4.43 ± 0.95	0.0015
lateral e' (cm/s)	8.37 ± 2.79	7.21 ± 3.47	0.2386
Septal E/e'	13.98 ± 4.26	17.45 ± 6.21	0.0327
Lateral E/e'	10.18 ± 3.81	12.90 ± 6.81	0.0926
Mean E/e'	12.40 ± 3.73	15.71 ± 6.21	0.0696
Diastolic dysfunction classification			
Undetermined	41.9%	7.1%	0.0242
Grade 1	12.9%	50.0%	
Grade 2	41.9%	42.9%	
Grade 3	3.2%	0.0%	

Values expressed as mean±standard deviation or proportion, as indicated. LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; S/PW: interventricular septum/posterior wall ratio; LA: left atrium; RV: right ventricle; EF: ejection fraction; LVOT: left ventricular outflow tract; E: mitral flow E wave; A: mitral flow A wave; EDT: E wave deceleration time; IVRT: isovolumetric relaxation time; e': mitral annulus tissue Doppler e' wave.

Discussion

The finding of significant reduction in myocardial strain in the hypertensive group suggests that these patients present greater impairment of ventricular function. Early detection of left ventricular dysfunction with preserved ejection fraction was only possible using the strain technique, not used in previous studies. Prior to the advent of strain, no significant abnormalities were observed in the comparison between these groups. In a study conducted in 1989 by Karan et al.,[17] 78 patients diagnosed with HCM on echocardiography and cardiac catheterization were evaluated, including 39 hypertensive patients. The most relevant finding was higher hypertrophy in hypertensive patients, suggesting that SAH may increase hypertrophy in HCM. This study was important to define the existence of hypertrophic cardiomyopathy with hypertension, which was previously described as hypertensive hypertrophic cardiomyopathy.

In 1998, Dimitrow et al.[18] published a study with 123 patients with HCM, 19.5% of whom were hypertensive, in which only functional class was evaluated. The study found that the association of SAH was more frequent in the elderly, but not rare in young people, which had worse functional class. In another study not using the strain technique, echocardiographic findings were similar between groups and SAH was also more frequent in the elderly.[19]

In 2014, Gonçalves et al.[20] performed GLS analysis in a group of 229 pure hypertensive patients without HCM and preserved EF, and observed a reduction in GLS in 15.3% of the patients. However, no studies were found in the literature using the strain technique to compare HCM patients with and without associated SAH. In addition to detecting early changes in ventricular function, strain impairment may be a predictor of ventricular arrhythmia. In a publication with 400 HCM patients, those with GLS >-10% were four times more likely to have events than patients with GLS ≤-16%.[21] Regional strain abnormalities in HCM may also be predictive of arrhythmia, as demonstrated by Correia et al.[22] A study with 32 patients found mean septal strain >-10% with 89% sensitivity and 74% specificity for the development of non-sustained ventricular tachycardia, regardless of age or maximum wall thickness. These regional strain abnormalities may be related to areas with higher percentage of fibrosis on magnetic resonance imaging, being a potential substrate for the development of arrhythmias.[23,24]

Diastolic dysfunction was more evident in hypertensive patients in this sample. Hypertensive patients had a higher percentage of grade I or II dysfunction and a lower percentage of undetermined cases, according to the latest recommendations for diastolic function evaluation.[15] It should be noted that left atrial volume, an important parameter in the assessment of diastolic function,[15,25,26] was increased in both groups on average, with no significant difference between them. This means, in principle, that most patients had some degree of diastolic dysfunction, but it was better defined in hypertensive patients.

Regarding the type of hypertrophy, in the classification proposed by Maron et al.,[14] which evaluated 125 patients, the most frequent type was type III (52%), followed by types II (20%), IV (18%) and I (10%). In another study, Reant et al.[27] evaluated 271 patients using this classification, and the most frequently observed type was II (47%), followed by types III (35%), I (11%) and IV (7%). We have found a percentage similar to Maron's classification regarding the most frequent types of hypertrophy, that is, types III and II, followed by types I and IV.

In the hypertensive group, mean age was higher, which may have influenced the evaluation of diastolic function and, perhaps, the strain analysis. Some studies have shown that myocardial strain presents a small reduction with age.[28,29] Others have not observed a clear relationship between myocardial strain and age.[30,31]

We observed that mean blood pressure was higher in the hypertensive group, but there is no definition in the literature as to whether increased blood pressure at the time of the test may influence strain analysis.

Study limitations

The strain technique requires regular heart rhythm, which limits its use in some situations, such as atrial fibrillation, which led to the exclusion of some patients. In the hypertensive group, mean age was higher and may have interfered with strain analysis and diastolic function analysis. Finally, long-term follow-up could provide further information about ventricular function behavior, since our study was cross-sectional.

Conclusion

Patients with HCM and SAH had lower myocardial strain, suggesting greater impairment of left ventricular function, even with preserved ejection fraction. This finding may be related to a worse prognosis, with early evolution to heart failure and/or onset of ventricular arrhythmias. Prospective studies are needed to confirm this hypothesis.

Author contributions

Conception and design of the research: Gil TCP, Castier MB, Rocha RM; Acquisition of data: Gil TCP, Gondar AFP, Sales AF; Analysis and interpretation of the data and Writing of the manuscript: Gil TCP; Statistical analysis: Santos MO, Lima FCS; Obtaining financing: Rocha RM; Critical revision of the manuscript for intellectual content: Castier MB, Rocha RM.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Pedro Ernestro/UERJ under the protocol number 2356113.2.0000.5259. 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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Are Myocardium Deformation Indices Influenced by Cardiac Load, Age or Body Mass Index?

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Short Editorial related to the article: Strain Analysis of Left Ventricular Function in the Association of Hypertrophic Cardiomyopathy and Systemic Arterial Hypertension

The typical findings of myocardium deformation indices (MDI) in many cardiac diseases, the low cost of the echocardiographic exam, the large availability, the vast implementation of this tool for clinical practice and the prognostic value has allowed the detection of earlier myocardium dysfunction than the traditional measurement of left ventricular (LV) ejection fraction.[1] Moreover, there are typical MDI patterns in different forms of hypertrophy: decreased values in septum MDI in hypertrophic cardiomyopathy (HCM) or where hypertrophy is more accentuated, or a segmental decrease in mutation carriers in a pre-clinical phase of disease, before development of hypertrophy;[2] apical sparing in amyloidosis;[3] striped pattern of myocardium deformation in glycogen storage cardiomyopathy (PRKAG2);[4] and decrease in subepicardial longitudinal strain in Anderson-Fabry disease.[5] In hypertension with concentric and eccentric hypertrophy, the MDI patterns are related to different geometric patterns,[6] but they are frequently preserved in athletes.[4]

The question whether MDI would be reliable in different machines and vendors was demonstrated that the accuracy of these indices were better than conventional echocardiography measurements and they are reliable for daily echocardiographic practice.[7]

The paper published in the same issue of this journal showed that the authors evaluated the LV global longitudinal strain in 45 patients divided into 2 groups: with HCM and the association with hypertension with HCM, and showed that strain was decreased in the latter group compared to the first one.[8] It is noticeable the difference between both groups about their age, body mass index (BMI) and blood pressure. Besides, many studies have demonstrated that global longitudinal strain could be affected by those variables mentioned, as demonstrated in a paper of 266 healthy subjects, 39.2 ± 17.5 years, 137 women, submitted to transthoracic echocardiography evaluation and showed that global longitudinal strain was progressively reduced with increasing age decades.[9] Metabolic syndrome may also play a role in myocardial deformation showed in a study of 384 patients grouped according to BMI (normal weight < 25 kg/m^2, overweight 25–29 kg/m^2, and obesity ≥ 30 kg/m^2), compared to healthy control group. Regardless of the presence or not of diabetes, overweight and obesity impair LV ejection fraction and global longitudinal strain.[10] Interestingly, Russell et al.[11] were the first to describe a new method that evaluated myocardial work using a non-invasive pressure-strain loop by echocardiogram.[11] In a canine model, it was demonstrated a significant reduction in LV strain after aortic construction. On the other hand, LV pressure-strain loop area did not change, which means that myocardial work seems to be not affected by increasing the afterload, but global longitudinal strain could transient change by hemodynamics status.[12] Therefore, we could be more precautious when we stratify the same cardiomyopathy simply by using global longitudinal strain, not considering afterload importance. Furthermore, the previous study compared 80 hypertensive patients, 80 HCM patients and 80 controls showed that longitudinal strain was lower in HCM patients, and also, the best parameter to differentiate both diseases was the MDI ratio of endocardium and epicardium layers. However, this parameter was not evaluated in the present study.[13]

The LV outflow tract obstruction is defined as peak LV gradient greater than or equal to 30 mmHg at rest or with provocation, is present in approximately two-thirds of patients with hypertrophic cardiomyopathy.[14] This dynamic obstruction leads to an increase in left ventricle afterload which could impair the global longitudinal strain itself, as previous mentioned. However, the authors of this present study did not mention this feature which certainly affects the myocardial deformation. The myocardial thickness and mainly, the presence of fibrosis affect negatively the patients' prognosis. Both parameters were not described in this present study and it is well known that they are related to a LV global longitudinal strain reduction.[15] When myocardial work was analyzed in hypertrophic cardiomyopathy subjects, one variable called global constructive work was the only predictor of LV fibrosis at multivariable analysis (OR 1.01, 95% CI: 0.99 – 1.08, p = 0.04).[16] A cutoff value of 1623 mmHg% (AUC 0.80, 95% CI: 0.66–0.93, p < 0.0001) was able to predict myocardial fibrosis with good sensitivity and fair specificity (82% and 67%, respectively).

In conclusion, MDI are an important tool helping to distinguish HCM from other cardiomyopathies, as well as, they present value for risk stratification impact. However, it is extremely recommended to take into account the hemodynamic status whenever analyze MDI data. Moreover, it is a diagnostic challenge the presence of overlapping of hypertrophic cardiomyopathy and hypertension. Myocardial work may play a role to solve this.

Keywords

Echocardiography/methods; Myocardium Deformation; Hypertension; Heart Failure; Strain; Hypertrophic Cardiomyopathy.

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Prevalence of Systemic Arterial Hypertension and Associated Factors Among Adults from the Semi-Arid Region of Pernambuco, Brazil

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Abstract

Background: Systemic arterial hypertension is a substantial public health problem responsible for millions of deaths per year worldwide. However, little is known about the epidemiology of this disease in areas distant from large urban centers in Brazil. Such information is necessary to plan health promotion strategies.

Objective: To estimate the prevalence of hypertension and determine its associated factors in adults residing in the semi-arid region of the state of Pernambuco, Northeastern Brazil.

Method: This is a cross-sectional study conducted with a random sample of male and female adults. Individuals with systolic blood pressure ≥ 140 mm/Hg and/or diastolic blood pressure ≥ 90 mm/Hg and those who reported being under treatment with antihypertensive drugs were considered hypertensive. We collected data on demographic, socioeconomic, behavioral, and anthropometric characteristics, as well as health and nutrition. The statistical analysis used Pearson's chi-square test, the chi-square test for trend, and multivariate Poisson regression analysis. A p-value < 0.05 in the final model was considered indicative of statistical significance.

Results: The sample consisted of 416 individuals, and the prevalence of hypertension was 27.4% (95%CI 23.2 – 32.0). In the final model, the independent predictors of hypertension were age of 40 years or older (p = 0.000), low economic class (p = 0.007), smoking (p = 0.023), overweight determined by the body mass index (p = 0.003), and reduced glucose tolerance/diabetes mellitus (p = 0.012).

Conclusion: The prevalence of hypertension was high and related to important risk factors. Thus, prevention and control strategies are recommended. (Arq Bras Cardiol. 2019; 113(4):687-695)

Keywords: Hypertension/prevention and control; Prevalence; Cardiovascular Diseases; Epidemiology; Blood Pressure; Risk Factors.

Introduction

Systemic arterial hypertension is a substantial public health problem around the world and the most common clinical condition found in primary care.[1,2] This condition is responsible for approximately 9.4 million deaths per year worldwide.[3] It is not only one of the major risk factors for other cardiovascular diseases,[2] but also a syndrome with its manifestations, characteristics, and multifactor etiology.[4]

The prevalence of hypertension increased from approximately 25.9% of the global adult population at the beginning of the 21st century to 31.1% in 2010, a 5.2% increase in ten years.[5] In developed countries, however, a 2.6% reduction occurred in this period, whereas developing countries faced a 7.7% increase.[5] In Brazil, studies compiling data from several cities report that hypertension affects approximately 30% of the adult population, corresponding to 36 million individuals.[4,6,7]

Analyzing the distribution of the disease in the country, the north and northeast regions have the lowest rates of hypertension.[8] However, this type of information is scarce in these regions due to the low number of surveys addressing the epidemiology of this condition.[9]

The semi-arid region covers a large area of Brazil, especially in the northeast part of the country. This region is often hit by crises related to long periods of drought. Besides the low socioeconomic development of the region, this situation can contribute to an increase in chronic non-communicable diseases.[10,11] Nevertheless, little is known about the epidemiology of hypertension and its geographic distribution in populations living distant from large Brazilian urban centers and in mesoregions, such as the semi-arid region.

Considering the need for information that can assist in improving and optimizing public health services and actions, the present study aimed to estimate the prevalence

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of hypertension and determine its associated factors in the adult population from the semi-arid region of the state of Pernambuco, Northeastern Brazil.

Methods

This is a population-based cross-sectional study conducted with male and female adults (aged 20 to 59 years) residing in the semi-arid region of Pernambuco.

The study population was determined by cluster sampling. Pernambuco is subdivided into 12 development regions (DR), six of which correspond to the semi-arid zone. Among them, three were randomly selected in the first stage of the sampling process. Next, one city was chosen from each DR: Serra Talhada (DR 4), Custódia (DR 12), and Belém de São Francisco (DR 1). Next, five census tracts were drawn per city with urban/rural distribution based on data from the 2010 Census. Lastly, 350 households were randomly selected to form a representative sample of the population in the semi-arid region of Pernambuco. The sample comprised all adult residents of the selected homes who were present at the time of data collection. Individuals with any physical limitation that hindered the anthropometric evaluation, debilitating diseases, and who declined to participate were excluded from the study. All stages of the selection process were performed using lists of random numbers generated with the aid of the EPITABLE tool of the Epi Info statistical package, version 6.04 (CDC/WHO, Atlanta, GE, USA).

The fieldwork occurred between July and September 2015 by a team of researchers who had previously undergone training for the administration of data collection instruments. A pilot study was conducted with 30 families in a city not selected for the main study to put into practice the logistics of the fieldwork and test the data collection instruments.

The sample size was calculated *a posteriori* assuming a 20% estimated prevalence of hypertension in the northeast region of Brazil,[8] a 5% sampling error, a 95% confidence interval, and a factor of 1.5 to compensate for the design effect of the cluster sampling. Moreover, 10% was added to compensate for possible dropouts, leading to a total of 410 individuals.

The following demographic and socioeconomic characteristics and respective categories were collected: gender (male or female), age in years (20 to 29, 30 to 39, 40 to 49, 50 to 59), ethnicity (white or multiracial/black), schooling (never studied, primary school, high school/university), employment status (works or does not work), and place of residence (urban or rural area). Data collection followed the guidelines of the *Instituto Brasileiro de Geografia e Estatística* (IBGE – Brazilian Institute of Geography and Statistics).[12] Economic class was categorized based on the Brazilian Economic Classification Criteria of the *Associação Brasileira de Empresas de Pesquisa* (ABEP – Brazilian Market Research Association):[13] upper/middle (A1, A2, B1, B2, C1, C2) and lower (D, E) classes.

We collected the following behavioral characteristics: alcohol intake in the previous 30 days (yes or no); active smoking (smoker/ex-smoker or never smoked); passive smoking (yes or no; individuals who do not actively smoke but are frequently in contact with cigarette smoke from people at home, work, or school/university); and addition of salt to food after preparation (never, sometimes/almost always). Physical activity level was determined using the International Physical Activity Questionnaire (IPAQ) validated for use in Brazil,[14] which enables the classification of individuals as sedentary/insufficiently active or active/very active.[14]

Anthropometric data were collected in duplicate following the guidelines of the World Health Organization.[15] Body mass was measured using a digital scale (TANITA™, model BF-683 W). Height was measured using a portable stadiometer (Alturaexata™). Waist circumference (WC) was measured at the midpoint between the last rib and the iliac crest with a flexible, non-elastic metric tape (Sanny™). When a difference greater than 0.5 cm was found between the two height and WC values, the participant was measured a third time, and the two closest results were considered to calculate the arithmetic mean.

The following health and nutritional characteristics and respective categories were collected: body mass index (BMI) (not overweight when < 25 kg/m^2 and overweight when ≥ 25 kg/m^2);[16] WC (normal when < 80 for women and < 94 cm for men and increased when ≥ 80 cm for women and ≥ 94 cm for men);[16] waist-to-height ratio (normal when < 0.52 for men and < 0.53 for women and increased when ≥ 0.52 for men and ≥ 0.53 for women);[17] and food security evaluated using the Brazilian Food and Nutritional Insecurity Scale,[18] which enabled classifying the homes into the following categories: food security, mild food insecurity and moderate/severe food insecurity.

Blood samples were collected through a venous puncture after a 10-hour fast. The analyses to determine the levels of fasting blood glucose, triglycerides, and total cholesterol used the Accutrend GCT [Roche Diagnóstica, Brazil], which allows immediate readings. The components of the biochemical profile were fasting blood glucose [normal when < 100 mg/dL and reduced glucose tolerance/diabetes mellitus (DM) when ≥ 100 mg/dL or when the individual used a hypoglycemic medication],[19] triglycerides (normal when < 150 mg/dL and high when ≥ 150 mg/dL),[20] and total cholesterol (normal when < 190 mg/dL and high when ≥ 190 mg/dL).[20]

Regarding the outcome variable, blood pressure (BP) was measured in duplicate using the auscultation method (Glicomed™ sphygmomanometer, model CE-0483), followed by the calculation of the arithmetic mean of the results. The procedures to prepare the individuals for BP measurement followed the recommendations of the Brazilian Society of Cardiology:[6] make sure that the individual rested for at least five minutes in a calm environment; did not have a full bladder, had not practiced physical exercise in the previous 60 minutes, had not consumed alcohol, coffee, or food in the previous hour, and had not smoked in the previous 30 minutes; and was seated at the time of the measurement, with the legs uncrossed, feet flat on the floor, and arm at the height of the heart. The criteria to diagnose hypertension was based on the Seventh Brazilian Hypertension Guidelines,[6] which classify an individual with hypertension when the systolic BP is ≥ 140 and/or diastolic BP is ≥ 90. We also considered hypertensive individuals who declared having a previous diagnosis and were under treatment with antihypertensive medications.

The data used in the present investigation derived from a study entitled "Evaluation of food and nutritional security in urban and rural communities affected by drought in the semi-arid region of Pernambuco" (certificate of presentation for ethical approval: 38878814.9.0000.5208; certificate of approval: 897.655). All participants received information about the study and signed the informed consent form.

Statistical analysis

All data were entered twice with the Epi Info™ software, version 6.04 (CDC/WHO, Atlanta, GE, USA), with the subsequent use of the VALIDATE module to check data consistency. We grouped the explanatory variables into the following four hierarchically ordered levels from distal to proximal: 1) biological factors; 2) demographic and socioeconomic factors; 3) behavioral factors, and 4) biochemical and nutritional factors (proximal level). Based on a conceptual model to determine hypertension, we assumed that predisposing factors imply different hierarchical levels of determination.

We conducted univariate statistical analysis with either Pearson's chi-square test or the chi-square test for trend to establish associations between explanatory variables and the outcome. Variables with a p-value < 0.20 were incorporated into the multivariate analysis using Poisson regression with robust variance. Results of the univariate analysis were expressed as percentages and respective 95% confidence intervals (95%CI) and of the multivariate analysis were described as prevalence ratios and respective 95%CI. A p-value < 0.05 in the final model was considered indicative of a statistically significant association. All analyses had the aid of the Statistical Package for Social Sciences (SPSS), version 13.0 (IBM Analytics, NC, USA) and Stata, version 14.0 (StataCorp, TX, USA).

Results

The final sample consisted of 416 adults with a median age of 35.0 (interquartile range of 28.0 to 48.0) years. Most of the sample was female (64;9%, 95%CI: 60.1 to 69.5), of black/multiracial ethnicity (78.4%, 95%CI: 74.0 to 82.2), and lived in urban areas (57.9%, 95%CI: 53.0 to 62.7).

A total of 19.7% (95%CI: 16.1 to 23.9) of the sample had the habit of consuming alcoholic beverages, 23.3% (95%CI: 19.4 to 27.7) smoked actively, 16.3% (95%CI: 13.0 to 20.3) smoked passively, and 71.5% (95%CI: 65.6 to 76.9) were sedentary or insufficiently active. Moreover, 10.1% (95%CI: 7.5 to 13.5) of the sample reported adding salt to food after preparation sometimes or nearly always.

The prevalence of hypertension was 27.4% (95%CI: 23.2 to 32.0). Table 1 shows the distribution of the condition according to demographic and socioeconomic variables. We found a statistically significant association between higher prevalence of hypertension and increasing age and lower levels of schooling and income. Regarding behavioral variables (Table 2), hypertension was more frequent among active smokers/ex-smokers and passive smokers. With respect to the health and nutritional profile (Table 3), hypertension was associated with overweight, determined by the BMI, and an increased weight-to-height ratio. Hypertension was also associated with the following biochemical variables: reduced glucose tolerance/DM and high total cholesterol (Table 4).

After statistical adjustments in the hierarchical model, the explanatory variables that remained significantly associated with hypertension were age, economic class, active smoking, BMI, and fasting blood glucose (Table 5).

Discussion

Hypertension is one of the most common conditions among older adults, but it also affects a considerable portion of the adult population (20 to 59 years), striking more than 30 million individuals in this age range in Brazil alone.[6] Thus, addressing this condition in the adult population is necessary.

Although slightly lower than the estimated national average of 30%,[6] the prevalence of hypertension among adults in the semi-arid region of Pernambuco was high, confirming that this is a serious public health problem. This finding was expected, given the low socioeconomic development of the mesoregion and its possible association with the high prevalence of chronic non-communicable diseases.[10] We underline, however, that some individuals classified as hypertensive may actually have "white coat hypertension," which was not evaluated and could be considered a limitation of the present study.

According to Andrade et al.,[8] the prevalence of self-reported hypertension among adults in Northeastern Brazil is 19.4% (95%CI: 18.4 to 20.5), which is lower than the rate found in the present study. This divergence may be explained by one of the limitations of using self-reports, which, although validated in population-based studies, might underestimate prevalence rates.[21] This aspect is influenced by the access to and use of health care services by the part of the population investigated, as self-reported hypertension would require a previous medical diagnosis.[21]

The greater susceptibility to hypertension with the increase in age found in the present study has been reported in the specialized literature, and there is a consensus on the direct, linear relationship between BP and age.[6] This relationship results from the development of atherosclerosis, with the stiffening of the arteries leading to an elevation in pressure levels, which is normally caused by physiological changes stemming from the aging process.[22]

The association between economic class and hypertension in the present study supports the conjecture that individuals with low status are more vulnerable to the development of the disease.[23] Furthermore, despite the association with a low level of schooling having lost its significance in the multivariate model, it could represent a more evident risk factor than income.[23] Thus, it is important to increase the monitoring of and care for these more vulnerable groups.

Being a smoker or ex-smoker was also associated with the prevalence of hypertension, which corroborates data from other population-based studies conducted in Brazil and a review study by Passos et al.[21] This result is consistent with experimental evidence that smoking can cause hypertension and other cardiovascular diseases.[24] In the first decade of the 21st century, 11% of worldwide deaths from cardiovascular diseases were attributed to smoking,[25] making this habit an important risk factor to address in health promotion and disease prevention actions.

Table 1 – Distribution of systemic arterial hypertension according to demographic and socioeconomic characteristics in adults from the semi-arid region, state of Pernambuco, Brazil, 2015

	Systemic arterial hypertension			
Variables	**n**	**%**	**95%CI**	**p-value‡**
Gender				**0.358**
Male	44	30.1	22.8 – 38.3	
Female	70	25.9	20.8 – 31.6	
Age (years)				**0.000§**
20 – 29	13	10.6	05.7 – 17.4	
30 – 39	20	15.9	10.0 – 23.4	
40 – 49	25	36.8	25.4 – 49.3	
50 – 59	56	56.6	46.2 – 66.5	
Ethnicity				**0.721**
White	26	28.9	19.8 – 39.4	
Multiracial or black	88	27.0	22.3 – 32.2	
Schooling				**0.000§**
Never studied	66	44.6	36.4 – 53.0	
Primary school	32	19.5	13.7 – 26.4	
High school/university	16	15.4	09.1 – 23.8	
Employment status				**0.150**
Works	45	23.9	18.0 – 30.7	
Does not work	69	30.3	24.4 – 36.7	
Place of residence				
Urban area	65	27.0	21.5 – 33.0	0.816
Rural area	49	28.0	21.5 – 35.3	
Economic class				**0.001**
Upper or middle*	45	20.5	15.3 – 26.4	
Lower†	69	35.2	28.5 – 42.3	

*95%CI: 95% confidence interval; * classes A1, A2, B1, B2, C1, and C2; † classes D and E; ‡ Pearson's chi-square test; § chi-square test for trend.*

Body composition is another important aspect related to hypertension, especially with regard to fat distribution, as the increase in visceral adipose tissue is directly associated with a greater incidence of the disease.[26] One of the limitations of the present study was not evaluating body fat distribution based on more accurate methods, such as the quantification of visceral or subcutaneous adipose tissue using computed tomography.[27] However, studies report that indicators such as BMI and WC are good tools to use in population-based studies and increases in these measures are associated with a higher risk of developing hypertension.[28-30]

The positive association between overweight based on BMI and hypertension in the semi-arid region of Pernambuco underscores the need for more effective dietary and nutritional education programs derived from health promotion policies and actions, in addition to greater encouragement to practice physical activity. Strategies of this nature would have a higher impact on the process of nutritional transition that has affected the country[31] and culminated in a 26.3% increase in overweight between 2006 and 2016, according to a telephone survey conducted by the Brazilian Ministry of Health.[32]

The concomitant occurrence of hypertension and reduced glucose tolerance and/or DM supports the scientific evidence indicating the close link between these conditions, which often develop together and through the same metabolic pathways.[33] An analysis of the Brazilian National Household Surveys conducted in 1998, 2003, and 2008 shows an increase from 1.7 to 2.8% in the prevalence coefficient standardized by gender and age range for DM associated with hypertension in the period, especially in the northeast and midwest regions of the country.[34] These data further highlight the considerable problems these conditions represent, especially in regions such as Northeastern Brazil and mesoregions such as the semi-arid region.

Table 2 – Distribution of systemic arterial hypertension according to behavioral characteristics in adults from the semi-arid region, state of Pernambuco, Brazil, 2015

Variables	Systemic arterial hypertension			p-value§
	n	%	95%CI	
Alcohol intake*				**0.330**
Yes	26	31.7	21.9 – 42.9	
No	88	26.3	21.8 – 31.5	
Active smoking				**0.000**
Smoker or ex-smoker	54	55.7	45.2 – 65.8	
Never smoked	60	18.8	14.8 – 23.6	
Passive smoking†				**0.000**
Yes	32	47.1	34.8 – 59.6	
No	82	23.6	19.3 – 28.4	
Physical activity level‡				**0.078**
Sedentary or insufficiently active	61	32.4	25.8 – 39.6	
Active or very active	33	44.0	32.5 – 55.9	
Addition of salt to food				**0.200**
Never	106	28.3	23.9 – 33.3	
Sometimes or almost always	8	19.0	08.6 – 34.1	

*95%CI: 95% confidence interval; * considering the 30 days prior to data collection; † individuals who do not actively smoke but are frequently in contact with cigarette smoke from people at home, work, or school/university; ‡ classified using the International Physical Activity Questionnaire (IPAQ); § Pearson's chi-square test.*

Table 3 – Distribution of systemic arterial hypertension according to health and nutritional characteristics in adults from the semi-arid region, state of Pernambuco, Brazil, 2015

Variables	Systemic arterial hypertension			p-value**
	n	%	95%CI	
BMI				0.019
Not overweight*	29	19.9	13.7 – 27.3	
Overweight†	76	30.6	25.0 – 36.8	
WC				0.082
Normal‡	29	21.8	15.1 – 29.8	
Increased§	81	30.0	24.6 – 35.8	
Waist-to-height ratio				0.012
Normal//	17	17.0	10.2 – 25.8	
Increased¶	87	29.8	24.6 – 35.4	
Food security#				0.245††
Food security	35	34.0	24.9 – 44.0	
Mild food insecurity	33	23.7	16.9 – 31.7	
Moderate or severe food insecurity	46	26.4	20.1 – 33.6	

*95%CI: 95% confidence interval; BMI: body mass index; WC: waist circumference; * BMI < 25.0 kg/m²; † BMI ≥ 25.0 kg/m²; ‡ < 80 cm for women and < 94 cm for men; § ≥ 80 cm for women and ≥ 94 cm for men; // < 0.52 for men and < 0.53 for women; ¶ ≥ 0.52 for men and ≥ 0.53 for women; # classified according to the Brazilian Food and Nutritional Insecurity Scale; ** Pearson's chi-square test; †† chi-square test for trend.*

The lack of associations between hypertension and alcohol intake, sedentary lifestyle, and the addition of salt to food after preparation was an unexpected finding, as these aspects are traditionally considered risk factors for the disease.[6] This paradox may be attributed to reverse causality, which consists of the repercussion of a disease positively changing the behavior of individuals, as many respondents were aware of their hypertension at the time of data collection. Another possible explanation for the lack of such associations would be the sample size, which was

Table 4 – Distribution of systemic arterial hypertension according to biochemical variables in adults from the semi-arid region, state of Pernambuco, Brazil, 2015

Variables	Systemic arterial hypertension			p-value[#]
	n	%	95%CI	
Fasting blood glucose				**0.000**
Normal[*]	56	28.4	22.2 – 35.3	
Reduced glucose tolerance and/or DM[†]	30	68.2	52.4 – 81.4	
Triglycerides				**0.416**
Normal[‡]	32	32.7	23.5 – 42.9	
High[§]	54	37.8	29.8 – 46.2	
Total cholesterol				**0.005**
Normal[//]	27	25.7	17.7 – 35.2	
High[¶]	59	43.4	34.9 – 52.1	

95%CI: 95% confidence interval; DM: diabetes mellitus; [*] < 100 mg/dL; [†] ≥ 100 mg/dL or when hypoglycemic medication was used; [‡] < 150 mg/dL; [§] ≥ 150 mg/dL; [//] < 190 mg/dL; [¶] ≥ 190 mg/dL; [#] Pearson's chi-square test.

Table 5 – Crude and adjusted prevalence ratios for systemic arterial hypertension according to explanatory variables in adults from the semi-arid region, state of Pernambuco, Brazil, 2015

Variables	n	Systemic arterial hypertension				p-value[§]
		Crude analysis		Adjusted analysis		
		PR	95%CI	PR	95%CI	
Age (years)						
20 – 29	13	1.00		1.00		
30 – 39	20	1.05	0.97 – 1.13	1.05	0.97 – 1.13	0.214
40 – 49	25	1.24	1.12 – 1.36	1.24	1.12 – 1.36	0.000
50 – 59	56	1.42	1.31 – 1.53	1.42	1.31 – 1.53	0.000
Economic class[*]						
Upper or middle	45	1.00		1.00		
Lower	69	1.12	1.05 – 1.20	1.09	1.02 – 1.17	0.007
Active smoking[†]						
Never smoked	54	1.00		1.00		
Smoker or ex-smoker	60	1.31	1.22 – 1.41	1.11	1.02 – 1.22	0.023
BMI[‡]						
Not overweight	29	1.00		1.00		
Overweight	76	1.09	1.02 – 1.17	1.21	1.07 – 1.37	0.003
Fasting blood glucose[‡]						
Normal	56	1.00		1.00		
Reduced glucose tolerance and/or DM	30	1.31	1.19 – 1.44	1.15	1.03 – 1.27	0.012

PR: prevalence ratio; 95%CI: 95% confidence interval; BMI: body mass index; DM: diabetes mellitus; PR 1.00 - reference; [*] adjusted for age, schooling, and employment status; [†] adjusted for age, schooling, employment status, economic class, passive smoking, and physical activity level; [‡] adjusted for age, schooling, employment status, economic class, passive smoking, physical activity level, BMI, WC, waist-to-height ratio, and fasting blood glucose; [§] Poisson regression with robust variance.

calculated only to estimate the prevalence of the outcome, possibly limiting the robustness of sub-analyses. Also, the predominance of females in the present study may have been due to the sampling method adopted.

The cross-sectional design constitutes another limitation of the present study by not allowing the inference of causality, as information on exposure and outcome are collected at the same time. However, this study makes important contributions to the knowledge about the epidemiology of hypertension in the population investigated. According to Vianna and Segall-Corrêa,[35] initiatives such as the present study are important and necessary for the acquisition of previously

unpublished information that can be used for regional, national, and international comparisons. Cross-sectional studies conducted in specific locations can provide better knowledge of local aspects, peculiarities, and risk factors that could go unnoticed in analyses involving broader territorial units, thereby complementing information on the geographic distribution of the disease.

Conclusion

The prevalence of hypertension was high in the semi-arid region studied and was associated with important risk factors, such as increasing age, low socioeconomic class, active smoking, overweight, and reduced glucose tolerance and/or DM. The constant monitoring of chronic non-communicable diseases, especially hypertension, DM, and obesity, and their associated factors is fundamental to the planning and continuous improvement of public health programs and actions, as well as the drafting of specific strategies for the region studied.

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Author contributions

Conception and design of the research: Santiago ERC, Oliveira JS, Leal VS, Lira PIC; Acquisition of data: Leal VS, Lira PIC; Analysis and interpretation of the data: Santiago ERC, Diniz AS, Oliveira JS, Leal VS; Statistical analysis: Santiago ERC, Andrade MIS; Obtaining financing: Diniz AS; Writing of the manuscript: Santiago ERC; Critical revision of the manuscript for intellectual content: Santiago ERC, Diniz AS, Oliveira JS, Leal VS, Andrade MIS, Lira PIC.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Pernambuco under the protocol number 897.655. 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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Social Determinants of Hypertension

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Short Editorial related to the article: Prevalence of Systemic Arterial Hypertension and Associated Factors Among Adults from the Semi-Arid Region of Pernambuco, Brazil

Hypertension (HT) is a disease with high prevalence in adults and is generally referred to as a 'complex disease'. This term has been used to indicate the diversity of factors that contribute to its onset.[1,2]

Studies in populations, twins, and families estimate that the impact of genetic background on the onset of HT ranges from 34% to 64%.[3] However, pressure regulation depends on a multiplicity of organs, systems, and mechanisms, which is why a large number of genes affect individual values. As a result, genetic tests are still largely ineffective as predictors of HT, since monogenic inheritance of this disease is rare.[4] Non-genetic factors are also numerous and are linked to lifestyle (nutrition, physical activity, alcohol and tobacco consumption, among others) or to the presence of conditions connected with a chronic inflammatory state, such as obesity and insulin resistance. In the presence of these factors, blood pressure increase with age is faster, leading to, at a given moment, blood pressure levels indicative of the presence of the disease. It is important to point out that the cutoffs that separate the states of 'normotension' and 'hypertension' are statistical, being suitable for use with populations, and potentially unsuitable in assessing individuals,[5] as the disease may be present in a subclinical state, i.e., even before reaching diagnostic blood pressure levels obtained in epidemiological studies. Therefore, given the difficulty of using genetic data, disease prevention should be undertaken by identifying risk factors that contribute to raising blood pressure. In this context, epidemiological knowledge about specific populations is an essential tool for handling the disease.

Despite its high impact on morbidity and mortality, and on economic and social costs, the epidemiology of HT and its determinants are still poorly known for the Brazilian population. Only in recent years has a robust and nationwide study been conducted in this area. The large territorial extent and the racial and cultural diversity of the Brazilian population also require regional studies. The National Health Survey (*PNS*) conducted in 2013 by the Ministry of Health with support from the *IBGE* [Brazilian Geography and Statistics Institute] in a representative and robust sample (N > 60 thousand) of the Brazilian adult population, showed a self-reported prevalence of HT of 21.4%, more frequent in women (24.2%) than men (18.3%). Upon changing the diagnostic criterion, considering those with blood pressure measured at home ≥ 140/90 mmHg, or those taking antihypertensive drugs, as individuals with HT, the prevalence rose to 32.3%, with a higher prevalence in men.[6] The study also showed differences between regions, with lower prevalences seen in the North and Northeast and higher ones in the South and Southeast. The disease was also less frequent in rural residents. Part of the regional differences may stem from different race/color compositions. Indigenous peoples apparently have lower blood pressure readings[7] and this may translate into a lower impact of the disease on populations with a greater presence of the indigenous trait, such as in the Northern region. Regional differences may also stem from the uneven distribution of general factors that affect blood pressure regulation, such as high salt intake, body fat accumulation, physical inactivity, alcohol abuse, and insulin resistance. The large territorial extent and cultural diversity may contribute to the non-uniform distribution of these factors and, consequently, the variability in the distribution of HT and other chronic diseases. More recently, the role of socioeconomic variables in the emergence, progress, and outcomes related to blood pressure is being viewed with increasing importance. Large studies, such as the Longitudinal Study of Adult Health (*ELSA-Brasil*), show the impact of low education and income levels on increased blood pressure and on the prevalence of the disease.[8] These data indicate that the Brazilian population segment living in more unfavorable conditions is more subject to the impact of the disease. And this has important consequences for addressing this health problem.

In this issue of the *Arquivos Brasileiros de Cardiologia* [Brazilian Cardiology Archives], Santiago et al.[8] publish data on a population-based study aimed at identifying the characteristics and prevalence of HT in the adult population (20-59 years) residing in the semiarid region of Pernambuco, in the Northeastern region of Brazil.[8] For this purpose, a representative sample of urban and rural households was selected by drawing from census tracts from three municipalities. The study showed that the overall prevalence of HT was 27.4%, with a predominance in males. Despite not having the statistical power for more detailed analyses of subgroups, it is clear from the data that the disease affects, with greater impact, the population segments with lower education and income, two variables that are represented in the socioeconomic classification of the households. The association between the presence of the disease and low education is impressive. While in the segment with higher education the presence of HT was found in 15.4%

Keywords

Hypertension; Hypertension/prevention and control; Prevalence; Risk Factors; Obesity; Diabetes Mellitus, Epidemiology.

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of the individuals, in the lowest segment the number increased to 44.6%, i.e., the probability of the disease being found was almost 3 times higher in the population segment with a low education level. Considering that education and income are two collinear variables in the Brazilian population, in the multivariate analysis model, schooling level dropped out of the modeling, leaving only the socioeconomic level as an independent predictor of the disease's presence. However, according to the Brazilian standard, both education and income enter into the socioeconomic classification model.

What still needs to be further investigated is the mediation between socioeconomic variables (education and income) and blood pressure. The *ELSA-Brasil* provided some clues on this.[9] Participants of African ancestry (Blacks and Browns) present higher blood pressure and higher blood pressure increase with age, thus predisposing to the onset of HT in adulthood. It is not known, however, whether this difference arises from birth or occurs later. Our research group has been seeking answers by studying children and adolescents of different races/color. We have shown that pre-pubertal students have equal blood pressure values, regardless of race/color.[10] The differences, therefore, appear later in adolescence or, more likely, in adulthood. Psychosocial stress could constitute an important factor in increased pressure with age and, therefore, in the onset of HT.[11] This could explain, albeit in part, the inverse relationship between education/income and HT prevalence. Individuals at the bottom of the social pyramid would live in greater uncertainty regarding their future. The struggle for survival is greater and the social support network related to adverse events in life (unemployment, adverse weather events such as prolonged drought in rural backlands) is less at the base of the pyramid, and this would determine a higher intensity allostatic load on these individuals (increased sympathetic activity, activation of the hypothalamic-adrenal-cortisol axis, attenuation of vagal function) contributing to a faster blood pressure increase over time and contributing to the earlier onset of hypertensive disease. Even without yet understanding where the initial deregulation that would lead to essential HT would be, this chain of events could explain the findings described by Santiago et al.[8] and other authors. This reasoning could explain, in theory, the small decrease in the prevalence of HT in Brazil described by Picon et al.[12] in a meta-analysis based on population-based studies with direct blood pressure measurement.[12] It is noteworthy that in this meta-analysis almost all studies were done in cities in the South and Southeast regions of Brazil, where the population's educational level has been improving in recent decades.

Regardless of the mechanism, the data described for the Brazilian population, showing an inverse relationship between education level and HT, pose an additional challenge in addressing the problem. Once diagnosed, the disease must be treated. At this stage, the adoption of healthy lifestyle habits is mandatory in relation to diet (rich in whole grains, fresh fruits and vegetables), physical activity, and quitting smoking and alcohol abuse. If such measures are insufficient for pressure normalization, then medication use enters as an effective measure. However, various factors contribute to the fact that both the adoption of healthy habits, as well as the use of medications, is more difficult for individuals in lower socioeconomic segments. Therefore, those who are most affected by the disease will have less conditions to treat it. Medications, although effective, must be used correctly, as their improper use can do more harm than good. Considering that the gateway to the diagnosis and treatment of HT in our country is the primary care sector, represented by the Primary Care Units, it is essential to engage all health teams, involving doctors, nurses, nutritionists, etc., so that the effectiveness of treatments for the hypertensive population becomes as homogeneous as possible, that is, regardless of socioeconomic factors. On the other hand, the data point to a fact of great significance. Improved education brings about health benefits in general and, particularly, for addressing chronic diseases, such as HT. Investments in education affects favorably the population health.

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Short Editorial

Co-occurrence of Smoking and Unhealthy Diet in the Brazilian Adult Population

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Abstract

Background: **Smoking and an inadequate diet are behavioral risk factors that contribute to the majority of deaths and disabilities caused by noncommunicable diseases.**

Objectives: **To estimate the prevalence of the co-occurrence of smoking and inadequate diet and identify associated factors in adults.**

Methods: **A cross-sectional population-based study was conducted with a sample of 28,950 Brazilian adults (18 to 59 years old). Data were obtained from Sistema de Vigilância por Inquérito Telefônico (Vigitel [Brazilian Health Surveillance Telephone Survey]) in 2014. Independent associations were investigated using Poisson hierarchical regression analysis with 5% significance level.**

Results: **The prevalence of the co-occurrence of smoking and unhealthy eating was 8.6% (95% CI: 7.9–9.3) and was higher among individuals residing in the southern region of the country than in those living in the central western region (PR = 1.50; 95% CI: 1.18–1.89), those with no private health insurance (PR = 1.14; 95% CI: 1.03–1.25), those who drank alcohol abusively (binge drinkers) (PR = 3.22; 95% CI: 2.70–3.85) and those who self-rated their health as fair (PR = 1.65; 95% CI: 1.36–1.99) or poor/very poor (PR = 1.70; 95% CI: 1.18–2.44). The prevalence of both factors was lower among individuals residing in the northeastern region of the country, women, individuals with brown skin color, those with a spouse, the more educated ones and those with overweight or obesity.**

Conclusion: **The more vulnerable segments to the co-occurrence of the risk factors studied were men residing in the southern region of the country, individuals with a lower socioeconomic status and those who reported binge drinking. Interventions addressing multiple behavioral risk factors adapted to specific contexts could have a greater impact on the Brazilian population. (Arq Bras Cardiol. 2019; 113(4):699-709)**

Keywords: **Tobacco Use Disorders; Feeding; Risk Factors; Risk reduction Behavior; Chronic Disease; Adult Health; Health Status Disparities.**

Introduction

Behavioral risk factors are responsible for the majority of deaths due to noncommunicable diseases (NCDs)[1,2] and part of the diseases resulting from these conditions.[3-5] Such factors included smoking, abusive alcohol intake, inadequate diet, physical inactivity, obesity, dyslipidemia, excessive animal fat intake and insufficient intake of fruits and vegetables.[6,7] According to a study conducted in 52 countries, these factors, combined with arterial hypertension, diabetes mellitus and psychosocial stress account for 90% and 94% of the attributable risk of cardiovascular disease among men and women, respectively.[8]

The World Health Organization attributes smoking to an estimated six million deaths per year. Insufficient intake of fruits and vegetables corresponds annually to 2.7 million deaths, 31% of ischemic heart diseases, 11% of cerebrovascular diseases and 19% of gastrointestinal cancers in the world.[9] Despite the reduction in the percentage of smokers in Brazil in recent years,[10,11] population-based health surveys have indicated that the prevalence of smoking is greater among adults (40 to 59 years old) and those with a lower education level.[10-12] Moreover, the prevalence of an unhealthy diet is high,[10,13,14] especially among men, adolescents and individuals with a lower education level.[13,14]

NCDs have multiple causes that occur simultaneously, resulting in distinct effects.[5] Studies indicate that the accumulation of two or more modifiable risk factors increases the occurrence of NCDs[8,15,16] and cardiovascular diseases[8] and is related to the overall death rate as well as death due to specific causes.[1,2] Risk behaviors are harmful actions that either increase the probability of disease or impede the recovery of health.[17] Therefore, behavioral (modifiable) risk factors are component causes that contribute to increased morbidity and mortality rates due to cardiovascular diseases, diabetes mellitus and cancer in adults and seniors.[1,5,15] The greatest impact of exposure to

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these factors is seen at more advanced ages. However, early signs of changes in health status occur more frequently from 40 years of age.[18,19]

Brazil has an adult population (18 to 59 years of age) of approximately 114 million. The co-occurrence of smoking and an unhealthy diet has been under-investigated in the literature. Exposure to behavioral risk factors begins early in life[16,18] and is consolidated in adulthood,[13] with effects on health in different phases of life. Therefore, the objective of this study was to estimate the co-occurrence of smoking and unhealthy eating practices in the Brazilian adult population as well as determine associations with socio-demographic characteristics and health indicators.

Methods

A cross-sectional population-based study was conducted with a sample of adults (18 to 59 years old) residing in the capitals of the 26 states of Brazil and the Federal District. The data were extracted from the records of 28,950 individuals interviewed in *Sistema de Vigilância por Inquérito Telefônico* (Vigitel [Brazilian Health Surveillance Telephone Survey]), in 2014.

A minimum sample of 1,500 individuals in each city was established to estimate the frequency of any risk factor in the adult population[20] considering a 95% confidence interval and a maximum error of three percentage points.[7] Data collection was performed in three steps. The first step consisted of systematic random selection of at least five thousand telephone lines. This systematic selection stratified by postal code was performed using records of residential landlines registered with telephone companies. The lines selected in each city were submitted to a second random selection divided into replicates of 200 lines, with each replicate reproducing the same proportion of lines per postal code of the original registry. The third step was the random selection of one of the adults residing in the selected homes (after identification) among the lines considered eligible for the system. The following were excluded in this step: business lines, out-of-service or nonexistent lines and lines for which there was no answer after six calls on different days and at different times, including weekends and evening hours[7] (Figure 1).

Weighting factors were used to compensate for the bias of the non-universal coverage of landlines. Using a post-stratification weight calculated based on 36 analysis categories by sex (female and male), age group (18–24, 25–34, 35–44, 45–54, 55–64 and ≥65 years old) and level of education (none or incomplete primary school, complete primary school or incomplete high school, complete high school or incomplete university degree and complete university degree), the estimates were adjusted to the population. The "rake" method was used for the calculation

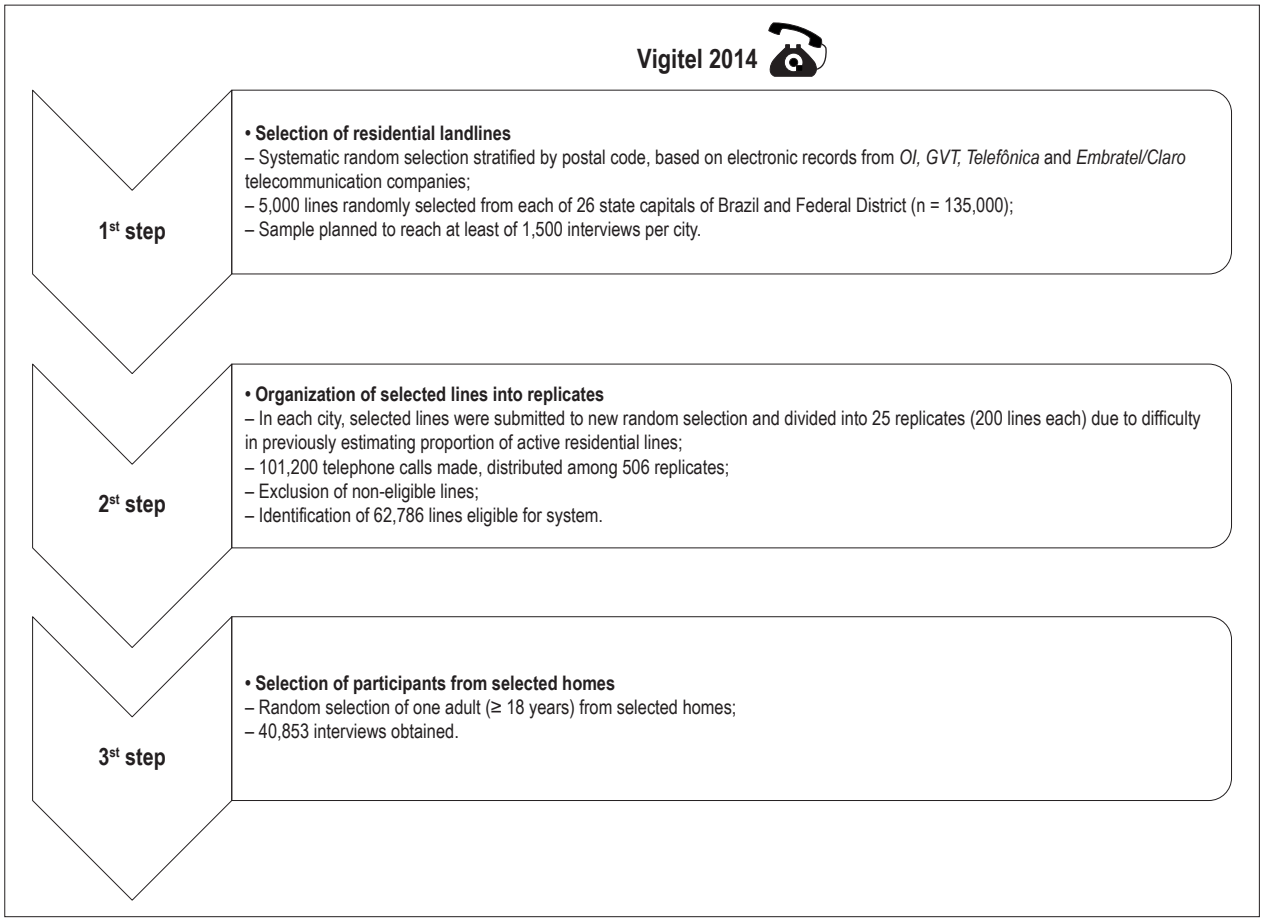

Figure 1 – *Flowchart of sample selection process. Vigitel, 2014.*

of the post-stratification weight of each individual in the sample. Information on the sample design of the Vigitel survey, the data collection instruments and procedures used in the interviews is published elsewhere.[7]

In the present study, the co-occurrence of smoking and an inadequate diet was considered the variable of interest. A smoker was considered any individual who answered affirmatively to the following question: "Do you currently smoke?," irrespective of the number of cigarettes, frequency and duration. The indicator of an unhealthy diet was created from a set of foods that serve as markers of the intake profile associated with protection from chronic diseases (beans, fruits, milk, raw vegetables and cooked vegetables) and risk for chronic diseases (red meat, sweets and sweetened beverages). Scores ranging from zero to four were attributed depending on the food and intake frequency. Markers of the protection category ingested daily and those of the risk category never or rarely ingested were not scored (zero). Maximum of four points was attributed to protective foods never or rarely consumed and risk foods ingested daily (Table 1). The total score was determined by the sum of food items and ranged from 0 to 32 points, with higher scores indicating poorer dietary quality. This variable was then categorized considering distribution terciles. Individuals in the 2nd and 3rd terciles (14 or more points) were grouped together, creating a dichotomous variable for unhealthy eating (yes or no). Co-occurrence was determined by the simultaneous occurrence of both of these conditions (smoking and unhealthy diet).

The following socio-demographic variables were considered: macro-region of the country (North, Northeast, Central West, South and Southeast), sex (male and female), age group (18 to 39 and ≥ 40 years old), skin color/ethnicity (white, black, yellow, brown and indigenous), marital status (with and without a spouse), education (0 to 8, 9 to 11 and 12 or more years of study) and having a private health insurance plan (yes or no). The following variables related to behavior and health status were considered: body mass index (BMI) (< 25 kg/m², ≥ 25 to < 30 kg/m² and ≥ 30 kg/m²), binge drinking [five or more drinks for men and four or more drinks for women on a single occasion in the previous 30 days (yes or no)], practice of physical activity (active or inactive) and self-rated health (very good/good, fair or poor/very poor). Weight and height were self-reported by the respondents. BMI was calculated for all records based on the imputation of the measures of weight and height using the "hot deck" method.[7] The following diseases were also considered: arterial hypertension, diabetes mellitus and dyslipidemia (all categorized as "yes or no").

Statistical analysis

Descriptive analysis was performed for the characterization of the study population. Age (continuous variable) was expressed as mean and respective 95% confidence interval. Categorical variables were expressed as relative frequency (percentage).

Prevalence values were estimated for smoking, unhealthy eating and the co-occurrence of both of these variables of interest according to socio-demographic characteristics, other behavioral factors and health conditions. Associations were determined between the co-occurrence of the risk factors and variables selected using Pearson's chi-square test with second-order correction (Rao & Scott), considering a 5% significance level. Next, prevalence ratios were estimated and adjusted for sex and age according to socio-demographic characteristics, behavioral factors and health conditions. A hierarchical Poisson regression model was used considering two sets of variables: 1) socio-demographic and 2) behavioral/health conditions. The variables from the first block were incorporated into the model. Those that remained significant after adjustments by the other variables on the same hierarchical level remained in the model, to which the second block of variables was incorporated. All variables with p-value < 0.05 after adjustments for variables on the same and higher hierarchical level remained in the final model. The analyses were performed using the Stata statistical package, version 12.0.

The objectives of the survey were made clear to all individuals contacted by telephone and written consent was substituted with verbal consent. The Vigitel study received approval from the National Human Research Ethics Committee of the Brazilian Health Ministry (certificate number: 355.590, June 26, 2013).

Table 1 – Scoring scale for unhealthy consumption of foods. Vigitel, 2014

Foods	0	1	2	3	4
Beans	Every day	5 to 6 days a week	3 to 4 days a week	1 to 2 days a week	Never or hardly ever
Fruits	Every day	5 to 6 days a week	3 to 4 days a week	1 to 2 days a week	Never or hardly ever
Raw vegetables[1]	Every day	5 to 6 days a week	3 to 4 days a week	1 to 2 days a week	Never or hardly ever
Cooked vegetables[2]	Every day	5 to 6 days a week	3 to 4 days a week	1 to 2 days a week	Never or hardly ever
Milk	Every day	5 to 6 days a week	3 to 4 days a week	1 to 2 days a week	Never or hardly ever
Red meat[3]	Never or hardly ever	1 to 2 days a week	3 to 4 days a week	5 to 6 days a week	Every day
Sweetened soft drink or artificial juice	Never orhardly ever	1 to 2 days a week	3 to 4 days a week	5 to 6 days a week	Every day
Sweets[4]	Never or hardly ever	1 to 2 days a week	3 to 4 days a week	5 to 6 days a week	Every day

[1]Lettuce and tomato salad or salad with any other raw vegetable. [2]Consumption of vegetables cooked with food or in soup, such as collards, carrot, eggplant, zucchini, except potato, cassava or yam. [3]Red meat: beef, pork, goat.[4] Consumption of sweets, such as ice cream, chocolate, cakes, cookies, etc.

Results

Mean age of the sample was 36.4 years (95% CI: 36.1–36.6); the majority was women (53.0%) and young adults (59.4%). The prevalence of the co-occurrence of the risk factors was 8.6% (95% CI: 7.9–9.3).

Table 2 shows the prevalence of smoking and an inadequate diet as well as associations with the other variables. No associations were found between smoking and BMI, physical inactivity, hypertension, diabetes or dyslipidemia ($p > 0.05$). All variables were associated with unhealthy eating, except for having a private health insurance plan ($p = 0.102$) and BMI ($p = 0.196$).

In the simple analysis, differences were found with regard to the region of the country, sex, skin color/ethnicity, education and health insurance ($p < 0.05$). Associations were found between the co-occurrence of risk factors and both binge drinking ($p < 0.001$) and self-rated health ($p < 0.001$). Higher frequencies of the co-occurrence of risk factors were found among individuals residing in the southern and southeastern regions of the country compared to those residing in the central western region. Higher frequencies were also found among individuals who did not have private health insurance, binge drinkers and individuals who reported their health to be fair, poor or very poor at the time of the interview. After controlling for sex and age, the prevalence of the co-occurrence of risk factors was lower among individuals who resided in the northern and northeastern regions of the country, women, individuals with brown skin color, those with a spouse and those with excess weight. The prevalence of the two risk factors also reduced significantly with higher education levels ($p < 0.001$) (Table 3).

Table 4 shows the hierarchical Poisson regression model of factors associated with the co-occurrence of smoking and unhealthy eating. The prevalence of both factors was lower in the northeastern region of the country (PR = 0.67; 95% CI: 0.54–0.83) and higher in the southern region (PR = 1.40; 95% CI: 1.11–1.77) compared to the central western region. The prevalence was approximately 40% lower among women and was also lower among individuals with brown skin and those who lived with a spouse. The prevalence reduced significantly with higher education levels and was approximately 16% higher among individuals without private health insurance (PR = 1.16; 95% CI: 1.05–1.27) after controlling for region of residence and other socio-demographic factors. Regarding behaviors and health conditions, excess weight was inversely associated with the co-occurrence of both risk factors. The prevalence was higher among those who considered their health to be fair or poor/very poor. Moreover, a strong, independent, statistically significant association was found between binge drinking and the co-occurrence of the risk factors considered (PR = 3.22; 95% CI: 2.70–3.85).

Discussion

The prevalence of the co-occurrence of smoking and an unhealthy diet was 8.6%. In a study conducted in England with a population aged 16 to 64 years, the prevalence of the co-occurrence of smoking and inadequate diet (measured by the consumption of beans, vegetables and fruits) was 25.5% among men and 23.6% among women.[21] In this study, which considered four lifestyle risk factors, the prevalence of smoking was 28.0% and insufficient intake of beans, fruits and vegetables was represented by the failure to have five portions of these foods, as recommended. The divergence in frequencies may be explained by cultural diversity and the diversity of eating habits in different populations. In a study conducted in the city of Botucatu (state of São Paulo, Brazil), Berto et al.[22] investigated the association between smoking and other behavioral risk factors in adults and found the co-occurrence of smoking and low intake of fresh fruits and vegetables (12.9% and 12.3% among men and 5.8% and 5.1% among women, respectively). In a study conducted with adults in the city of Florianópolis (state of Santa Catarina), the prevalence of the co-occurrence of smoking and an inadequate diet was 3.5%; inadequate diet was considered the reported intake of fruits and vegetables ≤5 days per week.[13]

In an American study with an adult population (≥20 years), smokers had a diet of poor quality, with less intake of fruits, vegetables, dairy products and whole grains as well as a greater percentage of energy from solid fats, alcohol and added sugar.[23] A study conducted with adult smokers found that fruits and vegetables, noncaffeinated beverages, sweets and dairy products worsened the sensory attributes of cigarettes, whereas meats, alcoholic beverages and caffeinated drinks improved the sensory attributes.[24] Haibach et al.[25] found that smokers who ingested more fruits and vegetables had lower levels of nicotine dependence and greater occurrence of smoking cessation.

To make the dietary indicator employed in the present study, we considered whole milk a marker of healthy diet. The results of epidemiological studies evaluating dietary sources of saturated fat have revealed the lack of an association or beneficial effects of dairy products on cardiovascular diseases.[26,27] Considering the gaps in the scientific literature on the association between milk consumption and health, Lamarche et al.[27] report the need to investigate whether whole milk and skim milk have different effects on health. Data from the 2008-2009 Brazilian Family Budget Survey revealed that the adult population has low consumption of dairy products (100 g/ml per day),[28] but high consumption of red and processed meats (90 g per day), with more than 80% of the participants exceeding the limit recommended by the World Cancer Research Fund (300 g per week).[29]

It should be stressed that the Vigitel survey did not address the consumption of processed meats or quantify the consumption of red meat. Therefore, only the frequency of weekly consumption was considered in the present study, regardless of the presence of visible fat. A previous study evaluating the attributable fraction of cancer in the adult population due to different exposures found that red meat is a risk factor for colon and rectal cancer when ingested at a rate of more than 70 g/day.[30]

In the present investigation, the co-occurrence of risk factors was higher in the southern region of Brazil and lower in the northeastern region than in the central western region. Reduced prevalence of smoking was found in all regions of the country between 2006 and 2013, but with the highest rates found in the South and the lowest in the

Table 2 – Prevalence of smoking and unhealthy diet in adults according to geographic region, socio-demographic characteristics, behavioral factors and health conditions. Vigitel, Brazil, 2014

Variable/categories	n	(%)	Smoking	p*	Unhealthy diet	p*
Geographic region						
Central West	4,068	11.8	9.9		70.3	
Northeast	9,912	25.7	7.8		68.4	
North	8,267	10.6	7.8	< 0.001	72.6	0.005
Southeast	4,110	44.1	13.3		69.8	
South	2,593	7.8	15.6		72.2	
Sex						
Male	11,704	47.0	13.2	< 0.001	76.6	< 0.001
Female	17,246	53.0	9.2		64.2	
Age group (in years)						
18 to 39	13,960	59.4	10.2	0.005	75.3	< 0.001
40 to 59	14,990	40.6	12.4		62.4	
Skin color/ethnicity						
White	10,780	41.9	11.9		69.6	
Black	2,713	11.7	12.8		70.1	
Yellow	790	3.0	9.0	< 0.001	82.0	0.002
Brown	12,015	41.8	9.1		69.9	
Indigenous	411	1.6	16.8		72.6	
Marital status						
With spouse	13,565	50.7	12.1	0.012	73.2	< 0.001
Without spouse	15,052	49.3	10.1		67.0	
Education (in years)						
0 to 8	5,720	29.7	16.3		66.4	
9 to 11	12,325	42.0	10.5	< 0.001	71.6	< 0.001
12 or more	10,905	28.3	6.6		71.2	
Private health insurance						
No	13,923	51.9	13.6	< 0.001	70.9	0.102
Yes	14,954	48.1	8.5		69.1	
BMI (kg/m^2)						
< 25	13,651	48.9	11.9		70.8	
≥ 25 to < 30	10,122	33.9	10.4	0.136	68.7	0.196
≥ 30	5,177	17.2	10.3		70.1	
Physical inactivity						
No	25,363	87.6	11.1	0.908	69.2	< 0.001
Yes	3,587	12.4	11.0		75.7	
Binge drinking						
No	24,048	81.5	8.0	< 0.001	67.8	< 0.001
Yes	4,902	18.5	2.5		79.3	
Self-rated health						
Very good/good	19,214	67.4	9.5		69.2	
Fair	8,328	28.5	13.4	< 0.001	71.8	0.028
Poor/very poor	1,193	4.1	18.7		73.8	

Continuation

Arterial hypertension						
No	22,887	81.7	11.1	0.743	71.1	< 0.001
Yes	6,063	18.3	11.4		65.2	
Diabetes mellitus						
No	27,356	94.9	11.1	0.811	70.9	< 0.001
Yes	1,594	5.1	11.4		53.3	
Dyslipidemia						
No	22,835	83.0	11.1	0.630	70.6	0.029
Yes	6,115	17.0	10.4		67.6	

**p-value of chi-square test with Rao-Scott correction. BMI: body mass index*

Northeast,[31] which may partially explain the present findings regarding the co-occurrence of smoking and an inadequate diet. Moreover, according to the 2008-2009 Family Budget Survey, northeastern and southern Brazil have different profiles in terms food purchase, with greater availability of red meat, processed meats, bacon, soft drinks and alcoholic beverages in the southern region.[32] Regional disparities in the distribution of modifiable risk factors are found in Brazil.[7,13,22,31] In the United States, a study addressing the co-occurrence of five healthy behaviors (not smoking, regular practice of physical activity, not consuming alcohol, maintaining one's weight and sleeping the recommended number of hours) in the adult population (≥21 years old) found geographic variations in the percentage distribution adjusted for age for the number of grouped factors.[33]

Regarding other socio-demographic characteristics, studies indicate that the prevalence of multiple risk factors is higher among young adults, men, individuals with a lower socioeconomic status (lower income and education) and those who live alone.[13,21,34] In the present study, the reduced co-occurrence of risk factors was found with higher education levels. Studies report an association between higher education level and healthy behaviors/health conditions.[10-14,19,21,34] The prevalence of co-occurrence was also lower among those with self-declared brown skin. In the city of Florianópolis (state of Santa Catarina), Silva et al.[13] found a greater occurrence of the accumulation of four risk factors in black adults. In the USA, racial/ethnic differences were found for five behaviors considered.[33] A study analyzing differences in the prevalence of risk factors for chronic diseases according to ethnicity/skin color found that, compared to whites, brown individuals smoked less and consumed fewer fruits, soft drinks and sweets as well as more beans, whole milk and meat with visible fat.[35] No studies were found in the national or international literature on the co-occurrence of smoking and an inadequate diet according to skin color/ethnicity.

The prevalence of the co-occurrence of risk factors was higher among individuals without a private health insurance plan. A study involving Brazilian adults found that individuals with private health insurance smoked less, ate better and practiced more physical activity during leisure hours.[36] The Health Ministry has taken several actions for reducing inequalities in the access and offer of healthcare services. The National Health Promotion Policy defends integral care, considering health promotion to be a strategy for organizing the actions and services of the public healthcare system, with a focus on factors that determine the health-disease process, intersectoral actions, social participation and the construction of healthy environments on individual and collective levels.[37] The National Food and Nutrition Policy and the Dietary Guide for the Brazilian Population[38] are important support instruments for the promotion of healthy eating within the Brazilian public health system (SUS, in its Portuguese acronym).

The prevalence of the co-occurrence of smoking and inadequate diet was lower among adults with excess weight. The inverse association found after adjustment for socio-demographic characteristics, behavioral factors and health conditions may be partially explained by the fact that smoking exerts an influence on metabolic processes; smokers weigh, on average, 4 kg less than non-smokers due to the increase in the metabolic rate, concomitantly with suppression of appetite.[39]

The prevalence of the co-occurrence of risk factors was higher among adults who reported binge drinking, which is a subgroup with greater vulnerability to NCDs. The planning of disease prevention actions should integrate population-based strategies and strategies directed at high-risk subgroups, as both are necessary and work in a synergistic way.[17] In the epidemiology of chronic diseases, the effect of a risk factor depends on the status of the individual for another factor (present/absent). Thus, the presence of two or more modifiable risk factors potentiates the occurrence of NCDs[8,15,16] and shorter time to the emergence of a disease leads to reduced healthy life expectancy. Data from four cohort studies on smoking, physical inactivity and obesity among individuals aged 50 to 75 in European countries revealed the impact of the co-occurrence of behavioral risk factors on the reduction in the expectancy of a healthy life free of chronic diseases.[40]

In the present study, the co-occurrence of risk factors was higher among those who did not rate their health positively. The literature describes the association between smoking and a

Table 3 – Prevalence and crude and adjusted prevalence ratios of smoking and inadequate diet according to geographic region, socio-demographic characteristics, behavioral factors and health conditions. Vigitel, Brazil, 2014

Variables/categories	n	Smoking/Inadequate diet	PR_{crude} (95% CI)	$PR^{*}_{adjusted}$ (95% CI)
Geographic region		< 0.001		
Central West	3,929	8.0	1	1
Northeast	9,200	5.8	0.73 (0.59–0.89)	0.73 (0.60–0.90)
North	7,791	6.2	0.78 (0.61–0.99)	0.78 (0.62–0.99)
Southeast	3,878	10.3	1.29 (1.04–1.59)	1.28 (1.03–1.57)
South	2,481	12.2	1.53 (1.23–1.90)	1.51 (1.21–1.87)
Sex		< 0.001		
Male	10,983	10.8	1	1
Female	16,296	6.7	0.61 (0.52–0.72)	0.60 (0.51–0.71)
Age group (in years)		0.167		
18 to 39	12,985	8.2	1	1
40 to 59	14,294	9.2	1.12 (0.95–1.31)	1.15 (0.98–1.34)
Skin color/ethnicity		0.008		
White	10,263	9.5	1	1
Black	2,534	9.3	0.98 (0.76–1.25)	0.98 (0.76–1.25)
Yellow	733	6.8	0.71 (0.44–1.16)	0.75 (0.46–1.22)
Brown	11,283	7.2	0.75 (0.61–0.92)	0.76 (0.62–0.93)
Indigenous	389	13.3	1.40 (0.84–2.32)	1.38 (0.85–2.24)
Marital status		0.062		
Without spouse	12,621	9.3	1	1
With spouse	14,351	8.0	0.85 (0.72–1.01)	0.72 (0.60–0.87)
Education (in years)		< 0.001		
0 to 8	5,227	12.4	1	1
9 to 11	11,526	8.4	0.67 (0.56–0.81)	0.70 (0.58–0.85)
12 or more	10,526	5.3	0.42 (0.33–0.53)	0.45 (0.35–0.56)
Private health insurance		< 0.001		
Yes	14,324	6.7	1	1
No	12,886	10.5	1.25 (1.15–1.36)	1.24 (1.14–1.35)
BMI(kg/m²)		0.055		
<25	12,867	9.5	1	1
≥25 to < 30	9,564	7.8	0.82 (0.68–0.98)	0.73 (0.61–0.89)
≥30	4,848	7.9	0.83 (0.66–1.03)	0.75 (0.60–0.94)
Physical inactivity		0.993		
No	23,992	8.6	1	1
Yes	3,287	8.6	1.00 (0.78–1.28)	0.97 (0.75–1.25)
Binge drinking		< 0.001		
No	22,644	6.0	1	1
Yes	4,635	19.9	3.30 (2.81–3.88)	3.17 (2.68–3.76)
Self-rated health		< 0.001		
Very good/good	18,312	7.3	1	1
Fair	730	11.1	1.53 (1.28–1.82)	1.57 (1.31–1.87)
Poor/very poor	1,048	13.1	1.80 (1.31–2.48)	1.91 (1.40–2.61)

Continuation

Arterial hypertension		0.815		
No	21,559	8.6	1	1
Yes	5,720	8.4	0.97 (0.79–1.19)	0.88 (0.71–1.08)
Diabetes mellitus		0.658		
No	25,780	8.6	1	1
Yes	1,499	8.0	0.92 (0.63–1.33)	0.83 (0.57–1.21)
Dyslipidemia		0.475		
No	21,485	8.7	1	1
Yes	5,794	8.1	0.93 (0.75–1.13)	0.87 (0.70–1.06)

*n: number of individuals in the unweighted sample. *$PR_{adjusted}$: prevalence ratio adjusted for sex and age. 95% CI: 95% confidence interval.*

poor perception of health in the adult population.[34,41] A study involving the Brazilian population ≥18 years of age also found poor assessments of health among individuals who did not consume fruits and vegetables regularly.[41] A study conducted in Madrid, Spain with 16,043 adults (18 to 64 years old) found that the accumulation of risk factors increased the frequency of perceived poor health in a progressive manner.[34]

No associations were found between the co-occurrence of risk factors and arterial hypertension, diabetes or dyslipidemia. In the analysis of individual risk factors, these conditions were only associated with an inadequate diet. National studies have not found an association between current smoking and arterial hypertension or diabetes, as found for former smokers.[42,43] A significant reduction in smoking occurred between 2006 and 2015[31,44] and a substantial increase in excess weight has occurred as a result of negative changes in the eating patterns of the population.[32,45] It should be stressed that the greatest incidence of these diseases and other health-related problems is found at more advanced ages. In the present study, the co-occurrence of the two risk factors did not necessarily express an additional risk for these outcomes in the adult population analyzed.

Estimates of the clustering of behavioral risk factors for NCDs performed in international studies[1,21,34,40] have led to the recognition that many of these factors are interrelated.[17] Effective prevention resides in reducing the concomitant occurrence of various risk factors related to these diseases, on both the individual and collective levels. The incidence of a given disease is important to primary prevention, as the risk is low for the majority of individuals, regardless of the disease.[15] Strategies on the population level seek to control determinants of the disease with interventions directed at environmental factors that make the disease prevalent.[46] Stratification of the population according to risk enables the identification of its distribution in the population and the adoption of specific prevention practices focused on priority subgroups.

Interventions that address multiple risk factors can have a greater impact than those focused on isolated behaviors.[2,15] The co-occurrence of health-related behaviors suggests complementary and substitutive relations. In Brazil, the goal of the Strategic Action Plan to Combat Non-Communicable Diseases is the reduction in the prevalence of smoking in the adult population from 15.1% (2011) to 9.1% (2022). Regarding dietary practices, the goal is to reduce mean salt intake from 12 g (2010) to 5 g (2022). The increase in the consumption of fruits and vegetables is on the list of monitoring indicators of the World Health Organization, but is not on the list of goals.[47] Global strategies adopted in specific contexts need to be implemented, broadened and, especially, maintained.

The present study has limitations that should be considered. The sample was restricted to the population with a landline at home, which diminished the participation of the northern and northeastern regions of the country, where coverage rates are lower. However, the use of weighting factors minimized the difference between populations with and without a telephone line.[7] Further limitations include the use of self-reported information and the impossibility of establishing causal relations due to the cross-sectional design of the study. It is not possible to affirm whether individuals with excess weight quit smoking and made changes in eating practices or whether smoking and a poor diet led to weight loss.

Conclusion

In the present study, the segments that are more vulnerable to the co-occurrence of smoking and an inadequate diet were residents of the southern region of the country, men, individuals with a lower socioeconomic status and those who reported binge drinking. Interventions addressing multiple behavioral risk factors, adapted to specific contexts, could have a greater impact on the Brazilian population. Regarding the management of healthcare services, information obtained from indicators can help guide the implementation, monitoring and assessment of healthcare models and actions directed at health promotion, as well as disease prevention and control.

Considering the increasing social inequality in Brazil and the consolidation of a dietary system centered on monocultures for the production of ultraprocessed foods that are disseminated throughout all social strata of the population through strong marketing strategies, the promotion of health and prevention of worsening of adverse health conditions are powerful and absolutely necessary strategies for reducing the impact of social profile on health and the access of the population to healthy aging.

Table 4 – Hierarchical Poisson regression model for factors associated with co-occurrence of smoking and inadequate diet in Brazilian adults. Vigitel, Brazil, 2014

Variables/categories	$PR^{a}_{adjusted}$ (95% CI)	$PR^{b}_{adjusted}$ (95% CI)
Geographic region		
Central West	1	1
Northeast	0.67 (0.54–0.83)	0.68 (0.55–0.84)
North	0.78 (0.61–1.00)	0.84 (0.65–1.08)
Southeast	1.24 (1.00–1.55)	1.30 (1.05–1.61)
South	1.40 (1.11–1.77)	1.50 (1.18–1.89)
Sex		
Male	1	1
Female	0.63 (0.53–0.75)	0.77 (0.65–0.92)
Skin color/ethnicity		
White	1	1
Black	0.89 (0.69–1.15)	0.84 (0.65–1.09)
Yellow	0.72 (0.42–1.21)	0.71 (0.42–1.18)
Brown	0.73 (0.59–0.89)	0.70 (0.57–0.85)
Indigenous	1.26 (0.78–2.05)	1.40 (0.87–2.26)
Marital status		
Without spouse	1	1
With spouse	0.78 (0.65–0.93)	0.85 (0.71–1.02)
Education (in years)		
0 to 8	1	1
9 to 11	0.62 (0.51–0.76)	0.60 (0.49–0.72)
12 or more	0.41 (0.32–0.53)	0.39 (0.30–0.51)
Private health insurance		
Yes	1	1
No	1.16 (1.05–1.27)	1.14 (1.03–1.25)
Body mass index (kg/m²)		
< 25		1
≥ 25 to < 30		0.73 (0.60–0.89)
≥ 30		0.76 (0.60–0.97)
Binge drinking		
No		1
Yes		3.22 (2.70–3.85)
Self-rated health		
Very good/good		
Fair		1.65 (1.36–1.99)
Poor/very poor		1.70 (1.18–2.44)

95% CI: 95% confidence interval; PR: prevalence ratio. [a]adjusted for geographic region and socio-demographic characteristics; [b]adjusted for geographic region, socio-demographic characteristics, behavioral factors and health conditions.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Francisco PMSB, Assumpção D; Acquisition of data and Writing of the manuscript: Francisco PMSB, Assumpção D, Malta DC; Statistical analysis: Francisco PMSB; Critical revision of the manuscript for intellectual content: Malta DC.

Potential Conflict of Interest

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

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

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Co-occurrence of Cardiometabolic Disease Risk Factors: Unhealthy Eating, Tobacco, Alcohol, Sedentary Lifestyle and Socioeconomic Aspects

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Short Editorial related to the article: Co-occurrence of Smoking and Unhealthy Diet in the Brazilian Adult Population

Cardiometabolic disease (CMD) is the principal cause of morbi-mortality worldwide. The risk factors in the development of CMD are diverse; understanding them significantly contributes to the design of clinical and/or community strategies for their prevention and/or treatment.[1] An unhealthy diet, cigarette smoking, sedentary lifestyle, and higher alcohol consumption significantly increase the risk of CMD, cancer, loss of healthy life years, and premature mortality.[2]

In a systematic review by Meader et al.,[3] 37 studies were proposed in order to evaluate risk behaviors such as smoking, physical inactivity, and unhealthy diet by a meta-analysis. A greater association was found when groups of risk factors co-existed (≥ 4) compared with individual risk factors. Alcohol abuse and smoking were the most commonly identified risk factors. They also reported that the socioeconomic level is a predictor of multiple risks.[3] On the other hand, in a cohort study of more than 20 years, mortality associated with 1, 2, 3, or 4 risk factors was 1.85 (C I 95%, 1.28-2.68), 2.23 (CI 95%, 1.55-3.20), 2.76 (CI 95%, 1.91-3.99), and 3.49 (CI 95%, 2.31-5.26), respectively. The risk of mortality by CMD was higher than for other causes of death such as cancer.[4]

Among the socioeconomic aspects, the socio-spatial pattern of the points of sale of goods and services is the factor that most predicts unhealthy lifestyles. Macdonald et al.,[5] in their study in Scotland, show that the distribution of alcohol, fast food, tobacco, and gambling outlets is concentrated in geographical areas with greater socioeconomic deprivation.[5] Another study shows that in developing countries, the poorest areas have a higher prevalence of inadequate diet and smoking habits and the co-occurrence of risk factors is 20%.[6]

Zwolonsky et al.,[7] in a study of UK men, found that 72% exhibited combinations of risk factors; physical inactivity (72.8%) together with the lack of fruit and vegetable consumption (73%) was the most common combination. In addition, 29.5% consumed more alcohol than the recommended limit and 25% were smokers.[7]

In this context, Zancheta et al.[8] detected a strong correlation between alcohol intake and smoking. In addition, unhealthy eating and physical inactivity were the most frequent risk factors. Approximately 3% did not exhibit any risk factors, while 38.0%, 32.9%, 9.4%, and 1.8% showed two to five factors, respectively. It was noteworthy that the highest incidence of these risk factors occurred in girls, older adolescents, those not living with both parents, children of less educated mothers, students attending public schools, and residents of cities in more developed urban areas of the country.[8]

In this issue of the Journal of *Arquivos Brasileiros de Cardiologia*, Stolses et al.[9] evaluated the co-occurrence of smoking and unhealthy eating in adults in a population sample, showing a high prevalence of inadequate eating (68.4-72.6%) and smoking habits (7.8-15.65%). The occurrence of both risk factors was mainly in men (47%), those residing in the southern part of the country (44.1%), subjects aged 18-39 years (59.4%) and those who consumed alcohol (18.5%). Finally, it is shown that residing in the south (PRadj 1.50; 95% CI 1.18-1.89), not having private health insurance (PRadj 1.14; 95% CI 1.03-1.25), having an abusive consumption of alcohol (PRadj 3.22; 95% CI 2.70-3.85), and reporting a poor state of health (PRadj 1.7; 95% CI 1.18-2.44) were associated significantly with smoking and inadequate diet in Brazilian adults.

In view of the reported scientific evidence, it is increasingly necessary to conduct studies about the co-occurrence of cardiometabolic risk factors because they respond to the multi-causal complexity of the principal health problems worldwide. Therefore, the strategy approach for prevention and/or treatment requires addressing risk factors in multiple rather than individual ways.

Keywords

Cardiovascular Diseases; Metabolic Syndrome; Morbidity and Mortality; Cluster Analysis; Risk Taking; Alcoholism/epidemiology; Tobacco Use Disorder/epidemiology; Lifestyle; Fast Foods; Sedentarism.

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Left Atrial Appendage Transcatheter Occlusion with AMPLATZER™ Amulet™ Device: Real Life Data with Mid-Term Follow-Up Results

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Abstract

Background: Left atrial appendage (LAA) occlusion is an alternative therapy for atrial fibrillation patients who have high embolic risk and contraindications to anticoagulant therapy.

Objective: To evaluate the feasibility, safety, and mid-term outcomes of percutaneous LAA occlusion, including device-related thrombosis.

Methods: Sixty consecutive patients who had undergone percutaneous LAA occlusion with AMPLATZER™ Amulet™ device from September 2015 to March 2018 were enrolled. Patients were followed for 21 ± 15 months (median – 20 months, interquartile range – 9 to 27 months). The postprocedural assessment was done at the 1st, 6th, and 12th month. Patients were clinically evaluated, and transesophageal echocardiography was performed at each visit. We evaluated the condition of normality of variables using the Kolmogorov-Smirnov test. P-values < 0.05 were statistically significant.

Results: The most common indication for the procedure was major bleeding with anticoagulants (n: 53, 88.3%). The procedure was completed successfully in 59 (98.3%) patients. Periprocedural mortality was observed in one patient. Postprocedural antiplatelet treatment was planned as dual or single antiplatelet therapy or low-dose anticoagulant therapy in 52 (88.1%), 2 (3.4%), and 5 (8.5%) patients, respectively. We found no clinically significant cerebrovascular events, device-related thrombus, or embolization in any patient during the follow-up. Two (3.4 %) patients presented significant peri-device leak (>3 mm) at the 1st month evaluation, which disappeared at the 12th month follow-up.

Conclusion: We concluded that LAA occlusion using the Amulet™ LAA occluder can be performed with high procedural success and acceptable outcomes. (Arq Bras Cardiol. 2019; 113(4):712-721)

Keywords: Atrial Fibrillation; Atrial Appendage; Mortality; Echocardiography/methods; Cardiac Catheterization; Anticoagulants/therapeutic use.

Introduction

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia, especially in older adults.[1] AF is associated with increased all-cause mortality and morbidity. The most significant AF morbidity is thromboembolic cerebrovascular events (CVEs). CVEs result in decreased quality of life and increased health care costs.[2] Oral anticoagulants (OACs) are effective therapeutic options to prevent thromboembolic events.[2] Randomized controlled studies and real-life studies showed that OAC drugs raise the risk of bleeding.[3] The major bleeding risk with vitamin K antagonists and direct OACs should not be ignored, especially in patients with high bleeding risk.[4-6] The balance between the protection from thromboembolic events and bleeding risk may be overbalanced towards bleeding. In this scenario, left atrial appendage (LAA) occlusion should be an alternative therapeutic option for some specific patient groups.[2]

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According to current AF guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC), LAA occlusion (surgical or percutaneous) may be considered for stroke prevention in patients with AF and contraindications to long-term anticoagulant treatment with Class IIb and Level B recommendation.[2,7]

Due to the lack of large randomized controlled trials on LAA occlusion with the Amulet device, there are some gaps on clinical approaches for perioperative preparation, appropriate treatments for possible complications, and postoperative follow-up, including post-implant antithrombotic therapy. In this retrospective observational study, we aimed to emphasize challenges to LAA occlusion, evaluate possible perioperative complications, and how to deal with them. In addition, we intended to reveal real-life mid-term outcomes in our patient group and share our postprocedural antiplatelet regimen as an alternative option for patients who have very high stroke risk despite the LAA occlusion.

Methods

Population

Patients who had a major bleeding event with anticoagulant treatment, recurrent minor bleeding with at least two different

anticoagulant treatments, or any life-threatening bleeding risk, such as high risk of falling or idiopathic thrombocytopenic purpura, were evaluated for suitability for LAA occlusion. Individuals who had less than one-year survival, were under critical non-cardiac status, and did not accept any interventional procedure were excluded. This retrospective observational study included 60 patients who had undergone percutaneous LAA occlusion with the Amulet device in the Hacettepe University Hospital Cardiology Clinic between September 2015 and March 2018. All patients signed the informed consent form, and the local ethics committee approved the procedures.

Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal etc.) and bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of two or more units of whole blood or red cells were considered a major bleeding, in accordance with International Society on Thrombosis and Haemostasis (ISTH) recommendations.[8]

Statistical analysis

We performed the statistical analysis using the SPSS statistical software (version 20; SPSS Inc., Chicago, IL, USA). Descriptive and categorical variables were presented as frequencies and percentages. Continuous data with normal distribution were expressed as means ± SD. Quantitative variables without normal distribution were described as median and interquartile range. We evaluated the condition of normality using the Kolmogorov-Smirnov test. The Student's t-test or Mann-Whitney test compared the numerical variables, as appropriate. P-values < 0.05 were statistically significant.

The AMPLATZER™ Amulet™ Left Atrial Appendage Occluder

The AMPLATZER™ Amulet™ Left Atrial Appendage Occluder (ST Jude Medical, Minneapolis, Minnesota) was used in all 60 patients for LAA occlusion. The AMPLATZER™ Amulet™ device is a self-expanding nitinol device with two parts (a lobe and a disc) pre-assembled on a single cable. Depending on the size of the device, a 12 to 14 French delivery catheter is used.

Measurement of left atrial appendage dimensions

Multidetector Computed Tomography (MDCT) was performed in 31 patients who had normal kidney function to evaluate the LAA anatomy. The LAA landing zone was measured with the MDCT in these 31 patients. All patients underwent transesophageal echocardiography (TEE) to guide the device selection and evaluate cardiac function. The device size was selected by using 3D TEE and MDCT when available. All patients had the size of LAA ostium and the device landing zone measured by TEE. TEE results were compared with MDCT ones in patients who had preprocedural MDCT. The relationship between LAA and pulmonary artery was evaluated in patients who had preprocedural MDCT.

Left atrial appendage occlusion procedure

As a routine preprocedural approach, standard transthoracic echocardiogram and TEE were performed before LAA occlusion in all patients to evaluate the shape and size of LAA and to reveal the presence of thrombus in LAA. TEE was performed after intravenous fluid infusion to avoid undersizing of LAA due to hypovolemia. The intravenous fluid infusion volume was determined according to the patients' physical examination, B-type natriuretic peptide (BNP) levels, and left ventricular ejection fraction. Left atrial pressure was also measured to determine the optimal intravascular volume status during the procedure. Patients with normal renal function underwent multislice cardiac computed tomography for optimal evaluation of LAA anatomy, size, and the relationship between LAA and related cardiovascular structures.

All patients undergoing percutaneous LAA occlusion procedure were under general anesthesia and intubated for better TEE guidance. Transseptal puncture was conducted with fluoroscopy and 3D TEE guidance at the inferoposterior site of the interatrial septum when the patient had no anatomic variations that could prevent optimum orientation. After a successful transseptal puncture, the delivery catheter was placed in the left atrium. The Amulet™ LAA occlusion device was then advanced to some extent out of the delivery sheath, the lobe of the device formed a ball shape, and the delivery sheath was placed in the LAA with a counterclockwise rotation. After confirming the optimum settlement in the LAA with TEE, the lobe of the device was opened with further advancement. After the proper placement of the lobe in the LAA, the disc was opened at the LAA ostium with the withdrawal of the delivery sheath. Relationships between the occlusion device and the circumflex artery and mitral valve were checked with 3D TEE, and radiopaque contrast was injected in the delivery sheath to evaluate para-device leak. Before being released, the device was pulled back with acceptable strength to check the stability. After all these steps, the occlusion device was released, and the relationships between the device and LAA, circumflex artery, and mitral valve were evaluated by 3D TEE. Periprocedural anticoagulation was maintained by IV heparin infusion with activated clotting time (ACT) control.

Postprocedural antiplatelet therapy

Postprocedural antiplatelet therapy was planned as dual or single antiplatelet therapy or low-dose anticoagulant therapy. This individualized therapy was designed according to patients' thromboembolism as well as bleeding risk.

Postprocedural follow-up

The patients were reevaluated with transthoracic echocardiography at the 1st, 6th, and 12th month. TEE was performed at all three visits. The patients were evaluated clinically and with TEE annually after the first year post-procedure.

Results

Baseline characteristics

This study involved 60 patients (mean age was 72.3 ± 20.1 years) who had undergone percutaneous LAA occlusion with the AMPLATZER Amulet device in the Hacettepe University Cardiology Clinic between September 2015 and March 2018. The sample consisted of 35 women (58.3%) and 25 men (41.7%). Table 1 lists all baseline characteristics.

The most common reason for LAA occlusion was major bleeding with OAC treatment (n: 53, 88.3%). The most common type of major bleeding was gastrointestinal bleeding (n:26, 57,8%).

Fifty-seven patients took OACs before LAA occlusion. The most common preprocedural anticoagulant used was rivaroxaban, in 30 (50.0%) patients. Warfarin, dabigatran, and apixaban were used by 4 (6.6%), 10 (16.7%), and 13 (21.7%) patients, respectively.

Thromboembolic events and bleeding risk scores

$CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, and ORBIT bleeding scores were calculated for all patients, and the average values of these scores were 2.75 ± 2.25, 4.61 ± 2.61, 4.32 ± 3.32, and 4.8 ± 2.8, respectively. Table 1 lists bleeding and thromboembolic event risk scores separately.

Device dimensions

The smallest implanted device had 16 mm and the biggest, 31 mm. Devices of 20 mm were implanted in 11 patients and of 25 mm in 16 patients.

Procedural Outcomes

The LAA occlusion device was implanted successfully in all 60 patients. No patient showed device embolization. One patient presented postprocedural major complication and mortality. Fifty-nine patients were discharged without any disabling complication. Six patients had periprocedural bleeding. All of them were associated with an access point, and only one of these patients needed a postprocedural blood transfusion. Periprocedural stroke, transient ischemic attack (TIA), and systemic embolization were not observed in any patient during hospital follow-up. The mean postprocedural hospital length of stay was 1.33 days (median of 2 days, interquartile range of 1 to 3 days).

Periprocedural complications

The percutaneous LAA transcatheter occlusion device was implanted successfully in all 60 patients. However, one patient presented a postprocedural major complication. This patient had been referred to emergency surgery due to pulmonary artery rupture. Despite the surgical repair of the pulmonary artery injury, the patient did not survive.

Two patients had postprocedural pericardial effusion, both self-limited and not requiring pericardiocentesis. Two patients started postprocedural ibuprofen and colchicine therapy.

Some clinical and anatomic patient features created problems for the procedural approach, but none of them prevented successful implantation. Five patients had a thrombus formation at the bottom of the LAA. The thrombus was attached to the LAA occlusion device in these patients. One patient had an atrial septal defect (ASD) closure device at the interatrial septum, which had been previously implanted. Generally, an ASD closure device in place is considered challenging for the transseptal puncture, but this patient had the transseptal puncture performed at the inferoposterior side of the interatrial septum, which is the most suitable puncture location for LAA occlusion. The LAA occlusion procedure was performed successfully in this patient without any damage to the ASD closure device (Figure 1).

Patients' postprocedural antiplatelet therapy

In most patients, postprocedural antiplatelet therapy consisted of acetylsalicylic acid (100 mg qd) and clopidogrel (75 mg qd). Dual antiplatelet therapy (DAPT) continued for 6 months after the procedure in 53 patients. DAPT was modified to the single antiplatelet therapy (acetylsalicylic acid or clopidogrel) if the absence of thrombus formation over the device was confirmed and peri-device leak was not found. Fifty-three patients under DAPT showed no device-related thrombus (DRT) or peri-device leak at the 6th month follow-up TEE. Accordingly, these patients continued with single antiplatelet therapy thereafter. Two patients under DAPT after the procedure had TIA during follow-up, which extended the DAPT for 12 months. Single antiplatelet therapy with acetylsalicylic acid was considered in only two patients due to the high bleeding risk. They continued to use single antiplatelet during their entire follow-up. Five patients used a low-dose OAC agent after the procedure. Four of them used apixaban 2.5 mg BID, and one took dabigatran 110mg BID until their 6th month evaluation. None of them had thrombus over the device or peri-device leak at the 6th month TEE. Thus, they continued their antithrombotic treatment with single antiplatelet therapy after their 6th month visit (Figure 2).

Follow-up outcomes

The patients were evaluated at the 1st, 6th, and 12th month after discharge, undergoing annual assessments afterward. Two patients died during the follow-up. Median follow-up duration was 20 months (interquartile range of 9 to 27 months). The first patient died due to decompensated heart failure six months after the LAA occlusion. The second patient died from a non-cardiac condition.

Clinically manifested stroke did not occur during the follow-up period. Two patients presented TIA-like symptoms and underwent cerebrovascular scanning and TEE. The exams showed no significant findings. These patients had a neurology consultation, and TIA was considered. Their DAPT was extended to 12 months. Both patients were discharged without neurological deficit, and brain imaging showed no evidence of new ischemic lesions. Besides these two cases, the most important thromboembolic clinical event was pulmonary embolism in one patient two months after LAA occlusion.

Four patients had bleeding. One required hospitalization and blood transfusion three months after the procedure. This patient had melena. Gastrointestinal bleeding was confirmed with endoscopy and colonoscopy. DAPT was switched to single clopidogrel therapy, and the patient was discharged five days after hospitalization. The bleeding was not significant in the other three patients, and they did not require hospitalization or blood transfusion. Two of them had epistaxis, and one had epidermal petechiae.

Routine TEE was performed at the end of the 1st, 6th, and 12th month after the procedure. In 10 patients, the follow up-duration was shorter than 12 months, and they were

Table 1 – Baseline Characteristics and LAA Occlusion Indications

Baseline Characteristics	n = 60
Mean Age	72.3 years ± 20.1 years
Female Gender, n (%)	35 (58.3%)
Hypertension, n (%)	56 (93.3%)
Diabetes Mellitus, n (%)	22 (36.6%)
Heart Failure, n (%)	23 (38.3%)
Cerebrovascular Event, n (%)	17 (28.3%)
Ischemic, n (%)	13 (21.6%)
Hemorrhagic, n (%)	3 (5.0%)
Ischemic and hemorrhagic, n (%)	1 (1.6%)
Chronic Kidney Disease, n (%)	29 (48.3%)
Stage 3 (GFR: 30% ≤ 59%)	14 (23.3%)
Stage 4 (GFR: 15% ≤ 29%)	7 (11.6%)
Stage 5 (GFR: ≤ 14%)	8 (13.3%)
Atherosclerotic Heart Disease, n (%)	40 (66.7%)
Peripheric Artery Disease, n (%)	7 (11.6%)
Atrial Fibrillation	
Paroxysmal, n (%)	13 (21.6%)
Persistent, n (%)	47 (78.3%)
Preprocedural Anticoagulation	
Yes, n (%)	57 (95.0%)
Rivaroxaban, n (%)	30 (50.0%)
Warfarin, n (%)	4 (6.6%)
Dabigatran, n (%)	10 (16.7%)
Apixaban, n (%)	13 (21.7%)
Follow Up, mean months ± SD, (median months, 1st and 3rd quartile)	21 ± 15 months (20 months, interquartile range of 9 to 27 months)
Left Atrial Appendage Occlusion Indications	
Major bleeding, n (%)	53 (88.3%)
Gastrointestinal, n (%)	36 (60.0%)
Hemoptysis, n (%)	11 (18.3%)
Hemorrhagic SVE, n (%)	4 (6.6%)
Pericardial, n (%)	1 (1.7%)
Retroperitoneal, n (%)	1 (1.7%)
Chronic Kidney Disease and Labile INR, n (%)	4 (6.6%)
Idiopathic Thrombocytopenic Purpura, n (%)	1 (1.7%)
Cerebral Angiopathy, n (%)	1 (1.7%)
Bronchiectasis, n (%)	1 (1.7%)
Thromboembolic and Bleeding Risk Scores	
$CHADS_2$ mean ± SD	2.75 ± 2.25
CHA_2DS_2-VASc mean ± SD	4.61 ± 2.61
HASBLED mean ± SD	4.32 ± 3.32
ORBIT mean ± SD	4.8 ± 2.8

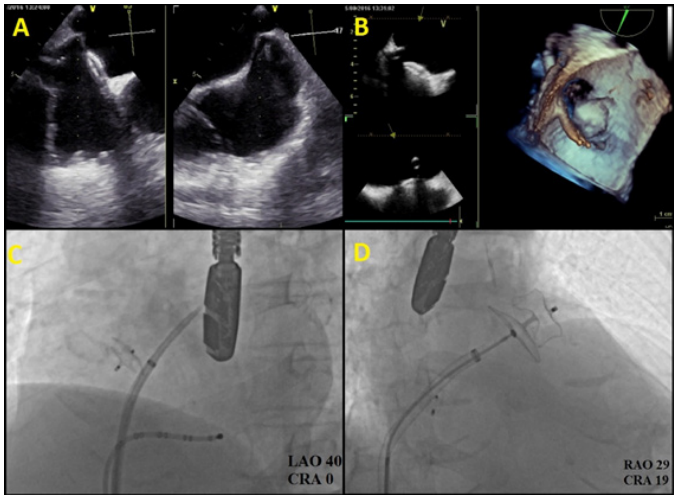

Figure 1 – *a) Transesophageal echocardiography image of the transseptal puncture needle tenting the inferoposterior site of the interatrial septum and atrial septal defect closure device, b) Tridimensional transesophageal echocardiography guidewire image after the transseptal puncture, c) Fluoroscopic image of the transseptal puncture on the inferoposterior site of the interatrial septum and atrial septal defect closure device, d) Fluoroscopic image of the device before being released.*

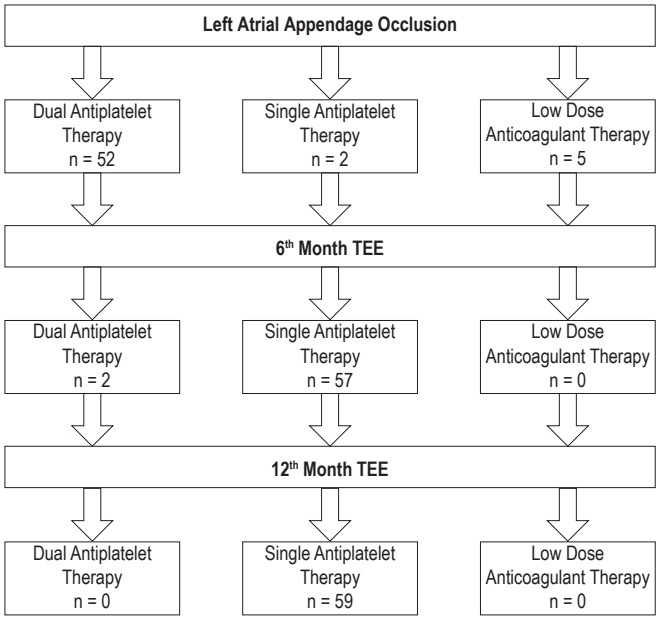

Figure 2 – *Postprocedural antithrombotic treatment.*

evaluated only at the 1st and 6th month (Figure 3). No patient showed device thrombus or embolization at any visit. Two (3.3%) patients had significant peri-device leak (>3 mm) at the 1st and 6th month visit. These two patients did not present peri-device leak at the 12th month TEE (Table 2).

Discussion

We used the AMPLATZER™ Amulet™ LAA occluder for percutaneous LAA occlusion in a series of patients and reported mid-term data on its safety and efficacy.

The PROTECT-AF and PREVAIL studies provided large-scale randomized clinical trial evidence that LAA occlusion with the Watchman device could be non-inferior to anticoagulation for CVEs in patients with non-valvular AF.[9,10] On the other hand, large-scale randomized data on other LAA occlusion devices are limited.

The AMPLATZER Amulet device is currently being evaluated in a randomized controlled trial (Amulet IDE Trial; ClinicalTrials. gov Identifier: NCT02879448) and long-term randomized trial data has not been published yet. Thus, real-life data, multicenter registries, and meta-analysis

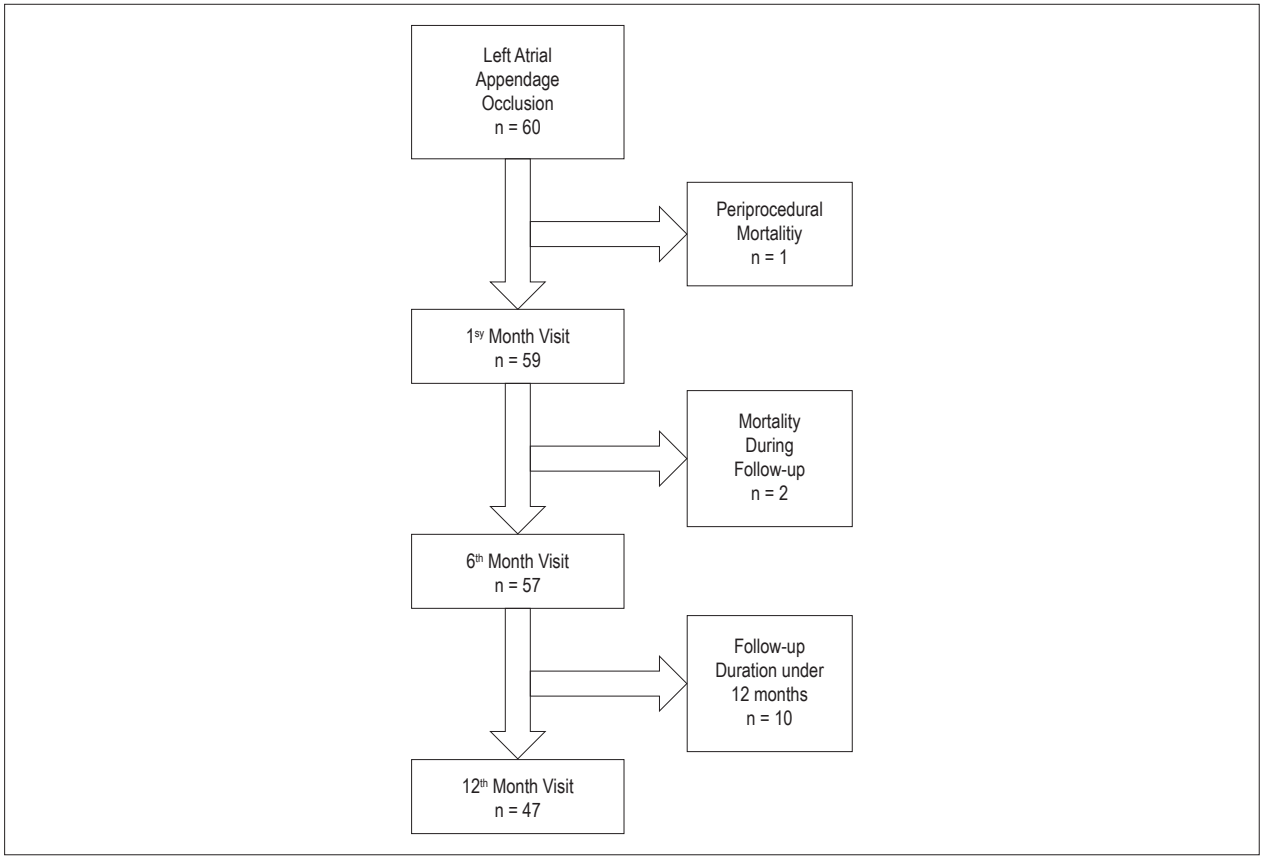

Figure 3 – *Patients' follow-up.*

of these studies still give us important information about the efficacy and safety of LAA occlusion with the Amulet device.

In our series of 60 patients, the LAA occlusion procedure was successfully completed without major complications in 98.3% of cases. Our procedural success rate was similar to previous studies.[11-13] Landmesser et al.[12] reported that the procedural success of LAA occlusion with the Amulet device was 99.0% in their multicenter registry, which included 1,088 patients.[12] They reported peri-device leak in 2% of patients during follow-up. In accordance with these data, we identified significant peri-device leak (>3 mm) in two patients (3.3%) with TEE at the 1st month after the procedure.[12] However, they showed no significant peri-device leak at the 6th month. We considered that this result might be due to the continued endothelization process on the closure device until six months after the procedure.

We found no significant disabling CVEs during follow-up. Only two patients had TIA, but with no neurological sequelae, and their cranial imaging did not reveal significant ischemic lesions. On the other hand, previous multicenter registries showed that there is still a risk of thromboembolic events despite LAA occlusion. Regueiro et al.[14] recently reported that 7 out of 101 patients (6.9%) had a stroke after LAA occlusion in 4.2 years of follow-up, 6 of them related to thromboembolic events.[14] AMPLATZER cardiac plug constituted most of the devices used in this study (82%), while Amulet was used only in 3 patients. They discharged 70% of the patients under DAPT and those using a single antiplatelet agent. We used the Amulet device in all our patients and discharged 96% of the patients with DAPT, which continued up to 6 months after LAA occlusion. This fact might be one of the reasons for the low incidence of CVEs in the follow-up of our patient group. The relatively short follow-up duration and the smaller sample size in our study could also be reasons for this difference.

DRT has been reported in 0-17% of patients after LAA occlusion.[15] Recently, some concern has been raised that DRT formation after LAA occlusion may be more frequent than expected. Fauchier et al.[16] reported that, among 469 patients who underwent LAA occlusion, the incidence of DRT was 7.2% in imaged patients during a mean follow-up of 13 ± 13 months.[16] Thrombus over the device was an independent predictor of ischemic events. The Watchman device constituted most (58%) of devices used for LAA occlusion in this study, while the Amulet device was used in 97 patients. Interestingly, DAPT at discharge was associated with a lower risk of thrombus, and only 23.2% of the study group was discharged with this treatment. Costa et al.[17] published patient outcomes over a 12-month follow-up and found no DRT.[17] We did not observe DRT in our patients with TEE imaging at the 1st, 6th, and 12th month after LAA occlusion, corroborating their results.[17] There is some controversy among studies regarding thrombus formation over the device. The individualized antiplatelet

Table 2 – Procedural and Follow-up Outcomes

Procedural Outcomes	Patients (n = 60)
Technical Success	60 (100%)
Procedural Success	59 (98.3%)
Periprocedural Mortality	1 (1.6%)
Periprocedural Morbidity	9 (15.0%)
Major Bleeding	0 (0.0%)
Minor Bleeding	6 (10.0%)
Stroke	0 (0%)
Systemic Embolization	0 (0%)
Device Embolization	0 (0%)
Pericardial Effusion	2 (3.2%)
Pericardial Tamponade	1 (1.6%)
Follow-up Outcomes	**Patients (n = 59)**
Mortality	2 (3.4%)
Stroke/TIA	2 (3.4%)
Ischemic Stroke	0
Hemorrhagic Stroke	0
TIA	2 (3.4%)
Pulmonary Thromboembolism	1 (1.7%)
Life Threating or Major Bleeding	1 (1.7%)
Minor Bleeding	3 (5.1%)
Major Findings in Follow up TEE	
Peridevice Leak (>3 mm) at 1st month	2 (3.4%)
Peridevice Leak (>3 mm) at 6th month	0
Device Related Thrombus	0
Device Embolization	0

TIA: transient ischemic attack; TEE: transesophageal echocardiography.

treatment may explain this difference in our patient series. We planned the antiplatelet regimen according to the patients' risk of stroke and thrombus formation over the device. DAPT was administered to most patients (88.3%) at discharge in our group. In addition, we planned an extensive antiplatelet therapy for patients who had peri-device leak at follow-up. Also, five of our patients had thrombus in the LAA before the procedure. These patients underwent low-dose anticoagulant therapy for six months. As peri-device leak and presence of thrombus in the LAA before the procedure were considered risk factors for thrombus formation on the closure device, we decided to individualize the antiplatelet therapy of these patients. Moreover, the relatively small sample size may be another cause for this discrepancy.

Our series had only one major periprocedural complication. The indication of LAA occlusion for this patient was preprocedural hemorrhagic CVE with an effective dosage of dabigatran. LAA occlusion was planned as thromboembolic prevention for this patient. Nonetheless, we observed a major periprocedural complication during the procedure. In this patient, the lobe hooks erupted from the LAA and damaged the pulmonary artery. These hooks are designed to allow better implantation and fixation of the device. When we reevaluated the preprocedural MDCT, we noted the close neighborhood between LAA and pulmonary artery. This close relationship resulted in pulmonary artery rupture. Although referred to urgent surgery, the patient did not survive. Previous case reports showed that postprocedural pulmonary artery rupture could be an early or delayed complication.[18,19] Most of these case reports mentioned that this complication is related to the anatomical relationship between LAA landing zone and pulmonary artery.[18,19] Halkin A. et al.[20] classified this relationship according to the contact point between LAA and pulmonary artery and they emphasized that the type 2 (proximal contact) relationship has a higher pulmonary artery rupture risk than the others.[20] We reevaluated the relationship between pulmonary artery and LAA in our patient after this study and found that it was a type 2 relationship (Figure 4).

Thrombus presence in LAA is considered a contraindication for LAA occlusion.[21] In our series, we detected thrombus at the bottom of the LAA in five patients. We considered that the thrombus at distal LAA could be attached to the LAA occlusion device, with a modified technique and minimal manipulation of catheters in the left atrium. Consequently, the procedures were performed successfully with no periprocedural neurological complications. We have reported one of these cases previously.[22] Tarantini et al.[23] recently reported in their multicenter study that LAA occlusion could be safely and effectively performed in 28 patients with distal LAA thrombus.[23] In line with these findings, we also suggest that LAA occlusion could be successfully conducted in patients with distal thrombus in experienced centers. However, the procedure should be canceled if the thrombus is located at the proximal LAA.

Percutaneous LAA occlusion is a complex procedure that has some periprocedural risks as we mentioned before. Consequently, preprocedural patient evaluation, patients with appropriate indications, and operator experience are very important to avoid possible complications.

In our study, we demonstrated that LAA occlusion using the Amulet™ LAA occluder could be performed with high procedural success. In our series, all but one of the procedures were completed safely without complications. We did not find any clinical events directly related to AF or the LAA procedure during postprocedural follow-up. On the other hand, further large-scale randomized trials and long-term outcome data are necessary to verify the efficacy and safety of LAA occlusion using the Amulet™ LAA occluder device.

Limitations

This study was not designed as a randomized prospective controlled trial; consequently, it has some limitations. First, we did not have a control group to compare the effectiveness of LAA occlusion in preventing thromboembolic events. Second, our mean follow-up duration was relatively short, and long-term outcomes of LAA occlusion cannot be inferred from our results. However, the LAA occlusion procedure and Amulet device are relatively new, and data about this device are limited. Therefore, studies like ours are still important and valuable

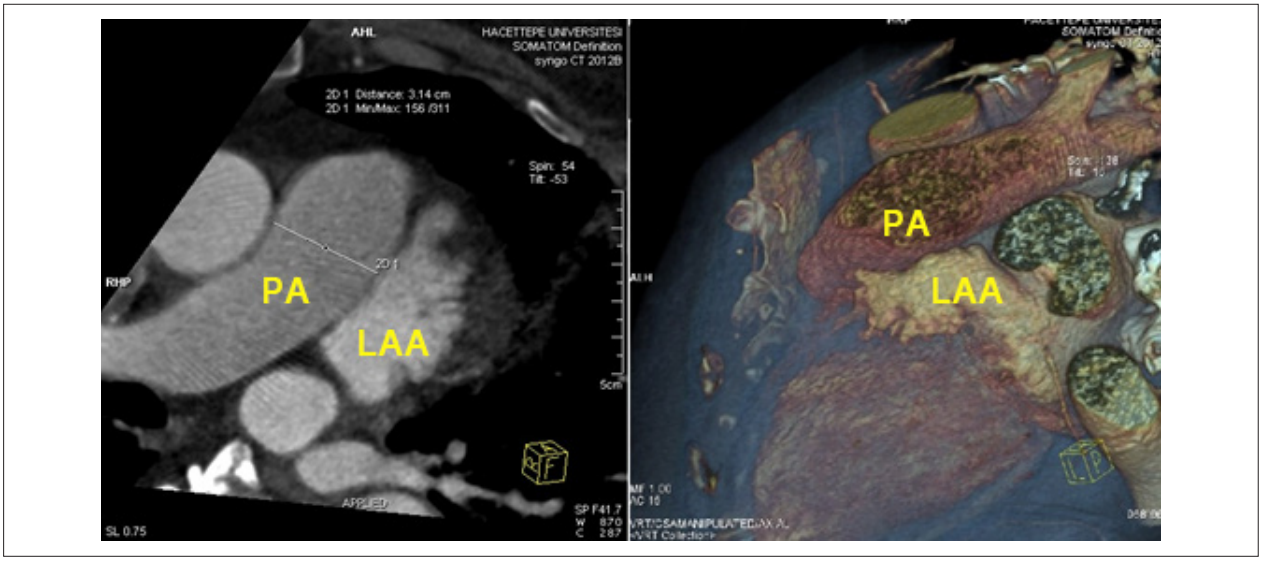

Figure 4 – *Computed tomography image of the neighborhood between pulmonary artery and left atrial appendage.*

to show the performance of LAA occlusion with the Amulet device. Third, we performed LAA occlusion in different clinical scenarios, such as thrombus formation in the LAA. There are some studies about these challenging conditions and the safety of LAA occlusion. Our series had similar results to those found in the literature. Due to the lack of consensus on adjuvant antithrombotic therapeutic strategies, we individualized the antiplatelet therapy after the procedure. However, our study population was relatively small for us to recommend an antithrombotic regimen after the procedure. Large-scale studies are necessary to make such recommendations.

Conclusion

LAA occlusion is an important and effective therapeutic option for selected AF patients with an increased risk of bleeding with anticoagulant treatment. Nevertheless, the procedure has some significant periprocedural risks, including death. Consequently, LAA occlusion should be performed in carefully selected patients with increased thromboembolic risk, who have at least one-year survival expectation and cannot tolerate OACs or had clinically important bleeding events.

Since LAA occlusion can be a challenging procedure, it should be performed by experienced operators with optimal skills and in collaboration with a heart team, including surgeons, neurologists, and experts on cardiovascular imaging.

Author contributions

Conception and design of the research: Şahiner ML; Acquisition of data: Şahiner ML, Kaya EB; Analysis and interpretation of the data: Kaya EB; Statistical analysis: Kaya EB, Çöteli C; Writing of the manuscript: Şahiner ML, Çöteli C; Critical revision of the manuscript for intellectual content: Aytemir K.

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 Hacettepe Universitesi Tip Fakultesi under the protocol number LUT/66. 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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Percutaneous Occlusion of Left Atrial Appendage: Growing Clinical Experience and Lack of Multicenter Randomized Clinical Trials

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Short Editorial related to the article: Left Atrial Appendage Transcatheter Occlusion with AMPLATZER™ Amulet™ Device: Real Life Data with Mid-Term Follow-Up Results

Left atrial appendage (LAA) closure as a prophylactic strategy for thromboembolic events in patients with atrial fibrillation (AF) has been performed for decades; initially during mitral valve repair surgeries[1] and, more recently, in nonvalvular AF patients at high risk of embolism who do not tolerate the use of oral anticoagulants (OACs).

The idea of LAA occlusion as an alternative to chronic warfarin use emerged from observations of anatomopathological studies and during cardiac surgery that disclosed the LAA as the main site of thrombus formation in patients with nonvalvular atrial fibrillation.[2,3]

The evolution of cardiac access interventionist techniques, together with the development of specific prostheses for LAA occlusion, allowed the appendage closure to be performed percutaneously, using a minimally invasive procedure, making it simpler and not restricted to patients who would have undergone heart surgery.

The first prosthesis developed for this purpose, called PLAATO, was tested early in the last decade by Horst Sievert et al.[4] and consisted of a nitinol structure, covered by an expanded polytetrafluoroethylene (ePTFE) occlusive membrane. The clinical study published in 2002 showed that the concept of percutaneous LAA occlusion was feasible; however, the prosthesis use was discontinued in 2005, due to the considerable number of complications such as cardiac tamponade, residual leaks, prosthesis protrusion towards the atrial cavity and, in some cases, lack of neo-endothelization of the prosthesis with formation of local thrombi.[5] On the other hand, the experience obtained with the implantation of this prosthesis was important for the development of more effective devices.

Currently, two prostheses with different profiles are being used in clinical practice: the Watchman prosthesis sold by Boston Scientific and the Amplatzer Amulet device (evolution of the Amplatzer Cardiac Plug) sold by ABBOTT. Of these, only the Watchman prosthesis has been evaluated in two prospective, multicenter, and randomized clinical trials. The PROTECT-AF study (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation),[6] evaluated the effectiveness and safety of percutaneous LAA occlusion with the Watchman prosthesis, compared with oral anticoagulation with warfarin in 707 patients (463 in the intervention group) with nonvalvular AF and CHADS2 ≥ 1. The LAA occlusion (3 events per patient-year) met the noninferiority criterion compared to warfarin (4.9 events per patient-year) in the efficacy criterion; however, the LAA occluder implantation was associated with a higher number of adverse events, especially the occurrence of hemopericardium (4.8%), which was related to the interventionist's learning curve in the prosthesis placement.

Due to safety concerns, the study was repeated (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy – PREVAIL trial)[7] with the same characteristics as the previous one, except for the greater experience of the operators. A total of 407 patients (269 in the intervention group) were included and at 18 months of follow-up, efficacy event rates (stroke, systemic embolization, and cardiovascular or unexplained death) of 0.064 were observed in the intervention group and 0.063 in the warfarin group, thus not meeting the pre-specified non-inferiority criteria previously obtained in the PROTEC-AF study, due to the very low number of events in the control group, a fact not observed in the previous and subsequent studies using warfarin.

However, the noninferiority criterion was met in the analysis of the second primary efficacy endpoint related to the event rate after 7 days of randomization. Also positive was the lower rate of prosthesis implant complications compared with the PROTECT AF study.

A complicating factor for the clinical implementation of the LAA occlusion strategy was the emergence of four new direct-acting oral anticoagulants (DOACs), supported by potent clinical studies showing no inferiority or even superiority of these new drugs over warfarin in patients with nonvalvular AF.[8,9] Due to the practical use of DOACs, the indication of appendage occlusion devices has been postponed and considered only in patients who are intolerant to oral anticoagulants, or in those who experienced embolic events while using these drugs, although the effectiveness of the device has not been studied in randomized controlled trials.

Therefore, due to this heterogeneity of indications and the lack of randomized controlled trials, the records have become important. Reddy et al.[10] evaluated 3822 consecutive cases of LAA occluder implantation based on Medicare data, showing

Keywords

Atrial Fibrillation/therapy; Atrial Appendage/diagnotic, imaging; Prostheses and Implants/adverse effects; Stroke/prevention and control.

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a cardiac tamponade rate of 1.02%, most of them adequately treated with pericardiocentesis; however, the tamponade resulted in death in three cases. These rates were lower than those observed in clinical studies, although most devices were implanted by less experienced operators. Another European registry (EWOLUTION)[11] also demonstrated a low complication rate, showing 34 (3.3%) adverse events among 1021 patients included in the study.

Two Brazilian registries have been recently published and suggested the safety of appendage occlusion device implantation. Guerios et al.,[12] performed a multicenter registry and evaluated the results of 91 patients with nonvalvular AF (62% ineligible for anticoagulation) and high risk of stroke (CHA2DS2VASc 4.5 ± 1.5), submitted to the implantation of 96 prostheses, with the ACP (Amplatzer Cardiac Plug) being implanted in 94.6%. The implant success rate was 97.8%, with 7.2% of complications, with five pericardial effusions requiring pericardiocentesis, one non-dedicated device embolization and one gas embolism without sequelae. In this series, during a median follow-up of 346 days (128.6 patient-years), three non-procedure-related deaths were observed, as well as five cases of peri-prosthesis leakage, with thrombus formation next to the prosthesis in two, resolved with the return of anticoagulation and only two patients had stroke at the follow-up.

In the second registry, Marcio Costa et al.,[13] evaluated 15 patients with nonvalvular AF and high risk of bleeding, submitted to implantation of the ACP prosthesis. In this small series, the procedure was successfully performed in all cases with no reports of hemopericardium or prosthesis displacement.

In this issue of the Brazilian Archives of Cardiology, Şahiner et al.[14] disclose retrospective data from a center in Turkey, which included 60 patients submitted to implantation of the Amplatzer Amulet device. The main indication for the procedure was the occurrence of bleeding (usually gastrointestinal) in the presence of oral anticoagulation. The authors demonstrated that the implantation procedure was successful and safe in most patients. One patient had pulmonary artery rupture due to a probable direct injury by the prosthesis struts. In most patients, antiplatelet therapy consisted of ASA (100 mg) and clopidogrel (75 mg) for 6 months after the procedure, being maintained on single therapy after transesophageal echocardiography demonstrated the absence of periprosthetic leaks or thrombi. During a mean follow-up of 21 ± 15 months, none of the patients had a stroke but two patients had clinical symptoms of transient ischemic attack.

Thus, due to the lack of robust evidence, the most recent guideline on atrial fibrillation recommends the implantation of appendage occlusion devices as a IIb indication, level of evidence B-NR, in patients with non-valvular AF at high risk for stroke and with contraindications for long-term oral anticoagulation use.[8]

An ongoing randomized trial (ASAP-TOO)[15] is seeking to demonstrate the effectiveness of the Watchman prosthesis in this clinical condition, but the study is estimated to be completed in 2023.

Apparently, we are reaching a stage of clinical knowledge and experience in optimizing the use of warfarin and direct-acting anticoagulants in patients with non-valvular AF at high risk of stroke and systemic embolization, recognizing and establishing the safe limits for their use. This opens up a new phase for the consideration of LAA occlusion devices. Therefore, additional prospective, multicenter, controlled clinical trials are needed to clarify the effectiveness and safety of the implantation of the devices in these new clinical situations, such as patients with absolute contraindication to OACs and antiplatelet use, even for a short period of time; patients that had a stroke while receiving apparently effective oral anticoagulation; LAA occlusion as an alternative to chronic use of NOACs; occlusion device implantation simultaneously with AF ablation; in addition to establishing the need and safe handling of short-term anticoagulant therapy and minimal antiplatelet therapy, which should be maintained after the implantation of different prostheses.

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Introduction of Application of Gini Coefficient to Heart Rate Variability Spectrum for Mental Stress Evaluation

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Abstract

Background: **The Gini coefficient is a statistical tool generally used by economists to quantify income inequality. However, it can be applied to any kind of data with unequal distribution, including heart rate variability (HRV).**

Objectives: **To assess the application of the Gini coefficient to measure inequality in power spectral density of RR intervals, and to use this application as a psychophysiological indicator of mental stress.**

Methods: **Thirteen healthy subjects (19 ± 1.5 years) participated in this study, and their RR intervals were obtained by electrocardiogram during rest (five minutes) and during mental stress (arithmetic challenge; five minutes). These RR intervals were used to obtain the estimates of power spectral densities (PSD). The limits for the PSD bands were defined from 0.15 to 0.40 Hz for high frequency band (HF), from 0.04 to 0.15 Hz for low frequency band (LF), from 0.04 to 0.085 Hz for first low frequency sub-band (LF1) and from 0.085 to 0.15 Hz for second low frequency sub-band (LF2). The spectral Gini coefficient (SpG) was proposed to measure the inequality in the power distribution of the RR intervals in each of above-mentioned HRV bands. SpG from each band was compared with its respective traditional index of HRV during the conditions of rest and mental stress. All the differences were considered statistically significant for $p < 0.05$.**

Results: **There was a significant decrease in HF power ($p = 0.046$), as well as significant increases in heart rate ($p = 0.004$), LF power ($p = 0.033$), LF2 power ($p = 0.019$) and LF/HF ($p = 0.002$) during mental stress. There was also a significant increase in SpG(LF) ($p = 0.009$) and SpG(LF2) ($p = 0.033$) during mental stress. Coefficient of variation showed SpG has more homogeneity compared to the traditional index of HRV during mental stress.**

Conclusions: **This pilot study suggested that spectral inequality of Heart Rate Variability analyzed using the Gini coefficient seems to be an independent and homogeneous psychophysiological indicator of mental stress. Also, HR, LF/HF, SpG(LF) of HRV are possibly important, reliable and valid indicators of mental stress. (Arq Bras Cardiol. 2019; 113(4):725-733)**

Keywords: **Gini Coefficient; Heart, Rate; Stress, Psychological/physiopathology; Action, Spectrum; Parasympathetic Nervous System; Simpathetic Nervous System.**

Introduction

The Gini coefficient is a statistical tool typically used in economics to measure income inequality. However, it can be applied to any data with an unequal distribution, including Heart Rate Variability (HRV). HRV is the spectrum of time interval between successive heartbeats (RR interval) over a specific period. This study proposes a novel application of the Gini coefficient to measure the inequality of the power spectral density of RR intervals.

Physical or mental imbalance caused by noxious stimuli can induce stress to normal homeostasis. If the stress on the system becomes chronic, the sympathetic nervous system stays activated, which can cause physical, psychological, and behavioral abnormalities.[1] Sympathetic nervous system sensitivity to mental stress increases over time and it can increase the risk of future cardiovascular diseases.[2]

HRV measurement has been adopted as a non-invasive and relatively easy method for objective assessment of the severity of stress.[3] It is a physiological phenomenon of variation in the time interval between heartbeats (RR interval) and is commonly used as a measure of autonomic nervous system activity.[4-7] Power spectral density (PSD) describes the transformation of periodic oscillations of the heart-rate signals

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into different frequencies. This transformation gives numerical values about their relative intensity.[8,9] Spectral methods produce a decomposition of total variation of a data series into its frequency components, which can be expressed in the form of a spectral density function that depicts spectral power as a function of frequency.[10]

A standard for HRV measurement and interpretation of frequency domain variables was published in 1996, and most subsequent studies are based on it.[4,9] These traditional HRV indices in frequency domain variables include very low frequency [0.0033-0.04 Hz], HF [0.15-0.4 Hz] and LF [0.04-0.15 Hz]. HF has been linked to the parasympathetic influence on the heart, while LF is modulated by baroreflex activity and has been linked to both sympathetic and parasympathetic activity.[4,6,7,11,12]

The power of traditional HRV indices in different bands changes by increasing or decreasing sympathetic or vagal modulation. However, it is unknown how equally this power in each frequency band is distributed during rest. It is also unknown how this power distribution gets affected with changes in sympathetic or parasympathetic modulation. To our best knowledge, the inequality in power distribution of HRV spectrum has not been measured before.

Therefore, the present study aims 1) to apply the Gini coefficient to power spectral density of HRV to measure the inequality of power distribution of frequency bands; 2) to compare the inequality in power spectrums of HRV signals during rest *versus* under mental stress; 3) to evaluate the Gini coefficient as a psychophysiological indicator of mental stress in comparison to traditional HRV indices.

Methods

Study population

A total of 13 healthy subjects (7 females, 6 males), age 19 ± 1.5 years, BMI 22.3 ± 1.3 kg/m^2, participated in this crossover study. An *a-priori* power analysis found that this number of participants would yield 80% power at an alpha level of 0.05. All the subjects were non-smokers and had no history of heart disease, systemic hypertension or any other disease. Participants did not take any medications, drugs or alcohol for 12 hours preceding the experiment and were advised not to drink any caffeinated beverages on the morning of the study. Prior to participation, subjects signed an informed consent. Study procedures were in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Medical University of Santiago de Cuba.

Experiments were performed in a quiet environment, between 9 a.m. and 12:30 p.m.. ECGs were taken in a sitting position, during rest and during arithmetic mental stress. After attachment of the electrodes, every subject relaxed for 10 min. ECG recordings were obtained during rest with spontaneous breathing for 5 min. Immediately afterwards, subjects performed a mental arithmetic task for 5 min.[13-15] The mental arithmetic task is one of the most efficient stimuli for inducing mental stress.[16-18] Briefly, subjects subtracted 7, starting from 1000. They were instructed to subtract as accurately as possible. For a single subtraction, time allowed was 5s and was signaled by a sound. Subjects said the result aloud and after each answer, subjects received verbal confirmation ("right" or "wrong"). They continued successive subtraction, even when the result was wrong. Aside from verbalization of the answers, subjects did not talk during the mental arithmetic challenge.

Signal acquisition and processing

A PowerLab Acquisition System 8® (ADInstruments) was used to collect the ECG recordings, with a sampling rate of 1000 Hz. A standard Lead II was used for ECG measurement. The Sabarimalai-Manikandan's[19] algorithm was used to detect the QRS complexes in the ECG signal, from which RR intervals were obtained**.** Pre-processing of RR series data was required before HRV analysis in order to reduce analytic errors. The standard deviation filter with percentage filter, with value of 20% from the previous interval, were used to detect ectopic intervals.[20] Cubic Spline Replacement was employed to replace ectopic intervals using cubic spline interpolation.[21] Finally, in other analysis of ECG signals, an ECG-derived Respiration Rate (EDR) was computed from raw ECG throughout the procedure via a built-in algorithm of Kubios HRV Premium® 3.0.2 software. The algorithm examined the alterations in the amplitude of the R-peak caused by chest movements during each respiratory cycle. Under stationary conditions (i.e., short-term registrations), the EDR is considered a reliable index of respiratory rates.[22] A previous study found a reasonable agreement between EDR and a reference respiratory rate derived from nasal/oral airflow.[23]

Heart rate variability analysis

Using the algorithm described by Berger,[24] the RR interval sequence was transformed into temporal RR sequence. Pre-processed temporal 5-min RR series were subjected to spectral analysis using the Welch periodogram method to obtain the estimates of power spectral densities (PSD). A total of 2048 samples (5-min RR series) were subjected to computation through the Welch modified periodogram with a Hann window, using segments of 512 samples and overlapping periods of 256 samples. The limits for the spectral HRV bands were delimited from 0.15 to 0.40 Hz for the HF, from 0.04 to 0.15 Hz for the LF, from 0.04 to 0.085 Hz for the LF1 and from 0.085 to 0.15 Hz for the LF2. Absolute PSD were calculated as the integral of each one-sided quadratic spectrogram in the frequency ranges previously defined.

Proposed Spectral Gini HRV Indices

The Gini coefficient is typically used by economists to measure income inequality. If the income level of the ith [$i = 1, 2. . . N$] house is xi, the Gini coefficient is calculated using the following equation:[25]

$$G(x) = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N}\left|x_i - x_j\right|}{2N\sum_{i=1}^{N}x_i}$$

If the incomes of all houses are equal, that is, $x1 = x2 = \cdots = xN$, the Gini coefficient becomes 0. Additionally, when only one house has income, that is, $x1 > x2 = \cdots = xN = 0$, the

income inequality is maximal and the Gini coefficient is equal to 1.[25,26] Kyung-Jin You et al.,[26] in 2016, have proposed the Gini coefficient to quantify the inequality in the power spectrum in the range of interest (fL–fH Hz) in electroencephalography for quantifying the depth of consciousness during anesthesia. Applying this to HRV, if each frequency of the power spectrum of the RR intervals is considered as an individual house and the power of the corresponding frequency is considered as the house income, it would be possible to quantify the spectral inequality in terms of the Gini coefficient. Therefore, the Spectral Gini coefficient (SpG) is expressed as:

$$SpG_{fL-fH\,Hz} = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N}\left|X(f_i) - X(f_j)\right|}{2(H-L+1)\sum_{i=L}^{H}X(f_i)}$$

The SpG can measure the inequality in the spectral powers of the RR intervals in each spectral HRV bands employed.

Statistical analysis

All values were expressed as Mean (X), Standard Deviation (SD) and Coefficient of Variation (CV %), Median [*] and Interquartile Range [¥]. All differences were considered statistically significant for $p < 0.05$.

The Wilcoxon Signed-Rank Test (non-parametric test) for two related samples was used to compare rest *versus* mental stress. Effect Size with Gates' delta was calculated and values above 0.80 were adopted with high magnitude.[27] In order to verify the association between traditional and Spectral Gini indices of HRV during mental stress and rest, Pearson's correlation was applied to the data with normal distribution, or Spearman's correlation, for the ones that did not accept this distribution. The normality of the data was initially determined using the Shapiro-Wilk test. Principal Component Analysis (PCA) is a technique to reduce the dimensionality of data consisting of correlated variables while capturing the bulk of variation present in the data.[28] There are as many principal components (PCs) as there are original variables. Each PC is a linear combination of the original variables with a set of weights called "loadings", which reflect the correlations between PCs and original variables. PC1 is the directional vector representing the best fit for data cloud. PC2 is the directional vector orthogonal to PC1 that provides the best fit for residual variability in the data, and so on. PCs are mutually uncorrelated. Effective dimensionality reduction is achieved when the first few (dominant) PCs capture most of the variation present in the data. Useful insights on the interrelationship between original variables can be obtained when the dominant PCs have substantive interpretations. The efficacy of the traditional and Spectral Gini Indices of HRV were defined by the Receiver Operating Characteristic (ROC) curve through Sensitivity, Specificity, Area Under Curve and its respective p value were used with Cutoff Points between rest and mental stress set by Youden Index.

All the statistical and mathematical calculations, as well as the processing of the signals, were performed using the Matlab 2012b software.

Results

Table 1 describes values of traditional and Spectral Gini Indices of HRV at rest and during mental stress. There was a significant decrease in HF ($p = 0.046$), a significant increase in the heart rate ($p = 0.004$), LF/HF ($p = 0.002$), LF ($p = 0.033$) and LF2 ($p = 0.019$) during mental stress, compared to rest. A significant increase in SpG(LF) ($p = 0.009$) and SpG(LF2) ($p = 0.033$) was observed. Coefficient of Variation analysis showed that Spectral Gini Indices are more homogeneous than traditional Indices of HRV.

The correlation values between traditional and Spectral Gini Indices of HRV during rest and mental stress are shown in Table 2. During rest, there were high correlations between the HR and the SpG(LF1) ($r = 0.721$; $p = 0.01$) and between SpG(LF) and SpG(LF2) ($r=0.829$; $p = 0.01$), good correlations between LF and SpG(LF2) ($r = 0.645$; 0.05), and between LF2 and SpG(LF2) ($r = 0.628$; 0.05). During mental stress, there was a good correlation between SpG(LF) and SpG(LF2) ($r = 0.682$; 0.05).

Figure 1 and Table 3 represent Principal Component Analysis (PCA) of Traditional and Spectral Gini Indices of Heart Rate Variability during rest and mental stress.

The PCA helps to reduce the multiple characteristics or variables of a sample to a few dimensions (in this case, only two dimensions). It can be explained as trying to reduce twelve variables of an object to two values or characteristics and to determine which out of these twelve variables are the most robust for those two characteristics (two dimensions), which allow a better study of the object of interest. The important variables for each dimension are those that are higher than 1 or lower than -1. On dimension 1, the variables LF (1.4742), HF (1.2896), LF1 (1.4674) and LF2 (1.3519) have greater weight. On dimension 2, the variables with a greater load are HR (1.3612), LF/HF (1.2657), SpG LF (1.4026) and SpG LF2 (1.0909).

With respect to Figure 1, the relationship between the variables is given by the cosine of the angle formed by each vector representing that specific variable. The more acute the angle, which is to say that it has a tendency to 0, the higher will be correlation, and if the vectors form a 90 degree angle, the variables will not be correlated. On the other hand, if they form an angle of 180 degrees, correlation is inverse. In dimension 2, the vectors of the variables HR, LF/HF and SpG LF form an angle close to 180 with the EDR and therefore, HR, LF/HF and SpG LF are negatively correlated with EDR. The size of the vector is the strength of that variable in that dimension.

Discussion

The present study aimed 1) to apply the Gini coefficient to power spectral densities of HRV to measure the inequality in distribution of frequency bands; 2) to compare the inequality in power spectrum of HRV signals during rest versus under mental stress; 3) to evaluate the Gini coefficient as a psychophysiological indicator of mental stress in comparison to traditional HRV indices.

In the present study, the traditional indices of HRV during mental stress showed expected results of significant increase in LF power and increase in LF/HF ratio, along with significant decrease in HF power. HRV is a reliable tool to measure psychophysiological stress[29] and the present results shows significant changes in HRV indices compared to rest.

Table 1 – Traditional and Spectral Gini Indices of Heart Rate Variability during rest and mental stress

	Variables	Rest			Mental Stress			Effect Size Gates' delta	p value
		X [*]	SD [¥]	CV (%)	X [*]	SD [¥]	CV (%)		
HRV Index	HR (bpm)	80.32 [75.5]	10.52 [15.6]	13.09	96.41 [91.4]	11.78 [21.1]	12.22	1.52 Large	0.004
	RMSSD (ms)	47.36 [44.10]	22.95 [26.45]	48.45	33.52 [32.20]	17.98 [27.30]	53.63	0.60 Medium	0.009
	EDR (Hz)	0.24 [0.25]	0.05 [0.06]	20.82	0.21 [0.22]	0.04 [0.08]	23.73	-0,6 Small	0.064
Traditional Indices [Bandwidth]	LF (ms2/Hz) |0.04-0.15 Hz|	844.78 [689.27]	627.95 [789.86]	74.33	1373.44 [1123.02]	1003.01 [1560.15]	73.02	0.84 Medium	0.033
	HF (ms2/Hz) |0.15-0.40 Hz|	1281.96 [986.91]	1429.36 [848.70]	111.49	758.91 [517.83]	691.12 [1001.75]	91.06	-0.36 Small	0.046
	LF1 (ms2/Hz) |0.04-0.085 Hz|	291.79 [283.39]	200.64 [180.87]	68.76	267.57 [235.48]	174.23 [224.52]	65.11	-0.12 Small	0.650
	LF2 (ms2/Hz) |0.085-0.15 Hz|	533.69 [435.59]	421.36 [580.17]	78.95	1086.58 [726.52]	861.88 [1308.89]	79.32	1.31 Large	0.019
	LF/HF (ratio)	1.00 [0.69]	0.88 [0.79]	88.2	2.31 [1.93]	0.93 [1.60]	40.34	1.48 Large	0.002
Gin Spectral Indices [Bandwidth]	SpG(LF) |0.04-0.15 Hz|	0.29 [0.29]	0.06 [0.08]	20.40	0.40 [0.39]	0.10 [0.16]	25.62	1.66 Large	0.009
	SpG(HF) |0.15-0.40 Hz|	0.50 [0.50]	0.08 [0.15]	17.35	0.45 [0.47]	0.09 [0.14]	20.00	-0.54 Small	0.133
	SpG(LF1) |0.04-0.085 Hz|	0.24 [0.21]	0.06 [0.07]	25.70	0.23 [0.22]	0.08 [0.12]	36.86	-0.19 Small	0.382
	SpG(LF2) |0.085-0.15 Hz|	0.28 [0.27]	0.07 [0.12]	26.22	0.35 [0.38]	0.10 [0.16]	29.71	0.85 Medium	0.033

p < 0.05. Mean (X), SD: standard deviation; CV: coefficient of variation; HRV: heart rate variability; HR: heart rate; RMSSD: Root Mean Square of the Successive Differences; EDR: ECG-derived; Respiration Rate; LF: low frequency; HF: high frequency; SpG: spectral; Gini coefficient.Median [*] and Interquartile Range [¥].

Table 2 – Correlations between Traditional and Spectral Gini Indices of HRV during mental stress and rest

HRV Indices	SpG(LF)			SpG(HF)			SpG(LF1)			SpG(LF2)		
	Rest	Mental Stress	Total	Rest	Mental Stress	Total	Rest	Mental Stress	Total	Rest	Mental Stress	Total
HR	0.313	-0.413	0.587‡*	0.306*	-0.140	-0.110	0.566†*	-0.112	,151	-0.025	0.463	0.409
RMSSD	-0.084	0.432	-0.029	-0.153	-0.446	-0.173	0.192*	0.053	,122	-0.216	0.267	-0.084
EDR	-0.177	-0.47	-0.466†	-,031	-0.293	-0.055	-0.330*	-0.037	-0.179	0.010	-0.404	-0.320
LF	0.264*	-0.005	0.296*	-	-	-	-0.335*	0.016	-0.177*	0.593†*	0.180	0.333*
HF	-	-	-	-0.192*	0.078	-0.026*	-	-	-	-	-	-
LF/HF	0.220*	-0.039	0.397†*	0.253*	-0.038	-0.002*	0.104*	-0.207	-0.008*	0.379*	-0.048	0.387*
LF1	0.258*	-0224	0.017*	-	-	-	-0.319*	-0.054	-0.217*	-	-	-
LF2	0.231*	0.041	0.335*	-	-	-	-	-	-0.158*	0.582†*	0.17	,335
SpG(LF)	-	-	-	-	-	-	0.390*	0.153	0.177*	0.829‡	0.682†	0.698‡

*Note: † p < 0.05; ‡ p < 0.01; *Spearman's correlation, for the HRV indices that did not accept normal distribution in Shapiro-Wilk test. HRV: heart rate variability; HR: heart rate; RMSSD: Root Mean Square of the Successive Differences; EDR: ECG-derived; Respiration Rate; LF: low frequency; HF: high frequency; SpG: spectral; Gini coefficient.*

To the best of our knowledge, this is the first study to apply the Gini coefficient to power spectrums of HRV signal/RR intervals to measure inequality in distribution of power. Conceptually, a Gini coefficient of zero means that the power is distributed equally for all frequencies within a spectral bandwidth. In contrast, a Gini coefficient of 1 suggests that there is a single frequency with the most power within a specific spectral bandwidth, and all other frequencies in the bandwidth have no power. In other words, increase in the Gini coefficient value suggests that there are few frequencies with the most power within that frequency band compared to before. The results showed that there was a significant increase in SpG(LF) during mental stress compared to rest, meaning that during mental stress, not only there was an increase in total power in LF, but also the total power distribution became more unequal and certain frequencies gained the most power. It is noteworthy that the LF2 sub-band (0.085-0.15 Hz) showed increased inequality, as changes in SpG(LF) and

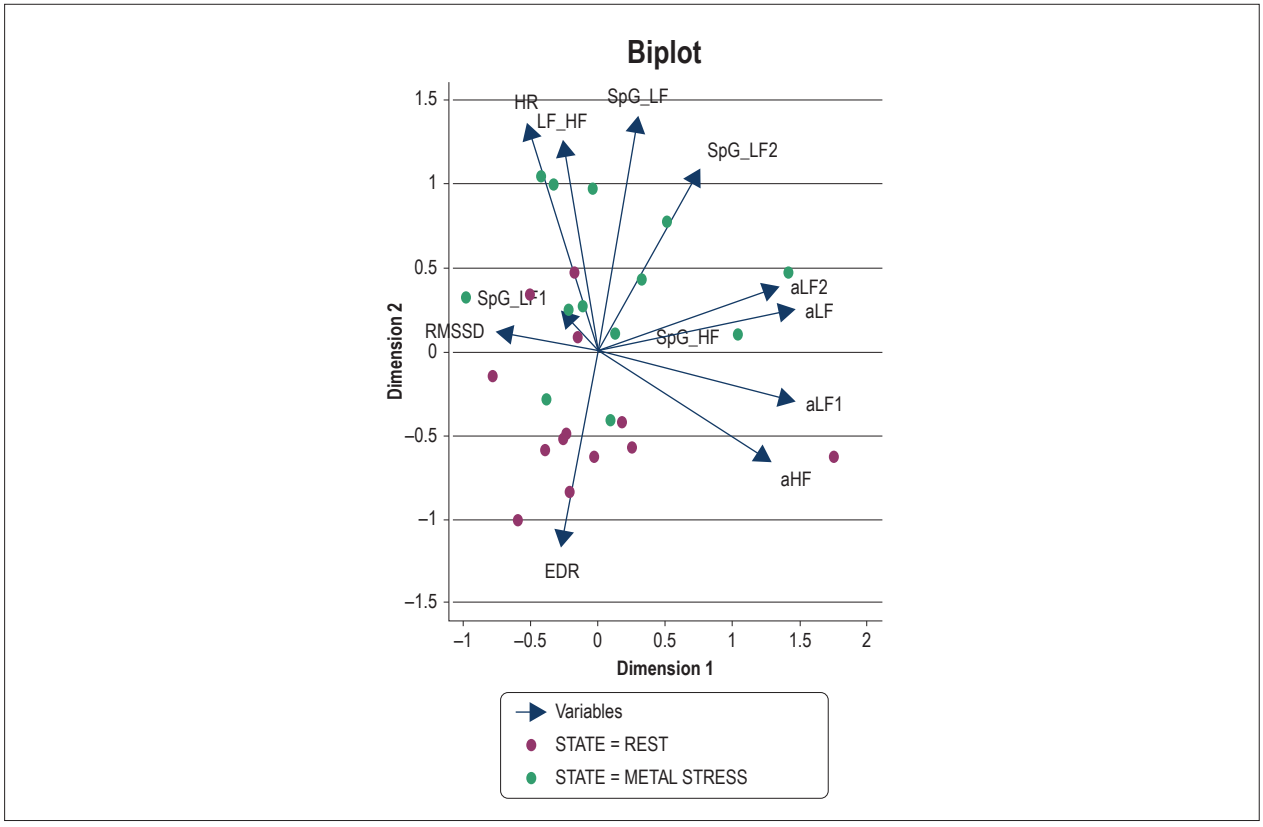

Figure 1 – *Principal Component Analysis of Traditional and Spectral Gini Indices of Heart Rate Variability during rest and mental stress (aHF = absolute HF; aLF1 = absolute LF1; aLF = absolute LF; aLF2 = absolute LF2). HR: heart rate; RMSSD: Root Mean Square of the Successive Differences; EDR: ECG-derived; Respiration Rate; LF: low frequency; HF: high frequency; SpG: spectral Gini coefficient.*

SpG(LF2) were significant but not for SpG(LF1) during mental stress. It should also be noted that the traditional HRV index showed a significant decrease in HF power during mental stress, but the decrease in SpG(HF) was not significant. These data suggest that there was decrease in power in the HF band, but the distribution of power within the HF band remained similar during rest and mental stress.

The coefficient of variation showed that, in comparison to traditional HRV indices, Gini spectral indices are homogeneous (see Table 1), meaning that the numeric values of changes in distribution of power during mental stress are located closer to the center (mean) and do not have high SD values like traditional indices. Pearson Correlation (and Spearman's correlation) Tests revealed poor correlation values between traditional and Spectral Gini Indices during mental stress, even though LF and LF2 of traditional HRV index showed good correlation with SpG (LF2) at rest. This indicated that Gini values are independent of traditional HRV indices and contribute to the additional information not reported until now.

Principal Component Analysis of traditional and Spectral Gini indices helps to reduce the multiple characteristics or variables of a sample (HRV) to a few dimensions (in this case, only two dimensions). It can be explained as trying to reduce twelve variables of an object to two values or characteristics and to determine which out of these twelve variables are the most robust for those two characteristics (two dimensions), which allow a better study of the object of interest. Dimension 2 is what differentiates the state of stress (green arrow on the figure, which tends to go upward) from the state of rest (red arrow on the figure, which tends to go below). Therefore, even though LF and HF have values >1 on Dimension 1, the variables with high load such as HR,LF/HF, SpG LF and SpG LF2 from Dimension 2 are considered physiologically and clinically more important as state indicators.

ROC curve was produced in order to evaluate the efficacy of Spectral Gini indices as an evaluator of mental stress. The cutoff points of the different indicators in the differentiation of the psychophysiological states, obtained from the Youden Index of the ROC curve, can be observed. However, it stands out how the HR ($p = 0.001$) the LF/HF ($p = 0.001$) and the SpG (LF) ($p = 0.011$) constituted the most optimal (ROC model) and effective indicators in the discrimination between rest and mental stress with the best values of sensitivity, specificity, Youden Index and area under the curve ($p < 0.05$).

The results shown on Table 4 are consistent with the results in Table 1, Figure 1 and Table 3, suggesting that HR; LF/HF and SpG LF were highlighted in the discrimination of the states of rest and stress.

The significant increase in LF and SpG(LF) power during mental stress allows discussion on the contributing factors for LF power. It is generally accepted that the HF component

is a reflex of the parasympathetic activity, and that the LF and LF/HF components are a reflex of both sympathetic and parasympathetic activity.[4] Breathing rate can influence HRV variables noticeably.[14,30] Bernardi et al.[14] have further reported that regardless of the amount of stress involved in the mental task, low breathing rate usually contributes to increase in LF power of HRV. Although there was a decrease in breathing rate during stress compared to rest in the present study, the EDR was 0.21 ± 0.04 Hz or 12.6 ± 0.24 br/min, which is not within the LF components in the RR power spectrum. In other words, in the present study, respiration rate was not responsible for increased LF power during mental stress.

There are few studies examining the contributing factors to LF power of HRV in depth. In their recent study, Roach et al.[31] reported that 75% of the contribution to LF power comes from fluctuations called ripples, and these ripples are probably due to arterial baroreceptor functions. Reyes del Paso et al. [32] have showed a strong association between baroreflex activity and mental stress. Vaschillo et al.[33] have investigated the subdivision of LF in two separate components in young binge drinkers and suggested that these two divisions functionally indicate two distinct physiological parameters. LF1 represents vascular tone baroreflex and LF2 represents heart rate baroreflex activity.

As noted earlier, data analysis from the current study showed increased LF power and decreased HF power during mental stress, along with increased SpG(LF) and SpG(LF2). It is possible that, under stress, a healthy cardiovascular system generates more LF oscillations, especially with power mostly around 0.1Hz frequencies, to regain homeostasis. This possibility is supported by Bates et al.,[34] who evaluated real-time changes in RR interval spectrum in response to placebo and alcohol. Bates et al.[34] suggested that under alcohol or other adverse conditions, one of the main adaptations includes maintaining low frequency oscillations even at the expense of high frequency oscillations. This can also explain the lack of changes in SpG(HF) under mental stress. That study also suggested that low frequency oscillations are useful to generate resonance for better adaptation, and 0.1 Hz is one of several resonance frequencies. The current study supports significant increase in LF subdivision during mental stress, and future studies are recommended to investigate the association of 0.1 Hz frequency to arterial baroreflex activity for better understanding of the mechanism of physiological adaptations during mental stress.

Table 3 – Values of Factor Loadings of Traditional and Spectral Gini Indices of Heart Rate Variability during rest and mental stress from Principal Component Analysis

Variable	Dimension 1	Dimension 2
HR	-0.5240	1.3612
RMSSD	-0.7615	0.1257
EDR	-0.2707	-1.1683
LF	1.4742	0.2518
HF	1.2896	-0.6571
LF1	1.4674	-0.2996
LF2	1.3519	0.3851
LF/HF (ratio)	-0.2641	1.2657
SpG(LF)	0.3048	1.4026
SpG(HF)	0.3397	0.0928
SpG(LF1)	-0.2806	0.2438
SpG(LF2)	0.7623	1.0909
Explained variance by	0.3125	0.2578
Total explained variance: 0.5703		

ROC curve and other efficacy values for Traditional and Spectral Gini Indices of Heart Rate Variability are described in Table 4. The cutoff points of the different indicators can be observed in the differentiation of the psychophysiological states obtained from the Youden Index of the ROC curve. Out of the 12 variables studied here, only HR (cutoff point: 83.350 bpm; p = 0.001), LF/HF (cutoff point: 1.02; p = 0.001) and SpG(LF) (cutoff point: 0.356; p = 0.011) show high values of sensitivity, specificity, Youden Index and area under the curve (p < 0.05). HR: heart rate; RMSSD: Root Mean Square of the Successive Differences; EDR: ECG-derived; Respiration Rate; LF: low frequency; HF: high frequency; SpG: spectral Gini coefficient

Table 4 – Efficacy of Traditional and Spectral Gini Indices of Heart Rate Variability in the discrimination of rest and mental stress

Variables	Cutoff point	Sensitivity	Specificity	Youden Index	Area Under Curve	p value
HR	83.350 bpm	1.00	0.769	0.769	0.870	0.001
RMSSD	37.70 ms	0.385	0.307	-0.308	0.325	0.130
EDR	0.2299 Hz	0.385	0.307	-0.308	0.308	0.096
LF	1120.44 ms^2/Hz	0.538	0.769	0.308	0.651	0.191
HF	623.83 ms^2/Hz	0.385	0.230	-0.385	0.343	0.174
LF1	239.99 ms^2/Hz	0.462	0.384	-0.154	0.450	0.663
LF2	581.42 ms^2/Hz	0.769	0.692	0.462	0.698	0.086
LF/HF (ratio)	1.02	1.00	0.769	0.769	0.870	0.001
SpG(LF)	0.356	0.692	0.923	0.615	0.793	0.011
SpG(HF)	0.505	0.231	0.53846	-0.231	0.373	0.270
SpG(LF1)	0.203	0.538	0.0769	-0.385	0.420	0.489
SpG(LF2)	0.274	0.692	0.615	0.308	0.722	0.054

HR: heart rate; RMSSD: Root Mean Square of the Successive Differences; EDR: ECG-derived; Respiration Rate; LF: low frequency; HF: high frequency; SpG: spectral Gini coefficient.

Conclusions

This study successfully applied Gini coefficient to power spectral densities of HRV to measure the inequality in distribution of frequency bands.

These results suggest that during stress (arithmetic challenge), compared to rest, not only total power of low frequency band increases, but the total power distribution becomes more unequal.

Spectral inequalities of heart rate variability analyzed from the Gini coefficient seem to be independent and homogeneous indicators of psychophysiological mental stress compared to traditional indices of HRV as per this pilot study.

Out of traditional and spectral Gini indices of HRV, HR, LF/HF, SpG (LF) seems to be valid and reliable tools as indicators of stress, and this study provides cutoff values for these variables to discriminate the states of stress and rest.

Study limitations

Among the limitations of this study, the small sample size can be cited. This is a pilot study on Gini coefficient application to HRV spectrum, therefore more studies with larger sample sizes are recommended for better understanding and interpretation of inequalities in power spectral density of RR intervals.

In addition, a mental arithmetic challenge was used to induce mental stress. Although this method is considered valid and reliable, results can possibly be varied under different circumstances, as mental stress is a complex and dynamic phenomenon.

Finally, HRV can be influenced by hormones depending on the menstrual phase in female participants. Although the menstrual phase was not monitored, data for both conditions (rest and mental stress) were collected on the same day in order to minimize baseline variability.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Sánchez-Hechavarría ME, Ghiya S, Carrazana-Escalona R, Cortina-Reyna S, Andreu-Heredia A, Acosta-Batista C, Saá-Muñoz NA; Acquisition of data: Sánchez-Hechavarría ME, Ghiya S, Carrazana-Escalona R, Cortina-Reyna S, Andreu-Heredia A; Analysis and interpretation of the data: Sánchez-Hechavarría ME, Ghiya S, Carrazana-Escalona R, Cortina-Reyna S, Acosta-Batista C; Statistical analysis: Sánchez-Hechavarría ME, Andreu-Heredia A, Saá-Muñoz NA; Writing of the manuscript: Sánchez-Hechavarría ME, Ghiya S, Acosta-Batista C, Saá-Muñoz NA.

Potential Conflict of Interest

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

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Ethical approval and informed consent

This study was approved by the Medical University of Santiago de Cuba Ethics Committee under protocol number 22/2017. All procedures involved in this study are 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 Neurolinguistics of the Heart

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Short Editorial related to the article: Introduction of Application of Gini Coefficient to Heart Rate Variability Spectrum for Mental Stress Evaluation

The association between mental stress and cardiac function has always been of major interest. In the 19th century, Claude Bernard, the father of evidence-based medicine, first acknowledged the vagus nerve as a structural and functional link connecting the heart and the brain. Nowadays, stress is considered one of the most significant health problems in modern society, related to the physiopathology of psychiatric, metabolic and cardiovascular diseases, and the search for its biomarkers remains a challenging task for researchers and clinicians.

But what is stress? How can we define it, before we tackle it?

From a phylogenetic point of view, the perception of threat and safety is the core element implicated in mental events related to stress. This threat appraisal works as a trigger of complex neurological processes leading to adaptive adjustments of heart rate, cardiac contractility and vascular resistance that follows sympathetic tone enhancement and parasympathetic withdrawal, and ultimately result in the survival of the individual and of the species. In summary, the heart and the brain are in constant communication in order to keep us from danger.

Although several physiological mechanisms are known to take part in this elaborate neurological circuitry, the autonomic nervous system is, undisputedly, the protagonist. The study "Introduction of Application of Gini Coefficient to Heart Rate Variability Spectrum for Mental Stress Evaluation",[1] identified an increase in the low frequency spectral power and in total spectral inequalities (using the Gini coefficient) during a cognitive mental challenge (arithmetic exercise). Interestingly, the 0.1Hz band expression, frequently associated with the arterial baroreflex activation, was significantly increased. Authors therefore proposed these indexes as biomarkers of stress and implicated baroreflex hyperactivity in its psychophysiology.

To the extent that we assume autonomic tonus changes as a reliable sign of mental stress, the heart rate variability (HRV) may indeed provide some interesting information. However, a careful appreciation of the involved neural structures may yield an insight into a sophisticated system and indicate that a reductionist interpretation of the autonomic response pattern may turn out to be misleading.

Observe the peripheric autonomic nervous pathways carefully. Its extrinsic components, mainly comprised by the vagus nerve and the numerous afferent and efferent nerves of the sophisticated sympathetic thoracic chain, are responsible to carry, through the central nervous system and back to the heart, sympathetic and parasympathetic information from baro and chemoreceptors, generating balanced responses that maintain internal homeostasis. Take into consideration that most of these structures are bimodal, with both vagal and sympathetic inputs.[2] Close to the epicardial surface, this innervation resolves into the intrinsic system, consisting of a dense net of thousands of neural cells and hundreds of epicardial ganglia, plentifully located in the atrial surface.[3,4] Cardiac ganglia work as integrative centers, where efferent data can be modulated, so the whole system can flexibly respond to a wide range of stimuli.[5] This modulation, this capacity to provide adaptive control over the periphery, is the hallmark of the autonomic nervous system.

Intrinsic and extrinsic systems are connected to the central nervous system. Here is where things start getting tricky. By using PET Scan and MRI, a series of neuroimaging studies[6,7] describe a *central autonomic network,*[7] containing cortical and subcortical areas, through which the brain controls visceromotor functions and goal-directed behavior. The network includes prefrontal cortices, the central nucleus of the amygdala, the paraventricular nucleus of the hypothalamus, the parabrachial nucleus, the nucleus of the solitary tract, and the nucleus ambiguous, among others. All these components are reciprocally interconnected, and the interplay of these inputs provides flexible adjustments. The system essentially operates as a continuous integration of concepts such as “self” and “danger” with external perceptions and memory into Gestalt representations, generating likely responses.

After appraising a potential threat, a primitive quick mental stress reaction arises from the amygdala. The reaction to uncertainty or danger is a relatively simple sympathoexcitatory state known as “fight or flight”, that in its pristine form results in a rather predictable HR increment. However, this initial perception often gives way to more elaborate mental interpretations as certain cortical areas action unfolds. The frontal cortex (FC), and medial preFC in particular, has a significant role by activating GABAergic pathways exerting inhibitory control over an activated amygdala.[7] The more abstract the stressful event, the more important and modulated the inhibition of subcortical cardioacceleratory circuits are, meaning that all these neural structures can be differentially recruited depending on the nature of the challenge, creating context-specific response patterns.

Keywords

Heart Failure;Gini Coefficient; Stress, Psychological, Action Spectrum; Sympathetic Nervous System; Parasympathetic Nervous System; Neurolinguistic Programming.

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Complex tasks requiring cognitive functions, such as arithmetic, online processing and manipulation of information are highly dependent on this reciprocal downregulation between the cortex and the amygdala.[8] The resultant HRV takes so many variables into account that defining specific spectral bands as reliable biomarkers, assuming a mechanistic causality, seems unlikely, especially so when it comes to abstract stressful contexts, such as expectations of future outcomes, emotional conditions and representation of economic values.[7]

To illustrate this limitation, in a very simplified way, imagine you are about to take a math test. At first, the challenge may disturb you, being felt as "danger", and so the amygdala nucleus promptly triggers a vagal withdraw (affecting both high and low frequency spectral powers) and a sympathoexcitatory reflex (modifying low frequency spectra). A few minutes later you realize you can handle it and start feeling confident. It is just going to take a little focus. A more accurate Gestalt representation has now been reached. By activating a GABA pathway, three main different areas of your preFC engage: 1-posterior and dorsal region of the rostral preFC (linked to cognitive functions), 2-dorso medial preFC (reliably related to social cognition) and finally 3- medial-orbitoFC and anterior ventral preFC (associated with autonomic aspects of emotional contexts and to "reward and punishment").[6,7]

Exerting a balanced inhibitory control over the amygdala through an integrated Central Autonomic Network, these anatomic structures guide goal-directed behavior and adaptability and ultimately dictates the amount of acetylcholine and norepinephrine to be released from the post-ganglionic fibers close to the sinus node, reshaping HRV spectra once again. Keep in mind that genetic background and cognitive performance may influence all these processes significantly.[7]

What is the value of HRV on assessing stress, then? As of 1965, Hon and Lee[9] had already identified inter-beat interval patterns preceding severe fetal distress even before a perceivable change in fetal heart rate. Undoubtedly, HRV has been proven to be an essential index of adaptability of the organism, and therefore, extensively studied under a wide range of stressful stimuli. Conflicting results, however, suggest distinct reactions to different forms of stress. While some authors demonstrated a global increase in HRV after exposure to noise,[10,11] public speech tasks[12] and sustained attention,[13] others found a global HRV reduction during memory[14] and cognitive tasks.[15] Emotional conditions have been proven to correlate with high-frequency band reduction by some authors,[16] and yet to be neutral by others.[12]

We are far from relying on surrogate endpoints to understand the different parts of the link between heart and brain. Even by using much more sophisticated techniques, such as regional cerebral blood flow neuroimaging, we are still scratching the surface of this intricate physiology. HRV could be an interesting tool for detecting general features of the stress response, although unreliable for distinguishing its complex mechanisms.

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Short Editorial

The Use of Two-Dimensional Strain Measured by Speckle Tracking in the Identification of Incipient Ventricular Dysfunction in HIV-Infected Patients on Antiretroviral Therapy, Untreated HIV Patients and Healthy Controls

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Abstract

Background: **Most cardiovascular abnormalities in patients infected with the human immunodeficiency virus (HIV) have been associated with myocardial damage directly caused by the virus. Some cases, however, may be associated with adverse effects from antiretroviral therapy (ART). New ventricular function assessment techniques are capable of detecting early changes in the cardiac function of HIV-infected patients using or not using ART. The usefulness of these techniques has been little employed in these patients.**

Objectives: **To investigate the potential influence of antiretroviral therapy (ART) on the occurrence of subclinical left ventricular systolic dysfunction evaluated by myocardial strain rate analysis using two-dimensional speckle tracking echocardiography (2-D Echo) in treated HIV patients compared to untreated patients and healthy individuals.**

Methods: **Sixty-eight HIV-infected patients with no cardiovascular symptoms, normal left ventricular (LV) ejection fraction (> 0.55 on 2-D Echo) were divided into three groups: 11 patients not using antiretroviral therapy (NT), 24 using protease inhibitor (PI) and 33 using non-nucleoside reverse transcriptase inhibitor (NNRTI). We also studied 30 normal non-HIV infected individuals (Ctrl). Demographic, clinical, biochemical and anthropometric data were collected. Preliminary transthoracic echocardiography included study of myocardial strain using two-dimensional speckle tracking. We studied strain and strain rate in the seventeen left ventricular (LV) myocardial segments in the longitudinal, circumferential and radial axes. Statistical analysis of the data was done with IBM SPSS – version 20 for Windows. Upon analysis of the data, namely the normality of independent variables in the different groups and the homogeneity of the variances between the groups, Kruskal-Wallis' non-parametric test was done, followed by Dunn's multiple comparison tests to test the significance of the differences between the values measured in the study groups. A significance level of 5% was adopted for decision-making on statistical tests.**

Results: **The mean age of HIV patients was 40 ± 8.65 years and the mean age of controls was 50 ± 11.6 years ($p < 0.001$). Median LV global longitudinal strain (GLS) of NT patients (–17.70%), PI patients (–18.27%) and NNRTIs (–18.47%) were significantly lower than that of the Ctrl group (–20.77%; $p = 0.001$). There was no significant difference in mean SLG between treated patients (PI, NNRTI) and untreated (NT) patients. No significant differences were observed in mean circumferential and radial strain, nor on circumferential and radial strain rates between the NT, PI, NNRTI and Ctrl groups.**

Conclusion: **The data suggest that HIV patients present, on myocardial strain measured by speckle tracking, signs of early LV systolic dysfunction that seem to be unrelated to the presence of ART. The prognostic significance of this condition in these patients deserves further studies. (Arq Bras Cardiol. 2019; 113(4):737-745)**

Keywords: **Acquired Immunodeficiency Syndrome; HIV; Ventricular Disfunction,Left; Echocardiography, Doppler; Antiretroviral Therapy; Highly Active; Strain; Speckle Tracking.**

Introduction

Around the world, deaths related to the acquired immunodeficiency syndrome (AIDS) declined from about 1.9 million in 2005 to about 1 million in 2016, largely due to expansion of treatment – for the first time, more than half of people infected with the human immunodeficiency virus (HIV) were under treatment for the disease. Since 2010, the annual number of new infections in all age groups decreased by 16%. However, progress is variable and, despite a global downward trend in this epidemic disease, several regions have been experiencing a sharp increase in the number of new infections and difficulties in expanding treatment.[1]

The antiretroviral therapy (ART) was an important development for HIV-infected patients, contributing to prolonged survival and improved quality of life.[2] Cardiovascular diseases have become a common finding because of the longer survival of these patients. Another important aspect of cardiovascular complications is that they appear to be associated with the effects of ART.[3,4] Although a decline in the incidence of severe heart

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conditions due to opportunistic agents, malnutrition or prolonged immunosuppression has been observed,[5] the incidence of coronary artery disease and peripheral vascular events has increased in HIV-infected patients.[6,7]

HIV-infected patients may have specific myocardial abnormalities and conventional two-dimensional tests may fail to detect subtle abnormalities in regional myocardial function. Speckle tracking is an innovative echocardiographic technique that has the capacity to evaluate myocardial strain in order to identify subtle abnormalities in ventricular function. Myocardial strain is a very important mechanical variable in HIV-infected patients, as it shows subclinical left ventricular dysfunction. Unfortunately, the technique of studying cardiac strain is still underused. Global longitudinal strain (GLS) is well correlated with left ventricular ejection fraction (LVEF). Reduced SLG can be found in patients with heart failure with preserved ejection fraction,[8] stable angina,[9] three-vessel coronary artery disease and patients using chemotherapy agents with cardiotoxicity.[10,11] The purpose of this study was to evaluate the presence of subclinical ventricular function abnormalities in HIV-infected patients using or not using ART.

Methods

Observational cross-sectional study involving 68 HIV-infected patients recruited from the Infectiology Service of Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF). Inclusion criteria were: age ≥18 years, HIV infection confirmed by serological tests, no cardiovascular symptoms. Patients were excluded if they were under any therapy with cardiac or neurological medications, if they had any cardiac symptom or history of hypertension, LV ejection fraction <0.55 and pulmonary artery systolic pressure >36 mmHg, stable angina, atrial fibrillation or moderate to severe valvular heart disease. Echocardiography was performed as part of an established research protocol rather than for symptoms or comorbidities. Patients were divided into four groups: 1) HIV-positive patients not using ART (NT); 2) HIV-positive patients on protease inhibitor therapy for at least 12 months (PI); 3) HIV-positive patients on therapy with non-nucleoside reverse transcriptase inhibitors (NNRTI) for at least 12 months and 4) healthy controls. Samples from the NT (n = 11), PI (n = 24) and NNRTI (n = 33) groups were defined by convenience, considering the patients at the time of data collection. For the control group, a sample of size similar to the largest of the study groups (n = 30) was defined.

The echocardiographic tests were conducted on an Echo Color Doppler device of the Italian company Esaote Biomédica, model Mylab 30 Gold, with a multi-frequency electronic sectoral transducer (2 to 4 MHz) with continuous electrocardiographic scanning. Traditional measures of left ventricular (LV) systolic function, ejection fraction and systolic shortening, diastolic function indicators, such as mitral flow E/A ratio, myocardial E wave velocity in the septal mitral annulus (septal E'), E/E' ratio and estimated left atrial pressure were taken. Right ventricular diastolic diameter and two echocardiographic variables that evaluate right ventricular systolic function were determined: tissue Doppler of lateral tricuspid annulus and longitudinal tricuspid annular motion (LTAM). LV ejection fraction was determined by using the Simpson's technique, on apical four-chamber and two-chamber views, on diastole and systole, thus obtaining end diastolic and end systolic volumes. Left atrial volume was obtained from end-systolic four-chamber and two-chamber views, and the arithmetic mean was then indexed by the body surface area to obtain left atrial volume index. LV mass was obtained from diastolic and systolic LV diameters, as well as from the interventricular septal and inferolateral wall diastolic thickness, following the technical guidelines of the American Society of Echocardiography.[12] Maximum tricuspid regurgitation (TR) rate, an indicator of pulmonary artery pressure, was obtained from apical four-chamber view. LV diastolic and systolic myocardial velocities were obtained by placing the tissue Doppler sample volume in the septal mitral annulus. Digital myocardial strain curves were taken by using the Xstrain software package from scanned cross-sectional and apical view images. Myocardial strain rate was also evaluated. GLS was obtained by the arithmetic mean of the longitudinal strain values in the seventeen segments, from the four-chamber apical view (Figure 1), three-chamber apical view (Figure 2) and two-chamber apical view (Figure 3). Global circumferential strain (GCS) was obtained by the arithmetic mean of the circumferential strain values in the seventeen segments, from the cross-sectional views at the level of the mitral valve, papillary muscles and tip. Radial global strain (SRG) was obtained from the arithmetic mean of the radial strain values in the seventeen segments, from cross-sectional views of the mitral valve, papillary muscles and tip. Strain percentage analysis was repeated twice, using the best echocardiographic images. The same echocardiographer conducted transthoracic evaluation, then took the scanned images to calculate the percentages of longitudinal, radial and circumferential strain on an offline workstation. The strain rate in the longitudinal, circumferential and radial planes was also obtained. (Figures 1 and 3).

Statistical analysis

Statistical analysis of the data was done with IBM SPSS – version 20 for Windows. After analysis of normality of independent variables in the different groups (using the Shapiro-Wilk test) and homogeneity of the variances between the groups (using Levene's test), it was decided to use Kruskal-Wallis' non-parametric test followed by Dunn's multiple comparison tests to test the significance of the differences between the values measured in the study groups. A significance level of 5% was adopted for decision-making on statistical tests. Continuous variables with normal distribution were described as mean and standard deviation and continuous variables with non-normal distribution were described as median and interquartile range.

This study was approved by the Research Ethics Committee from Hospital Universitário Antônio Pedro (#HUAP 159/11) and all patients signed an Informed Consent Form.

Results

The study included 98 individuals: 68 (69.4%) HIV-infected and 30 (30.6%) healthy controls with negative serology, of which 60 (61.2%) were males and 38 (38.8%) were females. Separately analyzing the groups of HIV-infected

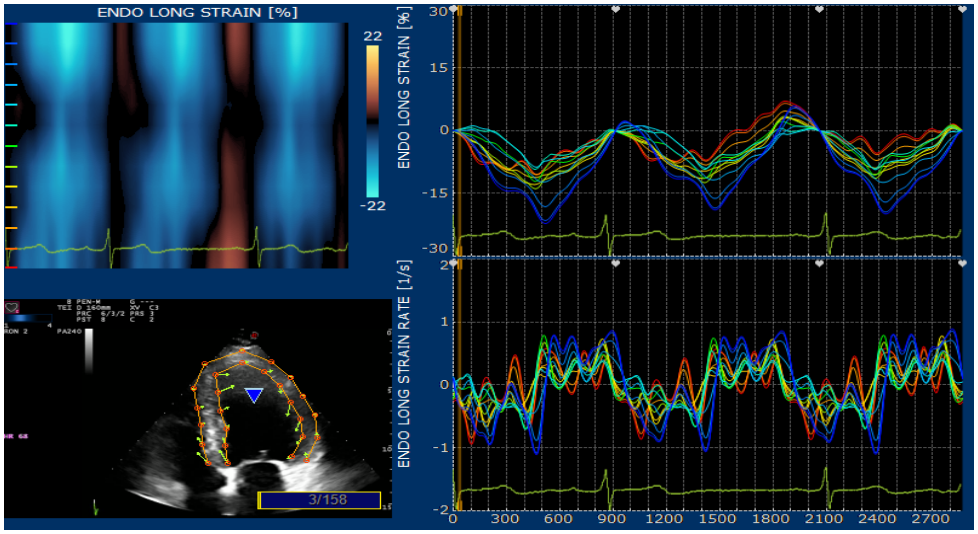

Figure 1 – *Apical four-chamber – percentage of longitudinal strain in the basal, middle and apical segments of the inferior and anterolateral septal walls.*

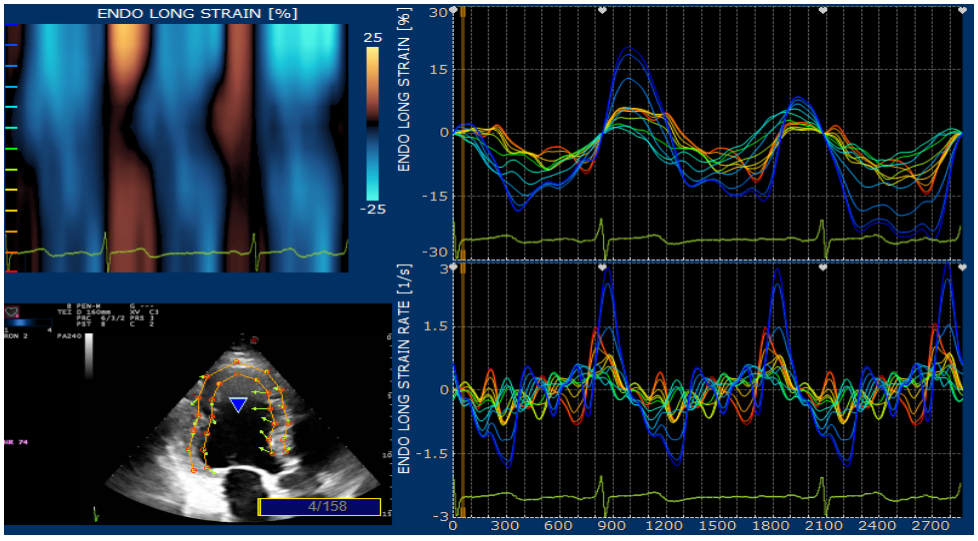

Figure 2 – *Apical three-chamber – percentage of longitudinal strain in the basal, middle and apical segments of the inferolateral and anterior septal walls.*

patients, 55.8% were males and 44,2% were females. The demographic, laboratory and clinical characteristics of the study population are found in table 1.

The age range was 27 to 81 years (43.26 ± 10.58 years). There were 34 individuals in the age group of 27 to 37 years, 37 individuals in the age group of 38 to 48 years, 19 individuals in the age group of 49 to 59 years, 6 individuals in the age group of 60 to 70 years and 2 individuals in the age group of 71 to 81 years.

Table 1 shows the demographic, clinical and laboratory variables of the different groups. Table 2 shows the echocardiographic variables of the different groups.

Regarding the echocardiographic variable "LV mass indexed by BSA," we identified higher values in groups HIV+ PI and HIV- CONTROL compared to groups HIV+ NO MEDICATION and HIV+ NNRTI. There were no differences between the groups HIV+ PI and HIV- CONTROL, nor among the groups HIV+ NO MEDICATION and HIV+ NNRTI (Table 2).

Regarding the variable "PP" (septal diastolic thickness), we identified higher values in the HIV-CONTROL GROUP. There were no differences between the groups HIV+ PI, HIV+ NO MEDICATION and HIV+ NNRTI (table 2).

Regarding the variable "SIV" (posterior wall diastolic thickness), we identified higher values in the HIV-CONTROL GROUP. There were no differences between the groups HIV+ PI, HIV+ NO MEDICATION and HIV+ NNRTI, although the group HIV+ NO MEDICATION presented PP values lower than the others (table 2).

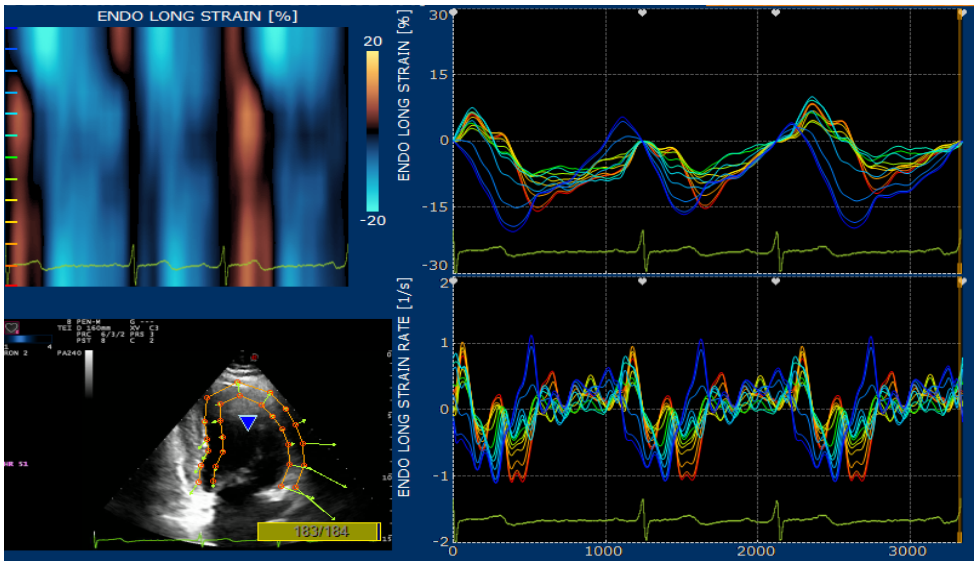

Figure 3 – *Apical two-chamber – percentage of longitudinal strain in the basal, middle and apical segments of the inferior and anterior walls.*

Table 1 – Demographic, clinical and laboratory variables according to the group

Variable		NT (n = 11)	PI (n = 24)	NNRTI (n = 33)	Control (n = 30)	Kruskal-Wallis test (p)
Age (years)	M ± DP	33.3 ± 4.1	44.8 ± 8.7	39.4 ± 8.0	49.9 ± 11.6	< 0.001
	Md ± IQR	33.0 ± 3.0	43.0 ± 10.5	39.0 ± 8.0	48.5 ± 15.0	
Gender	Male	9 (81.8%)	15 (62.5%)	14 (42.4%)	22 (73.3%)	0.033 (chi-square)
	Female	2 (18.2%)	9 (37.5%)	19 (57.6%)	8 (26.7%)	
	Md ± IQR					
Heart rate (bpm)	M ± SD	75.6 ± 7.3	72.0 ± 8.9	78.1 ± 6.2	73.2 ± 6.1	0.029
	Md ± IQR	78.0 ± 14.0	73.5 ± 16.0	77.0 ± 9.5	75.0 ± 8.8	
SBP (mmHg)	M ± SD	121.4 ± 6.0	129.3 ± 6.8	129.1 ± 6.8	123.8 ± 5.5	0.001
	Md ± IQR	120.0 ± 5.0	130.0 ± 10.0	130.0 ± 5.0	125.0 ± 10.0	
DBP (mmHg)	M ± SD	71.4 ± 4.5	70.0 ± 7.7	70.3 ± 7.5	67.8 ± 5.7	0.338
	Md ± IQR	70.0 ± 5.0	70.0 ± 20.0	70.0 ± 15.0	70.0 ± 5.0	
Blood glucose (mg/dl)	M ± SD	84.8 ± 14.2	79.7 ± 11.2	83.0 ± 9.5	82.4 ± 5.7	0.455
	Md ± IQR	82.0 ± 23.0	79.0 ± 9.0	81.0 ± 13.5	81.0 ± 7.0	
Total cholesterol (mg/dL)	M ± SD	164.6 ± 26.8	189.0 ± 56.3	183.9 ± 30.0	196.3 ± 17.4	0.021
	Md ± IQR	163.0 ± 40.0	198.0 ± 54.0	181.0 ± 42.0	199.0 ± 26.0	
LDL-c (mg/dL)	M ± SD	102.6 ± 27.6	108.7 ± 48.5	110.0 ± 27.9	118.9 ± 18.5	0.229
	Md ± IQR	104.0 ± 49.0	109.0 ± 66.0	102.0 ± 36.0	122.0 ± 27.0	
HDL-c (mg/dL)	M ± SD	47.5 ± 16.7	42.6 ± 17.5	55.0 ± 16.0	53.4 ± 3.5	0.007
	Md ± IQR	43.0 ± 30.0	41.0 ± 22.0	52.0 ± 18.0	54.0 ± 4.0	
Triglycerides (mg/dL)	M ± SD	101.1 ± 39.1	174.8 ± 78.2	119.7 ± 115.2	127.0 ± 15.5	< 0.001
	Md ± IQR	86.0 ± 79.0	165.0 ± 106.0	87.0 ± 71.0	123.5 ± 27.0	
CD4+ lymphocytes/mm^3	M ± SD	502.5 ± 206.3	534.4 ± 323.1	693.2 ± 317.7	-	0.044
	Md ± IQR	426.0 ± 310.0	404.0 ± 436.0	644.0 ± 297.0	-	

M: mean; SD: standard deviation; Md: median; IQR: interquartile range; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT: HIV-positive patients not using antiretroviral therapy. PI: HIV-positive patients on protease inhibitor therapy. NNRTI: HIV-positive patients on non-nucleoside reverse transcriptase inhibitor therapy. Control: healthy HIV-negative individuals.

Table 2 – Echocardiographic variables

Variable		NT (n = 11)	PI (n = 24)	NNRTI (n = 33)	Control (n = 30)	Kruskal-Wallis test (p)
Aorta (mm)	M ± SD	28.27 ± 1.85	30.58 ± 3.02	28.73 ± 2.97	29.53 ± 2.08	0.026
	Md ± IQR	29.00 ± 3.00	30.00 ± 3.50	29.00 ± 4.00	30.00 ± 2.00	
LA diameter (mm)	M ± SD	31.18 ± 3.82	33.21 ± 3.22	31.64 ± 4.59	34.33 ± 2.55	0.004
	Md ± IQR	30.00 ± 6.00	32.00 ± 4.50	31.00 ± 3.00	34.00 ± 4.00	
LVDd-i (mm/m^2)	M ± SD	29.75 ± 0.79	29.75 ± 1.81	28.67 ± 2.36	28.20 ± 1.73	0.020
	Md ± IQR	29.70 ± 1.13	29.87 ± 2.75	29.73 ± 4.22	28.65 ± 2.84	
LVSD (mm)	M ± SD	30.36 ± 2.38	31.17 ± 4.04	32.18 ± 3.26	32.17 ± 2.78	0.248
	Md ± IQR	30.00 ± 5.00	31.00 ± 7.00	32.00 ± 4.00	31.50 ± 4.00	
IVS (mm)	M ± SD	7.18 ± 0.98	7.88 ± 1.08	7.91 ± 0.95	9.03 ± 0.76	< 0.001
	Md ± IQR	7.00 ± 2.00	8.00 ± 2.00	8.00 ± 2.00	9.00 ± 2.00	
PP (mm)	M ± SD	7.00 ± 1.00	7.42 ± 1.18	7.67 ± 0.92	8.33 ± 0.80	< 0.001
	Md ± IQR	7.00 ± 0.00	8.00 ± 1.00	8.00 ± 1.00	9.00 ± 1.00	
LVEF – Simpson (%)	M ± SD	66.64 ± 3.83	62.46 ± 3.60	63.55 ± 4.10	64.17 ± 3.50	0.030
	Md ± IQR	67.00 ± 5.00	62.00 ± 5.00	63.00 ± 6.00	64.00 ± 6.00	
LV mass index (g/m^2)	M ± SD	82.23 ± 16.76	104.49 ± 24.01	90.01 ± 19.54	108.12 ± 14.25	< 0.001
	Md ± IQR	82.28 ± 13.59	106.35 ± 37.69	89.34 ± 26.89	110.61 ± 18.10	
E/A ratio	M ± SD	1.46 ± 0.40	1.33 ± 0.34	1.52 ± 0.41	1.18 ± 0.07	< 0.001
	Md ± IQR	1.34 ± 0.38	1.30 ± 0.22	1.50 ± 0.44	1.18 ± 0.09	
E' septal annulus (cm/s)	M ± SD	9.55 ± 1.87	9.03 ± 1.91	10.54 ± 2.21	8.38 ± 0.41	< 0.001
	Md ± IQR	9.00 ± 1.90	8.35 ± 2.00	10.00 ± 3.00	8.15 ± 0.60	
S' septal annulus (cm/s)	M ± SD	8.25 ± 1.09	8.10 ± 0.68	8.49 ± 1.41	9.03 ± 0.95	0.001
	Md ± IQR	8.00 ± 2.00	8.00 ± 0.40	8.10 ± 1.00	8.80 ± 0.60	
E/E' ratio	M ± SD	8.41 ± 1.33	8.72 ± 2.03	7.08 ± 1.65	9.29 ± 0.62	< 0.001
	Md ± IQR	8.40 ± 2.59	9.08 ± 3.04	7.27 ± 2.45	9.38 ± 0.88	
LA volume index (ml/m^2)	M ± SD	30.38 ± 6.16	29.93 ± 4.76	29.48 ± 5.60	29.56 ± 1.81	0.839
	Md ± IQR	29.11 ± 1.09	30.40 ± 3.48	29.17 ± 7.32	29.88 ± 2.76	
S lateral tricuspid annulus (cm/s)	M ± SD	11.29 ± 1.54	10.87 ± 1.42	12.23 ± 1.90	11.49 ± 0.90	0.014
	Md ± IQR	11.00 ± 2.00	10.80 ± 2.00	12.00 ± 2.00	11.70 ± 0.50	

M: mean; SD: standard deviation; Md: median; IQR: interquartile range; ST: HIV+ patient not using antiretroviral therapy. PI: HIV-positive patients on protease inhibitor therapy; NNRTI: HIV-positive patients on non-nucleoside reverse transcriptase inhibitor therapy. LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; ΔD%: left ventricle; LA: left atrium

Global longitudinal strain

Table 3 shows the GLS in the different groups.

Mean SLG was lower in the HIV groups compared to controls ($p < 0.05$). There were no differences between groups of HIV-infected patients.

No statistically significant differences were identified between longitudinal, circumferential and radial strain rates between the groups of HIV-infected patients and controls.

Discussion

The purpose of our study was to identify subclinical left ventricular dysfunction using speckle tracking. HIV+ patients were asymptomatic from the cardiovascular point of view and had normal LV systolic function by conventional echocardiographic analysis based on LV ejection fraction.

This study demonstrated that patients with HIV infection, even those not on ART, present longitudinal myocardial strain abnormalities assessed by speckle tracking. These findings confirm previous observations[13] and extend them by assessing the impact of new therapeutic protocols.

Cardiovascular manifestations of HIV infection were altered by the introduction of ART, which significantly modified the course of HIV infection, decreasing mortality and improving the quality of life of infected patients. On the other hand, data from multiple studies raised the concern that ART would be associated with an increase in peripheral and coronary artery disease. The clinical manifestations associated with ART are frequent and must be followed up by the multidisciplinary teams assisting these patients.[14]

This study suggests that subclinical left ventricular dysfunction should be investigated whenever possible.

Table 3 – Behavior of global longitudinal strain according to the group

Variable		NT (n = 11)	PI (n = 24)	NNRTI (n = 33)	Control (n = 30)	Kruskal-Wallis test (p)
Global longitudinal strain	M ± SD	-18.11 ± 1.28	-17.96 ± 4.89	-18.15 ± 3.07	-20.66 ± 0.79	0.001
	Md ± IQR	-17.70 ± 2.07	-18.27 ± 6.14	-18.47 ± 4.27	-20.77 ± 1.00	

M: mean; SD: standard deviation; Md: median; IQR: interquartile range.

Speckle tracking is an advanced echocardiographic technique that has much greater sensitivity than transthoracic echocardiography to detect functional abnormalities, mainly cardiac strain variables that assess left ventricular mechanical efficiency, identifying abnormalities earlier than other imaging techniques.

Sims et al.,[15] using transthoracic echocardiography, evaluated 28 HIV-infected young adults (aged seven to twenty-nine), compared to 28 controls, and no abnormalities of systolic and diastolic parameters were found. However, on the study of cardiac strain, a decrease in the percentage of longitudinal strain was observed in the patients in comparison with the control group. HIV-infected patients, regardless of ART, had a lower longitudinal strain rate than the control group.

Multiple studies have found high triglyceride levels in HIV-infected patients using protease inhibitors,[16-18] as these drugs stimulate the synthesis of hepatic triglycerides.[19] In our study, the group of patients using protease inhibitors presented the highest serum triglyceride levels. Studies in the literature show the importance of monitoring the lipid profile of HIV-infected patients using ART, especially when using protease inhibitors.[20]

In this study, it was observed that groups of HIV-infected patients, regardless of the type of ART, presented lower global longitudinal strain percentage than healthy controls. Barbaro et al.[3] evidenced in their study the need to monitor this group of patients, seeking to identify individuals with higher cardiovascular risk.

Previous studies evaluated left ventricular systolic and diastolic function in the population of HIV-infected individuals using one-dimensional and two-dimensional echocardiography and spectral Doppler. Hsue et al.[21] and Reinsch et al.[22] studied left ventricular diastolic and systolic functions using tissue Doppler, which uses filters for high velocities (blood) obtaining systolic and diastolic myocardial velocities in the septal and lateral mitral annulus. Lang et al.[12] focused their research on the complete study of LV diastolic function, following a scaled evaluation flowchart according to the guidelines of the American Society of Echocardiography.[12] Others identified anatomical and functional abnormalities in infected patients on ART.[23-28] The most recent studies use myocardial strain and myocardial strain rate percentage using speckle tracking to detect subclinical ventricular dysfunction in HIV-infected patients on ART.[12,29,30]

We know that the longitudinal cardiac fiber strain can be used to study the behavior of myocardial fibers arranged in the subendocardial area, as we know that 77% of these fibers are disposed longitudinally, and this makes speckle tracking play an important role in the study of ischemic disease, since ischemia begins in the subendocardial region.

This study revealed lower longitudinal strain percentages in HIV-infected individuals compared to healthy controls. There were no differences between the percentages of longitudinal strain in groups of HIV-infected patients using or not using ART.

Accurate and reproducible estimate of myocardial damage in patients with HIV infection and using ART has been considered to be increasingly important. The CHAART-2 study, which identified the long-term cardiovascular effects in HIV-infected children on ART, showed that cardiac structure and function were superior in HIV-infected children exposed to ART in the perinatal period compared with children in the pre-ART[31] era, which demonstrates the importance of early treatment in preventing cardiac damage. Besides, it reinforces the need for monitoring cardiac function in HIV-infected patients using ART to identify early myocardial injury, thereby decreasing long-term cardiovascular complications.

Several published papers have demonstrated the relationship between AIDS and cardiovascular diseases, with pericardial effusion and pericarditis being the best known.[32–39]

Okoshi and Montenegro[40] studied the incidence and etiology of heart lesions in patients with AIDS through a retrospective study of 72 necropsies. In none of the patients, death was considered a consequence of cardiac lesion, but macro and microscopic abnormalities were found in 90% of the cases.

Several studies report that the prevalence of cardiac abnormalities may be underestimated. Interstitial lymphocytic myocarditis[41,42] is found in 50 to 70% of asymptomatic infected individuals.

Myocardial abnormalities appear to be associated with more severe cases of immunosuppression and low TCD4 counts.[43]

Limitations

The limitations of the study are the limited sample size and the relatively broad age range of HIV-infected participants. Neither the effect of disease duration nor ART duration were analyzed. The absence of coronary artery disease documentation on computed tomography angiography did not allow to evaluate the influence of ART on the development of CAD. Currently, there are few patients not on antiretroviral therapy, therefore the group of HIV-infected patients not on ART was smaller than the other groups. We know that speckle tracking is a technique that depends on image quality and on the observer's experience in evaluating the main curves of myocardial strain. We have observed a large number of studies using speckle tracking in an attempt to identify patients with subclinical left ventricular dysfunction, but we should increasingly stimulate further research with a greater number of investigated patients to better understand the significance of the findings in the prognosis of patients.

Conclusion

The technique of studying myocardial strain by speckle tracking was able to detect early signs of deterioration of myocardial systolic function in HIV-infected patients, regardless of whether or not they were on antiretroviral drugs. Further studies are needed to evaluate HIV-infected patients and to assess the prognostic significance of these abnormalities in these patients.

Author contributions

Conception and design of the research: Rodrigues RC, Mesquita CT, Setubal S, Azevedo KML. Acquisition of data: Rodrigues RC, Mesquita CT, Azevedo KML. Analysis and interpretation of the data: Rodrigues RC, Mesquita CT, Setubal S, Moscavitch SD, Azevedo KML. Statistical analysis: Rodrigues RC, Mesquita CT, Moscavitch SD, Azevedo KML. Writing of the manuscript: Rodrigues RC, Mesquita CT, Setubal S, Moscavitch SD, Azevedo KML. Critical revision of the manuscript for intellectual content: Rodrigues RC, Mesquita CT, Setubal S, Moscavitch SD, Azevedo KML.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Ronaldo Campos Rodrigues, from Universidade Federal Fluminense (Hospital Universitário Antônio Pedro).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro under the protocol number HUAP 159/11. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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At Last, a Sensitive Method to Detect Incipient Systolic Dysfunction!

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Short Editorial related to the article: The Use of Two-Dimensional Strain Measured by Speckle Tracking in the Identification of Incipient Ventricular Dysfunction in HIV-Infected Patients on Antiretroviral Therapy, Untreated HIV Patients and Healthy Controls

Left ventricular systolic function evaluation has always been one of the main attributions of echocardiography. The degree of ventricular systolic dysfunction is an important predictor of outcome for a large number of diseases, including ischemic heart disease, cardiomyopathy, valvular heart disease, and congenital heart disease. In this area, the ejection fraction has been sovereign for many decades, but despite being a parameter that can, in most cases, inform the real state of global ventricular function, in many situations it may be normal in the presence of evident systolic or diastolic dysfunction.

Known clinical examples are the several cases of heart failure with preserved ejection fraction (HFpEF) or patients with hypertrophic cardiomyopathy, among others. For this reason, an index that can identify early ventricular dysfunction that is not connected with the ejection fraction has been sought for a long time.

Myocardial deformation evaluation by echocardiography emerged with the strain and strain rate techniques, still derived from tissue Doppler, which was developed at the Norwegian University of Science and Technology in Trondheim, Norway, approximately twenty years ago.[1,2] In 2004, we had already demonstrated the presence of incipient systolic dysfunction in patients with the indeterminate form of Chagas disease using this technique.[3]

Keywords

Heart Failure; Ventricular Dysfunction Left; Cardiomyopathy, Hypertrophic; HIV; Antiretroviral Therapy Highly Active; Myocardial Contraction; Echocardiography/methods.

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Later, in 2006, the speckle tracking technique appeared, which quantifies myocardial deformation by two-dimensional echo and does not depend on the insonation angle (a limitation of the prior technique).[4]This technique has advanced to the present day and allows measuring the longitudinal, radial and circumferential deformation of the several myocardial segments (strain). The mean value of the percentage of longitudinal deformation of each segment is what we call the global longitudinal strain (GLS) and this index has shown to be an excellent parameter for systolic function evaluation, which is sensitive enough to detect incipient impairment when the ejection fraction is still normal and has a higher prognostic value than EF in many clinical situations.[5-7]

In this issue of the Brazilian Archives of Cardiology, Dr. Ronaldo Campos Rodrigues presents us with an excellent work, in which left ventricular systolic function was assessed by quantifying GLS in HIV-positive patients, with and without antiretroviral therapy, compared with a control group.[8] It was observed that GLS values were significantly lower in infected individuals than in control ones, regardless of whether or not they were undergoing treatment. All of them had normal ejection fraction and the only group with abnormal GLS (less than -18%) was that of infected individuals without treatment. Their findings demonstrate the high sensitivity of this echocardiographic parameter in detecting incipient systolic dysfunction, which leads us to think that treatment must decrease myocardial aggression by the virus. Early systolic dysfunction was also found by Mendes et al.,[9] in a similar group.

These and other studies point to a paradigm shift in the study of ventricular function. I believe that soon, cardiologists will not be satisfied with the value of the ejection fraction alone but will also require the value of GLS for a deeper and more accurate assessment of ventricular systolic function.

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Predictors of Unfavourable Outcomes in Children and Adolescents Submitted to Surgical Mitral Valvuloplasty Secondary to Chronic Rheumatic Heart Disease

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Abstract

Background: **Mitral valve repair in paediatric patients with chronic rheumatic heart disease is superior to valve replacement and has been used with good results.**

Objective: **To identify predictors of unfavourable outcomes in children and adolescents submitted to surgical mitral valvuloplasty secondary to rheumatic heart disease.**

Methods: **Retrospective study of 54 patients under the age of 16 operated at a tertiary paediatric hospital between March 2011 and January 2017. The predictors of risk for unfavourable outcomes were: age, ejection fraction, degree of mitral insufficiency, degree of pulmonary hypertension, presence of tricuspid insufficiency, left chamber dilation, preoperative functional classification, duration of cardiopulmonary bypass, duration of anoxia, presence of atrial fibrillation, and duration of vasoactive drug use. The outcomes evaluated were: death, congestive heart failure, reoperation, residual mitral regurgitation, residual mitral stenosis, stroke, bleeding and valve replacement. For all analyzes a value of $p < 0.05$ was established as significant.**

Results: **Of the patients evaluated, 29 (53.7%) were female, with an average of 10.5 ± 3.2 years. The functional classification of 13 patients (25%) was 4. There was no death in the sample studied. The average duration of extracorporeal circulation was 62.7±17.8 min, and anoxia 50 ± 15.7 min. The duration of use of vasoactive drug in the immediate postoperative period has an average of 1 day (interquartile interval 1–2 days). The logistic regression model was used to evaluate the predictive variables for each unfavourable outcome. The duration of use of vasoactive drug was the only independent predictor for the outcomes studied ($p = 0.007$). Residual mitral insufficiency was associated with reoperation ($p = 0.044$), whereas tricuspid insufficiency ($p = 0.012$) and pulmonary hypertension ($p = 0.012$) were associated with the presence of unfavourable outcomes.**

Conclusion: **The duration of vasoactive drug use is an independent predictor for unfavourable outcomes in the immediate and late postoperative period, while residual mitral regurgitation was associated with reoperation, and both tricuspid regurgitation and pulmonary hypertension were associated with unfavourable outcomes. (Arq Bras Cardiol. 2019; 113(4):748-756)**

Keywords: **Heart Defects,Congenital; Mitral Valve Insufficiency/surgery; Hypertension,Pulmonary; Reoperation; Tricuspid Valve Insufficiency/surgery; Cardiopathy, Rheumatic.**

Introduction

Chronic rheumatic heart disease (RHD) consists of a non-suppurative complication of rheumatic fever (RF), with uni- or multivalvar involvement, which can lead to severe heart failure.[1] It is estimated that each year there are 470,000 new cases of RF and 233,000 deaths attributed to RF or RHD.[2]

Mitral valve regurgitation is the main cause of RHD in children;[3,4] when moderate or severe rheumatic valve disease is associated with pulmonary hypertension and left ventricular dysfunction, the development of congestive heart failure suggests the need for surgical intervention.[3] Chronic rheumatic disease and its complications generated, in Brazil, 6,648 hospitalizations and a cost of BRL 73,067,919.52 in 2017 alone.[5]

Problems inherent to mitral valve replacement include the need for long-term anticoagulation, risk of bleeding, thromboembolism, endocarditis and lack of growth potential of the prosthesis, which makes the mitral valve plasty (MVP) technique superior to valve replacement in pediatric patients.[6,7] However, patients submitted to valvuloplasty had a higher reoperation rate in the short term.[8]

This study aimed to identify predictors of unfavorable outcome in children and adolescents submitted to mitral valvuloplasty secondary to rheumatic heart disease.

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Methods

A retrospective cohort study was performed. Data were collected by reviewing information on medical records (physical and electronic). The collection was performed by four researchers after standardized training. The Escola Bahiana de Medicina e Saúde Pública Research Ethics Committee approved this study together with CAAE from 64019316.0.0000.5544.

Population

The study included 54 patients with mitral insufficiency of rheumatic etiology who underwent surgical correction by MVP technique, from March 2011 to January 2017.

Preoperative evaluation

Patients were clinically identified using the New York Heart Association (NYHA) Functional Classification.[9] All medications that patients used continuously for at least one month were recorded. Valvular lesions were assessed by preoperative transthoracic echocardiography, classifying the lesions as "absent/discrete" or "moderate/significant". Patients who presented another cause of valve damage at the time of surgical correction by MVP (infective endocarditis; congenital, post-traumatic, degenerative lesions or dystrophic lesions; cardiomyopathies or inflammatory or ischemic disease) or who underwent aortic valve surgery or other procedures in the same surgical time of MVP or an undocumented previous MVP, or patients who did not reach 60 postoperative days until January 2017 were excluded from the study.

Surgical technique

The reconstructive valve surgery technique was MVP, described by Carpentier,[10] which includes annuloplasty and commissurotomy. The patients studied were preferably operated by the same medical team. The intraoperative data collected were: surgical technique used, duration of cardiopulmonary bypass (CPB), duration of anoxia and presence of atrial fibrillation. The intraoperative outcomes studied were: arrhythmia, cardiorespiratory arrest (CRA) and bleeding.

Follow-up

Follow-up was carried out within 60 days after surgery, in an outpatient setting, in a single centre. The predictors of risk for unfavourable outcomes studied were: age, ejection fraction, type of valve lesion, degree of mitral insufficiency (MI), left chamber dilatation, NYHA Preoperative Functional Classification, surgical technique used, duration of CPB, duration of anoxia, presence of atrial fibrillation, presence of pulmonary hypertension (PH) (sPAP > 35 mmHg) and presence of tricuspid insufficiency (TI).

Early (up to 7 postoperative days) and late (>7 days post-operative) outcomes related to heart valve disease were studied. The following were investigated: death, heart failure, cardiogenic shock, endocarditis, mitral valve damage, sepsis, stroke, bleeding, reoperation and valve replacement. The presence of any of these outcomes alone or in combination would characterize an unfavourable outcome as a single dependent variable.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 14.0 for Windows, was used for the elaboration of the database and for descriptive analysis. The results were presented in tables. Categorical variables were expressed in frequencies and percentages. Continuous variables with normal distribution were expressed as mean and standard deviation; those with non-normal distribution were expressed in median and interquartile range. The normality of the numerical variables was verified through descriptive statistics, graphical analysis and the Kolmogorov-Smirnov test.

The independent Student's *t* test was used to compare groups of numerical variables with normal distribution (age, weight, body mass index – BMI, duration of anoxia, duration of CPB, ejection fraction). The Mann-Whitney test was used to compare numerical variables with asymmetric distribution, such as duration of use of vasoactive drugs (VAD).

The χ^2 test was used to compare the use of medications in the preoperative and upon hospital discharge, and the intergroup comparison of the following categorical variables: gender, origin, outpatient follow-up, reoperations, functional classification, surgical team, events during surgery, duration of extubation and echocardiographic variables. When the distribution showed $n < 5$ individuals in each category, Fisher's exact test was used.

The paired Student's t-test was used for the numerical variable "ejection fraction" in the comparison of the paired groups (pre- and postoperative), and the McNemar test was used to compare the categorical variables of the echocardiogram. For all univariate analyses, a value of $p < 0.05$ was established.

The logistic regression model was used to evaluate the predictive variables for unfavourable outcomes in children and adolescents who underwent surgical mitral valvuloplasty secondary to rheumatic heart disease. After the univariate analysis, the independent variables were included in the logistic model if they presented $p < 0.05$, remaining in the model if they remained significant ($p < 0.05$). The manual procedure for insertion and withdrawal of the variables was adopted. Results were presented using Odds Ratio (OR) and their respective 95% confidence intervals (95%CI).

Results

From March 2011 to January 2017, 90 patients underwent surgery by the MVP technique in the tertiary hospital where the present study was carried out. Of these, 36 were excluded, of which 7 had congenital mitral lesions (mitral dysplasia), 8 had underwent aortic valve replacement associated with MVP and 21 due to loss to follow-up or incomplete data.

Characteristics of the sample studied

Table 1 shows clinical and demographic aspects of the 54 patients included, of which 29 (53.7%) were female, with a mean age of 10.5 ± 3.2 years. Of these patients, 34 (64.2%) lived on the countryside of the State of Bahia, 5 (9.4%) were from the Metropolitan Region and 14 (26.4%) were from the capital, Salvador. The mean BMI was 15.7 ± 3.5 kg/m^2.

Table 1 – Characterization of sociodemographic and clinical variables of 54 children and adolescents with rheumatic mitral insufficiency undergoing mitral valvuloplasty

Variables	Mean ± SD
Age (years)	10.5 ± 3.2
Weight (kg)	32.9 ± 14.3
Height (m)	1.4 ± 0.2
Body mass index (BMI) (kg/m²)	15.7 ± 3.5
	Median (IQ25–IQ75)
Time from disease to surgery (months)	8.00 (5.00–36.00)
Sex	n (%)
Female	29 (53.7)
Male	25 (46.3)
Origin	
Countryside	34 (64.2)
Salvador	14 (26.4)
Metropolitan Region	05 (9.4)
Outpatient follow-up	
Regular	27 (51.9)
Irregular	25 (48.1)
Cardiac insufficiency	
NYHA 1	10 (18.5)
NYHA 2	22 (40.7)
NYHA 3	9 (16.7)
NYHA 4	13 (24.1)

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

Prior to the surgery, 27 (51.9%) had regular outpatient follow-up. The disease duration until the surgery was a median of 8 months (interquartile range 5-36). The functional classification of 44 (81.48%) patients was between NYHA 2 and 4, with 13 (25%) being NYHA 4. None presented atrial fibrillation or had to undergo emergency surgery. There were no deaths in the sample studied.

Only 3 (5.6%) patients had to undergo reoperation, all of them undergoing a single reoperation. The causes were moderate to severe aortic regurgitation, leading to valve replacement in one patient on the 23rd postoperative day, and the other on the 45th. The third patient maintained severe MI even after correction, evolving with associated severe aortic insufficiency, undergoing reoperation for aortic and mitral valve replacement on the 45th day after repair.

Preoperative medications were grouped into 4 combinations: combination 1 – captopril and furosemide; combination 2 – captopril, furosemide and spironolactone; combination 3 – captopril, furosemide, spironolactone and digoxin; combination 4 – captopril, furosemide, spironolactone and carvedilol. Of these combinations, approximately half of the patients (55.8%) used combination 1. All patients had regular use of benzathine penicillin.

Intraoperative data

The patients underwent surgery with a standard surgical team in most cases, with only 2 procedures (3.8%) being performed by another team. The most used surgical technique was annuloplasty (96.2%), followed by commissurotomy 02 (3.8%), considering only the main procedure. There were events during surgery in 24 (44.4%) of the cases, including: severe bleeding (2), CRA (6), use of VAD (8) or others (8). The mean duration of CPB was 62.7 ± 17.8 min and anoxia was 50 ± 15.7 min. Extubation occurred within 6 hours postoperatively in 48 (92.3%) patients. The duration of VAD use in the immediate postoperative period had a median of 1 day (interquartile interval 1–2 days).

Description of preoperative and postoperative echocardiograms

Table 2 describes the data found in the preoperative and immediate postoperative echocardiogram (up to 7 postoperative days), comparing their results. The postoperative ejection fraction was reduced when compared to the preoperative one, 54.8 ± 13.9% and 70.2 ± 8.5%, respectively, with a value of $p < 0.05$. As for left chamber dilatation, 98% of the patients presented it preoperative and 87% postoperatively. This reduction showed $p = 0.063$, demonstrating a trend towards significance.

Among the valve changes described in Table 2, moderate or significant aortic insufficiency was present in 13 (26.5%) patients in the preoperative period. In the postoperative period, only 8 (21.1%) had aortic insufficiency, but with no statistical significance (p = 1,000).

Moderate or significant MI was present in 48 (98%) patients in the preoperative period. Of these, none of the patients' MI had worsened and 6 (15.8%) patients maintained moderate or significant postoperative MI ($p < 0.001$).

PH was present in 38 (77.6%) patients in the preoperative period and only 7 (18.4%) in the postoperative period. No patient progressed to PH or worsened in the postoperative period. On the other hand, 31 (81.6%) participants who had preoperative PH did not present it in the postoperative period ($p < 0.001$).

Analysis and description of outcomes

The presence of outcomes in the sample was divided into outcomes in the immediate postoperative period (up to 7 days) and in the late postoperative period (up to 60 days), as shown in Table 3. Seventeen patients presented an immediate postoperative outcome, mitral lesion (stenosis and/or residual insufficiency), being present in 8 (14.8%) patients. In the late postoperative period, 16 had outcomes, and mitral regurgitation was again the most common, presented by 11 (20.4%) patients.

The comparison between the use of medications in the preoperative period and after discharge and the outcomes did not present statistical significance, regardless of the combination used.

The variables that were related to the presence of late postoperative outcome were duration of CPB and duration of

Table 2 – Description of surgical and echocardiographic variables in the preoperative and immediate postoperative periods of 54 children and adolescents with rheumatic mitral insufficiency undergoing mitral valvuloplasty

Variables	Preoperative Mean ± SD	Post-operative Mean ± SD	p value
Duration of ECC (min)	62.7 ± 17.8	---	---
Duration of anoxia (min)	50.0 ± 15.7	---	---
Duration of VAD use (days)	---	1.0 (1.0 - 2.0)	---
Ejection fraction (%)	70.2 ± 8.5	54.8 ± 13.9	0.015§
Dilation of left chambers	**n (%)**		
No	01 (2.0)	06 (11.1)	0.063¥
Yes	48 (98.0)	32 (84.2)	
Mitral stenosis			
Absent/discrete	46 (93.9)	36 (94.7)	1.000¥
Moderate/significant	03 (6.1)	02 (5.3)	
Aortic insufficiency			
Absent/discrete	36 (73.5)	30 (78.9)	1.000¥
Moderate/significant	13 (26.5)	08 (21.1)	
Aortic stenosis			
Absent/discrete	49 (100.0)	38 (100.0)	---
Mitral insufficiency			
Absent/discrete	01 (2.0)	32 (84.2)	0.000¥
Moderate/significant	48 (98.0)	06 (15.8)	
Tricuspid insufficiency			
Absent/discrete	36 (73.5)	31 (81.6)	0.508¥
Moderate/significant	13 (26.5)	07 (18.4)	
Pulmonary hypertension			
No	11 (22.4)	31 (81.6)	0.000¥
Yes	38 (77.6)	07 (18.4)	

ECC: extracorporeal circulation; VAD: vasoactive drug; § paired Student's t test; ¥ McNemar test.

anoxia, both with $p < 0.05$. Age, weight, height, gender, origin, outpatient follow-up, disease duration until surgery, functional classification, surgical team, surgery events and duration of extubation had no statistically proven relationship.

When the variables of the echocardiogram were studied in the immediate and late postoperative period, as shown in Table 4, the relationship between the presence of outcomes with MI, TI, and PH is statistically significant. In preoperative echocardiography, no relationship of statistical significance with the outcomes was found.

Predictive variables

The predictive variables are presented in Table 5. In the final model, the variable duration of VAD use was found as an independent predictor for the immediate outcome, presenting OR 2.5 (95%CI, 1.3-4.9), while no independent predictor was found for the late outcome. The duration of ECC was close to statistical significance.

Discussion

MVP is universally accepted as superior to valve replacement (bioprostheses or metal prostheses), especially in children in whom growth, problems with anticoagulation, thromboembolism, rapid valve degeneration, increased risk of endocarditis and less preservation of ventricular function are unfavourable factors to this technique.[6-8,10-12] In the tertiary hospital in which the study was performed, MVP is the preferred technique.

Patients in the study were followed up for two months after MVP, and in that period, there were no deaths in the sample studied. This is in accordance with the literature, in which the precocious or hospital mortality rate ranged from 0.9 to 3.5%.[7,12,13]

The literature lacks in studies that identify probable clinical predictors of negative outcomes in patients undergoing MVP surgery. In the present study, PH presented statistical significance for both immediate (≤7 days) and late (up to 60 days) postoperative outcomes in the univariate analysis,

Table 3 – Description of the immediate and late outcomes (and combined outcomes) of 54 children and adolescents with rheumatic mitral disease undergoing mitral valvuloplasty

Variables	n (%)
Immediate outcome (n = 54)	
None	37 (68.6)
CHF	01 (1.9)
Sepsis	01 (1.9)
Mitral lesion*	04 (7.4)
Others	04 (7.4)
Bleeding and others	02 (3.7)
CHF and mitral lesion *	01 (1.9)
Others and CHF	01 (1.9)
Mitral lesion* and others	02 (3.7)
Mitral lesion* and bleeding	01 (1.9)
Late outcome (n = 54)	
None	38 (70.4)
CHF	01 (1.9)
Reoperation/valve replacement (up to 30 days)	03 (5.6)
Mitral lesion*	11 (20.4)
Others	01 (1.9)

**mitral lesion: mitral stenosis and/or residual mitral insufficiency; n: number of participants; CHF: congestive heart failure.*

but did not maintain significance in the multivariate analysis. In their study of 122 mitral repairs, Kim et al.,[14] after univariate and multivariate analysis, found preoperative pulmonary hypertension as the only independent risk factor for death (HR: 3.75 95%CI: 1.21–11.57; p = 0.022), but this study was carried out with adults with a mean age of 48.9 ± 11.5 years. The results in this study may differ from those found in the literature due to the sample size, as well as the age: the younger the sample, the higher the mortality rate and the higher the early rate of valve failure.[15-17]

In addition, postoperative TI was also a predictor of univariate analysis in this study, both in the immediate postoperative period and in the late postoperative period, but it lost significance in the multivariate analysis. No associations were found in the literature reviewed, but, like PH, TI is a criterion that should be valued. Although they were not independent predictors of outcomes, both variables were associated with unfavourable outcomes, both in the immediate and late postoperative period, with statistical significance, and should be used as initial points for surgical indication and follow-up in these patients.

Yakub et al.[13] described residual mitral regurgitation ≥2 crosses as a predictor of valve failure and reoperation. In our study, the presence of moderate or significant residual MI in the postoperative period was associated with outcome both in the immediate and late postoperative period, in the univariate analysis, with statistical significance. Of the three children who underwent valve replacement, one presented moderate to severe mitral regurgitation even after attempted repair by MVP technique and the other two developed moderate to severe aortic regurgitation and underwent aortic valve replacement before completing sixty postoperative days. This data is in agreement with the literature in other studies as well, such as in those by Silva et al.[11] and Severino et al.,[15] always being a marker for reoperation. It is known that the late MVP results also depend on good coaptation of the cusps, which can be obtained through association of surgical techniques and reassessed at the end of the repair, whenever possible with intraoperative transesophageal echocardiography,[18] which is not available in the hospital in which the study was carried out.

The mean duration of ECC found was 62.7 ± 18.8 minutes and the duration of anoxia was 50.0 ± 15.7 minutes, showing an association with the outcomes in the immediate postoperative period. In fact, in the literature, duration of CPB has been described as an independent predictor for cardiac surgeries, usually due to inflammatory factors in the bloodstream. Thus, it is well established that a CPB time longer than 90 minutes is associated with a more complicated postoperative period. The study by Talwar et al.[16] showed duration of CPB of 47.6 ± 11.9 and duration of anoxia of 37.2 ± 12.8, and when assessed for association with early death or reoperation, no significance was found.[16] This divergence with the literature may be due to the longer duration of both CPB and anoxia found in our sample.

The ECC time found in this study may have been influenced by variables that were not studied, such as anatomical differences, anterior leaflet involvement, thickening of the ribs, calcifications and papillary muscle involvement. Non-standardization of intraoperative and echocardiographic records, as well as the retrospective nature of the study, prevented the analysis of these data.

The duration of VAD use in the immediate postoperative period was found as a predictor for outcome in this study. Silva et al.[11] also described the use of VAD, finding OR of 1.47 (95% CI 0.32-6.83), but they did not present statistical association in their sample. Other variables may have influenced this divergence in results, such as longer duration of CPB and anoxia in the study by Silva et al.[11]

The use of drugs for clinical optimization of CHF, due to the volume overload generated by mitral annular dilatation, also did not present significance and no description of the study of this variable was found in the reviewed literature, except in the study by Silva et al.,[11] in which there is only a description of the use of anticongestive medications in 40% of patients in the preoperative period, not presenting a statistical analysis of this data.

The variables age, weight, height, duration of illness until surgery, NYHA preoperative classification, presence of atrial fibrillation and use of drugs were not significant in this study. In the studies by Talwar et al.[16] and Kalfa et al.,[17] these data were evaluated descriptively without statistical analysis and using only residual MI, reoperation, valve replacement and mortality as the outcome, without considering other variables such as bleeding, CHF and sepsis as possible outcomes.

Table 4 – Comparison between clinical and echocardiographic variables in the postoperative period with clinical outcomes in 54 children and adolescents with rheumatic mitral insufficiency undergoing mitral valvuloplasty

Variables	Imediate postoperative period (up to 7 days)		p value	Late postoperative period (up to 60 days)		p value
	Yes mean ± SD	No mean ± SD		Yes mean ± SD	No mean ± SD	
Duration of VAD use (days)	3.0 (1.0–3.0)	1.0 (1.0–2.0)	0.009¶	2.0 (1.0–3.0)	1.0 (1.0–2.0)	0.035¶
Ejection fraction (%)	54.7 ± 17.6	54.9 ± 10.6	0.982*	54.5 ± 15.8	55.0 ± 13.0	0.936*
Dilation of left chambers	**n (%)**	**n (%)**		**n (%)**	**n (%)**	
No	02 (14.3)	04 (16.7)	0.846¥	02 (16.7)	04 (15.4)	0.920¥
Yes	12 (85.7)	20 (83.3)		10 (83.3)	22 (84.6)	
Mitral stenosis						
Absent/discrete	12 (85.7)	24 (100.0)	0.057¥	10 (83.3)	26 (100.0)	0.094¥
Moderate/significant	02 (14.3)	00 (00.0)		02 (16.7)	00 (00.0)	
Aortic insufficiency						
Absent/discrete	10 (71.4)	20 (83.3)	0.385¥	09 (75.0)	21 (80.8)	0.685¥
Moderate/significant	04 (28.6)	04 (16.7)		03 (25.0)	05 (19.2)	
Aortic stenosis						
Absent/discrete	14 (100.0)	24 (100.0)	---	12 (100.0)	26 (100.0)	---
Mitral insufficiency						
Absent/discrete	09 (64.3)	23 (95.8)	0.010¥	08 (66.7)	24 (92.3)	0.044¥
Moderate/significant	05 (35.7)	01 (4.2)		04 (33.3)	02 (7.7)	
Tricuspid insufficiency						
Absent/discrete	09 (64.3)	22 (91.7)	0.036¥	07 (58.3)	24 (92.3)	0.012¥
Moderate/significant	05 (35.7)	02 (8.3)		05 (41.7)	02 (7.7)	
Pulmonary hypertension						
No	09 (64.3)	22 (91.7)	0.036¥	07 (58.3)	24 (92.3)	0.012¥
Yes	05 (35.7)	02 (8.3)		05 (41.7)	02 (7.7)	

*n: number of participants; SD: standard deviation; IQ: interquartile range; VAD: vasoactive drugs; *independent Student's t test; ¶ Mann-Whitney's test; ¥χ^2 test or Fisher's exact test.*

Table 5 – Predictive variables for immediate and late outcomes in 54 children and adolescents with rheumatic mitral insufficiency undergoing mitral valvuloplasty

Variables	Input Model		Final Model	
	OR (95%CI)	p value	OR (95%CI)	p value
Immediate outcome				
Sex	3.6 (0.8–15.0)	0.084	-	-
Duration of VAD use (days)	2.4 (1.2–4.9)	0.014	2.5 (1.3–4.9)	0.007
Late outcome				
Days of VAD	1.8 (0.9–3.7)	0.95	-	-
Number of reoperations	1.8 (0.1–31.7)	0.683	-	-
Duration of ECC (min)	1.0 (0.9–1.1)	0.538	1.0 (1.0–1.1)	0.051
Duration of anoxia (min)	1.0 (0.9–1.1)	0.958	-	-
Extubation (hour)	5.2 (0.4–67.3)	0.211	-	-

OR: Odds Ratio; 95%CI: 95% confidence interval; logistic regression.

The literature presents other outcome predictors that were not identified or not studied in our sample, such as ventricular dysfunction, studied by Talwar et al.,[16] with HR 4,9 (95%CI 2.65–9.2), $p < 0.005$. On the other hand, Yakub et al.[13] described the NYHA preoperative classification, emergency surgeries and double valvular lesions as predictors of early death.

In our country, rheumatic disease is the main cause of acquired heart diseases in childhood and adolescence, unlike in developed countries, where Kawasaki disease is the most frequent cause of acquired heart disease in the paediatric age group.[19,20] In this context, degenerative lesions are the main indications of mitral valve repair, which justifies the small number of studies found, taking into account only valvular corrections by MVP technique for valve sequela due to chronic RHD in the pediatric age group.[21]

Although Brazil is considered a high risk country for RF, with 40% of heart surgeries being performed for valve repairs due to chronic RHD sequelae, according to data from the Department of Informatics of the Unified Health System (DATASUS),[5] only a few Brazilian studies were found involving the theme addressed in the present study, and only one of them comprising the paediatric age group, all focusing on surgical results. Murad et al.[7] studied 86 patients with a mean age of 35.8 years and concluded that MVP can be performed with low mortality and should be the procedure of choice in patients with MI. Similarly, Pomerantzeff et al.[22] studied 330 patients with a mean age of 26.9 ± 15.4 years for 20 years and concluded that the MVP technique is feasible in rheumatic patients with low early and late mortality. Severino et al.,[15] in a study with 104 adult patients (mean age 32.73 ± 14.74 years) evaluating MVP results in rheumatic patients, found that late reoperation was associated with postoperative residual MI ($p < 0.001$), presence of PH ($p < 0.01$), age ($p < 0.04$) and postoperative functional classification ($p < 0.001$). Silva et al.[11] evaluated the outcome of valve reconstruction in rheumatic lesions in 40 patients younger than 18 years after 4 years of evolution and did not find statistically significant risk factors that could interfere with the evolution of patients in relation to valve replacement before 4 years. The studied variables included: functional classification in the pre- and postoperative period, amount of drugs used by patients at the time of surgery, duration of CPB and anoxia and need for VAD in the immediate postoperative period.

To date, no study has been published in the North and Northeast Regions involving patients with chronic RHD, although the socioeconomic characteristics of these regions are strong factors for a higher prevalence of chronic RHD in the country. In the Brazilian articles published by Severino et al.[15] and by Silva et al.[11] there is no report of the origin of the patients operated by the MVP technique, nor were they intended to look for possible predictors for other unfavourable outcomes besides reoperation and mortality.

Because the surgical indications for mitral repair in the paediatric population do not have well-defined criteria in the literature, they require previous discussions and interaction between paediatric cardiologists, cardiologists and cardiac surgeons in order to delineate and minimize factors that may contribute to a postoperative period in the short, medium and long term with good results.

This is a pioneer study, due to the characteristics already described, in an exclusively paediatric population, in a high-risk region for chronic RHD, which should elicit new discussions regarding the topic addressed. Because this pathology has the special characteristic of being one of the rare rheumatic diseases whose etiologic agent is known and, therefore, has a specific treatment and can be avoided with the adoption of low-cost preventive measures with high effectiveness. Being the primary prophylaxis performed with low-cost and easily accessible antibiotics, valve sequelae and, consequently, cardiac surgeries could be avoided, reducing cost to society and improving the quality of life for the affected population.

Conclusion

The time of VAD use was an independent predictor for outcomes studied postoperatively. Residual MI was associated with reoperation, while TI and PH were associated with unfavourable outcomes in the immediate and late postoperative period. The data in this study allow new investigations to improve the prognosis of children and adolescents with chronic RHC submitted to the MVP repair technique.

Study limitations

The limitations of our study are related to its retrospective nature, sample size, and due to it being carried out in a single centre.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Cruz RCC, Cordeiro BS, Santos FS, Fernandes CR, Gama JMA, Ladeia AMT; Acquisition of data, Statistical analysis and Writing of the manuscript: Cruz RCC, Cordeiro BS, Santos FS, Fernandes CR, Gama JMA; Critical revision of the manuscript for intellectual content: Cruz RCC, Ladeia AMT.

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

The Escola Bahiana de Medicina e Saúde Pública Research Ethics Committee approved this study together with CAAE from 64019316.0.0000.5544.

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Mitral Valve Repair in Young Rheumatic Patients

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Short Editorial related to the article: Predictors of Unfavourable Outcomes in Children and Adolescents Submitted to Surgical Mitral Valvuloplasty Secondary to Chronic Rheumatic Heart Disease

Mitral valve repair surgery presents excellent immediate and late results in young patients with valve disease resulting from chronic rheumatic heart disease such as those reported in the article by Cruz et al.[1] in this issue.

There is agreement in the literature on the lower morbidity and mortality of patients submitted to mitral repair surgery in relation to valve replacement, but there is no uniformity of results of mitral valve reconstruction in patients with lesions resulting from rheumatic fever, perhaps, due to the recurrence of new rheumatic episodes in the evolution of these patients.[2]

In the work of Cruz et al.,[1] they found that the time of use of vasoactive drug is an independent predictor for unfavorable outcomes in the immediate and late postoperative, while residual mitral valve insufficiency was associated with reoperation and both tricuspid insufficiency and pulmonary hypertension were associated with unfavorable outcomes. We should consider some points. Mitral valve insufficiency surgery in rheumatic patients should be performed from the anatomic point of view when there is still a pliable anterior leaflet, at the appropriate time, neither early nor late, so that the surgery is performed before the development of pulmonary hypertension and tricuspid insufficiency, although it is known that many patients only seek care already in advanced stages of the disease.

As reported in our study,[2] valvar reconstruction requires the surgeon a perfect knowledge of anatomy and the multiplicity of existing techniques. In addition, an evaluation of the leaflets, a mitral valve annulus, chordae tendineae and papillary muscles should be performed systematically during the surgery. Surgery should be performed with Doppler echocardiographic examination through the transesophageal tube.

When the anterior leaflet is thickened and there is a significant mitral insufficiency, it is technically possible to correct the reflux by means of reconstructive techniques, but this valve will most likely become stenotic due to the restriction of movement caused by this thickening of the anterior leaflet of the mitral valve, impairing its opening.

Other anatomical details are important. The normal mitral valve presents a zone of coaptation between the anterior and posterior leaflets, around 6 to 8 mm, coaptation that we should pursue in the performance of a mitral valve repair surgery because this adequate coaptation will favor a good long-term evolution. This coaptation is easily proven in the intraoperative period, with the test of saline solution with the filling of the left ventricle, making the mitral valve competent after the repair surgery, and the use of brushing with methylene blue in the atrial line of coaptation. Besides this good coaptation, a successful mitral valve repair must have an adequate valve area after the procedure, without ever causing stenosis.

We must not forget that myocardial protection in cardiac surgery is fundamental. If this protection is performed properly and we get good mitral valve reconstruction, confirmed by echocardiography in a patient with good preoperative ventricular function, the need for vasoactive drugs in the immediate postoperative period will certainly below.

Several studies[3] have shown a direct relationship with good results, that is, the durability of the repair and the volume of mitral repairs made by a given service.

Undoubtedly, the cardiovascular surgeon who is interested in mitral valve reconstruction should accompany for some time an institution that routinely uses this technique.

Keywords

Heart Defects Congenital; mitral Valve Insufficiency/surgery; hypertension, Pulmonary; Reoperation; Cardiopathy, Rheumatic.

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Review Article

Evaluation of Myocardial Perfusion by Computed Tomography - Principles, Technical Background and Recommendations

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Abstract

Coronary computed tomography angiography (CCTA) has gained a prominent role in the evaluation of coronary artery disease. However, its anatomical nature does not allow the evaluation of the functional repercussion of coronary obstructions. It has been made possible to evaluate Myocardial computed tomography perfusion (Myocardial CTP) recently, based on myocardial contrast changes related to coronary stenoses. Several studies have validated this technique against the anatomical reference method (cardiac catheterization) and other functional methods, including myocardial perfusion scintigraphy and fractional flow reserve. The Myocardial CTP is performed in conjunction with the CCTA, a combined analysis of anatomy and function. The stress phase (with assessment of myocardial perfusion) can be performed before or after the resting phase (assessment of resting perfusion and coronary arteries), and different acquisition parameters are proposed according to the protocol and type of equipment used. Stressors used are based on coronary vasodilation (e.g. dipyridamole, adenosine). Image interpretation, similar to other perfusion assessment methods, is based on the identification and quantification of myocardial perfusion defects. The integration of both perfusion and anatomical findings is fundamental for the examination interpretation algorithm, allowing to define if the stenoses identified are hemodynamically significant and may be related to myocardial ischemia.

Keywords

Computed Tomography Angiography/methods; Myocardial Perfusion Imaging/methods; Coronary Artery Disease; Dipyridamole; Adenosine; Vasodilatation.

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Introduction

Coronary computed tomography angiography (CCTA) was introduced in clinical practice in the end of the last century to promote noninvasive visualization of coronary arteries. Its use proved it an appropriate option for the evaluation of coronary artery disease.[1-4] Technological improvements of the equipment in recent years have allowed its application in different clinical conditions (emergency room chest pain evaluation, investigation in patients with conflicting diagnostic tests, among others). It is noteworthy that in all these conditions the background for its use rests on its high negative predictive power, making the presence of obstructive disease in the face of a negative test very unlikely.[1,2,5-8] Hence the need for invasive coronary angiography in a large number of individuals with clinical presentation or results of noninvasive tests compatible with coronary artery disease, but without obstructive coronary disease, shows a favorable cost-benefit profile using CCTA in these clinical scenario.[1,2,5,8-10]

On the other hand, the routine use of CT scan could result in a greater number of invasive procedures, since it would show lesions without clinical manifestation and that would be submitted to interventional treatment.[11] This limitation would stem mainly from the fact that the positive predictive value of Coronary artery CT is not as high as its negative predictive value, as it is also somewhat limited in characterizing plaques of moderate obstruction, especially when compared to other diagnostic tests.[1,4,6] This is relevant because the correct management of patients with coronary artery obstruction requires the characterization of the functional impact of stenosis, given that atheromas that do not cause flow reduction should receive maximum clinical treatment, whereas plaques that impact myocardial perfusion could be treated with surgical or percutaneous revascularization even if it promotes a moderate decrease in vessel lumen.[12-15]

Given the importance of myocardial ischemia detection, either by echocardiography, magnetic resonance imaging, myocardial scintigraphy, or by invasive examinations that include Fractional Flow Reserve (FFR) analysis,[4,15-18] the use of hybrid images, combining anatomical and functional findings, has become extremely desirable.[4] However, this involves

additional costs and time, which often makes this diagnostic workflow impractical. In view of the above, there was a desire to perform myocardial perfusion analyses with the MDCT itself, in the same procedure as the anatomical evaluation. This approach would involve the use of just one piece of equipment, reduced support staff, and reduced time and cost for exams. The initial attempts were made in commercially available equipment and showed favorable results, which confirmed the potential of a combined analysis, providing important data for an appropriate therapeutic management of such cases.[4,19,20]

Initial positive expectations were strengthened as technology progressed, including dual energy use, increased detector numbers, and improvements in spatial and temporal resolutions.[4,21-23] This favorable scenario led to the development of an international multicenter trial designed to test the validity of a combined analysis of anatomy and perfusion by CT scan with the conventional way of investigating such patients, that is, angiography associated with scintigraphy.[24] This study has shown that it is possible to perform combined CT anatomy and perfusion evaluations safely and with very favorable results.[24]

Nowadays, there are tomographs in Brazil with all characteristics necessary to ensure that such images are generated in accordance with what is described in this document. In addition, similar to what happened with the standardization of coronary angiotomography procedures by the National Agency for Supplementary Health Guidelines, the creation of a document on use is also educational and may hinder the indiscriminate use of diagnostic tests, thus avoiding the waste of resources in situations with no solid scientific evidence of the benefit these could bring.

Therefore, the purpose of this paper is to discuss in more depth the characteristics of ischemia CT research, the technological and software prerequisites, and to define which subgroups of patients would benefit from this exam.

Physiopathological rationale of coronary tomography myocardial perfusion

Myocardial CTP is based on the principles of the theory of tracer-dilution, first developed by Stewart,[25] in the 19th century. Images of the heart are taken during iodinated contrast injection to assess its transit through myocardial microcirculation, allowing the construction of an time-attenuation curves in the aorta and myocardium, from which myocardial blood flow (MBF) and myocardial blood volume (MBV) can be defined.[26] Based on the principles of the theory of tracer-dilution on CT,[27] the higher the concentration of iodinated contrast in the intravascular space and myocardial microcirculation, the greater its attenuation; and the opposite is also true. However, diffusion into the extracellular space increases over time, and after one minute its extracellular concentration is greater than the intravascular.[28] Therefore, to obtain an accurate perfusion assessment, images must be acquired right in the beginning of the first contrast pass.

Thus, in the first-pass imaging approach, the concentration of iodinated contrast is ideally proportional to MBF in a wide range of blood flows. Areas with lower (darker) attenuation upon first contrast passage are classified as hypoperfused territories and are visually and quantitatively evaluated in comparison to adjacent myocardial territories.[26] Another study has shown that first-pass perfusion imaging by helical CT correlates well with myocardial blood flow evaluated by microspheres.[29] This study confirmed the feasibility of performing an atherosclerosis and MBF assessment in a single CT scan, with the possibility of quantification and semi-quantitative analysis of perfusion data by attenuation curves. These theoretical considerations were later indorsed in a human clinical study from 2012, which confirmed the accuracy of MDCT assessment to detect coronary obstructions that cause myocardial ischemia.[30]

CT myocardial perfusion imaging – Validation

Although recently inserted in the clinical evaluation, Miocardial CTP has been subject of research for several years. In 2006, George et al.[31] used a canine model to determine the correlation between induced epicardial stenosis and perfusion defects identified by CT, with myocardial perfusion having microspheres as reference. The favorable results encouraged further clinical studies comparing, the additional value of the combination between Coronary computed tomography angiography (CCTA) and Myocardial CTP with the use of CCTA alone. Rocha-Filho et al.[22] showed an increase in accuracy in the combined assessment (CCTA + Myocardial CTP) compared to CCTA alone in the diagnosis of significant coronary stenosis. Adding Myocardial CTP to the strategy improved the accuracy from 0.77 to 0.90 (area under the ROC curve) in detecting stenoses.

Promising data from single-center clinical studies prompted the study CORE320.[24] This is a multicenter study in which the combined use of CCTA + Myocardial CTP to detect flow-limiting stenoses defined by obstructions >50% associated with perfusion defects was tested, defined by the combination of myocardial perfusion scintigraphy (SPECT-MPI) and cardiac catheterization. When considering all patients, the combination protocol achieved an accuracy of 87% for the definition of disease and 93% when considering only patients with no history of previous coronary disease.

Data from this same study evaluated the performance of Miocardial CTP alone in the diagnosis of significant stenosis identified by catheterization alone, compared to MPC.[32] The accuracy of MDCT, defined by the area under the ROC curve, was greater than that of MPC (0.78 vs. 0.69, p = 0.001), mainly due to the higher sensitivity of the first method.

Although the isolated use of MDCT for myocardial ischemia detection is not the end goal of tomography use, a recent study published by Takx et al.,[33] described the diagnostic performance of MDCT related to other methods of myocardial ischemia analysis, taking invasive coronary FFR as a reference. In a per-patient analysis, Myocardial CTP was shown to have a 93% accuracy in detecting flow-limiting coronary stenosis, while cardiac magnetic resonance and positron emission tomography had similar accuracy (94 and 93%, respectively). These values were statistically higher when compared to methods traditionally used in myocardial ischemia analysis, such as MPC and stress echocardiography, with accuracy of 82 and 83%, respectively.

The use of dynamic myocardial perfusion in the detection of myocardial ischemia has shown encouraging results validated by different reference techniques.[26,34-39] Clinical studies evaluating dynamic Myocardial CTP using invasive FFR as reference have

shown good diagnostic performance, with sensitivity and specificity ranging from 88 to 95%, and 74 to 90%, respectively. Although promising, the evaluation of this technique has been performed mainly through small sample unicentric studies, so the potential benefits of its use in relation to static Myocardial CTP need further investigation. Similarly, the use of dual energy in the evaluation of myocardial perfusion finds favorable ground for clinical research. Recent studies have shown promising data in the attempt to detect obstructive coronary artery disease (CAD) (86-94% sensitivity and 74-98% specificity),[40,41] however with data obtained in small samples. A prospective multicenter study to evaluate the use of this technique to identify flow-limiting coronary stenosis using invasive FFR as a reference is underway.[42]

Table 1 shows the results of selected studies evaluating Myocardial CTP performance in the search for myocardial ischemia and obstructive CAD.

Equipment required

Any 64-channel or more (4 cm z-axis coverage) CT scan is able to perform coronary angiography, and therefore synchronizes with the electrocardiogram (ECG) and appropriate settings, being also able to study pharmacological-stress myocardial perfusion.[43-47] For dynamic stress studies, with follow-up of the first pass of contrast through the myocardium (as opposed to a single acquisition at peak myocardial contrast – static perfusion), CT scans with at least 8 cm cover are required, either axially or in shuttle mode. Regarding image post-processing, it is recommended to use specific analysis software that allows segmenting the heart, coding the density of each area of the myocardium by color and displaying the result in a 3D map integrated with the coronary anatomy, or Bull's Eye representation form. Some newer tools allow correction of beam hardening hypo-attenuation, which is common in the inferior/inferolateral walls (from the aorta), septum (from contrast in the right ventricle) and anterior walls (from the ribs). This correction is highly recommended and can be done by probability algorithms[48] or by dual energy spectral acquisition with reconstruction of high energy monochrome images.[49]

A contrast infusion pump, preferably with two heads, is required for dynamic injection of high flow contrast. There is no need for an infusion pump for dipyridamole, but its presence can help optimize and ensure protocol quality. Despite the safety of dipyridamole/adenosine demonstrated in past studies, emergency care supplies regularly present in radiological clinics should be readily available, as well as qualified personnel to use them. Since dipyridamole/adenosine may induce advanced atrioventricular blocks (especially in conjunction with beta-blockers), the presence of percutaneous pacemaker can be helpful. Aminophylline should be ready for infusion after dipyridamole/adenosine administration. Continuous monitoring by ECG of satisfactory quality is indispensable during infusion.

Acquisition protocols – CT myocardial perfusion imaging

Monitoring of coronary artery tomography images, as well as CTMP, should be conducted by a specialized professional.[50] CTMP imaging techniques vary according to manufacturer and equipment model used. Thus, we warn that for each manufacturer some adjustments should be made for protocol optimization. In addition, we emphasize that the description of patient preparation, techniques of acquisition and use of medications are suggestions based on previous studies and the authors' experience, and may vary to meet the specific demands and workflows of each institution.

– Pre-exam preparation

As preparation for the exam, all patients should be fasting for at least four hours and not have caffeinated beverages in the last 24 hours.

Patients should be punctured with 18-20 gauge Jelco intravenous catheter in the antecubital vein of the right arm for administration of iodinated contrast. Another IV line in the left arm should be made for infusion of the stressor agent (dipyridamole/adenosine/regadenoson) and aminophylline as dipyridamole antagonist when necessary.

ECG, heart rate and blood pressure should be monitored by the attending physician throughout the examination.

Table 1 – Evaluation of myocardial perfusion by computed tomography in the study of obstructive coronary artery disease and myocardial ischemia

Study	Year	N	Reference	Sens.	Spec.	PPV	NPV
George et al.[43]	2009	27	ICA and MPC	86	92	92	85
Rocha-Filho et al.[22]	2010	35	ICA	96	100	100	91
George et al.[30]	2012	50	MPC	72	91	81	85
Bettencourt et al.[44]	2013	101	FFR	89	83	80	90
Rochitte et al. (CORE 320)[24]	2014	381	ICA and MPC	80	74	65	86
Cury et al.[45]	2015	110	MPC	90	84	36	99
Takx et al.[33]	2015	2048	FFR	88	80	-	-
Sørgaard et al.[46]	2016	1188	MPC, MRI, ICA, FFR	85*	81*	-	-
Pontone et al.[47]	2018	100	ICA and FFR	98	54	68	96

*ICA: invasive coronary angiography; MPC: myocardial perfusion scintigraphy; Spec.: specificity; FFR: fractional flow reserve; MRI: Magnetic Resonance Imaging; Sens.: sensitivity; PPV: positive predictive value; NPV: negative predictive value. * Results of myocardial perfusion by computed tomography with MPC and MRI as reference.*

Patients with blood pressure above 100 mmHg may receive sublingual nitrate (isosorbide dinitrate [5mg] or propatylnitrate [10mg]), with a minimum interval of 20 minutes for subsequent pharmacological stress, as validated in previous safety profile studies.[24] Although there is a theoretical anti-ischemic effect of nitrates, its use according to steps described above was not relevant to mask perfusion defects under pharmacological stress by tomography, when using SPECT-MPI associated to cardiac catheterization as a reference.[24]

– Use of beta-blockers as preparation for computed tomography coronary angiography

Patients may receive intravenous or oral metoprolol prior to examination. Although there is no formal guideline for this purpose, the proposal is to use the following scheme used in a previous multicenter study:[24] If body mass index (BMI) is < 30 kg/m^2 and heart rate (HR) is > 60 bpm, 75 mg oral metoprolol should be administered. If BMI is ≥30 kg/m^2 and HR > 60 bpm, oral 150 mg metoprolol should be administered. If HR remains >60 bpm, intravenous metoprolol 5 mg every 5 minutes up to a total of 20 mg may be administered.

– Use of stressors to evaluate myocardial perfusion by computed tomography

Regardless of the mode of image acquisition or equipment available, fixed stressor administration protocols are used. In Brazil, stress protocols use mainly dipyridamole (0.56 to 0.84 mg/kg) in 4 minutes, with acquisition in the 6th minute of the beginning of injection or possibly adenosine (140 μg/kg/min for 4 minutes, with acquisition at the end of the last minute). Regadenoson can be used as a stressor at a single dose of 0.4 mg intravenous (IV) in a bolus, with stress imaging acquired within 1-2 minutes after injection.

1 – 64-Row Multidetector Scanners

The assessment of myocardial perfusion at rest and stress by tomography, as well as the coronary anatomical evaluation, should always be performed in a single protocol. Aiming at a low radiation dose, we always suggest performing resting perfusion study (CCTA study itself) with the usual low-dose protocols available on the device (preferably with dose modulation and/or prospective acquisition), and the protocol under pharmacological stress whenever possible, with a slightly lower radiation dose, but diagnostic quality, always prioritizing prospective acquisition.

We encourage the option of the protocol to be used (stress/rest or rest/stress) according to the experience of each center and particular characteristics of each patient or the CT scanner used. Figure 1 shows the rest/stress protocol, however stress imaging prior to rest is feasible.

As an example, we can describe the following acquisition parameters for first-generation 64-channel scanners:[19,51,52]

- Resting study – Retrospective Gating, 70-90 ml of contrast at 5 ml/s injection pump infusion after metoprolol (max. 20 mg), 64 x 0.5 mm or 32 x 0.6 mm collimation, mAs up to 850 depending on gender and weight and Kv of 100 (preferred).
- Study under pharmacological stress – Retrospective Gating, 60ml contrast at 3ml/s injection pump infusion,

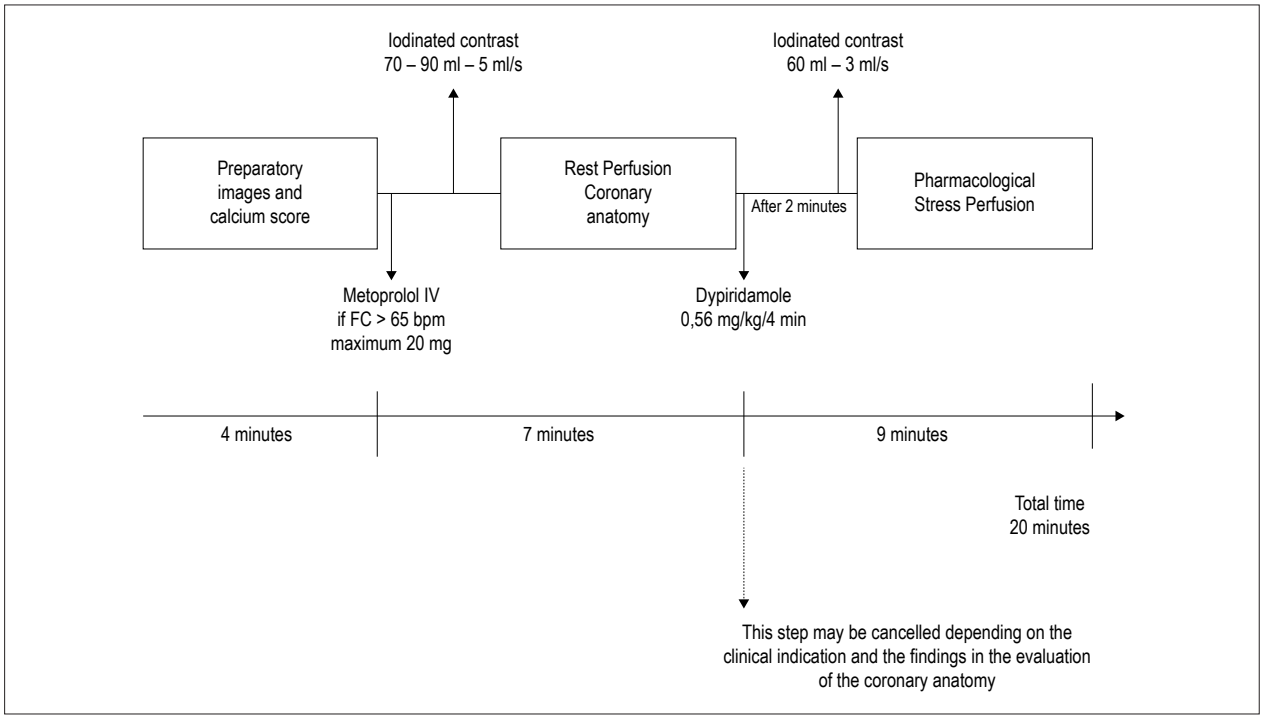

Figure 1 – *Acquisition protocol CCTA + myocardial CTP. CCTA: Coronary Computed Tomography Angiography; CTP: computed tomography perfusion.*

peak pharmacological stress acquisition, 32x1.0 mm collimation, 100 mA and 100 Kv (preferred).

Devices with latest hardware and state-of-the-art software can take advantage of available technological advances (e.g. prospective acquisition) and be based on a protocol with less radiation and the same diagnostic capability.

After iodinated contrast infusion, imaging acquisition can be performed manually as soon as the contrast is visually detected in the left atrium.

2 – Volumetric acquisition scanners (eg 240-320 detectors, or high-pitch beat acquisition):

The rest protocol will simultaneously acquire anatomical image (coronary angiography) and myocardial perfusion. The start and end of acquisition should be programmed based on previously acquired calcium score images, trying to minimize the radiation dose. Acquisition parameters used include 240-320 0.5 mm detectors with 100-120 kV voltage probe, gantry rotation from 0.280 to 0.375 seconds, with prospective ECG trigger.

Intravenous contrast will be infused by pump injection in a biphasic or three-phase protocol: 100% contrast in the first phase, 30% contrast plus 70% saline in the second phase, and 100% saline in the third phase. The contrast dose will be adjusted according to the patient's weight (see Table 2).[53]

Contrast injection monitoring must be performed by rapid real-time acquisitions initiated 5 seconds after the start of infusion. An apnea command is to be performed 14 seconds after the start of intravenous contrast infusion. When the contrast density peak reaches 300 UH in the descending aorta, acquisition of resting myocardial perfusion images and coronary angiography by CT will be initiated.

The pharmacological stress protocol will focus on stress myocardial perfusion image. Again, the beginning and end of the acquisition should be programmed based on previously acquired images, calcium score and rest perfusion. Acquisition parameters used include 240-320 0.5 mm detectors with 100-120 kV tube voltage, gantry rotation from 0.280 to 0.375 seconds with a prospective ECG trigger.[53]

Following administration of the stressor, a 12-lead ECG should be performed, along with blood pressure and heart rate checks.

3 – Other protocols

Different techniques and forms of image acquisition are available and constantly evolving, including dual energy and dynamic acquisition. Although promising, such techniques require further investigation and radiation reduction strategies. Therefore, we will not address the protocols used for such techniques in this document.

CCTA/CTMP Interpretation and Integration

The assessment of CTMP involves a sequence of steps, which must be systematized to produce a result that reflects a physiopathological change or a state of normality. In this approach, initial assessment of CCTA is recommended (Figure 2),[57] given that the additional value of CT perfusion defects in the absence of atherosclerosis has not been investigated so far.

Once the CCTA is evaluated and any coronary stenosis and non-interpretable segments (stents, calcifications, artifacts) are quantified, the next step is to assess stress and rest myocardial perfusion. At this stage, qualitative and quantitative visual analyses (below) are used to establish the severity and extent of myocardial perfusion deficit, as well as its reversibility.

The third step in the process of image interpretation is the reclassification of anatomical findings. Due to potential limitations of luminal assessment by CCTA and the existence of intermediate stenoses,[22,51,58] myocardial perfusion analysis may be the information required to define obstruction. In this sense, in coronary segments whose evaluation was doubtful for any reason, the presence of myocardial ischemia observed by the Myocardial CTP should strongly suggest significant stenosis.

The final step in the interpretation process is anatomical-perfusion alignment based on the integration of CCTA and Myocardial CTP findings. This process is essential to define the presence of flow-limiting stenoses,[24] i.e. the presence of epicardial obstructions causing myocardial perfusion defects, whether fixed (fibrosis) or reversible (ischemia). This correlation should be performed mainly by multiplanar reconstructions, in order to align each epicardial vessel with its respective myocardial territory, defined by well-established myocardial segmentation models.[59] This process should produce a correlation between epicardial stenoses and eventual perfusion defects, whose description should clear and detailed in the final report.

Quantitative analysis of myocardial stress perfusion by tomography

Among the methods used for quantitative evaluation we can mention transmural perfusion ratio (TPR) and summed stress score (SSS), obtained through static acquisition. MBF estimates, although likely to be performed by dynamic myocardial perfusion, will not be addressed in this document.

Table 2 – Contrast dose and flow by patient weight53

weight (Kg)	First phase: 100% Contrast (ml)	Second phase: 30% contrast and 70% Serum (ml)	Third phase: 100% serum (ml)	Flow (ml/s)
< 60	44	20	50	4
60-70	54	20	50	4.5
71-100	54	20	50	5
> 100	64	20	50	5

Modified table from George et al.[53]

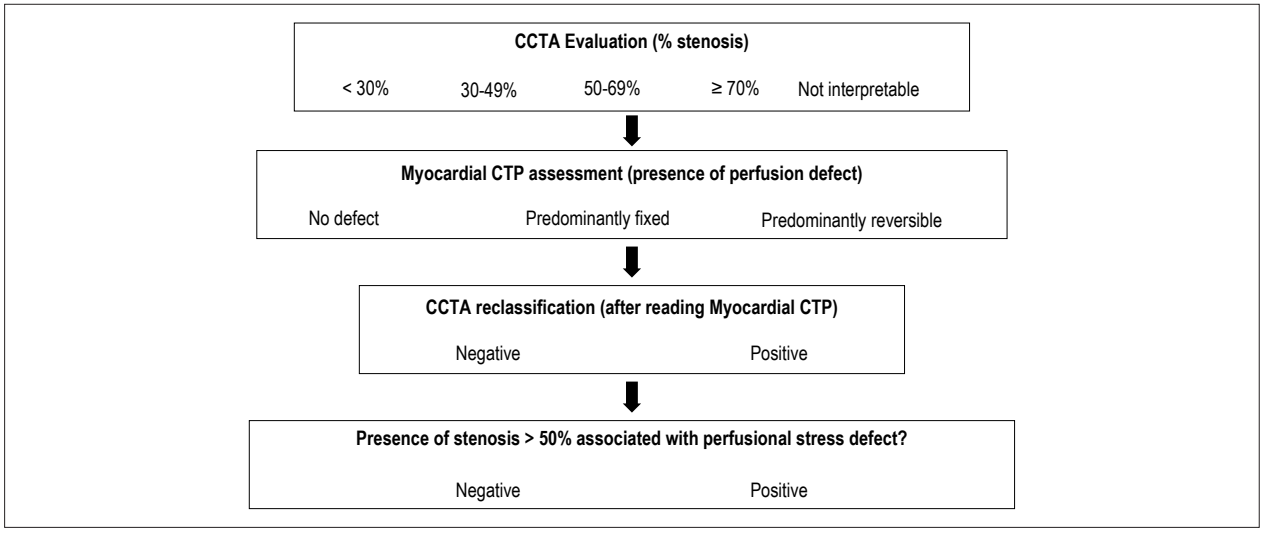

Figura 2 – *Workflow for combined CCTA + myocardial CTP analysis (modified from Magalhaes et al[57]).*

The TPR is calculated by the average subendocardial density (in Hounsfield Units) divided by the average of the subepicardial density of each myocardial segment. This relationship showed that Myocardial CTP can detect and quantify perfusion defects compared with SPECT,[30] and has excellent accuracy to identify perfusion defects after pharmacological stress associated with significant coronary obstruction by invasive coronary angiography.[52] TPR less than 0.85 should be considered the cutoff value for identifying ischemic segments.[52]

Tomography SSS should be calculated based on the sum of perfusion defect of the 17 segments predefined by the American Heart Association, ranging from a scale of 0-4 for each segment (0 – normal; 1 – discrete; 2 – moderate; 3 – important and 4 – transmural perfusion defect). SSS values for ischemia quantification are: less than 4 normal, between 4 and 8 discrete, between 9 and 13 moderate, and greater than 13 important.

Report

Myocardial CTP assessment should be divided into qualitative and quantitative analysis. The report must contain the examiner's visual and subjective impressions, followed by the quantitative assessment (TRP and SSS). The reversibility of perfusion defects is fundamental information and should be addressed in the report, as it reflects the myocardial ischemia itself.

The most important part of the report is the integration of anatomical and perfusion findings. The examiner should clearly define whether there is a correlation between luminal obstructions and perfusion defects, as well as the extent of perfusion defects and reversibility as they define the therapeutic approach.[60]

The main elements of the report are expressed in Table 3.

Limitations

Myocardial perfusion study is advantageous when in conjunction with the anatomical assessment of the coronary arteries, as it benefits from the combined assessment. Thus, it is a limited strategy when considered in isolation, given exposure to ionizing radiation and iodinated contrast, which can be avoided in other diagnostic methods.

Because it uses additional doses of radiation and contrast when compared to coronary tomography alone, Myocardial CTP should be used with caution in patients with renal failure or undergoing other examinations employing ionizing radiation over a short time.

The use of vasodilatory pharmacological stress should be carefully evaluated in patients with any clinical or hemodynamic instability, as well as in patients with atrioventricular blocks, chronic obstructive pulmonary disease and asthma.

Future perspectives

As previously mentioned, the use of dynamic perfusion by tomography allows the evaluation of myocardial iodine contrast kinetics, making it possible to quantify MBF. Additionally, the use of dual energy techniques (two x-ray tubes operating simultaneously at different voltages) allows to create an "iodine map" for the quantification of perfusion defects. Although such techniques are already available, further studies are needed to assess the impact of these approaches on clinical decision-making, as well as the increased supply of equipment that allows the use of this technique, which is still scarce in Brazil.

Recently, a new approach has emerged in the functional assessment of coronary artery disease by CT, known as CT-derived FFR. Although it uses a completely different technique, it has the same purpose of Myocardial CTP, using

Table 3 – Elements of the combined report CCTA + Myocardial CTP

Protocol used (rest-stress, stress-rest, dynamic perfusion or dual energy perfusion) and iodinated contrast volume
Scanner
Stressor agent, doses and reversing agent (when applicable)
Presence of symptoms and electrocardiographic changes in stress.
CCTA description (quantification of stenosis)
Myocardial CTP description (qualitative/quantitative analysis, artifacts)
Anatomic-perfusional integration
Conclusion

CCTA: coronary computed tomography angiography; CTP: computed tomography perfusion.

routine coronary tomography images without the need for pharmacological stress. Usually, coronary tomography images are transferred to a dedicated computer, where simulations based on computational fluid dynamics are performed, in order to create a three-dimensional model based on the anatomical and physiological characteristics of each patient. This model identifies stenoses and quantifies changes in intracoronary pressures, reflecting the changes found in stenoses invasively assessed by FFR.[61] The most recent data point to an optimal accuracy of this method, and equivalent to the combined assessment CCTA + Myocardial CTP to define flow-limiting stenoses using invasive FFR as a reference.[62] Although promising, this technique also faces limitations, such as the impossibility of use in revascularized patients with stents, as well as examinations with motion artifacts/calcification that prevent the proper identification of lumen boundaries to generate the three-dimensional model. Moreover, because it is a technique with specific and hard-availability software and hardware, FFR-CT is still restricted to some centers in the world (in Brazil, only used as a research tool).

Conclusion

CCTA combined with stress tomography evaluation of myocardial perfusion is a safe and accurate modality for the simultaneous investigation of coronary obstructions and their repercussions on regional myocardial flow. The positive impact of this approach lies on the value added by the ischemic burden information provided by myocardial perfusion upon CT, a well-established method of anatomical and coronary stenosis assessment, with acceptable doses of radiation and the use of iodinated contrast.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Magalhães TA, Cury RC, Schvartzman P; Writing of the manuscript: Magalhães TA, Cury RC, Cerci RJ, Parga Filho JR, Gottlieb I, Nacif MS, Masciarelli Pinto I, Rochitte CE, Vilas-Boas F, Schvartzman P.

Potential Conflict of Interest

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Study Association

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Ethics approval and consent to participate

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

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Cardiology Training in Brazil and Developed Countries: Some Ideas for Improvement

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Abstract

Huge variations exist in cardiology training programs across the world. In developing (middle-income) countries, such as Brazil, to find the right balance between training improvements and social and economic conditions of the country may be a difficult task. Adding more training years or different mandatory rotations, for instance, may be costly and not have an immediate direct impact on enhancing patient care or public health. In this text, we compare the Brazilian cardiology training system with other proposals implemented in developed countries from North America and Europe, aiming to point out issues worth of future discussion. Factors such as training rotations and competencies, and program duration and distribution across the countries are presented. The number of first year cardiology trainees per inhabitants is similar between Brazil and the United States (0.24 medical residents/100,000 inhabitants in Brazil and 0.26 medical residents/100,000 inhabitants in the USA). These numbers should be analyzed considering the inequality in training program distribution across Brazil, since most centers are located in the Southeast and South regions. Having more residency programs in distant areas could improve cardiovascular care in these areas. Duration of cardiology Residency Training is shorter in Brazil (two years) in comparison with developed countries (> 3 years). Brazilian residency programs give less emphasis to scientific research and diagnostic methods. Unifying minimum training requirements across the globe would facilitate the development of international learning opportunities and even professional exchange around the world.

Introduction

Brazil is the fifth largest country in the world, regarding both land territory and population, and it is the tenth largest economy globally.[1,2] As well as in many other developing and developed nations, cardiovascular diseases are a major concern in Brazil, being the leading cause of death in the country.[3] On the other hand, many Brazilian citizens do not receive proper cardiovascular care.[4]

Improving health professionals' training may contribute to change this scenario, although the understanding of what modifications should be made in cardiology training programs is not an easy task. Drawing parallels between the cardiology residency programs in Brazil and other countries' programs may help to identify possible targets for improvement. However, there are few publications currently available on cardiology training programs.[5] The main objectives of this report were 1) to delineate a non-systematic narrative point-of-view, comparing the Brazilian training system with countries in Europe and North America; 2) to briefly introduce the cardiology training program in Brazil to international readers who may not be familiar with it. PubMed database was searched for articles published up to February 2018 with the keywords "cardiology Residency" and "cardiology Training" in the target countries, written in English, Spanish and Portuguese. Official position statements and legal documents issued by cardiovascular societies and public organizations pertinent to this topic were also reviewed and cited as appropriate. Selection of countries was made based on the availability of information in the literature. Given the nature of the present article, and the scarcity of published data, authors' opinions were also included when appropriate.

Length of Training

To become a cardiologist in Brazil, the first step is to obtain a medical degree. After finishing high school, the student must apply for a highly competitive entrance exam (called "vestibular") and be admitted to a medical degree course, which lasts six years. The following step is a two-year internal medicine residency and, finally, the general cardiology residency (named Fellowship in some countries, such as the USA), which lasts two more years. To be a specialist in a field of cardiology, additional training is required. For example, for training in imaging techniques (echocardiography, cardiac magnetic resonance, nuclear medicine, etc.), usually one or two additional years are necessary for each track. The same amount of time is normally required for some clinical subspecialties, such as Acute Coronary Care, and two years are mandatory for Interventional cardiology. For Heart Failure and Transplantation, one extra year is required. In summary, to become a Cardiologist in Brazil one needs to complete four (General Cardiologist) to six (General

Keywords

Cardiology; Education, Medical; Program Accreditation; Internship and Residency; Fellowships and Scholarships; Brazil.

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Cardiologist with a subspecialty training) years of postgraduate medical education. It is important to note that the National Board of Medical Residency ("*Comissão Nacional de Residência Médica*" – CNRM) supervises the residency training (as will be discussed later) and some (but not all) of the subspecialties training programs.

When comparing education and training lengths between developed and developing countries, important differences are observed (Table 1). Ten years are required to become a general cardiologist in Brazil (which is similar to most countries in Latin America).[6-9] In the USA, internal medicine residency and cardiology Fellowship usually last three years each. Adding that to the period in the undergraduate degree program and in Medical School (eight years), the total post-secondary education time to become a cardiologist in the USA is 14 years. In Germany, three years of internal medicine residency training and three years of cardiology residency training are required (12 years in total). There are also differences in patterns of work shifts across the countries, which may influence the real time spent in training. Post-call day-off, for example, is a common practice in the USA and Canada, while in Brazil the resident is allowed six hours of rest (instead of the whole day) following a night-shift work. After the completion of the whole educational program straightly, that is, without interruptions for conscription, or extra or sabbatical years, a doctor will be able to become a cardiologist approximately at the age of 28 in Brazil, 33 in the USA and 31 in Germany.[10,11]

Another example of a lengthy training process can be observed in the United Kingdom. After finishing medical school (usually five years), the trainee must complete a two-year Foundation Program, followed by the Core Medical Training (two years) or Acute Care Common Stem (three years). After that, the trainee is finally able to go through the specialty training in cardiology. That is comprised of three initials years of Core Cardiology Training and two years of advanced training in specialist area modules. During the three initial years, the emphasis is given to acute cardiovascular care and basic procedural techniques. For the last two years, most of the time is spent in one or more of these fields of practice: interventional cardiology, electrophysiology, non-invasive imaging, adult congenital heart disease or heart failure. Counting all those years together, a total of 14 or 15 years is required to become a cardiologist in the UK. Of note, after the completion of this pathway, not all cardiologists will have the same amount of knowledge in every area, since the curriculum for the last years is flexible to the individual's interest. Additional years may be necessary for those doing part-time training, or for dual certification in cardiology and internal medicine, or for combining out-of-program research (by doing a research fellowship in another institution, for example) or extra training in subspecialties of cardiovascular care.[12,13]

Clearly, the duration of training to become a cardiologist is not uniform across countries, and there is not a definitive standard of practice. It depends not only on the total amount of knowledge and practical skills that the professional needs to acquire, but also on the country's social and economic conditions, since having more training years increases educational expenses. As a general guidance, the American College of Cardiology (ACC) endorses the period of three years for training in general cardiology while the European Society of Cardiology recommends a four-year term, despite important variations among European countries.[14,15] Using a comparative approach only, it is not possible to accurately state that the same length of training in these countries would be applicable to the Brazilian reality. It may be the case that medical residents in Brazil spend more time in service during the two-year residency and oversee more patients. Conversely, the amount of knowledge in cardiology has increased dramatically in the last decades[16] and it seems unlikely that a resident in cardiology resident in Brazil would be able to master the necessary knowledge and abilities in a 2-year training duration. As a result, there is an ongoing discussion in Brazil to have a single focused year of internal medicine training (instead of the current two years, as in France and Spain) before starting a new model of a 3-year cardiology residency.

Required competencies and training schedule

To better understand how knowledge is acquired, one may also look at the core rotations trainees must complete. The government sector responsible for the coordination of medical training throughout Brazil is the Ministry of Education (with active participation of the Ministry of Health), and the CNRM.[17] The CNRM was founded in 1977 and has made several improvements to the medical residency, as follow:

Table 1 – Length of cardiology residency trainings in selected countries.[10-12,21,25,33,34]

Country	Continent	Graduation (years)	Previous training length (ys) (e.g.: internal medicine)	Cardiology residency program (years)	Total length (years)
Australia	Oceania	6	4	3	13
Brazil	South Am.	6	2	2	10
Canada	North Am.	7 or 8	3	3	13 or 14
France	Europe	6	1	3	10
Germany	Europe	6	3	3	12
Spain	Europe	6	1	4	11
UK	Europe	5	4 or 5	5	14 or 15
USA	North Am.	8	3	3	14

Am.: America. Data obtained from each country's official legislation or decree on medical training and/or National Cardiovascular Society

- Regulation of work hours: currently, a medical resident in Brazil (of any specialty) should work up to 60 hours per week, with no more than 24 hours of in-hospital shift activities (in-home on-call is not permitted);
- Wages and salaries: the resident doctor is paid monthly by the Government (Federal, State, or County) or by a private institution. All residents receive the same amount, regardless of the year of training or the field of training (currently there are 53 different medical specialties officially recognized in Brazil). Usually, no extra payment is granted for night shifts. Housing and food assistance are commonly offered, especially for those in greater need. Working at night shifts outside the residency program ("moonlighting") and "locuming" are not prohibited, as long as they do not interfere with the residency program;
- Training supervision: the definition of residency is "training at service under supervision", which means that the resident must be overseen by an attending physician at all time, including night, weekend and holiday shifts.

Once the CNRM requirements are fulfilled, each program has the flexibility to adapt the program according to the local reality. For cardiology, CNRM requires the trainee to spend at least half of the total training time in inpatient care, in the emergency department, wards or coronary care units (CCU). Around one-fifth of the training time must be dedicated to outpatient clinics, and at least 5% of the time should be spent learning diagnostic methods. Congenital heart disease and post-operative care are also considered mandatory rotations for all cardiology trainees.[18] Importantly, as in North America and some European countries, cardiology residency programs in Brazil are planning to implement a "competency-based curriculum". This approach is focused on evaluating the trainees according to specific learner outcomes, with emphasis on a formative, instead of a summative assessment, leaving behind the traditional time-based curriculum and passive learning methodology.[19] The discussions are still ongoing, and it will probably take some time until the new proposal is fully implemented in Brazil.

In the USA, the Accreditation Council for Graduate Medical Education (ACGME) oversees training programs across the country and establishes general basic requirements for training sites and educators.[10] The ACC also publishes the Core Cardiovascular Training Statement, currently in the fourth version (COCATS 4), with recommendations for levels of trainings and milestones within each component of the cardiovascular training.[14] Both documents from the ACC and ACGME are aligned to and focused on competency-based learning. The general core competencies are: patient care; medical knowledge; practice-based learning and improvement; interpersonal communication skills; professionalism; and system-based practice.[14] Of note, the Brazilian Society of Cardiology (BSC) also published a guideline for cardiovascular training in the Brazil.[20]

In Canada, cardiology training programs are supervised by the Royal College of Physicians and Surgeons of Canada. Along the three-year cardiology Residency Program, the minimum requirements comprehend: 15 training blocks of clinical residency (CCU, wards, consults, clinics), 15 blocks of laboratory-based residency (cardiac catheterization, electrophysiology, nuclear cardiology, echocardiography), two research blocks, and four blocks of electives.[21] Additionally, clinical and academic contents of the program must fulfill all of the CanMEDS roles for the cardiology specialty. CanMEDS is a "framework that identifies and describes the abilities physicians require to effectively meet the healthcare needs of the people they serve".[22] According to CanMEDS, medical competencies are grouped under seven key roles: medical expert, communicator, collaborator, leader, health advocate, scholar and professional.[23] Training programs are supposed to offer their trainees opportunities to master each one of these roles in the scope of practice. Canada is also moving towards implementing a competency-based medical education curriculum for all residency programs, through the "Competence by Design" initiative.[24] This is based on milestones to be achieved as the resident advances through the training program, from the entrance in the residency program until the transition to the unsupervised medical practice. The target year for Canadian cardiology Residency programs to launch the "Competence by Design" is 2020. In Spain, trainees gain access to the cardiology Residency via the MIR test ("Médico Interno Residente"), right after leaving medical school, and the training lasts five years. In the first year, most of the rotations are usually related to internal medicine. In the second year, activities are divided between CCU, cardiology wards and consults. The third year is dedicated to non-invasive tests, such as echocardiography and cardiac stress tests. In the fourth year, around six months should be spent in the cardiac catheterization laboratory and 4 months in an electrophysiology service. The last year has a more flexible curriculum, at the discretion of each hospital. Residents may rotate on areas such as congenital heart disease and heart transplantation and/or can spend more time doing research and elective rotations.[25]

When compared to trainees from North America and some European countries, medical residents in Brazil spend less time in non-invasive tests and in the catheterization laboratory, since those abilities are developed in depth by those who choose to pursue further training in these subspecialties. Training in North America and Europe generally includes completing mandatory, procedural logs and documentation.[10,15,18] In addition, in Brazil, little emphasis is given to research, contrary to countries with longer training length.

Residency training programs in Brazil are aimed at practical aspects of cardiology (around 80% of the time), and didactic activities, such as lectures, seminars, etc., are developed in the remaining 20% of total time. Again, changing the residency program duration from two to three years, would also contribute to a better training in important areas, such as research, among others.

Availability and distribution of training centers

In Brazil, in 2017, 502 new residents[a] started their training in 167 cardiology Programs, unevenly distributed throughout the regions of the country (average of 0.24 medical residents/100,000 inhabitants);[26] the respective numbers for the USA (2016/2017 period) were 855 new cardiology Fellows in 193 Programs (0.26 new medical residents/100,000 inhabitants).[27] However, the proportion of Cardiologists/100,000 inhabitants in both countries is, respectively, 7.47 for Brazil and 6.83 for the USA [26, 28-30, b] (Figure 1).

[a] Since the mentioned countries have different training lengths, comparisons are made using the number of first-year residents/fellows of each country

[b] Personal communication, Dr. Rosana L. Melo, CNRM General Secretary

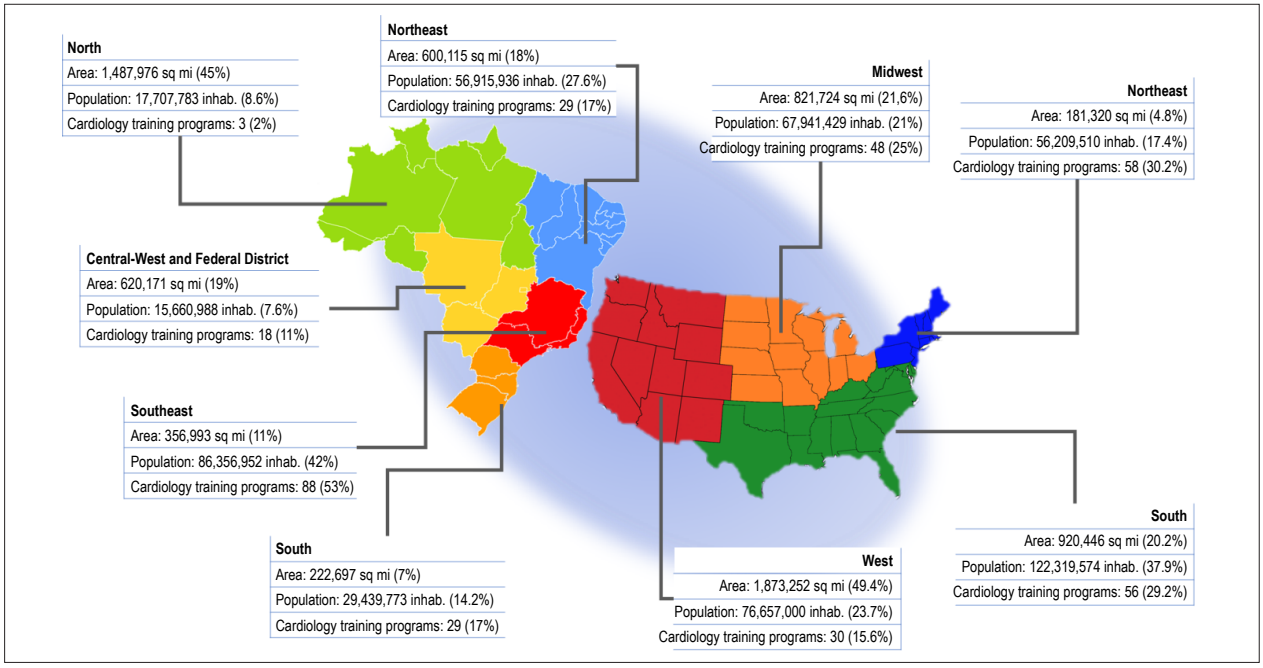

Figure 1 – *Comparison between Brazil and the USA (without Puerto Rico) regarding Cardiology Residency (Fellowship) Program distribution. Inhab.: inhabitants.*[d,27,28,30,35]

In Canada, there are 15 cardiology Residency Programs. A total of 58 new residents (PGY-4, postgraduate year four in the Canadian numerical scheme) started their training in Adult cardiology in the 2016/2017 period (0.16 new residents/100,000 inhabitants), most of them (50 residents) receiving regular government funding (Figure 2). Most of the programs are held in the provinces of Ontario (21 new cardiology residents within five programs), and Quebec (16 new cardiology residents within four programs), especially in the cities of Toronto and Montreal, respectively. Canada is a large country territory-wise, but with the vast majority of its 35 million inhabitants living within 100 miles of the USA border.[31,32]

Brazil also has significant variability in population density and financial resources across the country and, consequently, the distribution of the residency programs is very unequal, and most of the programs are held in institutions of the South and the Southeast regions (Figure 1). In fact, a single State out of the total 26, the São Paulo State, supports more than one-third of all available positions in the whole country. This reflects the distribution of the medical schools in these areas; the Southeast region concentrates most of the medical schools, while the North region, occupied mainly by the Amazon rainforest and with the smallest population density in the country, exhibits the smallest number of medical schools and cardiology Residency programs. In the USA, the distribution of the Residency Programs in cardiology is also unequal, but not like Brazil. Despite having the smallest geographical area, the US Northeast region houses the majority of positions, and the New York State alone concentrates approximately one-eighth of them all.[27] Creating more training programs and facilities in more distant locations in Brazil could help improve cardiovascular care in the inner regions of the country. Local authorities have been working on this issue during the past years, but with limited success.

Board certification

Each country has a method to certify that a doctor is legally recognized as a specialist in a field. In the USA, the American Board of Internal Medicine is the agency responsible for offering physicians the certification in cardiovascular care. In Europe, each nation has its own agency, such as the Joint Royal Colleges of Physicians Training Board in the United Kingdom and the "College National des Enseignants de Cardiologie" in France. To date, there is not a single, unified European examination valid for all countries, although some initiatives have been proposed. In Brazil, after finishing the residency, the doctor is automatically certified by the CNRM and Federal Council of Medicine as a Cardiologist. Additionally, to be certified as a Cardiologist by the Brazilian Medical Association, the physician must apply for the BSC exam, which consists of a written examination, applied once a year, during the BSC National Congress. If approved, this professional will be certified by the BSC, Brazilian Medical Association and by the Federal Council of Medicine.

In Brazil, besides the residency programs supervised by the CNRM, there are 20 programs, accredited and supervised by the BSC (not by the CNRM) throughout the country.[c] In general, the core curriculum is similar to the CNRM programs,[20] but some differences should be noted: 1) in the BSC training programs no salary is paid to the trainee and 2) no automatic certification is granted by the Federal Council of Medicine; the trainees must undergo the BSC Board Certification test in order to be certified as a Cardiologist.

Final comments

The model of the medical residency programs reflects the socioeconomic conditions, and the organization of the educational and health systems of each country. A limitation of

[c] Personal communication, Dr. Pedro S. Farsky.

[d] Personal communication, Dr. Rosana L. Melo, CNRM General Secretary.

Figure 2 – *Geographical representation of all Cardiology training programs in Canada. 1: University of British Columbia (Vancouver, BC); 2: University of Calgary (Calgary, AB); 3: University of Alberta (Edmonton, AB); 4: University of Saskatchewan (Saskatoon, SK); 5: University of Manitoba (Winnipeg, MB); 6: University of Western Ontario (London, ON); 7: McMaster University (Hamilton, ON); 8: University of Toronto (Toronto, ON); 9: Queen's University (Kingston, Ontario); 10: University of Ottawa (Ottawa, ON); 11: McGuill University (Montreal, QC); 12: Université de Montréal (Montreal, QC); 13: Université de Sherbrooke (Sherbrooke, QC); 14: Université Laval (Quebec City); 15: Dalhousie University (Halifax, NS).*[31]

the present text is the lack of data in the literature describing and comparing different cardiology training programs around the globe. This impairs our ability to make a more evidence-based comparison and many inferences presented in this manuscript are derived from the authors' opinions and experiences. With these points in mind, in our understanding the main strengths of the cardiology Residency Programs in Brazil are: 1) one centralized national coordination (CNRM), responsible for the supervision and the rules that are valid for all programs; 2) the rigorous selection process candidates must go through to advance to the next level of training. On the other hand, this international perspective identifies opportunities for improvement, such as the fact that two years for training in General cardiology is likely too short, given the complexity of modern cardiology.

In countries like Brazil, with huge regional differences, it is imperative to make proposals for an equal provision of good Medicine all over the country. Yet, given the differences observed among the cardiology Residency Programs worldwide, it would be very useful if our professional governing bodies defined a minimum standardized curriculum for the training of new Cardiologists, considering the characteristics of the country. Possibly, a three-year residency, with a competency-based curriculum, offering a balanced amount of patient care, procedures and diagnostic test training, organized in time-limited rotations and longitudinal activities (such as an integrated outpatient clinic), and a time dedicated to research, would be a starting point for discussion about harmonization of the residency programs. Further, it would be important that medical societies across the world recognize these training differences, so that they could tailor educational programs in cardiology (including scientific meetings and conferences) for the needs of the developing world. Besides giving better care to our underserved population, these initiatives would facilitate collaboration and exchange experiences with cardiologists internationally.

In conclusion, the development of an international standardized minimum curriculum for the cardiology residency training programs, to be customized according to individual country characteristics, would be very useful and promote exchange of experience internationally. In our opinion, the cardiology training in Brazil needs to be improved based on the programs conducted in developed countries. In order to achieve this goal, it is necessary an urgent mobilization of different sectors of the cardiology community, such as the cardiology Residency programs, the BSC, and the CNRM, among others.

Author contributions

Conception and design of the research: Godoy LC, Farkouh ME, Manta ICKA, Furtado RHM, Nicolau JC; Acquisition of data: Godoy LC, Manta ICKA, Furtado RHM, Nicolau JC; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Godoy LC, Farkouh ME, Manta ICKA, Dalçóquio TF, Furtado RHM, Yu EHC, Gun C, Nicolau JC; Writing of the manuscript: Godoy LC, Nicolau JC.

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Case 5/2019 – 55-Year-Old Diabetic Man with Heart Failure After Non-ST Segment Elevation Myocardial Infarction

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A 55-year-old male patient which is insulin-dependent diabetes mellitus (DM) with visual complications and chronic kidney disease (CKD) was admitted a month ago (February 2017) after an episode of nocturnal dyspnea. A diagnosis of non-ST-segment elevation myocardial infarction (AMI) was identified. Admission examinations revealed elevated myocardial injury markers - CKMB of 70 ng/mL and 2 ng/mL troponin. The electrocardiogram (ECG) showed a ST-segment depression from $_{V2}$ to $_{V6}$. The coronary angiography revealed a 30% lesion in the right and left coronary arteries did not present lesions (Figure 1). The echo revealed diffuse left ventricular hypokinesia and 36% ejection fraction. Creatinine was 1.8 mg/dL.

After discharge, the patient developed orthopnea and lower limb edema and sought emergency care and was transferred to InCor two weeks after hospital discharge with a diagnosis of decompensated heart failure (March 22, 2017).

During a physical examination, the patient had dyspnea, was hydrated, did not have a fever, had good peripheral perfusion, blood pressure was 100x70 mmHg, a 90 bpm heart rate and 92% oxygen saturation. There was jugular turgescence, bilateral and symmetrical vesicular murmur present, presence of crackles in both lung bases, normophonetic rhythmic sounds in two stages, without murmurs. There was no hepatomegaly or hepatojugular reflux. The patient's abdomen was flaccid, painless and had airborne noises present. The lower limbs presented a ++ / 4+ edema, the calves were free and there were symmetrical pedis pulses.

The patient was using 100mg acetylsalicylic acid, 20 mg enalapril and NPH human insulin.

The ECG (March 22, 2017) revealed sinus rhythm, low voltage of the QRS complex in the frontal plane and ST segment depression, 1 mm, horizontal from V_2 to V5, and a reduction of the left ventricular potentials (Figure 2).

Chest radiography (March 23, 2017) revealed massive bilateral pleural effusion and cardiomegaly (Figure 3), persistently identified on the radiograph on March 31, 2017.

Keywords

Diabetes Mellitus/complications; ST- Elevation Myocardial Infarction; Heart Failure; Cardiogenic Schock.

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Laboratory tests revealed anemia and creatinine increases (Table 1).

Echocardiography (March 23, 2017) revealed a 30 mm aortic diameter, 39mm left atrium, right ventricle in the basal portion, which was 44 mm and in the middle portion, which was 29 mm. The septum and posterior wall thickness were 7 mm, left ventricular diameters of 56 mm in diastole and 51 mm in systole, the area method ejection fraction (Simpson) was 22%. There was mild to moderate mitral regurgitation and pulmonary artery systolic pressure was 36 mmHg.

The serologies for Chagas disease and cytomegalovirus were negative.

With this history and the exam findings, the hypothesis of type 2 infarction or myocarditis was raised.

Magnetic nuclear resonance showed marked biventricular systolic dysfunction - 11% left ventricular ejection fraction (LVEF) and slight dilatation (indexed final diastolic volume of 106 mL/m^2 and final systolic volume of 100 mL/m^2), with increased right ventricular dilation (final diastolic volume indexed was 137 mL/m^2 and final systolic volume of 122 mL/m^2, 6% ejection fraction). The right atrium had a normal volume while the left atrium was greatly enlarged (indexed volume 65 mL/m^2).

The cardiac diameters were: aorta 2.5 mm, right ventricle in the longest axis 71 mm and shortest axis 40 mm; left ventricle diastole 57 mm, systole 56 mm; septum thickness 6 mm and 5mm lateral wall. There was a transmural, circumferential multifocal late enhancement, sparing the apical segments beyond the apex and compromising the papillary muscles, which all had subendocardium involvement (Figure 4). There was no pericardial effusion and there was massive bilateral pleural effusion.

During hospitalization, the patient had a fever and leukocytosis (Table 1), and was diagnosed with bronchopneumonia, treated with vancomycin and tazobactam with a reduction in C-reactive protein and leukocytosis.

Renal function worsened (Table 1) with oliguria and a shilley catheter was used in the femoral vein, but due to hemodynamic instability, hemodialysis was not possible.

Since admission, the patient had severe dyspnea requiring long-term non-invasive ventilation and right hemithorax drainage due to respiratory discomfort with a serohematic discharge of about 3 liters during two days. The March 31 radiograph revealed massive bilateral pleural effusion prior to drainage. In the middle of the night on March 31st, 2017, the patient had cardiopulmonary arrest with pulseless electrical activity and was promptly resuscitated for 15 minutes with a return to spontaneous circulation. The patient received orotracheal intubation and required maximum doses of noradrenaline and dobutamine to maintain a mean blood

Anatomopathological Correlation

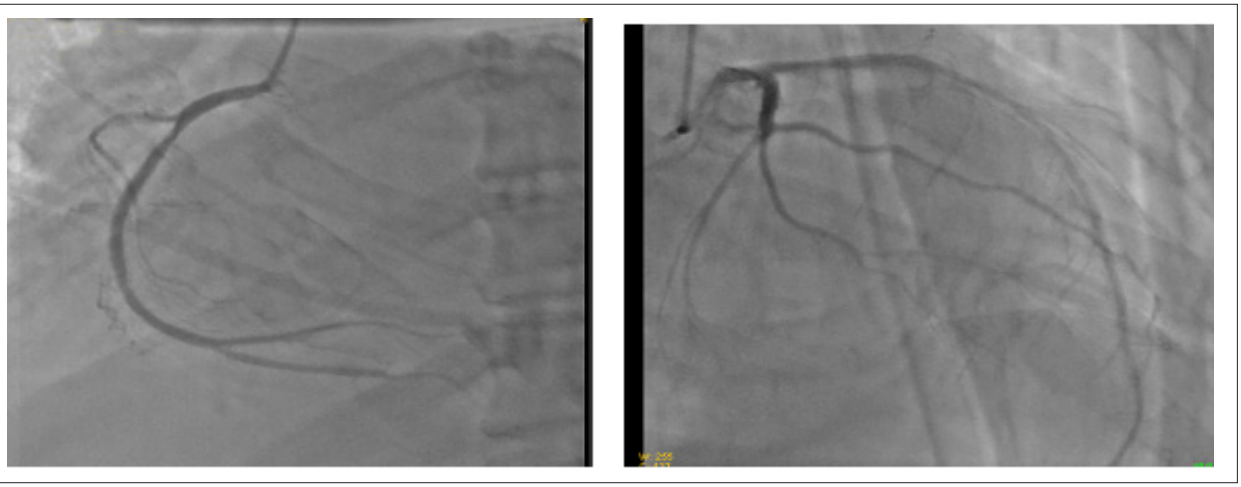

Figure 1 – *Right coronary in right anterior oblique view. A) Left coronary in right oblique view (B)*

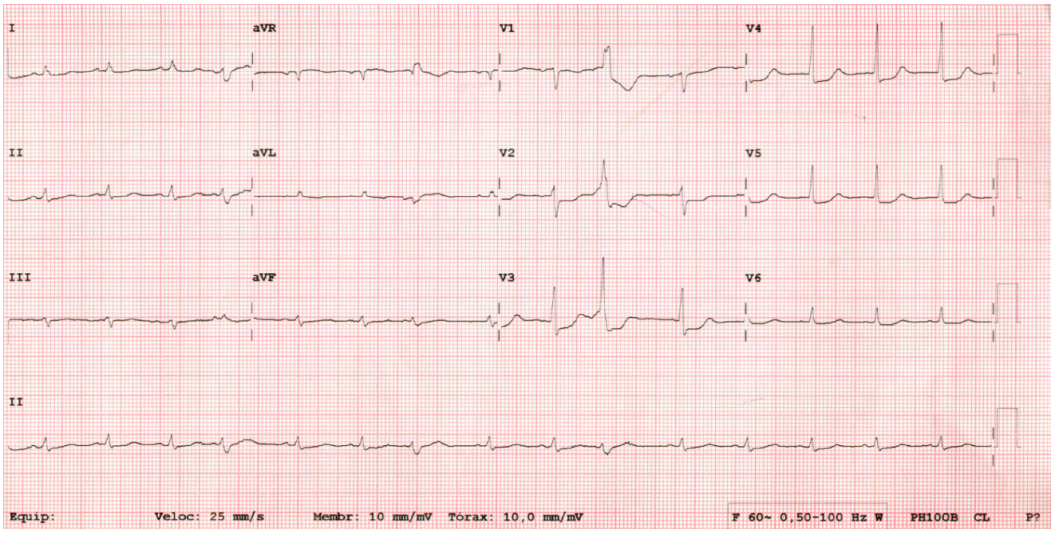

Figure 2 – *Low-voltage electrocardiogram of the QRS complex in the frontal plane and ST-segment depression from V_2 to V_5.*

pressure of 65 mmHg. He evolved with a refractory shock, with mechanical ventilation difficulties and died at 12:05 (March 31st, 2017).

Clinical Aspects

This is a 55-year-old male patient known to have insulin dependent DM and CKD who in February 2017 had a nocturnal episode of dyspnea. Due to the episode, he sought medical care in the emergency room, where changes in markers of myocardial necrosis were identified - increased CKMB and troponin, as well as ST-segment depression from V_2 to V_6 on the ECG. A coronary angiography was performed at the time showing only a 30% lesion in the right coronary artery.

After discharge, the patient developed orthopnea and lower limb edema requiring further hospitalization seven days after discharge. On admission to our service, he presented signs of pulmonary and systemic congestion, the ECG maintained previous parameters, a chest X-ray showed cardiomegaly and massive bilateral pleural effusion, and laboratory tests showed a worsening of renal function and anemia. The transthoracic echocardiogram showed 22% LVEF, through the Simpson method, with diffuse hypokinesia and no segment changes. After this initial evaluation, the following hypothesis was raised for this patient - type 2 AMI and myocarditis. In order to enable a better investigation of the patient´s conditions, propaedeutic complementation was performed. The serologies for Chagas disease and cytomegalovirus were negative. A cardiac resonance showed increased systolic dysfunction in both ventricles with 11% LVEF, with slight left ventricular dilation, increased

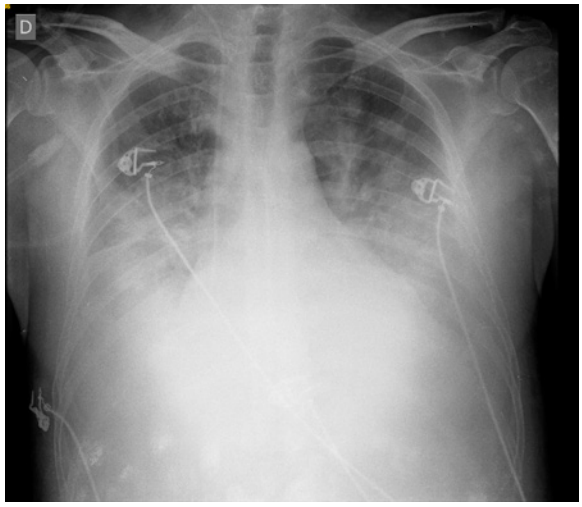

Figure 3 – *Chest X-ray: massive bilateral pleural effusion and cardiomegaly.*

right ventricular dilation, a significant enlargement of the left atrium and an absence of changes in the right atrium. Regarding the enhancement, the patient presented late transmural, circumferential multifocal enhancement, with subendocardial involvement sparing the apex. There was no pericardial effusion, but there was massive bilateral pleural effusion.

During hospitalization, the patient developed pulmonary focal sepsis, with an initial improvement after the introduction of an antimicrobial regimen. Due to the need for infectious treatment, the team decided to postpone endomyocardial biopsy. Despite the improvement of infectious parameters, there was a worsening in renal function and hemodynamic instability. During the entire hospitalization period, the patient maintained a borderline respiratory pattern requiring noninvasive ventilation and right hemithorax drainage to control respiratory symptoms with serohematic secretion drainage. The patient evolved with pulseless electrical activity, reversed after resuscitation for 15 minutes. However, the patient evolved with a refractory shock, which led the patient to die 12 hours after cardiopulmonary arrest.

Due to the diagnostic doubts concerning the case and a lack of improvement after the selected therapy to control the condition, the patient was referred for autopsy with the intention of elucidating the case.

Regarding the clinical evaluation of the case, the main diagnostic hypotheses raised were myocardial infarction and myocarditis, due to the clinical presentation of acute onset heart failure with left ventricular dysfunction. The changes found on magnetic resonance imaging, although not typical, reinforced the maintenance of the initial hypotheses. We describe below information about the two clinical entities evaluated in this clinical case.

According to the fourth universal definition of MI, it consists in an increase in troponin above the 99% associated with at least one of the other factors (typical ischemic symptoms and/or new ECG abnormalities and/or imaging showing a myocardial loss with a pattern of coronary ischemia and/or thrombosis evidenced during the catheterization or autopsy).[1] Myocardial injury does not include the changes described above and can occur in very common events in practice such as: decompensated heart failure, chronic renal failure, shock, anemia, stroke, myocarditis, Takotsubo cardiomyopathy, among others.[1] Among the five types of AMI, type 2 occurs in the presence of an imbalance between oxygen supply and demand, in the absence of atherosclerotic plaque complications. The threshold for this imbalance to occur varies between individuals and is influenced by ongoing stressors, comorbidities (including cardiac and noncardiac), and pre-existing coronary disease.[1] The mechanisms that influence the aforementioned imbalance are diverse and may occur concomitantly, besides being related to atherosclerosis with a reduction of myocardial perfusion and without plaque rupture, coronary spasm, microvascular dysfunction, coronary embolism, coronary dissection, tachyarrhythmias, bradyarrhythmias, hypoxemia, significant anemia, shock.[1]

The prevalence of type 2 AMI is variable in the studies and depends on the type of criteria used.[1] In a real-life study conducted in Sweden with 20,138 patients, 7.1% of AMI hospitalizations were type 2. Patients in this group were older, predominantly female, and had more comorbidities, especially heart failure and atrial fibrillation.[2] In a 2016 study, the main causes of type 2 AMI were - tachyarrhythmias in 36.7%; aortic stenosis in 14.5% and heart failure in 13.7%.[3] Another study observed that approximately 50% of the patients with type 2 AMI had no significant coronary disease.[4]

Regarding the initial evaluation of these patients, the most common symptom presented was dyspnea.[3] In addition, ST segment elevation is known to occur in 3-24% of cases. Coronary atherosclerosis is a common angiographic finding among these patients and, in general, they have a worse prognosis.[1] Please note that angiography is not necessary to establish the diagnosis of type 2 infarction.[1]

The long-term consequences of type 2 AMI are poorly understood. A study published in 2018 evaluated and

Anatomopathological Correlation

Table 1 – Laboratory Exams

Exams	03/23/2017	03/27/2017	03/30/2017	03/31/2017
Hemoglobin, g/dL	11.3	9.4	9.3	8.5
Hematocrit (%)	35	29	27	25
Leukocytes (/mm^3)	9600	16000	9470	10030
Rod cells (%)	n	8	6	
Segmented	n	81	80	
Neutrophils (%)	67	89	86	81
Eosinophils:	2	0	0	0
Basophils (%)	0	0	0	0
Lymphocytes (%)	21	5	9	13
Monocytes (%)	10	6	3	6
Platelets/mm^3	202000	151000	180000	129000
CKMB (ng/mL)	14.5			
Troponin I (ng/mL)	3.65			
Calcium (mg/dL)	8.5		8.5	
Ionic calcium (mMol/L)	1.24			
Phosphorus (mg/dL)			5.1	5.1
Magnesium (mg/dL)	1.8	1.8	2.3	2.4
PCR (mg/L)	3.13	91.39	53.16	48.25
Sodium (mEq/L)	139		138	
Potassium (mEq/L)	4.4		3.2	
Urea (mg/dl)	56	66	131	144
Creatinine(mg/dl)	2.34	2.62	3.46	4.01
Gasometry		venous	artery	
pH		7,36	6.92	
pCO_2 (mmHg)		43.2	56.1	
pO_2 (mmHg)		39.7	59.1	
O_2 saturation (%)		63.2	11	
HCO_3- (mEq/L)		23.9	-22.9	
BE (mEq/l)		-1		
tAP (INR)			2.5	
TTPA (rel)			1.22	
Dimer D (ng/mL)			704	
Fibrinogen (mg/L)			327	
Arterial lactate (mg/dL)		24	134	
AST (U/L)		33		46
ALT (U/L)		37		35
Lactic Dehydrogenase (U/L)				293
Total bilirubins (mg/dL)		0.45		0.67
Direct bilirubin (mg/dL)		0.23		0.34

CKMB: creatinokinase MB; PCR: C reactive protein; BE: base excess; tAP (INR): prothrombin time; TTPA: Partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine transaminase

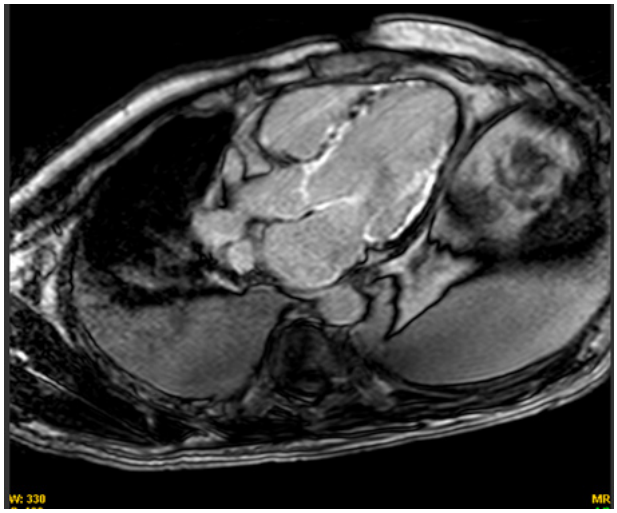

Figure 4 – *4-chamber magnetic resonance imaging - circumferential late enhancement.*

compared outcomes of patients diagnosed with type 1 AMI, type 2 AMI, and myocardial injury and showed that the risk of death was higher among those with a history of type 2 AMI compared to those with a history of type 1 AMI, even after variable adjustment. Most deaths in the first 2 groups were due to noncardiac causes. Regarding major cardiovascular events, there was no difference between the groups. Coronary artery disease was an independent predictor of major cardiovascular events among patients with type 2 AMI or myocardial injury with a 1.71 odds ratio and a confidence index of 1.31-2.24.[5]

Management of type 2 AMI remains uncertain and there are no well-defined clinical management strategies. Initial management should be performed by controlling the precipitating factor that leads to an imbalance in the demand and supply.[6]

Another study published in 2019 showed that almost 30% of the patients in the sample were diagnosed with type 1 AMI when they actually had a type 2 AMI diagnosis.[6]

Regarding myocarditis, it is known that this entity consists of a myocardial inflammatory process with multiple presentation aspects, from asymptomatic presentations to sudden death, including heart failure and fulminant presentations in this spectrum. The etiological agents are diverse, including viral or bacterial, fungal or protozoal infections, hypersensitivity reaction, autoimmune diseases and toxins.[7] Regarding the epidemiological evaluation, it is known that it is an underdiagnosed disease, with a bimodal peak (ranging from 1 year and 20 years) and corresponds to an important cause of cell loss by direct action necrosis of the virus, cytotoxic agents with inflammatory mediators and oxidative stress products.[8] After the initial action process of the immune system, there may be an improvement in conditions, fighting the myocyte aggressive organism and reducing the immune response or persistence of the injury due to persistent aggressive mechanisms or exacerbated immune responses.[9]

In regards to complementary exams, there is usually an increase in inflammatory markers and there may be an increase in myocardial necrosis markers. As for ECG, there may not be changes or changes that are not specific, and the echocardiogram findings may also be variable and include diffuse hypokinesia, pericardial effusion, or segment changes. Magnetic resonance imaging is a fundamental exam, as it presents high sensitivity and specificity for myocardial inflammatory processes, and may show segment changes, regional hypertrophy, dilatation of the cardiac chambers. In the endomyocardial biopsy assessment, the exam has high levels of specificity, with moderate sensitivity. Class I indications by the Brazilian Myocarditis Guideline for biopsy include the IC level for cases lasting up to 2 weeks with no established cause with progressive haemodynamic worsening, and IC for cases beginning less than 3 months ago and more than 15 days after, no definite cause and presenting ventricular arrhythmias or second and third degree atrioventricular blocks.[10]

Regarding treatment, uncomplicated cases do not require specific approaches, only symptomatic management and rest guidelines. Heart failure cases that present decreased ejection fraction require special attention and must receive medications that are known to reduce mortality. Cases requiring antiviral treatment and immunosuppressive therapy need to be evaluated.[10] The prognosis of myocarditis is favorable in most cases. A study published in 2019 showed that 13% of the evaluated patients had a poor evolution.[11] Summarizing, despite raising other hypotheses for the recent onset of IC, the hypothesis of coronary disease is still the main one for this patient due to risk factors, epidemiological context and alteration of complementary exams. **(Dr. Ana Vitória Vitoreti Martins and Dr. José Roberto de Oliveira da Silva Filho)**

Diagnosis hypothesis: Type 2 infarction with heart failure; death from cardiogenic shock. **(Dr. Ana Vitória Vitoreti Martins and Dr. José Roberto de Oliveira da Silva Filho)**

Necropsy

The necropsy showed the presence of myocardial infarction in the final healing phase in all left ventricular walls (Figures 5 and 6).

Anatomopathological Correlation

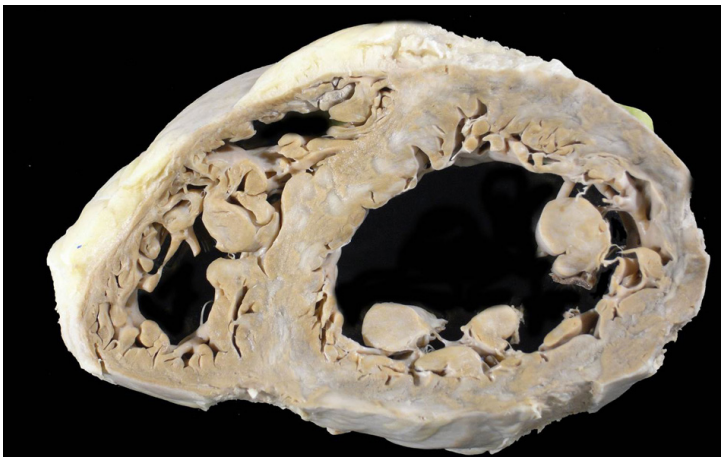

Figure 5 – *Cross section of the heart in the middle portion of the ventricles, showing grayish-white areas that correspond to end-stage infarcts in all left ventricular walls.*

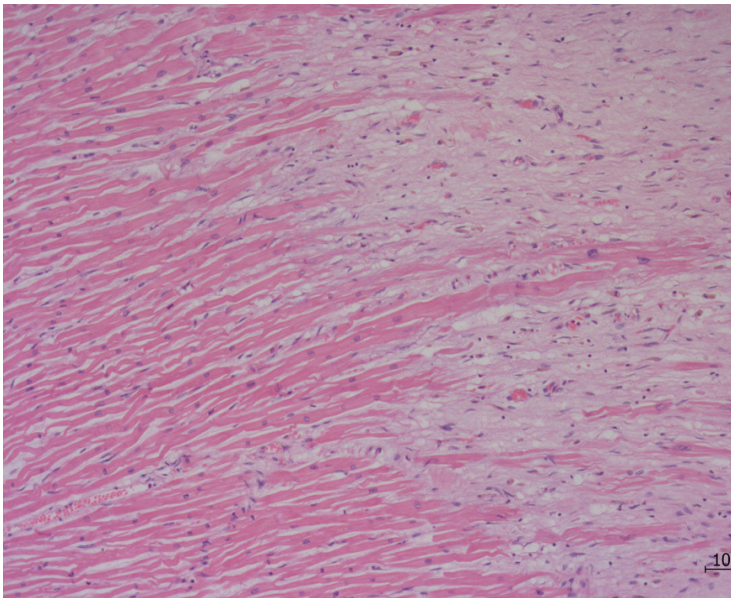

Figure 6 – *Histological section of the left ventricular myocardium showing the boundary between preserved (more rosy, left) myocardium and healing necrosis area. Hematoxylin and eosin coloring; lens magnification: 10x.*

The coronary arteries had atherosclerosis, moderate in the anterior interventricular (anterior descending) and circumflex branches of the left coronary artery (66% maximal obstructions in the first centimeter and 59% in the third centimeter, respectively) and specifically severe in the right coronary artery (77% obstruction in the fourth centimeter). There was no thrombosis or other occlusive lesions (Figure 7).

As the patient had cardiogenic shock, there was a small occipital cerebral infarction with a few days of evolution.

No cavitary lesion or thrombus occluding the left ventricular apex was evidenced.

Lung sections did not show recent bronchopneumonia.

An important finding was pancreatic lipomatosis, with almost complete replacement of exocrine pancreatic tissue by fat, leaving only the islets (Figure 8). **Dr. Paulo Sampaio Gutierrez)**

Anatomopathological diagnoses: Ischemic heart disease, with myocardial infarction in the final stage of healing in all left ventricular walls. Pancreatic lipomatosis. **Dr. Paulo Sampaio Gutierrez)**

"Causa mortis": cardiogenic shock **(Dr. Paulo Sampaio Gutierrez)**

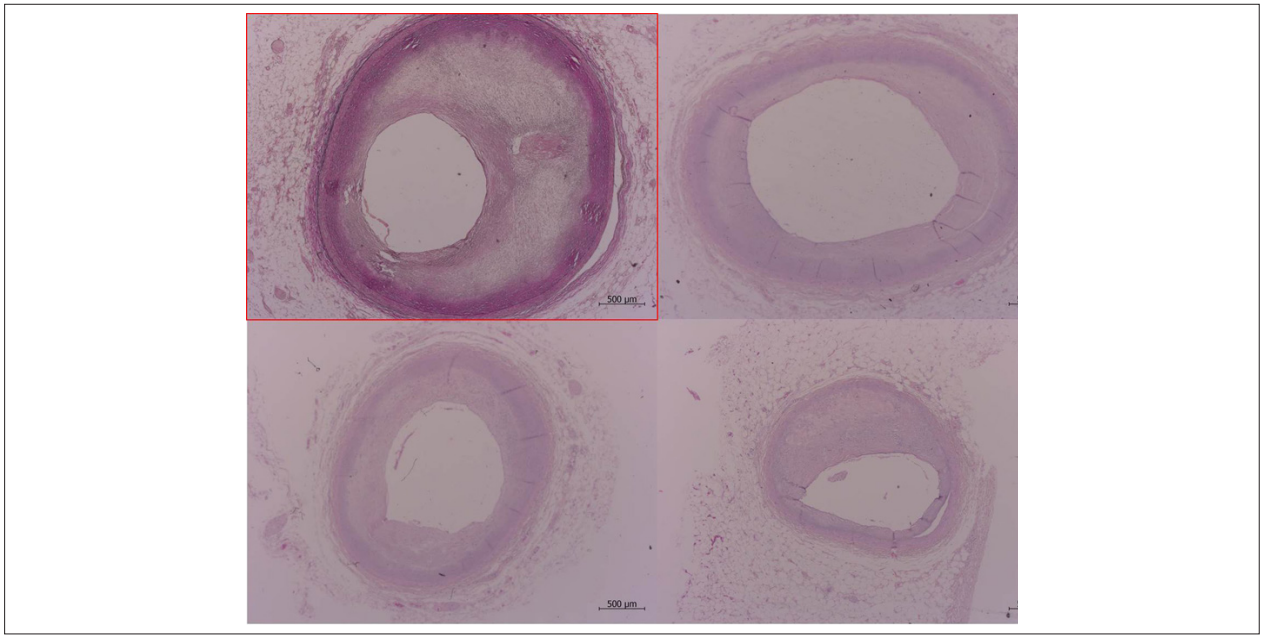

Figure 7 – *Histological sections of coronary artery segments showing moderate and focally severe atherosclerosis (4th centimeter of right coronary artery, 77% obstruction). Right coronary artery CD; Cx: circumflex branch; IVA: anterior interventricular branch (anterior descending); PVI: posterior interventricular branch (posterior descending). Verhoeff coloring for elastic fibers (right coronary artery segment) or hematoxylin and eosin (other segments); lens magnification: 2.5x.*

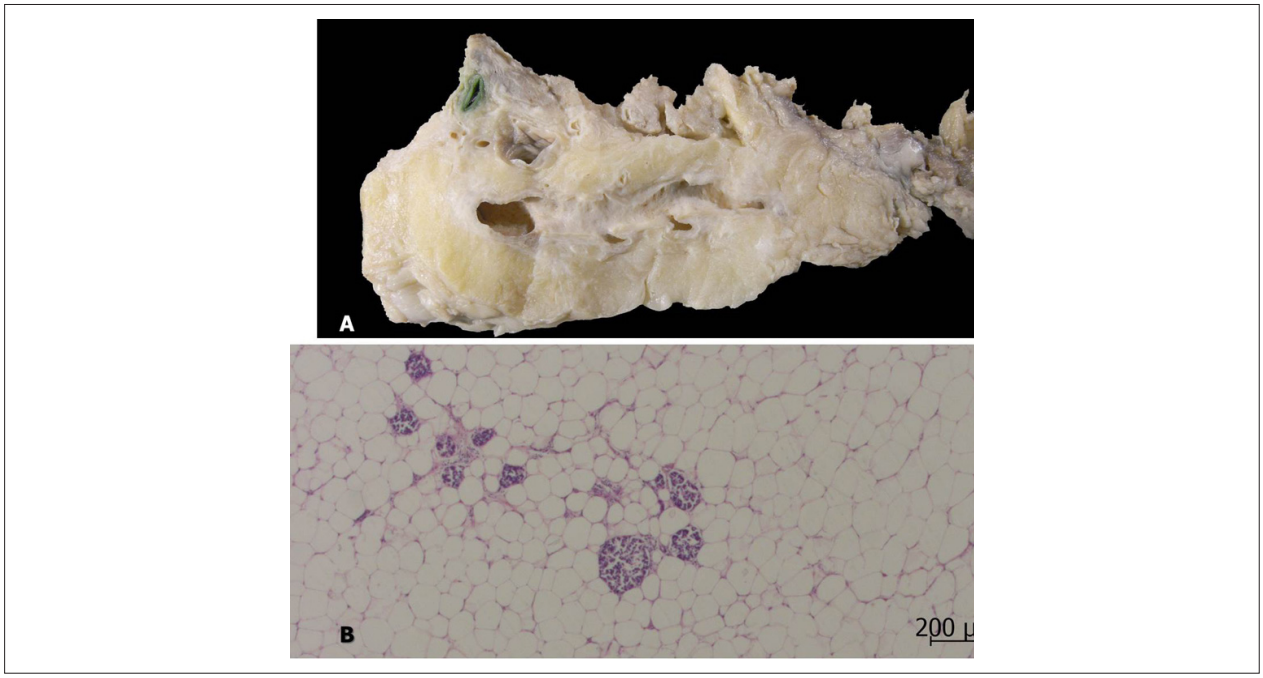

Figure 8 – *Pancreas seen both macroscopically (A) and histologically sectioned (B), hematoxylin and eosin staining, (2.5x objective enlargement) with lipomatosis, replacement of exocrine glands with fatty tissue, with only a few Langerhans islets (endocrine pancreas) left.*

Anatomopathological Correlation

Comment

This is a very unusual case, in which some points were not clarified in the necropsy. The main point concerns the fact that the patient had a lesion with microscopic appearance of a myocardial infarction with an evolution of 4 to 6 weeks, that is, compatible with the clinical history of a sudden onset heart failure, diagnosed with infarction and elevated necrosis. However, the pattern of the lesion was not usual, irregularly affecting all the walls of the left ventricle. Therefore, we came to think of myocarditis and there was no adequate explanation for the occurrence of this ischemic necrosis; Atherosclerosis was only moderate, with a single segment with severe right coronary artery injury, and there were no recent or organizing thrombi. Diabetic patients sometimes have cardiac microcirculatory lesions, but in the present case these were not significant.

Another issue is that the pancreas had its exocrine portion almost completely replaced by fat, with the Langerhans islets left. There are three diagnoses to consider: cystic fibrosis, Schwachman-Diamond syndrome, and carboxyl lipase ester mutations. The former is eliminated due to the absence of cysts, whether in the pancreas, lungs or other organs. Schwachman-Diamond syndrome mainly affects young children. Therefore, the patient will most likely carry a carboxyl lipase ester mutation, which may even be responsible for delayed onset juvenile diabetes, as was the case with this patient, and influence the development of atherosclerosis.[12-15] **(Dr. Paulo Sampaio Gutierrez)**

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Myocarditis Following Recent Chikungunya and Dengue Virus Coinfection: A Case Report

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Introduction

Dengue virus (DENV) and chikungunya virus (CHIKV) are arboviruses that cause ongoing epidemics in several countries of Latin America. DENV belongs to the *Flaviviridae* family and CHIKV is an alphavirus of the *Togaviridae* family. Both viruses are transmitted by mosquitoes of the genus *Aedes* (mainly *Aedes aegypti* and *Aedes albopictus*) and during the acute phase they may cause similar nonspecific febrile syndromes that can progress to severe or debilitating conditions.[1,2]

DENV infection has been endemic in Brazil since the 1980's. However, CHIKV is an emergent agent. Autochthonous transmission was first detected in September 2014 in the city of Oiapoque, Amapá state. Since then, there have been thousands of autochthonous cases in the country.[3] A total of 38,499 and 277,882 cases of suspected CHIKV infection were reported by the national surveillance system in 2015 and 2016, respectively. In 2017, a total of 185,369 suspected cases were reported until December 9. Ceará (1,271 cases/100,000 inhabitants) and Roraima (789 cases/100,000 inhabitants) have the highest incidence among the Brazilian Federation states.[4] Coinfections with these two viruses have been reported and the overall effect on the heart is still unknown.[5-7] There have been some reports of myopericarditis following DENV and CHIKV infection, but this manifestation in coinfected patients is rare and few data are available.[8-10]

The aim of this report is to present a case of a young and immunocompetent man with myocarditis, following a recent DENV and CHIKV coinfection. We discuss the clinical course and laboratory abnormalities of this rare condition, along with its successful management in an infectious disease specialized center, highlighting the importance of being aware of this condition in developing countries endemic for DENV and CHIKV.

Case report

The patient was a 28-year-old male, resident in Fortaleza, Ceará State and was admitted in the emergency room of São José Hospital of Infectious Diseases in May 2017. The symptoms had started 5 days prior to admission with fever, adynamia, myalgia, and worsening of general condition. He denied retroorbital pain, bleeding phenomena or abdominal pain. He had taken no medications in the previous year and had not traveled outside of Brazil. There was no previous history of cardiopathies.

Upon the initial examination, the Glasgow Coma Scale (GCS) score of the patient was E4 V5 M6. He had a heart rate of 120 beats per minute and had hypotension (70/40 mm of Hg). There was no heart murmur or pericardial rub and his pulmonary examination was unremarkable. The skin showed no rashes, and there were no petechiae or jaundice.

The electrocardiogram (EKG) showed supraventricular tachycardia (230 bpm) not responsive to intravenous adenosine. An electric cardioversion was performed and successfully restored the normal heart rhythm. A new EKG was performed showing ST elevation with upper concavity and PR segment depression in DII, DIII and aVF, such as ST depression in V1 and aVR. The patient was then admitted to the intensive care unit. His laboratory parameters are described in Table 1. A first transthoracic echocardiogram revealed an altered left ventricular ejection fraction (EF) (43%), left ventricular hypercontractility, and mild bilateral pericardial and pleural effusions (Figure 1). After 5 days, a new echocardiogram was performed, revealing a 36.4% EF, as well as diffuse hypokinesia and moderate pericardial effusion.

Dobutamine (2.9 mcg/Kg/min) IV was initiated and maintained for 4 days and a single dose of 400 mg of hydrocortisone IV was administered. Treatments with immunoglobulin IV or colchicine were not considered. Paired blood cultures were negative for pyogenic agents. Antibiotics were not used.

Serologies for coxsackie virus, rubella, Chagas disease, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus (EBV), toxoplasmosis, hepatitis B virus and hepatitis C virus were negative. The patient's serum samples were tested and found to be ELISA-IgM positive and ELISA-IgG positive for DENV and ELISA-IgM positive for CHIKV. The DENV NS1 antigen test yielded a negative result. There was a good response to therapy and the patient progressed with gradual improvement until recovery of ventricular function. After 11 days, a last echocardiogram showed an EF of 70% and persistence of pericardial effusion. The patient was discharged from the hospital 11 days after admission. Table 1 shows laboratory results during hospital stay.

Keywords

Myocarditis; Coinfection; Dengue; Chikungunya Virus.

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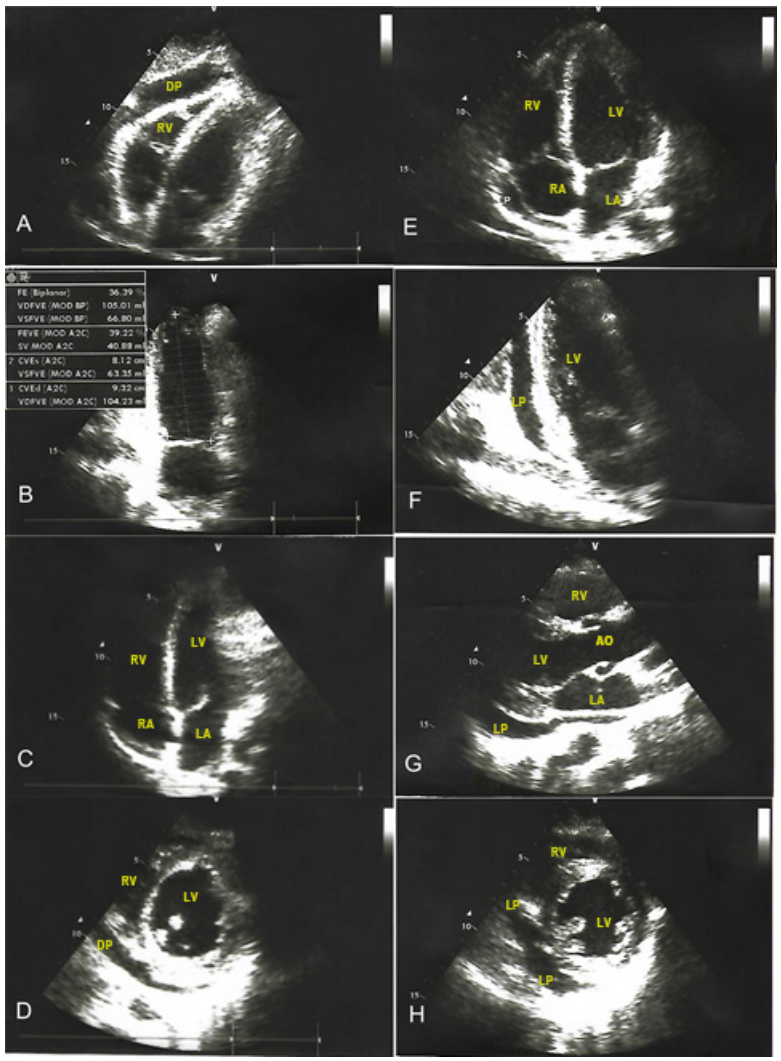

Figure 1 – *Transthoracic echocardiogram with altered left ventricular ejection fraction (36.39%), left ventricular hypercontractility, and mild bilateral pericardial effusion (A-D). E-H shows a second transthoracic echocardiogram with ejection fraction of 70%. DP and LP: pericardial effusion. RV: right ventricle; LV: left ventricle; RA: right atrium; LA: left atrium; EF: ejection fraction.*

Discussion

Typical clinical manifestations of acute CHIKV infection are fever, headache, polyarthralgia/polyarthritis, myalgia, rash, and fatigue.[11] Atypical manifestations have also been described, affecting the cardiovascular, nervous, ocular, cutaneous, and other systems.[6,12-14] The clinical spectrum of chikungunya heart disease ranges from asymptomatic ECG alterations to potentially lethal cardiac complications.[6]

The manifestations of acute DENV infection are very similar to those of CHIKV, with a lower prevalence for joint manifestations.[15] Heart involvement in DENV infection is not uncommon. Cardiac manifestations can vary widely, from silent disease to severe myocarditis resulting in death.[7] Arora et al.[7] studying 120 patients with DENV found 37.5% of patients with cardiac manifestation in the form of myocarditis and 5% with rhythm disturbance, with AV block being the most common.[16]

The specific viral diagnosis is commonly made through ELISA, a specific serological test.[11,15] In cases of DENV, secretion of the NS1 non-structural viral protein from infected cells makes an early diagnosis possible. NS1 protein can be detected in blood and tissue samples within 9 days of the onset of fever.[15]

There is a low probability that the patient had an isolated viral infection since both viruses are part of different viral families, thus considerably reducing the cross-reaction probability. Kam et al.[17] found that 6% of DENV-infected patients had antibodies that were cross-reactive to CHIKV.[17] Although they share the same vector, CHIKV is part of the *Togaviridae* family, while DENV is part of the *Flaviviridae* family.

Heart disease associated with arboviruses has no specific treatment and may be a self-limited condition. Thus, quick supportive therapy to prevent further cardiac function

Table 1 – Laboratory results during hospital stay of a patient with myocarditis and coinfection with dengue virus and Chikungunya virus

Characteristic	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Hemoglobin, g/dL	18.6	17.2	15.7	15.4	14.4	13.6	12.6	12.9	12.7	14.1	13.9
Hematocrit, %											
WBC count, x10^3/mm^3	12.5	17.4	19.6	18	14	11.1	9.4	8.1	6	6.1	6.7
Polymorphs, %											
Lymphocytes, %											
Lymphocyte count, x10^9/L	1.5	1.57	1.76	1.26	1.4	1.78	1.22	1.37	1.45	1.83	2.29
Platelet count, x10^9/l	135	122	158	177	182	169	160	156	164	199	207
Creatinine level, mg/dL	1.51	1.65	1.52	1.69	1.42	1.32	1.23	1.29	1.04	1.02	1.23
CRP levels, mg/dl	0.89	0.99	0.45	0.35	0.25	0.43	0.53	0.52	0.31	0.21	0.14
Serum Lactate level mmol/l	11.4	4.5		2.4							
NT-proBNP, pg/mL	32692	20858	14543	13832							
LDH, IU/L	522	1371		360							
ESR, mm	3			2							
CK level, U/L	1306		347								
Troponin I, ng/mL	1.05	0.5	0.47								
INR	1.56	1.73		1.51			1.26	1.19	1.14		1.12

WBC: White Blood Cell; CRP: C - Reactive Protein; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; LDH: Lactate Dehydrogenase; ESR: Erythrocyte Sedimentation Rate; CK level: Creatine Kinase level; INR: International Normalized Ratio.

loss and cardiogenic shock is still the most recommended management.[6] There is also evidence that IV hydrocortisone may be helpful to accomplish full recovery in DENV myocarditis[18] but there is yet no consensus about whether this drug should be used in this setting or if it has a real impact on recovery and mortality rates, even more in cases of combined arbovirus infection. Although arbovirus myocarditis is an acute condition, most patients persist chronically with cardiac disease, such as chronic heart failure and ECG T-wave changes.[16,19] The role of coinfection in the severity of arbovirus cardiac manifestations is not currently known, but studies regarding other symptoms showed that it might contribute to a more severe disease.[6,7,20] It is also noteworthy that the herein described myocarditis may have been caused solely by the CHIKV, since the NS1 protein test yielded a negative result. It is also important to note that the DENV IgM may be positive from 139 up to 179 days, respectively for secondary and primary infections.[21]

The present study has limitations. Polymerase chain reaction (PCR) was not available for the etiological diagnosis. The degree of myocardial impairment was not assessed by Magnetic Resonance Imaging (MRI). Although reported by other authors,[8,9] MRI was not available at our center.

Conclusion

The case presented herein suggests that DENV and CHIKV coinfection may result in myocarditis, which can be severe and may be possibly reverted with supportive therapy and correct management of cardiac function. Nevertheless, the correct etiopathogenesis of the cardiac disorder is undefined and the disease may be caused solely by either the DENV or CHIKV virus. It is important to be aware of this possible complication of arboviruses mainly in endemic areas.

Author contributions

Conception and design of the research: Farias LABG, Beserra FLCN, Fernandes L, Teixeira AAR, Girão ES, Pires Neto RJ; Acquisition of data: Farias LABG, Beserra FLCN, Fernandes L, Teixeira AAR, Ferragut JM, Pires Neto RJ; Analysis and interpretation of the data: Ferragut JM, Girão ES, Pires Neto RJ; Statistical analysis: Pires Neto RJ; Writing of the manuscript: Farias LABG, Beserra FLCN, Fernandes L, Teixeira AAR, Pires Neto RJ; Critical revision of the manuscript for intellectual content: Ferragut JM, Girão ES, Pires Neto RJ.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de São José de Doenças Infecciosas under the protocol number 2.405.527. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019

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Note: The purpose of these Guidelines is to inform. They do not substitute the clinical judgment of doctors who, in final analysis, must determine which tests and treatments are appropriate for their patients.

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In this update, grade of recommendations and level of evidence were applied in accordance with the following standards:

	Grade of recommendation
Grade I	Conditions for which there is conclusive evidence or, in the absence of conclusive evidence, general consensus that the procedure is safe and useful/effective
Grade IIa	Conditions for which there are conflicting evidence and/or divergent opinions regarding the procedure's safety and usefulness/effectiveness. Weight or evidence/opinion in favor of the procedure. The majority of studies/experts approve.
Grade IIb	Conditions for which there are conflicting evidence and/or divergent opinions regarding the procedure's safety and usefulness/effectiveness. Safety and usefulness/effectiveness less well established, with no prevailing opinions in favor.
Grade III	Conditions for which there is evidence and/or consensus that the procedure is not useful/effective and may, in some cases, be potentially harmful

	Level of evidence
Level A	Data obtained from multiple concordant large randomized trials and/or robust meta-analysis of randomized clinical trials
Level B	Data obtained from less robust meta-analysis, from a single randomized trial, or from non-randomized (observational) trials
Level C	Data obtained through consensus of expert opinion

Declaration of potential conflict of interest of authors/collaborators of the Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019 If the last three years the author/developer of the Statement:

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Content

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and in Brazil, leading to increased morbidity and disability-adjusted life year (DALY). Despite the decrease in mortality rates and DALY standardized by age in Brazil, possibly as a result of successful health policies, their total number is increasing, mainly due to aging and illnesses in the population.[1]

Classical risk factors (hypertension, dyslipidemia, obesity, sedentary lifestyle, smoking, diabetes, and family history) raise the pre-test probability of CVD – particularly of coronary artery disease (CAD) – and determine primary and secondary prevention. Several other factors, including sociodemographic, ethnic, cultural, dietary, and behavioral aspects, can also explain the differences in CVD burden among populations and their trends over the decades. The implementation of health policies, among them, encouraging healthy lifestyle habits and providing access to primary and secondary CVD prevention measures, associated with the treatment of cardiovascular (CV) events are essential to control CVD in all countries, including Brazil.

The I Brazilian Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia* – SBC), published in 2013,[2] aimed at helping reduce CV mortality, as established by the World Health Assembly in May 2012; SBC reaffirmed its commitment to decreasing the premature CVD mortality rate by 25%.[3] However, the reduction in CVD mortality has reached a plateau in the past five years in Brazil, with significant regional variation, suggesting the need for renewing strategies to combat these diseases.[4] With this purpose, SBC revisited its CV prevention guideline,[2] proposing to update themes related to the primary prevention of CVD and suggesting strategies that could assist Brazilian cardiologists in reducing morbidity and mortality from these groups of causes.

The Brazilian Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019 updates the strategies that address classical risk factors and discusses new concepts, such as the need to gather knowledge about emerging risk factors – for instance, spirituality –, socioeconomic and environmental factors, as well as additional strategies, like the use of vaccines.

We hope to contribute to renew the SBC commitment with the Brazilian society and the Strategic Action Plan for tackling Chronic Non-Communicable Diseases (NCD),[5] of which CVD is the main component, with an instrument that will allow systematized access to the current literature, disseminating the knowledge necessary to resume the decreasing trend in CV mortality in Brazil.

1. Risk Stratification

1.1. Cardiovascular Risk Stratification to Prevent and Treat Atherosclerosis

The first manifestation of atherosclerotic disease in approximately half of the people who have this complication is an acute coronary event. Therefore, identifying asymptomatic individuals with higher predisposition is crucial for effective prevention associated with the correct definition of therapeutic targets. The so-called risk scores and algorithms based on regression analysis of population studies were created to estimate the severity of CVD, substantially enhancing the identification of overall risk. The Framingham gloal risk score (GRS)[6] included the estimate of 10 years of coronary and cerebrovascular events, peripheral arterial disease, or heart failure (HF) and was the score adopted by the Department of Atherosclerosis of SBC (*Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia* – SBC-DA).[7]

In addition, individuals who have multiple risk factors for CV, subclinical atherosclerosis, or already had manifestations of CVD have a high risk for events and can be classified differently.

Thus, the new CV risk stratification proposed by the SBC-DA defines four levels of CV risk:

- Very high risk
- High risk
- Moderate risk
- Low risk

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Strategies for primary or secondary prevention of the disease are proposed based on the characterization of CV risk.

1.2. Very High Risk

Individuals who have a significant atherosclerotic disease (coronary, cerebrovascular, or peripheral vascular) with or without clinical events belong to this category (Chart 1.1).

1.3. High Risk

Patients in primary prevention who present ORS > 20% (men) or > 10% (women) or aggravating risk conditions based on clinical data or subclinical atherosclerosis (Chart 1.2).

Chart 1.1 – Individuals with very high cardiovascular risk according to the Department of Atherosclerosis of the Brazilian Society of Cardiology[7]

Significant atherosclerosis (≥ 50% obstruction) with or without clinical events in the following territories
• Coronary
• Cerebrovascular
• Peripheral vascular

Chart 1.2 – Individuals with high cardiovascular risk according to the Department of Atherosclerosis of the Brazilian Society of Cardiology[7]

- Men with overall risk score > 20%
- Women with overall risk score > 10%
- Subclinical atherosclerosis documented by:
  - Carotid ultrasound with the presence of plaque
  - ABI < 0.9
  - CACS > 100 Agatston U
  - Atherosclerotic plaques in coronary computed tomography angiography
- Abdominal aortic aneurysm
- CKD defined by Glomerular Filtration Rate < 60 mL/min in the non-dialysis stage
- Patients with LDL-c ≥ 190 mg/dL
- Type 1 or 2 diabetes, with LDL-c between 70 and 189 mg/dL, and presence of RS* or SAD**

*ABI: Ankle-Brachial Index; CACS: Coronary Artery Calcium Score; CKD: chronic kidney disease; LDL-c: low-density lipoprotein-cholesterol; RS: Risk Stratifiers; SAD: Subclinical Atherosclerotic Disease. * Age ≥ 48 years in men and ≥ 54 years in women; time to diabetes diagnosis > 10 years; family history of premature CVD (< 55 years for men and < 65 years for women) in first degree relative; smoking (at least one cigarette in the previous month); systemic arterial hypertension; metabolic syndrome, according to the International Diabetes Federation; albuminuria > 30 mg/g creatinine and/or retinopathy; glomerular filtration rate < 60 mL/min. ** Carotid ultrasound with presence of plaque > 1.5 mm; ABI < 0.9; coronary calcium score > 10 Agatston units; atherosclerotic plaques in coronary computed tomography angiography; LDL-c between 70 and 189 mg/dL, with overall risk score > 20% for males and > 10% for females.*

1.4. Moderate Risk

The estimated risk for atherosclerotic disease results from the sum of the risk associated with each risk factor and the powering caused by synergisms between some of these factors. Given the complexity of these interactions, intuitive risk allocation often leads to under- or overestimation of higher or lower risk cases, respectively. Among the algorithms created to stratify CV risk, the last Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention recommends the use of ORS, which estimates the risk for myocardial infarction, cerebrovascular accident (CVA), HF – fatal or non-fatal –, or peripheral vascular insufficiency in 10 years.

Based on this score, individuals with GRS ranging from 5 to 20% (males) and 5 to 10% (females) are classified as moderate risk. Patients with diabetes mellitus (DM) without SAD criteria or RS are also considered at moderate risk. Many middle-aged individuals belong to this risk category (Chart 1.3). Part of the latest recommendations leans towards inflammatory conditions and the use of coronary calcium to restratify patients at moderate risk.[8]

1.5. Low Risk

Any estimated CV risk based on findings of observational studies inevitably has limitations related to calibration and discriminatory power: the attempt to allocate a certain risk percentage to each patient collides with individual aspects, not covered by risk prediction equations. The idea of restoring the concept of aggravating risk – understood as individual phenotypic expressions causally related to greater chances of a CV outcome – to improve somewhat the individualization of the algorithms created from large population samples has been gaining strength.[8] However, in the low-risk population stratum, an aggravating risk in those with less than 5% chance of having a CV outcome in 10 years[6,8] would hardly have a decisive influence in this relatively short time interval. On the other hand, as age is one of the most important determinants of risk for CV events, a man aged 62 years, without SAD, normotensive, non-smoker, non-diabetic, and with optimal levels of serum lipids would already be classified by ORS as moderate risk, even without any aggravating factor.[6]

Chart 1.3 – Moderate Risk according to the Department of Atherosclerosis of the Brazilian Society of Cardiology

- Male patients with GRS from 5 to 20%
- Female patients with GRS from 5 to 10%
- Diabetic patients without RS* or SAD** factors

*GRS: overall risk score; RS: risk stratifiers; SAD: subclinical atherosclerotic disease. * Age ≥ 48 years in men and ≥ 54 years in women; time to diabetes diagnosis > 10 years; family history of premature CVD (< 55 years for men and < 65 years for women) in first degree relative; smoking (at least one cigarette in the previous month); systemic arterial hypertension (SAH); metabolic syndrome, according to the International Diabetes Federation; albuminuria > 30 mg/g creatinine and/or retinopathy; glomerular filtration rate < 60 mL/min. ** Carotid ultrasound with presence of plaque > 1.5 mm; ABI < 0.9; coronary calcium score > 10 Agatston units; atherosclerotic plaques in coronary computed tomography angiography; LDL-c between 70 and 189 mg/dL, with ORS > 20% for males and > 10% for females.*

Therefore, adults considered at low CV risk are those aged 30 to 74 years, of both genders, whose risk for CV events calculated by GRS is lower than 5% in 10 years[6,7] (Chart 1.4).

Although the calcium score is not recommended for low-risk patients, non-diabetic individuals at moderate risk, without a family history of premature coronary disease, who have a zero calcium score can be considered at low risk and postpone the start of the cholesterol-lowering therapy with statins.[8]

Aggravating risk factors are not used in patients considered at low CV risk. The North American guideline of 2018 considers restratifying moderate risk to low in patients with zero calcium score (non-diabetics and without a family history of premature coronary disease).[8]

Charts 1.5, 1.6, 1.7, and 1.8 present the GRS for men and women in 10 years.

Chart 1.4 – Patients at low cardiovascular risk according to the Department of Atherosclerosis of the Brazilian Society of Cardiology[7]

- Men with an overall risk score < 5%
- Women with an overall risk score < 5%

Table 1.1 summarizes the recommendations for cardiovascular risk stratification.

Chart 1.6 – Overall risk for women in 10 years[2]

Score	Risk (%)	Score	Risk (%)
≤ -2	< 1	13	10.0
-1	1.0	14	11.7
0	1.2	15	13.7
1	1.5	16	15.9
2	1.7	17	18.5
3	2.0	18	21.6
4	2.4	19	24.8
5	2.8	20	28.5
6	3.3	21+	> 30
7	3.9		
8	4.5		
9	5.3		
10	6.3		
11	7.3		
12	8.6		

Chart 1.5 – Score according to overall risk for women[2]

Score	Age (years)	HDL-c	TC	SBP (untreated)	SBP (treated)	Smoking	Diabetes
-3				< 120			
-2		60+					
-1		50-59			< 120		
0	30-34	45-49	< 160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	< 35		140-149	120-139		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

HDL-c: high-density lipoprotein-cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

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Chart 1.7 – Score according to overall risk for men[2]

Score	Age (years)	HDL-c	TC	SBP (untreated)	SBP (treated)	Smoking	Diabetes	
-2		60+		< 120				
-1		50-59						
0	30-34	45-49	< 160	120-129	< 120	No	No	
1		35-44	160-199	130-139				
2	35-39	< 35	200-239	140-159	120-139			
3			240-279	160+	130-139		Yes	
4			280+		140-159	Yes		
5	40-44				160+			
6	45-49							
7								
8	50-54							
9								
10	55-59							
11	60-64							
12	65-69							
13								
14	70-74							
15	75+							
Score								Total

HDL-c: high-density lipoprotein-cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Chart 1.8 – Overall risk for men in 10 years[2]

Score	Risk (%)	Score	Risk (%)
≤ -3	< 1	13	15.6
-2	1.1	14	18.4
-1	1.4	15	21.6
0	1.6	16	25.3
1	1.9	17	29.4
2	2.3	18+	> 30
3	2.8		
4	3.3		
5	3.9		
6	4.7		
7	5.6		
8	6.7		
9	7.9		
10	9.4		
11	11.2		
12	13.2		

Table 1.1 – Recommendations for cardiovascular risk stratification

Recommendation	Recommendation grade	Level of evidence	Reference
Routine evaluation of cardiovascular risk factors in adults aged 40 to 75 years, according to GRS for 10 years (Charts 1.5, 1.6, 1.7, 1.8; Figure 1.1)	I	B	2,9,10
Routine evaluation of cardiovascular risk factors in adults aged 20 to 39 years, according to GRS for each 4 to 6 years (Charts 1.5, 1.6, 1.7, 1.8; Figure 1.1)	IIa	B	2,9,10
For adults with borderline (5 to < 7.5%/10 years) or moderate (≥ 7.5 to < 20%/10 years) risk, including aggravating factors is recommended to guide therapeutic decisions	IIa	B	2,9,10
Adults with borderline (5 to < 7.5%/10 years) or moderate risk (≥ 7.5 to < 20%/10 years) can have their calcium score assessed to guide therapeutic decisions	IIa	B	2,9,10
The risk to life or for 30 years can be considered in adults aged 20 to 59 years with an estimated risk < 7.5%/10 years	IIb	B	2,9,10

GRS: global risk score.

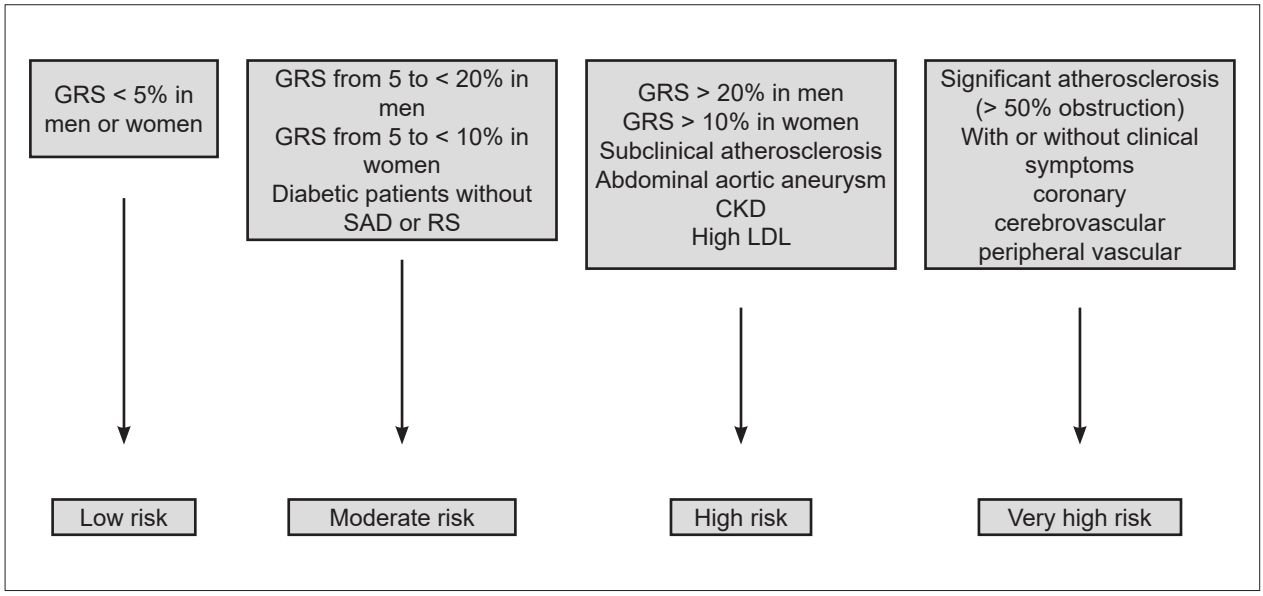

Figure 1.1 – *Cardiovascular risk stratification. CKD: chronic kidney disease (glomerular filtration rate < 60 ml/min/m², non-dialysis); GRS: global risk score; RS: risk stratifiers; SAD: subclinical atherosclerotic disease.*

2. Dyslipidemia

2.1. Introduction

Dyslipidemias represent an important CV risk factor, with low-density lipoprotein cholesterol (LDL-c) as the most relevant modifiable risk factor for CAD.[11] Genetic[12] and clinical studies with statins and other lipid-lowering drugs provide ample evidence that lower LDL-c levels are associated with the proportional decrease in CV outcomes, including myocardial infarction, CVA, and CV death.[13,14]

The 2017 Updated Brazilian Guideline for Dyslipidemia incorporated some changes in the approach of dyslipidemias compared to the previous version.[7] One of the changes was that fasting was no longer mandatory for total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c) tests, provided that the laboratory specifies the situation in the report, without fasting or with 12-hour fasting. As for triglycerides (TG), it might increase in the absence of fasting. In hypertriglyceridemia, particularly with a value > 440 mg/dL, a new collection after 12-hour fasting is crucial.[15] Apolipoprotein (ApoA1 and ApoB) levels can be determined in a sample without prior fasting, and moderately high TG levels do not influence immunochemical methods. The analytical performance of this methodology is good, and the levels can be measured in automated platforms with an immunoturbidimetry or nephelometry profile.

There is evidence of an independent association between elevated lipoprotein (a) [Lp(a)] and CVD risk in the general population,[16] not only for the lipid content of Lp(a) but also for its prothrombotic and proinflammatory properties. The gold standard for quantification of plasma concentrations is the measurement of Apo(a) mass by turbidimetry, nephelometry, or chemiluminescence, using isoform-insensitive assays, which

are little affected by the heterogeneity in Apo(a) isoforms. It does not require fasting and provides accurate data. Its analysis is not recommended for routine assessment of CVD risk in the general population, but it should be determined in the risk stratification of individuals with a family history of premature atherosclerotic disease and familial hypercholesterolemia (FH).[7] Lp(a) values above 50 mg/dL, equivalent to 80%, are considered high; if the result is in nmol/L, it should be multiplied by 2.5, with Lp(a) values above 125 nmol/L classified as high.[7]

Table 2.1 reports the reference values of the lipid profile with and without fasting, according to the evaluation of CV risk in adults.

The primary (LDL-c) and secondary (non-high-density lipoprotein cholesterol – non-HDL-c) therapeutic targets for lipid control are established following the risk stratification of patients (discussed in Chapter 1). This stratification considers the presence or absence of clinical or subclinical atherosclerotic disease, the presence of diabetes, and the GRS, with subsequent risk classification into four possible categories: low (< 5%), moderate (5-10% in women and 5-20% in men), high (> 10% in women and > 20% in men), and very high (clinical atherosclerotic cardiovascular disease, > 30%) risk. Chapter 1 presents the complete risk stratification. Specific targets for each category were defined in accordance with Table 2.1.[7]

The Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention[7] also included a change in CV risk stratification for individuals already using statins. Considering the imprecision of risk calculation in these patients, the guideline proposes using a correction factor for TC to estimate the risk score in this context, derived from studies that compared the efficacy of different statins in the doses used and that allowed an average LDL-c reduction of ~ 30% with the treatment.[17] This situation applies to most patients who take moderate doses of statins. Given the average TC reduction of 30% with statins, patients who use these medicines should have their TC multiplied by 1.43.[17] Moreover, in the initial approach, the target for individuals who are not on lipid-lowering treatment should be decreasing the percentage of LDL-c and non-HDL-c. For those already on lipid-lowering therapy, the recent guideline also established a reduction in absolute LDL-c and non-HDL-c values with the treatment, as shown in Table 2.2.

2.1.1. Familial Hypercholesterolemia

FH is a genetic condition characterized by very high LDL-c levels and, therefore, increased risk for premature atherosclerotic disease, especially of a coronary event. However, despite its importance, this condition is still underdiagnosed and undertreated.[18,19] This version of the guideline reinforces that greatly increased cholesterol values could indicate FH, after excluding secondary dyslipidemias. Adult individuals with TC values ≥ 310 mg/dL or children and adolescents with levels ≥ 230 mg/dL should be evaluated for this possibility. Among the clinical scores available for FH, we highlight the Dutch Lipid Clinic Network score, used in our field, and presented in Table 2.3. In addition to clinical scores, the genetic test for FH is a very useful, but not mandatory, tool to confirm suspected cases and screen relatives of established index cases.

2.2. Dyslipidemia Treatment

2.2.1. Non-Pharmacological Therapy

Nutritional therapy, weight loss, and the practice of physical activity should be recommended for all patients. Table 2.4 describes the dietary recommendations for the treatment.

2.2.2. Drug Treatment Focused on Hypercholesterolemia

Statins are the first treatment choice for hypercholesterolemia, due to the evidence showing that their use decreases all-cause

Table 2.1 – Reference values, according to the evaluation of cardiovascular risk estimated for adults over 20 years of age

Lipids	With fasting (mg/dL)	Without fasting (mg/dL)	Risk category
Total cholesterol	< 190	< 190	Desired
HDL-c	> 40	> 40	Desired
Triglycerides	< 150	< 175	Desired
LDL-c*	< 130	< 130	Low
	< 100	< 100	Moderate
	< 70	< 70	High
	< 50	< 50	Very high
Non-HDL-c	< 160	< 160	Low
	< 130	< 130	Moderate
	< 100	< 100	High
	< 80	< 80	Very high

*HDL-c: high-density lipoprotein-cholesterol; LDL-c: low-density lipoprotein-cholesterol. * LDL-c values calculated by the Martin formula.[7,15] Adapted from the Updated Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]*

Table 2.2 – LDL-c and non-HDL-c percentage reduction and absolute therapeutic targets in patients who use and do not use lipid-lowering drugs

Risk	Without lipid-lowering drugs	With lipid-lowering drugs	
	Reduction (%)	LDL-c target (mg/dL)	Non-HDL-c target (mg/dL)
Very high	> 50	< 50	< 80
High	> 50	< 70	< 100
Moderate	30-50	< 100	< 130
Low	> 30	< 130	< 160

LDL-c: low-density lipoprotein-cholesterol; non-HDL-c: non-high-density lipoprotein-cholesterol. Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]

Table 2.3 – Diagnostic criteria for familial hypercholesterolemia (based on the Dutch Lipid Clinic Network criteria – Dutch MEDPED)

Parameter	Score
Family history	
First degree relative with premature vascular/coronary disease (men < 55 years, women < 60 years) OR	
First or second degree relative with TC > 290 mg/dL*	1
First degree relative with tendon xanthoma and/or corneal arcus OR	
First degree relative < 16 years with TC > 260 mg/dL*	2
Clinical history	
Patient with premature CAD (men < 55 years, women < 60 years)	2
Patient with premature cerebral or peripheral arterial disease (men < 55 years, women < 60 years)	1
Physical examination	
Tendon xanthoma	6
Corneal arcus < 45 years	4
LDL-c Levels (mg/dL)	
≥ 330 mg/dL	8
250 - 329 mg/dL	5
190 - 249 mg/dL	3
155 - 189 mg/dL	1
DNA analysis	
Functional mutation in the LDL receptor, the ApoB100, or the PCSK9* gene	8
FH diagnosis	
Confirmed if	> 8 points
Potential if	6 - 8 points
Possible if	3 - 5 points
Not FH	< 3 points

*CAD: coronary artery disease; DNA: deoxyribonucleic acid; FH: familial hypercholesterolemia; LDL-c: low-density lipoprotein-cholesterol; TC: total cholesterol. * Modified from the Dutch MEDPED, adopting a criterion from the Simon Broome Register Group proposal. Adapted from the Updated Guideline for Dyslipidemia and Atherosclerosis Prevention (5) and the I Brazilian Guidelines for Familial Hypercholesterolemia.*[19]

Table 2.4 – Dietary recommendations for the treatment of dyslipidemia

Recommendations	LDL-c			Triglycerides	
	Within the target and without comorbidities* (%)	Above the target or with comorbidities* (%)	Borderline 150-199 mg/dL (%)	High 200-499 mg/dL (%)	Very high† > 500 mg/dL (%)
Weight loss	Maintaining a healthy weight	5-10	Up to 5	5-10	5-10
Carbohydrate (%TEV)	50-60	45-60	50-60	50-55	45-50
Added sugars (%TEV)	< 10	< 10	< 10	5-10	< 5
Protein (%TEV)	15	15	15	15-20	20
Fat (%TEV)	25-35	25-35	25-35	30-35	30-35
Trans fatty acids (%TEV)	Exclude from diet				
Saturated fatty acids (%TEV)	< 10	< 7	< 7	< 5	< 5
Monounsaturated fatty acids (%TEV)	15	15	10-20	10-20	10-20
Polyunsaturated fatty acids (%TEV)	5-10	5-10	10-20	10-20	10-20
Linolenic acid, g/day	1.1-1.6				
EPA and DHA, g	-	-	0.5-1.0	> 2.0	> 2.0
Fiber	25 g, with 6 g of soluble fiber				

DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; TEV: total energy value. The reassessment period after implementing lifestyle modification measures should be 3 to 6 months. Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]

mortality, coronary ischemic events, need for revascularization, and CVA. LDL-c reduction varies among statins, a difference closely related to the initial dose, as shown in Table 2.5.

Chart 2.1 presents the recommendations for lipid management and the evidence that supports such recommendations.

Side effects are rare in statin treatment, but among them, muscular effects are the most common and can occur weeks or years after the start of treatment. They range from myalgia, with or without elevation of creatine kinase (CK), to rhabdomyolysis. CK levels should be evaluated at the start of treatment or when the dose needs to be increased, in case of muscle symptoms (pain, tenderness, stiffness, cramps, weakness, and localized or generalized fatigue), and when introducing drugs that might interact with statin (Recommendation Grade: IIa, Level of Evidence: B). The baseline evaluation of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be performed before the beginning of statin therapy. During the treatment, the liver function should be assessed in case of signs or symptoms suggesting hepatotoxicity (fatigue or weakness, loss of appetite, abdominal pain, dark urine, or jaundice) (Recommendation Grade: IIa, Level of Evidence: B).[7] Repeated analyses of enzyme samples in asymptomatic patients lead to additional costs with no benefit to patients.

Table 2.6 describes the indications for the association of other lipid-lowering drugs.

2.2.3. Drug Treatment Focused on Hypertriglyceridemia

Hypertriglyceridemia is an independent risk factor for CVD, particularly for CAD.[21] However, it is not clear if hypertriglyceridemia causes atherosclerosis, since TG does not tend to accumulate in arterial walls, or if the abnormalities

Table 2.5 – Intensity of the lipid-lowering treatment

	Low	Moderate	High
Expected LDL-c reduction with daily dose, %	< 30	30-50	≥ 50
Examples, daily doses in mg	Lovastatin 20 Simvastatin 10 Pravastatin 10-20 Fluvastatin 20-40 Pitavastatin 1	Lovastatin 40 Simvastatin 20-40 Pravastatin 40-80 Fluvastatin 80 Pitavastatin 2-4 Atorvastatin 10-20 Rosuvastatin 5-10	Atorvastatin 40-80 Rosuvastatin 20-40 Simvastatin 40/ Ezetimibe 10

Note: the use of Ezetimibe alone reduces LDL-c in 18-20%. LDL-c: low-density lipoprotein-cholesterol. Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]

Chart 2.1 – Recommendations for blood lipid management, recommendation grade, and level of evidence

Recommendation	Recommendation grade	Level of evidence	Reference
Individuals at very high CV risk: LDL-c should be reduced to < 50 mg/dL and non-HDL-c to < 80 mg/dL	I	B	7
Individuals at high CV risk: LDL-c should be reduced to < 70 mg/dL and non-HDL-c to < 100 mg/dL	I	A	7
Individuals at high and very high CV risk: whenever possible and tolerated, give preference to high-intensity statins or Ezetimibe associated with statin (Simvastatin 40 mg or another statin at least as potent)	I	A	7
Individuals at moderate CV risk: LDL-c should be reduced to < 100 mg/dL and non-HDL-c to < 130 mg/dL	I	A	7
Individuals at moderate CV risk: whenever possible and tolerated, give preference to statins of at least moderate intensity	I	A	7
Individuals at low CV risk: the LDL-c target should be < 130 mg/dL and non-HDL-c < 160 mg/dL	I	A	7
Drug therapy to increase HDL-c levels is not recommended	III	A	7
Individuals with TG levels > 500 mg/dL should receive appropriate therapy to reduce the risk for pancreatitis	I	A	7
Individuals with TG levels between 150 and 499 mg/dL should receive therapy based on CV risk and associated conditions	IIa	B	7

CV: cardiovascular; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides. The reassessment period after the drug treatment must be of at least a month. Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]

Table 2.6 – Indications for the association of other lipid-lowering drugs (non-statins)

Recommendation	Recommendation grade	Level of evidence	Reference
Ezetimibe			
When the statin treatment in the maximum tolerated dose does not reach the LDL-c target in very high-risk patients	I	B	7
When the statin treatment in the maximum tolerated dose does not reach the LDL-c target in patients in primary prevention	IIb	C	7
Alone or in combination with statins represents a therapeutic option for patients who do not tolerate the recommended doses of statins	IIa	C	7
Can be used in case of fatty liver disease	IIb	C	7
Resins			
Adding cholestyramine to the statin treatment can be recommended when the LDL-c target is not reached despite the use of potent statins in effective doses	IIa	C	7
PCSK9 Inhibitors			
Indicated for patients at high CV risk, on optimized statin treatment at the highest tolerated dose, associated or not with Ezetimibe, and who have not reached the recommended LDL-c or non-HDL-c targets*	IIa	A	7

CV: cardiovascular; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol. In very high-risk patients and some high-risk situations, when the individuals already take statin at the highest tolerated dose and Ezetimibe, the addition of a PCSK9 inhibitor is reasonable, despite the lack of an established long-term safety (> 3 years) for this drug and its low cost-effectiveness according to current data.[20] Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]

associated with it, such as low HDL-c,[22-24] small and dense LDL particles,[25,26] insulin resistance,[27,28] and increased blood coagulability and hyperviscosity,[29-31] predispose the individual to atherosclerosis. According to Table 2.7, drug treatment for hypertriglyceridemia should be considered after the exclusion of secondary causes for the increase in TG – diabetes, renal failure, excessive alcohol intake, and use of certain medicines – and adjustments for behavioral measures.

Table 2.8 presents the recommended doses of fibrates available in our country and their effects on lipid profile

Table 2.7 – Indication of medicines for the treatment of hypertriglyceridemia

Recommendation	Recommendation grade	Level of evidence	Reference
Fibrates			
TG levels above 500 mg/dL	I	A	32,33
Mixed dyslipidemia with a prevalence of hypertriglyceridemia	IIa	B	32,33
In patients with diabetes, TG > 200 mg/dL, and HDL-c < 35 mg/dL, the combination of fenofibrate and statin might be considered when changing the lifestyle have failed	IIa	B	32,33
Nicotinic acid (niacin)			
There is no evidence that the drug benefits patients with controlled LDL-c	III	A	32,33
Exceptionally, it can be administered to patients with isolated low HDL-c and as an alternative to fibrates and statins, or in combination with these drugs in patients with hypercholesterolemia, hypertriglyceridemia, or resistant mixed dyslipidemia	IIa	A	32,33
Omega-3 fatty acids			
Patients with severe hypertriglyceridemia who did not reach the desired levels with the treatment can take high doses (4 to 10 g/day) of omega-3 fatty acids in combination with other lipid-lowering drugs	I	A	32,33
Supplementation with an E-EPA (ethyl eicosapentaenoic acid) formulation (4 g/day) can be recommended for high-risk patients with elevated TG levels using statins, as it seems to reduce the risk for ischemic events, including CV death*	I	B	32,33

*CV: cardiovascular; EPA: eicosapentaenoic acid; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides. * This formulation is not commercially available in our country. Adapted from I Brazilian Guidelines on Fat Consumption and Cardiovascular Health.[32]*

Table 2.8 – Fibrate doses and lipid abnormalities (mean percentages)*

Drugs	Dose (mg/day)	TG reduction (%)	HDL-c increase (%)	LDL-c reduction (%)
Bezafibrate	200-600	30-60	7-11	Varying
Bezafibrate retard	400	30-60	7-11	Varying
Gemfibrozil	600-1200	30-60	7-11	Varying
Gemfibrozil retard	500	30-60	7-11	Varying
Etofibrate	500	30-60	7-11	Varying
Fenofibrate	160-250	30-60	7-11	Varying
Ciprofibrate	100	30-60	7-11	Varying

** Effects depend on the dose used and the initial baseline TG value. HDL-c: high-density lipoprotein-cholesterol; LDL-c: low-density lipoprotein-cholesterol; TG: triglycerides. Adapted from the Updated Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention.[7]*

3. Diabetes and Metabolic Syndrome

3.1. Myocardial Risk

Patients with DM2 have a 2 to 5 times greater risk for HF compared to non-diabetic individuals.[34] As CAD patients are excluded, the incidence of HF in the diabetic population decreases but remains significantly higher than in non-diabetic individuals. In type 1 diabetes, above 7%, each 1% increment in glycated hemoglobin (HbA1c) was associated with a 30% increase in HF risk,[35] while type 2 diabetes was associated with a 16% increase in the risk, regardless of other risk factors, including obesity, smoking, hypertension, dyslipidemia, and coronary disease.[36,37]

Diabetic cardiomyopathy is characterized by myocardial fibrosis and left ventricular hypertrophy with diastolic dysfunction, initially asymptomatic, and that progresses slowly to diastolic or systolic dysfunction, followed by HF with clinical repercussion.[38]

Occasionally, diabetic cardiomyopathy can manifest as arrhythmias and sudden death. Mechanisms involved in the pathophysiological process include mitochondrial dysfunction, oxidative stress, inflammation, dysfunction in the mitochondrial Ca^{2+} management, activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and disorders of cardiac energy metabolism.[39-41]

3.1.1. Myocardial Risk Estimate

Despite the lack of an universally accepted method to estimate HF risk specifically in diabetic individuals, methods such as plasma brain natriuretic peptide (BNP), echocardiographic evaluation of diastolic dysfunction, and risk calculators such as the Health ABC Heart Failure Score and the Framingham Heart Failure Risk Score are often used to estimate the future risk for symptomatic HF.

Elaborating a standardized strategy to screen and intervene in patients at HF risk might be difficult due to its different definitions, the heterogeneity of its prevalence in various populations, its inconstant duration until the development of clinic HF or left ventricular dysfunction, and the varying interventions to modify or treat risk factors. As we shall see below, the Health ABC Heart Failure Score is the mechanism with the highest sensitivity and specificity and should be recommended as the primary strategy in risk stratification of symptomatic HF. Nonetheless, BNP can be used concomitantly to reclassify individuals at high risk for HF.

The evidence that supports the use of BNP in diabetic patients to predict the HF risk is based on two randomized controlled trials. As shown in Table 3.1, these programs recruited 1,674 patients without HF for randomization and identified a total of 29 subsequent events of hospitalization for HF. The combined statistical power of these studies is limited but provides the perspective for the potential benefit of screening based on biomarkers such as BNP.

Diastolic dysfunction on the echocardiogram – Historically, experts disagree on recommendations for echocardiographic diagnosis of diastolic dysfunction, as

Table 3.1 – BNP screening to guide the primary prevention strategy for diabetes mellitus

	Study design and intervention	Study population	N without prior HF	Hospitalizations for HF/follow-up duration	Effect on hospitalization for HF	Effect on major CV events*
STOP-HF[42]	Randomized controlled trial with BNP screening versus usual primary treatment	Age > 40 years without HF but with CV disease or CV risk factors	1,374	21 / 4.2 years	OR 0.48 (95% confidence interval 0.20–1.20)	OR 0.60 (95% confidence interval 0.45-0.81)
PONTIAC[43]	Randomized controlled study, with treatment in a cardiology outpatient clinic for titration of RAAS inhibitors and beta-blockers associated with care in a DM treatment unit versus care in an isolated DM unit	DM2 without known CV disease and NT-proBNP > 125 pg/mL	300	8 / 2 years	HR 0.14 (95% confidence interval 0.02–1.14)	HR 0.35 (95% confidence interval 0.13–0.97)

*BNP: brain natriuretic peptide; CV: cardiovascular; DM: diabetes mellitus; HF: heart failure; RAAS: renin-angiotensin-aldosterone system. * Major CV events, defined as unplanned hospitalizations for CV causes and deaths.*

shown in the 2009 guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) and the Canberra Study Criteria (CSC).[44,45] Based on these recommendations, epidemiological studies and a meta-analysis[46,47] suggest that preclinical diastolic dysfunction (Stage B HF), defined as diastolic dysfunction with normal systolic function and without HF symptoms, is common in DM, and that its presence increases by 61 to 70% the risk for developing symptomatic HF (stages C and D). Despite being simple and non-invasive,[46,47] the echocardiographic diagnosis for patients at higher risk for HF does not seem to be as cost-effective as the measurement of BNP,[48,49] although these data are not specifically available for the Brazilian population.

The diagnostic criteria became more specific and less sensitive in the 2016 ASE/EACVI guideline,[50,51] despite the simplification. With these criteria, the prevalence of diastolic dysfunction in the general population ranges from 1 to 7%. However, no studies have been designed to focus on primary prevention based on this diagnostic criterion.

Risk scores for future HF – The HF risk in patients with DM and metabolic syndrome (MS) can be predicted with clinical scores. Although no scores have been developed specifically for patients with DM or MS, several studies have demonstrated good performance in these populations. Among the most used scores are the

(i) Health ABC Heart Failure Score;[52] the

(ii) The Framingham Heart Failure Risk Score;[53] and the

(iii) And the Atherosclerosis Risk in Communities (ARIC) Heart Failure Risk Score.[54]

The variables included in the Framingham Heart Failure Risk Score are age, gender, CAD, diabetes, left ventricular hypertrophy based on electrocardiogram (ECG), valvular disease, heart rate, and systolic blood pressure (SBP). The Health ABC Heart Failure Score includes the Framingham variables with the following differences: addition of serum albumin, serum creatinine, and smoking; replacement of glucose for diabetes; and exclusion of valvular disease. The ARIC Heart Failure Risk Score includes age, ethnicity, gender, CAD, diabetes, SBP, use of medicines for blood pressure (BP), heart rate, smoking, and body mass index (BMI).

Designed for a community population of older adults, the Health ABC Heart Failure Score reached a positive and negative predictive power of 10 and 15% in comparison with the Framingham Heart Failure Risk Score[52] and 2 to 4% above the ARIC Heart Failure Risk.[54] The Health ABC Heart Failure Score is an instrument validated in observational and intervention studies and, thus, considered a reference for estimating the future HF risk in patients with DM and MS (detailed description in Figure 3.1).

Although all scores are designed with only the variables listed above, the addition of BNP or NT-proBNP as linear variables would significantly increase the predictive power of all scores.[52,54] Based on the thresholds used in the studies PONTIAC[43] and STOP-HF,[42] we suggest reclassifying individuals with BNP ≥ 50 pg/mL or NT-proBNP ≥ 125 pg/mL into a higher risk category.

3.1.2. Preventive Therapies for Individuals at High and Very High Risk for Heart Failure in 5 Years and Secondary Prevention for Those with Clinical Heart Failure

Drug Therapies for DM2 that impact HF – As stated previously, above 7%, the HF risk increases by 8% for each 1% increment in HbA1c, while a 1% reduction decreases the risk by 16%. Although, several clinical trials have investigated the effect of metformin on the CV system based on the pathophysiology of insulin resistance, the effect of this class directly on HF remains inconclusive. Studies with insulin and sulfonylureas showed a neutral effect on HF, and glucagon-like peptide-1 (GLP-1) agonists/analogs[55] and acarbose[56] proved to be neutral regarding the risk for HF hospitalizations and mortality.

More recently, three large studies – EMPA-REG, CANVAS, and DECLARE – revealed that sodium-glucose 2 (SGLT2) cotransporter inhibitors reduced CV outcomes, including HF hospitalizations.[57,58] HF mortality among individuals who used empagliflozin was significantly lower than in those using a placebo. The studies EMPA-REG and DECLARE associated the risk of taking these drugs with a higher rate of genital infections in the group using empagliflozin and dapagliflozin, while the CANVAS study showed an increased risk of lower limb amputation.[57,58] Together, all three SGLT2 inhibitors available (empagliflozin, canagliflozin, and dapagliflozin) reduce the risk for HF hospitalization, even in asymptomatic patients at the start of treatment. Therefore, the use of these drugs is recommended for patients with DM or MS at high or very high risk for HF.

Among the hypoglycemic agents that increase the chance of HF, we highlight the thiazolidinediones (RECORD study – rosiglitazone; and PROactive – pioglitazone)[59,60] and a dipeptidyl peptidase-4 inhibitor (DPP-4i) – the saxagliptin (SAVOR-TIMI 53).[61] In the studies RECORD and SAVOR-TIMI, patients with HF also had higher subsequent mortality rates. Thus, rosiglitazone, pioglitazone, and saxagliptin are contraindicated for patients with or at high risk for HF.

3.1.3. Therapies Focused on Cardiac Remodeling

Although only two clinical trials substantiate these recommendations, patients with DM and MS at high and very high risk for HF seem to benefit from the early introduction of anti-remodeling therapies, such as RAAS inhibitors and beta-blockers. Based on these pharmacological strategies triggered by BNP or NT-proBNP levels above the risk threshold, the studies PONTIAC[43] and STOP-HF[42] suggested reducing the risk for HF hospitalization and mortality.

In patients with clinical HF, clinical trials have demonstrated that the drug therapies tested were equally effective, regardless of the presence of DM and MS.

Angiotensin blockers – The CHARM Trial (candesartan),[62] Val-HeFT (valsartan),[63] and ATLAS (lisinopril)[64] have demonstrated that the use of angiotensin-converting enzyme inhibitors (ACEI) or aldosterone-receptor blockers (ARB) favored the decrease in mortality and hospitalization among patients who had HF and reduced ejection fraction, regardless of the presence of DM2 or MS.

Age	
Age	Score
≤ 71	-1
72-75	0
76-78	1
≥ 79	2

Systolic BP	
mmHg	Score
≤ 90	-4
95-100	-3
105-115	-2
120-125	-1
130-140	0
145-150	1
155-165	2
170-175	3
180-190	4
195-200	5
> 200	6

Heart rate	
bpm	Score
≤ 50	-2
55-60	-1
65-70	0
75-80	1
85-90	2
≥ 95	3

Albumin	
g/dL	Score
≥ 4.8	-3
4.5-4.7	-2
4.2-4.4	-1
3.9-4.1	0
3.6-3.8	1
3.3-3.5	2
≤ 3.2	3

Creatinine	
mg/dL	Score
≤ 0.7	-2
0.8-0.9	-1
1.0-1.1	0
1.2-1.4	1
1.5-1.8	2
1.9-2.3	3
> 2.3	6

Coronary artery disease	
Status	Score
No	0
Possible	2
Diagnosed	5

Smoking	
Status	Score
No	0
Former	1
Present	4

SBP-nearest 5 mmHg

HR-nearest 5 bpm

Glucose-nearest 5 mg/dL

Fasting blood glucose	
mg/dL	Score
≤ 80	-1
85-125	0
130-170	1
175-220	2
225-265	3
≥ 270	5

Left ventricular hypertrophy	
Status	Score
No	0
Yes	2

Health ABC Risk Score	HF risk	HF risk in 5 years
≤ 2 points	Low	< 5%
3-5 points	Moderate	5-10%
6-9 points	High	10-20%
≥ 10 points	Very High	> 20%

Figure 3.1 – *Health ABC Heart Failure Score.*

***Mineralocorticoid antagonists* –** Patients with and without DM2 showed a reduction in mortality, with the use of both spironolactone (RALES trial)[65] and eplerenone (EMPHASIS-HF).[66] We underline the risk for hyperkalemia, which might particularly affect patients with renal function deterioration and already using ACEI or ARB.

***Beta-blockers* –** In patients with DM and HF, the use of metoprolol succinate (MERIT-HF), bisoprolol (CIBIS II), and carvedilol (COPERNICUS) is recommended. They presented equal efficiency in patients with and without DM. A meta-analysis that included six trials indicated a reduction in all-cause mortality among patients with DM2, as well as in non-diabetic individuals.[67]

***Nitrates and Hydralazine* –** Approximately 40% of the patients randomized in the A-HeFT trial had DM2. In this subpopulation, the combination of a fixed dose of hydralazine and nitrate significantly reduced all-cause mortality.[68]

***Ivabradine* –** Its use decreased mortality and hospitalizations in patients with and without DM2 in the SHIFT study, which involved 6,558 patients.[69]

The sacubitril-valsartan combination is not well established yet in patients with preserved ejection fraction or at high risk for HF; even for patients with reduced ejection fraction, there is no specific study or subanalysis focused on the diabetic population.

3.2. Atherosclerotic Risk

3.2.1. Metabolic Syndrome, Diabetes Mellitus, and the Continuous Corollary of Coronary Artery Disease

MS and the DM comprise a spectrum of multisystemic diseases, particularly in the vascular endothelium, that contribute dramatically to the progression of pathophysiological substrates of CAD. Robust evidence suggests that CV risk increases even in stages that precede the clinical diagnosis of DM in 10 to 20 years, based on current criteria. As MS is one of the main risk factors for DM, considering it within a *continuum* of metabolic changes related to coronary atherothrombosis is reasonable.[70,71]

In fact, estimates indicate that glucose metabolic changes precede the diagnosis of diabetes in 4 to 12 years[72] (Figure 3.2). While in early stages the overproduction of insulin can compensate its resistance, after a certain point, the pancreatic functional reserve is exhausted, and the production of insulin

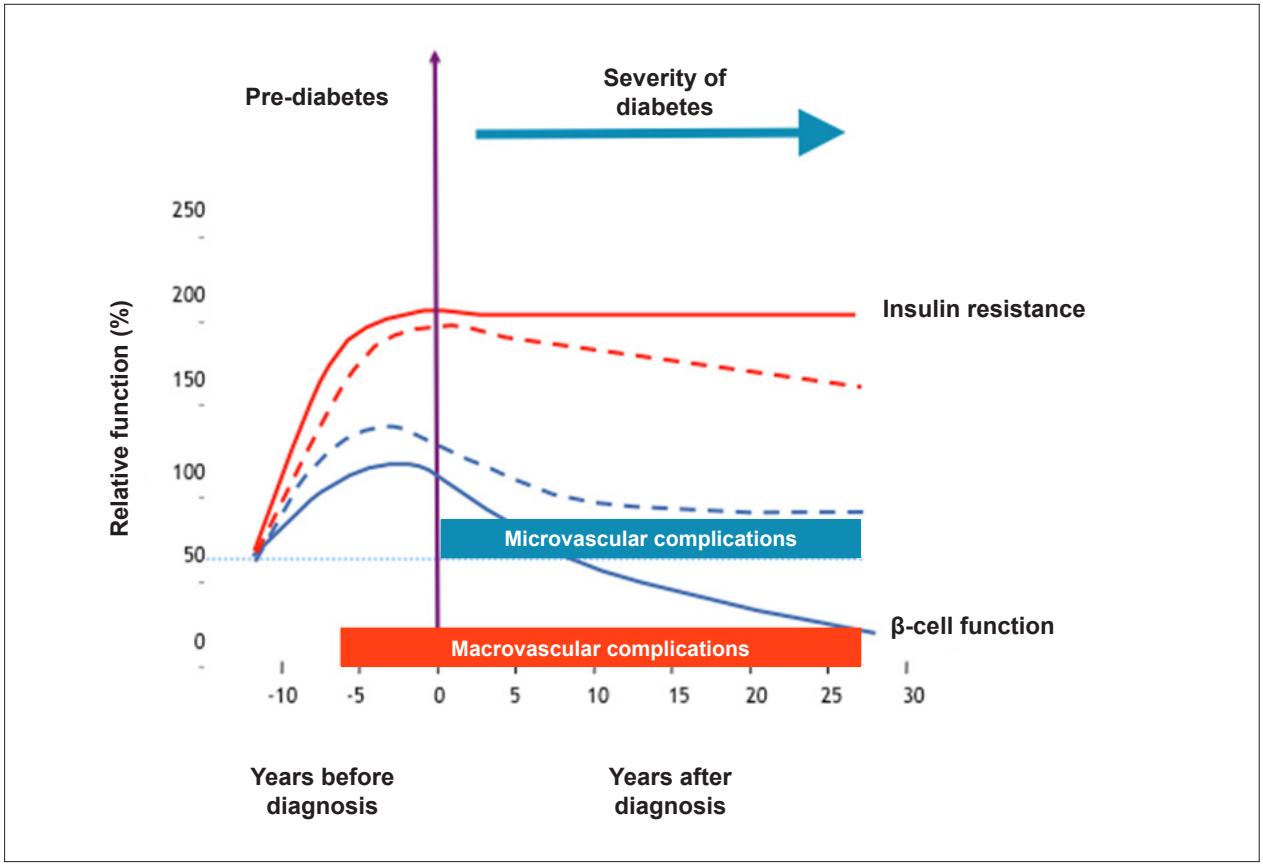

Figure 3.2 – *Progression of micro- and macrovascular disease in type 2 diabetes and its relationship with the functional reserve of pancreatic beta-cells and hyperglycemia.*

no longer compensates its resistance. After this moment, the diagnosis will be established by hyperglycemia, but CV changes adaptive to insulin resistance and cellular oxidative stress become irreversible.

Another mechanism that seems to occur even in early stages (pre-hyperglycemia) is the accumulation of fatty acids in various tissues, such as pancreas, heart, and liver, accelerating the dysfunction in insulin production, hepatic glucose production, and left ventricular diastole.[73] Therefore, even remotely before the period of hyperglycemia, several cellular mechanisms cooperate to determine the endothelial dysfunction, the phenotypic changes in lipids with hypertriglyceridemia, and small, dense LDL, creating the ideal scenario for accelerated atherogenesis.[74] Together, these data suggest that CAD becomes accelerated many years before the onset of hyperglycemia.

3.2.2. Primary Prevention Strategies for Coronary Artery Disease in Individuals with Metabolic Syndrome and Diabetes Mellitus

Corroborating the pathophysiological evidence, weight control strategies with physical activity and intensive dietary guidance have proven to be the best available method to reduce the risk of a patient with MS and pre-DM developing the clinical diagnosis of DM.[75,76] Lifestyle interventions decreased the risk for DM by 45% (p = 0.001), the risk for CV death by 41% (p = 0.033), and all-cause mortality by 29% (p = 0.049).

In patients with established DM and microalbuminuria, the randomized clinical trial STENO-2[77] showed that a multifactorial approach to lifestyle significantly decreased CV morbidity and mortality in comparison with conventional treatment.

3.2.3. Individual Risk Prediction for Coronary Artery Disease in Patients with Diabetes Mellitus and Metabolic Syndrome

At least 68% of diabetic patients aged 65 years or older die from heart diseases, most of them from CAD, followed by congestive HF.[78] DM is considered an independent CV risk factor both in men and women, raising in about two to four times the probability of clinical CAD, when compared to individuals without DM.[79] Moreover, based on a meta-analysis with almost 1 million individuals from 87 studies, MS is associated with a twofold increase in CV outcomes and a 1.5 increase in all-cause mortality, exceeding the isolated risk of its components.[80]

The CAD risk in the population with DM or MS, however, is not evenly distributed. Several strategies for CAD screening were implemented in recent decades, although

most of them have proven to be fruitless, as these groups are at high risk for CAD. Revascularization strategies guided by myocardial perfusion scintigraphy or coronary computed tomography angiography in asymptomatic diabetic individuals were not superior to clinical management, based only on traditional risk factors.

In the study FACTOR-64 – a randomized clinical trial with 900 patients with DM1 or DM2 for at least three years and without CAD symptoms –, the revascularization strategy guided by coronary computed tomography angiography did not reduce the risk for acute coronary syndrome (ACS) or CV mortality.[81] Similarly, in the studies DIAD[82] and DYNAMIT,[83] the revascularization strategy guided by exercise stress test with scintigraphy did not improve CV and non-CV outcomes compared to conventional medical treatment in 1,900 asymptomatic diabetic patients.

Currently, the more efficient and practical resources to determine CV risk in diabetic patients have been the isolated control of its risk factors. Subanalyses of the Diabetes Heart Study[84] and FACTOR-64[81] revealed that the factors with greater predictive power for ACS risk were the use of statins and LDL-c levels, followed by glomerular filtration rate, microalbuminuria, and C-reactive protein (CRP).

The treatment of CV risk factors related to aggressive diabetes is the method more strongly associated with the reduction in CV morbidity and ACS mortality in diabetic patients, as demonstrated in the study STENO-2.[77] However, as detailed below, the most effective way of predicting risk and managing more or less intensive targets in primary prevention should be combining risk and coronary calcium scores.

3.2.4. Risk Calculator

Risk scores are among the most commonly used strategies, consisting of estimating risk based on prospective data collected from cohorts of diabetic patients, such as the UKPDS, the DECODE, the DARTS, the ADVANCE, the Swedish National Diabetes Register, and the DCS.[85,86] Other calculators developed for mixed populations (diabetics and non-diabetics) are also widely used: ORS/SBC, Framingham, Pooled Cohort Equations (ASCVD), REYNOLDS, SCORE, PROCAM, and others.[74] The main advantage of these methods lies in their easy application in clinical practice, as they consider the usual clinical data, such as age, laboratory test values, and anthropometric information. The UKPDS calculator is more recommended for diabetic patients (IDF21 guidelines, NICE, Canadian Diabetes Association, Australian National Vascular Disease Prevention Alliance, and others) and the ORS is the more widely used in the Brazilian diabetic and non-diabetic population.

Nevertheless, these and other strategies to estimate the progression of vascular diseases are still limited, underestimating the risk in young patients with DM or recently diagnosed patients, while overestimating the risk in individuals diagnosed for > 10 years or with HbA1c > 9.0%.[87-89] Also, the scores do not take into account the advances of the last 5 to 10 years, such as new drugs and diagnostic methods, and have relatively low predictive performance (C-statistic between 0.54–0.70), considering that 30 to 60% of individuals are at moderate risk.[87] In this scenario, adding the coronary calcium score to clinical risks has become the most efficient and cost-effective alternative to estimate the CAD risk in patients at moderate risk.

3.2.5. Coronary Artery Calcium Score

Coronary artery calcium (CAC) is a highly specific characteristic of coronary atherosclerosis. The CAC score (CACS) is an available, consistent, and reproducible method to evaluate the risk for future coronary events, essentially by guiding primary prevention strategies.[90] CACS in asymptomatic populations is cost-effective for moderate risk patients[90] and has a positive impact on adherence to treatment.[91]

The Multi-Ethnic Study of Atherosclerosis (MESA) developed a valuable and useful support tool for CACS to predict risk, incorporating CACS to a clinical model using 10-year follow-up data until the first manifestation of CAD.[92] The MESA score involves individuals aged 45 to 85 years, providing CAD risk in 10 years with and without CACS. The Heinz Nixdorf Recall (HNR) and the Dallas Heart Study validated the score.[92] The greatest limitation of the MESA score is that its algorithm does not include all forms of atherosclerotic disease, which differentiates it from the ORS/SBC.[93]

In an analysis of patients from the MESA study[94] who had an estimate of atherosclerotic cardiovascular disease (ASCVD) of 5 to 7.5% in 10 years, a CACS = 0 was associated with an ASCVD observed rate of 1.5%, while any calcium score > 0 was associated with an actual rate of events of at least 7.5%. In individuals from MESA with an ASCVD risk between 7.5 and 20%, a CACS = 0 was associated with an event rate of around 4.5%, while a CACS > 0 was associated with a net benefit of statin therapy of approximately 10.5%.

CACS should represent a way of segregating diabetic individuals with a higher atherosclerotic burden and possibly those suffering for longer the vascular effects of insulin resistance associated with endotheliopathy, which begins in the early stages of pre-diabetes.[72]

As explained above, pathophysiologically, vascular disease, especially diabetic coronary disease, starts long before its clinical diagnosis. However, the strategies to map the progression of the vascular disease in earlier stages are still limited, and there are few viable tools for clinical practice. Thus, a clinical score – such as the ORS/SBC – combined with CACS is the most efficient way to predict the CAD risk in moderate-risk patients.

3.2.6. Lipid Targets in Primary Prevention for Individuals with Metabolic Syndrome and Diabetes Mellitus

Statins are among the most prescribed drugs worldwide, reflecting their fundamental role in primary and secondary prevention of atherosclerotic disease and the high prevalence of dyslipidemias. Several randomized clinical trials (RCT) and meta-analyses, such as the Cholesterol Treatment Trialists' (CTT) Collaboration,[14] solidified the indication of statins. Among 21 RCT comparing statin and

placebo, with a total of 129,526 individuals followed for 4.8 years, each 40 mg/dL reduced of LDL-c decreased the incidence of CV events by 12% and CAD deaths by 20%. Moreover, the CTT analyses showed that a greater reduction in LDL-c with the use of more potent statins had an additive effect on the prevention of CV events. Findings of 5 RCTs with more than 39,000 individuals combined showed that reducing LDL-c levels in over 20 mg/dL with a more intensive lipid-lowering treatment can decrease the incidence of non-fatal myocardial infarction by 19%, ischemic CVA by 31%, and major CV events by 28%.

The use of statins in patients with CAD seems to stabilize atherosclerotic plaques, and can even lead to their volumetric reduction,[95] with an approximately linear relationship between the decrease in LDL-c and the rate of CV events, as well as between LDL-c levels and the progression of the atheroma volume in carotid arteries. In parallel, not only the dose of statin and the reduction in LDL-c decrease CV risk, but the period of statin use also seems to have a central role in reducing the risk for CV death and non-fatal myocardial infarction. In the WOSCOPS study, for instance, the number needed to treat (NNT) with pravastatin after four years of follow-up was 40:1, whereas, after 16 years, NNT decreased to 27:1.[96]

Regarding lipid targets for patients in secondary prevention, the scenario was redesigned after the publication of the IMPROVE-IT study[97] (with simvastatin and ezetimibe), whose LDL-c was 50 mg/dL, and the FOURIER study[98] (alirocumab, a PCSK9 inhibitor), which reached mean LDL-c levels as low as 38 mg/dL. Based on the significant and consistent reduction in coronary events in two clinical trials, currently the LDL-c target is < 50 mg/dL; there is no reason, however, in terms of safety, to seek even lower targets, either through diet, statins, ezetimibe, or PCSK9 inhibitors.

In a primary prevention scenario, the reduction in vascular events is comparatively lower than in secondary prevention, but it still is robustly cost-effective in diabetic and non-diabetic patients with CV risk > 7.5% in 10 years.[99] As revealed in the CTT meta-analysis, a decrease in LDL-c by 80 mg/dL (with a mean starting LDL-c from 130 to 160 mg/dL) combined with an effective statin regimen for about five years in 10,000 patients in primary prevention typically prevents 500 vascular events (5% of patients).[14]

Although the duration of clinical studies with statins is relatively short (3 to 7 years), patients with DM and MS will be subject to a metabolically unfavorable environment for the rest of their lives (10 to 30 years). Assuming that 68% of causes of death in diabetic patients are CV-related,[78] it is reasonable to think that, once the high vascular risk is identified (based on the ORS with or without CACS), more aggressive therapeutic targets should be considered.

No RCT has investigated an LDL-c target below 70 mg/dL (JUPITER)[100] in primary prevention. However, Mendelian randomization studies consistently support that lower LDL-c levels (including the 30-50 mg/dL range) were related to lower CV morbidity and mortality.[101] Furthermore, a subanalysis of the JUPITER study showed that the lower the LDL-c level achieved (< 50 mg/dL), the greater the risk reduction in both diabetic and non-diabetic individuals.[102]

3.2.7. Aspirin in Primary Prevention

The use of acetylsalicylic acid (ASA) in primary prevention is a controversial issue, but that seems to have recently reached a common denominator. In 2018, three RCT provided an answer to this question: the ASCEND,[103] in diabetic patients; the ARRIVE,[104] in non-diabetic patients at moderate CV risk (median risk of 15% in 10 years); and the ASPREE,[105] in patients aged 70 years or older. All three studies compared low doses of aspirin (100 mg per day) with placebo from 5 (ARRIVE and ASPREE) to 7.5 years (ASCEND), and collectively found:

1) no difference in rates of myocardial infarction and acute myocardial infarction;
2) no difference in CV mortality;
3) no difference in all-cause mortality in ASCEND and ARRIVE, and a small risk increase with aspirin in ASPREE; and
4) greater risk for gastrointestinal malignancy among aspirin users in the ASPREE study (probably due to early diagnosis).

These data are consistent with a systematic review by the Antithrombotic Trialists' Collaboration,[106] which included 95,000 individuals from six RCT. The reduction in risk for vascular events ranged from 0.57 to 0.51% per year (placebo vs. aspirin), while extracranial and major gastrointestinal bleedings increased by 0.03% per year (0.10 to 0.07%).

Although observational studies suggest that the use of aspirin benefits primary prevention in patients at high CV risk,[107] this result was not confirmed in subanalyses of ASCEND and ARRIVE. Even in patients at higher estimated risk for CV events, aspirin provided no net benefit since it induced more bleedings in this subpopulation, and the proportional decrease in vascular events was mild compared to that in individuals at lower risk.[103,104]

3.2.8. Hypoglycemic Agents in Patients with Diabetes Mellitus

Despite the strong effect of glycemic control on microvascular complications among diabetic patients, its benefits for the macrovascular disease were still a paradigm until recently. Medicines such as sulfonylurea and insulin have limitations, despite being very effective in glycemic control, as they induce weight gain and increase the risk for hypoglycemia, two major risk factors for the worsening of symptoms and prognosis in HF and CAD. Several RCT tested these drugs, combined with metformin, by comparing intensive glycemic control and less aggressive targets. In a meta-analysis with 13 RCT and 34,533 diabetic individuals, although the risk for non-fatal myocardial infarction decreased with intensive glycemic control (relative risk – RR 0.85; 95% confidence interval, 0.74–0.96, p < 0.001), there was no significant change in all-cause mortality (RR 1.04; 99% confidence interval, 0.91–1.19) or CV mortality (RR 1.11; 95% confidence interval, 0.86–1.43).[108]

On the other hand, with the advent of new drugs that allow effective glycemic control associated with weight loss and minimal risk for hypoglycemia, the paradigm of glycemic control regarding CVD was broken. In a recent meta-analysis, GLP-1 analogs consistently reduced the incidence of CV deaths and non-fatal infarction by 14 and 18%, respectively.[109] Data from the studies LEADER (liraglutide),[110] SUSTAIN-6 (semaglutide),[55] HARMONY (albiglutide),[111] and REWIND (dulaglutide) demonstrated safety and efficacy among diabetic patients in secondary prevention and patients in primary prevention at high or very high CV risk. Chart 3.1 presents the recommendations for DM and MS management.

4. Obesity and Overweight

4.1. Introduction

In the past decades, Brazil underwent a process called nutritional transition[112] – a concept related to secular changes in dietary patterns and nutritional status – and important modifications regarding food intake and PA patterns, as a consequence of economic, social, demographic, and health transformations.[113] Obesity and overweight are complex and chronic conditions, whose prevalence has grown inexorably in the last 4 to 5 decades.[114] Between 1980 and 2013, the

Chart 3.1 – Recommendations for diabetes mellitus and metabolic syndrome management

Recommendation	Recommendation grade	Level of evidence	Reference
The Health ABC Heart Failure Score should be recommended for patients with MS or DM as a primary strategy in the risk stratification of HF	I	B	52-54
BNP values ≥ 50 pg/mL or NT-proBNP ≥ 125 pg/mL must be used together to reclassify individuals at moderate risk for HF into high risk Individuals at high and very high risk should receive an intensive primary prevention approach	IIa	A	52-54
Echocardiographic diagnosis of diastolic dysfunction in patients with DM or MS without clinical symptoms of HF should suggest an increased risk for the development of HF. However, the data available are not enough to recommend its routine use to estimate the future risk for symptomatic HF	IIA	B	50,51
The use of an SGLT2 inhibitor is recommended for patients with DM or MS without clinical symptoms of HF, but at high or very high risk for HF, based on the Health ABC Heart Failure Score and BNP levels	I	B	57,58
Prescribing rosiglitazone, pioglitazone, or saxagliptin is contraindicated for patients with DM or MS without clinical symptoms of HF, but at high or very high risk for HF, based on the Health ABC Heart Failure Score and BNP levels	III	A	59-61
Strategies for weight control, PA, dietary guidance, and quitting smoking should be offered to all patients with glucose intolerance, MS, or DM, so as to mitigate the progression of CAD	1	A	75-77
Stratifying the risk for coronary events with anatomical or functional methods is not recommended for asymptomatic patients with MS or DM	III	A	78-84
Using CACS is recommended for patients with DM or MS and at moderate CV risk (ORS 5 – 20%). When CACS = 0, the recommendation is usually not to start statin treatment	I	B	89-94
CACS should not be requested for patients with DM or MS and at low (ORS < 5%) or very high (> 20% in 10 years) CV risk	III	B	14,95-97
In primary prevention, patients with DM or MS referred to statin therapy should receive highly potent doses of these medicines and/or ezetimibe, with an LDL-c target < 70 mg/dL Alternatively, in individuals with DM or MS and at high or very high risk, the LDL-c target should be < 50 mg/dL	I I	A B	14,95-97
In primary prevention for patients with familial hypercholesterolemia, with or without DM or MS, the LDL-c target should be < 50 mg/dL, with an indication for a highly potent statin, ezetimibe, and PCSK9 inhibitors until the target is reached	I	A	14,95-97
Using ASA is not recommended as a primary prevention strategy for patients with MS or DM, regardless of CV risk	III	A	103,104
The introduction of a GLP-1 analog is recommended for diabetic patients with or without a history of CV disease, but at high or very high risk for ASCVD	I	A	55,108-111

ASCVD: atherosclerotic cardiovascular disease; BNP: brain natriuretic peptide; CACS: coronary artery calcium score; CAD: coronary artery disease; CV: cardiovascular; DM: diabetes mellitus; GLP1: glucagon-like peptide-1; HF: heart failure; LDL-c: low-density lipoprotein-cholesterol; MS: metabolic syndrome; ORS: overall risk score; SGLT2: sodium-glucose 2 cotransporter.

global percentage of individuals with a BMI ≥ 25 kg/m² rose from 28.8 to 36.9% in men and 29.8 to 38.0% in women.[115] In Brazil, 52.4% of the population was overweight in 2014, with 17.9% of them classified as obese.[116] According to data from the 2018 Risk Factors Surveillance and Chronic Disease Protection by Telephone Survey (VIGITEL), the incidence of overweight reached 55.8% and of obesity, 18.7% among men over 20 years of age; while for women, these values were 53.9% and 20.7%, respectively.[117] In 34 years, the prevalence of obesity increased over four times for men (from 2.8 to 12.4%) and more than twice for women (from 8 to 16.9%).[118,119] Brazil currently holds the fourth place among the countries with the highest prevalence of obesity and the number of overweight adults will exceed those with low weight.[118] There is a significant rise in overweight and obesity among children and adolescents, regardless of gender and social status, and a considerable proportion of these individuals will become obese adults.

Obesity has a multifactorial nature and is one of the leading factors to explain the growth in the chronic NCD burden, given its frequent association with CVD, such as arterial hypertension (AH), CVA, HF,[120] dyslipidemias, type 2 diabetes, atrial fibrillation,[121,122] osteoarthritis, and certain types of cancer. Also, obesity is an important condition that predisposes the individual to mortality.[118,119]

In addition, weight gain over time is associated with MS, increased risk for CVA, and death in late stages of life.[123-125] Many patients who present some of these changes have hypertriglyceridemia and increased levels of plasma fatty acids, stored as lipid droplets in the heart. Intramyocardial lipids that exceed the storage and oxidation capacity can become toxic and lead to non-ischemic and non-hypertensive cardiomyopathy, known as diabetic or lipotoxic cardiomyopathy.[126] Significant weight loss (≥ 5% of initial weight) improves BP, LDL-c, TG, and glucose levels, delaying the onset of type 2 diabetes.[127]

4.2. Primary Prevention

According to the World Health Organization (WHO), an inadequate diet is the main risk factor for early mortality worldwide.[128] Therefore, a healthy diet is recommended for everyone, and the ability to prepare healthy meals has beneficial correlations with the consumption of equally healthy foods.[129] However, studies have shown a reduction in the habit of cooking in some countries, which has encouraged health specialists to elaborate nutritional education strategies focused on nutrients and tools, such as the proper purchase and storage of food, and planning and preparing meals at home.[130]

Also, we emphasize that the biological moment that could prevent weight gain is of the utmost importance. In females, the moment of greatest risk seems to be the reproductive age, specifically during pregnancy and the first two years postpartum, and the period post-menopause.[131,132] Among children and adolescents, prevention of excessive weight gain was expected precisely because the growth phase requires extra energy, and the possibility of energy expenditure is higher compared to other life stages. These potential facilitators, however, do not seem to overcome the factors associated with obesity and those responsible for the epidemic growth also in these age groups and life stages.[133] In this regard, we underline the so-called "obesogenic environment," that is, the role of the food industry, fast food chains, advertisements, TV shows, movies, and videogames, leading to situations that keep the children more sedentary and subjected to excessive energy intake. The most appropriate interventions should combine environmental and behavioral changes.[134-136]

A study conducted with 422 adolescents, with a mean age of 12.5 years, compared students who practiced competitive physical activity daily for 2 hours with those from a standard school who have only one hour of physical activity per week. The percentage of overweight/obesity in the first group was 49.8% and in the second, 37.3%, which reveals the high prevalence of this change in the two groups.[137] A similar sample submitted to a multidisciplinary program of moderate intensity, that could be easily incorporated in the daily routine, showed positive advances in risk factors when compared to the control group.[138]

Among adults, studies show a decline in the consumption of rice and beans, increase in the intake of processed products (particularly cookies and soft drinks), excessive consumption of sugar, more saturated fats, and insufficient intake of fruits and vegetables, creating an environment with habits that do not favor a healthy dietary pattern, directly associated with the increase in chronic NCD, especially obesity.[139-142]

A recommendation from the 2014 Dietary Guidelines for the Brazilian Population proposes 10 steps for a healthy diet:

1. Prioritize natural or minimally processed foods;
2. Use oil, salt, and sugar moderately;
3. Limit the consumption of processed foods;
4. Avoid the intake of ultra-processed foods;
5. Eat regularly and carefully;
6. Buy food at the street market;
7. Cook;
8. Plan the purchase of foods and preparation of meals;
9. Avoid fast food;
10. Be critical of food advertising.

Some other useful pieces of advice are:[143,144]

- Eat regularly throughout the day and at similar times every day to establish a healthy dietary pattern;
- Pay attention to food labels and choose products without trans and hydrogenated fats;
- Avoid soft drinks and processed juices, cakes, cookies, sandwich cookies, and sweet desserts;
- Give preference to drinking water between meals;
- Practice at least 30 minutes of vigorous physical activity on most weekdays or 40 minutes of moderate physical activity;
- However, individuals with a tendency towards obesity or with family profile should practice moderate physical activity for 45-60 minutes per day; those who were obese and lost weight should practice for 60-90 minutes to avoid regaining the weight lost;
- The practice of physical activities and exercises can prevent weight gain and obesity even in older adults.

Table 4.1 lists the recommendations on how to approach overweight and obese adults.

Table 4.1 – Recommendations on how to approach overweight and obese adults

Recommendation	Recommendation grade	Level of evidence	Reference
Weight loss is recommended for overweight and obese individuals to improve their CV risk profile	I	B	2,9,128
Counseling and interventions addressing lifestyle, including caloric restriction, aimed at achieving and maintaining weight loss are recommended for overweight and obese adults	I	B	2,9,128
Calculate the BMI and anthropometric measures during medical appointments to identify overweight and obese adults with the purpose of intervention	I	C	2,9,128
Measure the waist circumference to identify individuals with higher cardiometabolic risk	IIa	B	2,9,128

BMI: body mass index; CV: cardiovascular.

5. Arterial Hypertension

5.1. Introduction

AH is the most prevalent chronic disease in the world, affecting approximately one-third of the adult population. BP is maintained by several factors, particularly the intravascular volume, cardiac output, peripheral vascular resistance, and the elasticity of arterial vessels. Among the various regulatory mechanisms, RAAS – involving the renal system – has significant participation; an imbalance in this complex regulatory system, however, can result in chronic elevation of BP levels, known as AH. AH is one of the most important CV risk factors, as hypertensive individuals present much more atherosclerosis, leading to CVA, HF, coronary disease, peripheral vascular insufficiency, and kidney disease.[145]

Although we have efficient drugs with few adverse effects, the worldwide control of this condition still leaves much to be desired, since we are dealing with completely asymptomatic disease, a fact that makes care adherence very difficult.

According to the 7th Brazilian Guideline of Arterial Hypertension, an individual is hypertensive when his or her SBP and diastolic blood pressure (DBP) are equal to or higher than 140/90 mmHg (Table 5.1).[146] Figure 5.1 shows the flowchart for the diagnosis of hypertension.

Table 5.1 – Classification of blood pressure according to measurements taken casually or at the doctor's office in individuals aged 18 years and older[146]

Classification	SBP (mmHg)	DBP (mmHg)
Normal	≤ 120	≤ 80
Pre-hypertension	121-139	81-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	160-179	100-109
Stage 3 hypertension	≥ 180	≥ 110
When SBP and DBP are in different categories, the BP classification should assume the higher one		
Isolated systolic hypertension is determined when SBP ≥ 140 mmHg and DBP < 90 mmHg, and should be classified into stages 1, 2, or 3		

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure.

The genesis of primary AH is multifactorial, with genetic and environmental influences. Although the genetic mechanisms involved are still obscure, there is evidence that children of hypertensive individuals have a greater chance of becoming hypertensive. However, the environmental aspect has an essential role in the development of AH. As the individual ages, the prevalence of AH increases significantly; therefore, detecting predisposing factors is important to prevent this critical CV risk factor properly. Besides family history, age, ethnicity, and insulin resistance, there are also environmental factors related to the development of AH that can be modified, such as obesity, psychosocial aspects, diet, sodium intake, sedentary lifestyle, and alcohol consumption.

5.2. Physical Activity and Hypertension

Epidemiological studies suggest that regular aerobic physical activity can be beneficial in preventing and treating hypertension, as well as reducing CV risk and mortality. A meta-analysis with 93 articles and 5,223 individuals showed that aerobic training, dynamic resistance, and isometric resistance reduce SBP and DBP at rest by 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg, respectively, in the general population.[147]

Resistance training, but not other types of training, further reduces BP in hypertensive individuals (8.3/5.2 mmHg). Regular physical activity of lower intensity and duration reduces BP less than moderate or vigorous training but is associated with a decrease in mortality by at least 15% in cohort studies.[148,149]

This evidence suggests that hypertensive patients should be advised to practice dynamic aerobic exercise of moderate intensity (walking, running, cycling, or swimming) for at least 30 minutes 5 to 7 days per week. The practice of resistive exercises 2 to 3 days per week could also be recommended. Also, healthy adults could benefit from gradually increasing moderate aerobic physical activity to 300 minutes per week, vigorous aerobic physical activity to 150 minutes per week, or an equivalent combination of the two, ideally with supervised daily exercise.[6,9] The impact of isometric exercises on BP and CV risk is less well established.

Table 5.2 demonstrates the classification of physical activity intensity and the levels of absolute and relative intensity. Table 5.3 shows the v goals to prevent and treat AH.

Table 5.2 – Classification of physical activity intensity and examples of levels of absolute and relative intensity[9]

Classification		Absolute intensity	Relative intensity	
Intensity	MET	Examples	% HRmax	Talk test
Light	1.1 – 2.9	Cycling (< 4.7 km/h), light domestic chores.	50 – 63	
Moderate	3.0 – 5.9	Fast walking (4.8–6.5 km/h), slow-cycling (15 km/h), decorating, vacuuming, gardening, golf, tennis (in pairs), ballroom dancing, water aerobics.	64 – 76	Breathing is faster but compatible with complete sentences.
Vigorous	≥ 6.0	Running, cycling (> 15 km/h), heavy gardening, swimming, tennis.	77 – 93	Breathing is heavier, incompatible with a comfortable conversation.

Metabolic equivalent (MET) is the energy expenditure of an activity divided by the resting energy expenditure: 1 MET = 3.5 mL O_2 kg^{-1} min^{-1} oxygen consumption (VO_2). HR: heart rate; % HRmax: percentage of the maximum heart rate measured or estimated (220-age). Adapted from the 2016 European Guidelines On Cardiovascular Disease Prevention In Clinical Practice.[9]

Table 5.3 – Physical activity to prevent and treat hypertension[147,151-153]

Intervention	Objective	Approximate impact of SBP	
		Hypertension	Normotension
Aerobic	• 90 to 150 min/week • 65 to 75% of HR reserve	-5/8 mmHg	-2/4 mmHg
Dynamic resistance	• 90 to 150 min/week • 50 to 80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mmHg	-2 mmHg
Isometric resistance	• 4 × 2 min (handgrip), 1 min of rest between exercises, 30 to 40% of maximum voluntary contraction, 3 sessions/week • 8 to 10 weeks	-5 mmHg	-4 mmHg

5.3. Psychosocial Factors

Some psychosocial factors, such as work and family stress, depression, anxiety, hostility, and type D personality, as well as low socioeconomic and cultural status, increase the risk for AH – and consequently CVD – and reduce the adherence to a healthy lifestyle and drug treatment. On the other hand, CVD also increase the risk of manifesting these psychosocial factors, indicating a bidirectional and robust relationship.[154]

Moreover, the prevalence of CVD and AH is higher in developing countries, where the control rate of these diseases tends to be poor, decreasing life expectancy and increasing the pathologies and frailties related to aging.[155] Several prospective studies and systematic reviews have addressed socioeconomic status, showing that low schooling and income, low-status jobs, as well as living in poor residential areas are associated with the increase in BP levels and consequently CV risk.[156,157]

Individuals with mood and personality disorders present an increase in the incidence and worsening of the prognosis of CVD, especially among those with depression or anxiety.[157] Similarly, personality traits associated with hostility or distress also worsen the prognosis.[158]

The management of psychosocial stress with several existing techniques, among them meditation, music therapy, yoga, and slow breathing, can be crucial in preventing and controlling BP. In general, such techniques can mildly reduce BP levels in hypertensive individuals.[159,160]

5.4. Diets that Promote the Prevention and Control of Arterial Hypertension

In 2017, the Global Burden of Disease Group considered unhealthy diet as one of the main as risk factors for premature death and disability.[161] Adjustments in the diet of individuals with normotension (NT) or pre-hypertension (PH) have the potential of reducing BP and preventing AH.[162] National and international guidelines recommend that all patients with PH or AH reduce their sodium intake and consume adequate amounts of fresh fruit, vegetables, and low-fat dairy products.[163] Furthermore, these documents emphasize the importance of maintaining body weight and waist circumference within the normal range.[164]

Many dietary patterns have been proposed to prevent and control AH, as well as maintain global and CV health. Among the dietary models proposed, with different levels of evidence and effectiveness to prevent and control AH, we highlight the Dietary Approaches to Stop Hypertension (DASH), low-fat, high-protein, low-carbohydrate, moderate carbohydrate, low-glycemic index/low-glycemic load, low-sodium, vegetarian/vegan, Mediterranean, paleolithic, Nordic, and Tibetan[165] (Chart 5.1).

A meta-analysis of 67 studies published between 1981 and 2016 compared the effects of these dietary patterns on patients with PH and AH. DASH, Mediterranean, low-carbohydrate, paleolithic, high-protein, low-glycemic index, low-sodium, and low-fat were significantly more effective in reducing

Chart 5.1 – Methods and characteristics of dietary interventions proposed to prevent and control arterial hypertension

a. DASH: high consumption of vegetables and fruits, low-fat dairy products, whole grains, and low sodium intake

b. Mediterranean: high consumption of fruits, vegetables, olive oil, legumes, cereals, fish, and moderate intake of red wine during meals

c. Low-carbohydrate: < 25% of carbohydrates in the total energy intake; high consumption of animal and/or plant protein; in many cases, it has a high intake of fat

d. Paleolithic: lean meat, fish, fruits, leafy and cruciferous vegetables, tubers, eggs, and nuts, excluding dairy products, cereal grains, beans, refined fats, sugar, sweets, soft drinks, beer, and extra salt

e. Moderate carbohydrate: 25 to 45% of carbohydrates in the total energy intake; 10 to 20% of protein consumption

f. High-protein: > 20% of protein in the total energy intake; high consumption of animal and/or plant protein; < 35% of fat

g. Nordic: wholegrain products, plenty of fruits and vegetables, rapeseed oil, three fish meals per week, low-fat dairy products, no sugary foods

h. Tibetan: foods rich in protein and vitamins, preferably cooked and hot

i. Low-fat: < 30% of fat in the total energy intake; high consumption of cereals and grains; 10-15% of protein

j. Low-glycemic index: low-glycemic load

k. Vegetarian/vegan: without meat and fish/without animal products

l. Low-sodium: less than 2 g of sodium/day

Adapted from reference.[165]

SBP (-8,73 to -2,32 mmHg) and DBP (-4,85 to -1,27 mmHg) compared to the control diet.[165]

Regarding food supplements, several meta-analyses have evaluated the potential effects of additives on BP reduction with supplementation of certain substances in populations of individuals with NT, PH, and AH.[166] The effects of these supplements on BP reduction are usually mild, heterogeneous, and their statistical significance is difficult to assess. The substances whose supplementation has evidence of significant BP reduction are: potassium, vitamin C, food-derived bioactive peptides, garlic, dietary fiber, linseed, dark chocolate (cocoa), soy, organic nitrates, and omega-3.[167] Chart 5.2 shows the recommended mean daily portions, their potential impact on BP, the level of evidence, and the recommendation grade of each of these supplements, as well as other food interventions. Supplementation with calcium, magnesium, combined vitamins, tea, and coenzyme Q10 did not present a significant BP reduction.[168]

5.5. Alcohol and Hypertension

The relationship between alcohol consumption and hypertension is known since 1915, when a pioneer publication reported this association.[169] Several epidemiological studies corroborate the almost linear and dose-dependent relationship between alcohol and AH.[170]

The difficulty in determining the effect of alcohol on the development of AH is the difference in the quantification of the

Chart 5.2 – Dietary supplements and interventions with evidence of a potential reducing effect on blood pressure

Recommendation supplement or intervention SBP/DBP reduction	Recommendation grade	Level of evidence	Reference
Potassium: 90-120 mmol/day SBP/DBP= -5.3/-3.1 mmHg	IIa	A	166
Vitamin C: 500 mg/day SBP/DBP= -4.9/-1.7 mmHg	IIa	A	166
Bioactive peptides: 2.6-1500 mg/day SBP/DBP = -5.3/-2.4 mmHg	I	A	166
Garlic: 12.3-2400 mg/day SBP/DBP= -4.6/-2.4 mmHg	I	A	166
Dietary fiber: 11.5 g/day SBP/DBP= -2.4/-1.8 mmHg	I	A	166
Linseed: 28-60 g/day (crushed) SBP/DBP= -2.9/-2.4 mmHg	IIb	B	166
Dark chocolate: 46-100 g/day SBP/DBP= -2.9/-2.4 mmHg	I	B	166
Soybean: substituting 25g of dietary protein SBP -10%, DBP -7%	IIa	B	166
Organic nitrates: 15.5 ± 9.2 mmol +140-500 mL of beet juice/day SBP/DBP= -4.4/-1.1 mmHg	IIb	B	166
Omega-3: 3 to 4 g/day SBP/DBP= -4.5/-3.1 mmHg	I	A	166
Weight loss: - 5.8% / SBP/DBP= -4.4/-3.6 mmHg	I	A	166
Reduced alcohol consumption: - 67% / SBP/DBP= 3.9/2.4 mmHg	IIa	B	166

DBP: diastolic blood pressure; SBP: systolic blood pressure. Adapted from reference.[166]

consumption pattern, and the varying alcohol concentration of these beverages. Heterogeneous results originate from the influence of the type of beverage ingested, volume consumed, lifestyle, intake pattern, and socioeconomic status of the population studied.[171-172]

The INTERSALT study evaluated the consumption of 300 ml of ethanol weekly (34 g, 3 or 4 drinks/day) and found a BP increase in drinkers compared to non-drinkers.[173] Estimates indicate that excessive alcohol consumption is responsible for approximately 10-30% of AH cases.[174] The ARIC study followed 8,834 individuals for eight years and, at the end of the investigation, the patients with high alcohol consumption had a greater incidence of AH, regardless of the type of beverage, gender, or ethnicity. Moderate alcohol consumption was associated with risk of developing AH, not only in African Americans but also in the Brazilian population.[175] Approximately 6% of all-cause mortality worldwide is attributed to alcohol.[176] When ingested in a single dose, alcohol has a dose-dependent biphasic effect characterized by BP reduction, vasodilation, and increase in HR with a subsequent BP elevation.[177]

In a study using the Ambulatory Blood Pressure Monitoring (ABPM) in pre-menopausal women, the group who consumed 20-300 ml of red wine/day (146-218 g of alcohol/week) showed a significant increase in BP.[178] The same situation occurred in normotensive men who ingested an average of 40 g/day of ethanol, compared to the group who did not consume alcohol for four weeks.[179]

A meta-analysis with 15 RCTs, involving 2,234 participants, assessed the effects of reducing the consumption of ethanol on BP and estimated that a 2-mmHg reduction in DBP could decrease the prevalence of AH by 17%, the CAD risk by 6%, and the ischemic CVA and transient ischemic attack by 15%.[180]

5.6. Weight Loss and Prevention of Arterial Hypertension

Overweight is recognized as a factor related to BP elevation, and the greater the BMI, the higher risk for AH.[181] Central obesity and weight gain over time stand out as important factors for the development of AH. The Nurses' Health Study revealed that women who gained 5.0 to 9.9 kg and those who gained more than 25 kg in 18 years of follow-up had a higher risk for AH – 1.7 and 5.2, respectively. However, estimates suggest that only 26 to 40% of AH cases are attributable to overweight, emphasizing the multifactorial nature of AH.[182]

Weight loss as a non-pharmacological approach reduces BP in normotensive individuals and can prevent the development of AH. Changes in lifestyle are crucial for weight loss, focusing on the adoption of a hypocaloric diet and regular PA, with the reduction in caloric intake being more important than following specific diets.[183]

Regular isolated PA, without a concomitant dietary approach rich in fruits, vegetables, grains, seeds, nuts, fish, and dairy products, and poor in meats, sugars, and alcohol in general, is not enough for a significant weight loss.[184]

A meta-analysis of controlled studies with 4,184 individuals showed a reduction in SBP and DBP of 1.05 and 0.92 mmHg, respectively, for each 1 kg of weight lost. In healthy obese individuals, the combination of a low-calorie diet and BMI reduction was associated with an average decrease of 4.73/2.75 mmHg in SBP and DBP.[185]

A systematic review of studies with hypertensive subjects showed that the magnitude of BP reduction with weight loss was on average 4.5/3.2 mmHg for SBP and DBP, respectively, underlining that the greater the weight loss, the higher the BP reduction.[186]

The Framingham Study revealed a reduction in the risk of developing AH of 22 to 26% in individuals aged 30-49 and 50-65 years, respectively, who maintained a weight loss of 6.8 kg, in 8 years. In this context, regular PA stands as a measure of great importance in the maintenance of weight loss.[187]

5.7. Low-Sodium Diet in the Prevention of Arterial Hypertension

Prospective cohort studies have demonstrated that high sodium intake increases the risk of death and CV events. These studies also reported that decreasing sodium intake to below a certain value (approximately 3 g of sodium per day) further reduced BP. Paradoxically, low sodium intake was associated with an increased CV risk and risk of all-cause mortality in the general population and hypertensive individuals, suggesting a J-curve phenomenon. The mechanism of this apparent increased risk with low sodium intake is probably related to higher activity in the renin-angiotensin system under a very high restriction of salt in the diet. No epidemiological study has evidenced that very low sodium intake can be harmful.[10]

On the other hand, there is evidence of a causal relationship between sodium intake and an increase in BP. Excessive sodium intake (> 5 g of sodium per day) increases BP and is associated with a higher prevalence of systolic AH with aging.[188]

Many studies have shown that sodium restriction decreases BP. A meta-analysis revealed that a reduction of 1.75 g of sodium per day (4.4 g of salt/day) was associated with an average decrease of 4.2 and 2.1 mmHg in SBP and DBP, respectively, with a more pronounced effect in hypertensive individuals – 5.4 and 2.8 mmHg. The reducing effect of sodium restriction on BP is more significant in black people, older adults, and individuals with DM, MS, and chronic kidney disease (CKD).[164]

In Western populations, such as the Brazilian, the usual sodium intake is estimated between 3.5 to 5.5 g/day (which corresponds to 9 to 12 g of salt per day), with marked differences among countries or even regions.[189]

Sodium intake should be limited to approximately 2.0 g/day (equivalent to about 5.0 g of salt per day) in the population in general, but especially in hypertensive individuals.

The effective reduction of salt is not easy, and information about which foods have high levels of salt is often scarce. It is crucial that the population pay very careful attention to the amount of salt added to meals and with foods high in salt (processed products). Reducing salt intake remains a public health priority, but it requires a combined effort between the food industry, governments, and the general population since 80% of the salt consumed originates from processed foods. The adequate consumption of fruits and vegetables enhances

the beneficial effect of a low-sodium diet on BP, mainly due to the increased intake of potassium, known for reducing BP.

It is possible to prevent or postpone AH with a change in lifestyle, which can effectively promote the primary prevention of systemic arterial hypertension (SAH), especially in individuals with borderline BP.[10] Healthy lifestyle habits should be adopted since childhood and adolescence, respecting the regional, cultural, social, and economic characteristics of individuals (Chart 5.3).

5.8. Antihypertensive Control in Primary Prevention of Diabetes Mellitus and Metabolic Syndrome

BP control is one of the more robust tools for reducing CV risk. Reducing 20 mmHg in SBP can decrease CAD mortality by 40%, CVA mortality by 50%, and HF mortality by 47%. However, AH is still the most common and potent risk factor for loss of life expectancy, due to the suboptimal population control of this condition.[190-192]

Chart 5.3 – Recommendations on how to approach adults with high blood pressure or arterial hypertension

Recommendation	Recommendation grade	Level of evidence	Reference
Non-pharmacological measures are indicated for all adults with high BP or hypertension to reduce BP: weight loss, healthy eating habits, low sodium intake, dietary potassium supplementation, increased physical activity with a structured training program, and limited alcohol consumption	I	A	9,10,155,164,189
Antihypertensive drugs are recommended for adults at estimated risk ≥ 10% in 10 years and average SBP ≥ 130 mmHg or average DBP ≥ 80 mmHg, for primary prevention of CVD	I	A	9,10,155,164,189
A BP target < 130/80 mmHg is recommended for adults with confirmed hypertension and CV risk ≥ 10%	I	B	9,10,155,164,189
A BP target < 130/80 mmHg is recommended for adults with arterial hypertension and chronic kidney disease	I	B	9,10,155,164,189
A BP target < 130/80 mmHg, which should start if BP ≥ 130/80 mmHg, is recommended for adults with arterial hypertension and type 2 diabetes	I	B	9,10,155,164,189
Antihypertensive drugs are recommended for adults at estimated risk < 10% in 10 years and average BP ≥ 140/90 mmHg for primary prevention of CVD	I	C	9,10,155,164,189
In adults with confirmed hypertension, without additional markers of increased CV risk, the recommended BP target is < 130/80 mmHg	IIb	B	9.10,155,164, 189

BP: blood pressure; CVD: cardiovascular disease; DBP: diastolic blood pressure; SBP: systolic blood pressure.

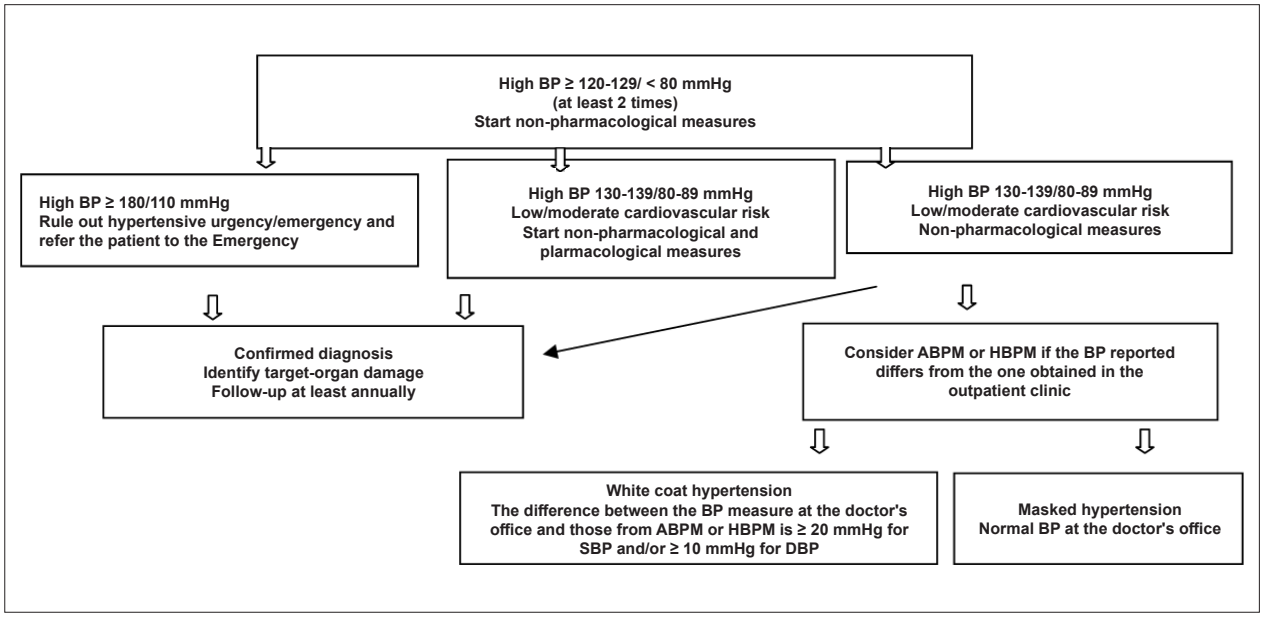

Figure 5.1 – *Flowchart for the diagnosis of arterial hypertension. BP: blood pressure; ABPM: ambulatory BP monitoring; HBPM: home BP monitoring. Modified from references.*[9,10,189]

Based on the non-automated measurement taken in the doctor's office, the recommended BP target is < 130/80 mmHg for individuals with stages 1 and 2 hypertension at low and moderate CV risk, and those with stage 3 hypertension at low, moderate, and high CV risk.[146] This recommendation is based on meta-analyses of randomized studies,[193,194] which demonstrated the superiority of this BP target compared to values above 150/90 mmHg. Decreasing this target to 130/80 mmHg seems to be safe in this lower-risk population, as observational[195] and some randomized studies corroborate,[194,196] although the additional benefit is relatively small and counterbalanced by the risk for symptomatic hypotension and adverse effects of drugs.

On the other hand, individuals with stages 1 and 2 hypertension at high or very high CV risk or with three or more risk factors, and/or MS, and/or target-organ damage should have BP levels < 130/80 mmHg.[146] In the SPRINT study,[197] among the 9,361 non-diabetic individuals at high CV risk (median of 24.8% in 10 years), 39% met the criteria for MS. The study population was randomized for a more (< 120 mmHg) and less intense (< 140 mmHg) reduction in SBP – automated BP measurement (on average, 10 mmHg lower than the SBP measured at the doctor's office with a non-automated method). Among patients with MS, the reduction in the primary outcome – comprising acute coronary syndromes, CVA, HF, or CV death – was similar to that of patients without MS after 3.26 years of follow-up. The most intense SBP treatment arm presented a decrease of 25% in the risk of primary outcome compared to that with less intense reduction (HR 0.75; 95% confidence interval: 0.57-0.96; p < 0.001).[198,199]

Among patients with coronary disease, the recommended BP target should be between 130 x 80 and 120 x 70 mmHg, particularly avoiding a DBP below 60 mmHg due to the risk for coronary hypoperfusion, myocardial damage, and CV events.[146] A J curve has been consistently identified in this population, with SBP < 120 mmHg and DBP < 70 mmHg being associated with higher mortality.[200]

6. Vitamins and Omega-3 Fatty Acids

6.1. Introduction

Several observational studies have found a strong association between the consumption of grains, fruits, and vegetables – foods rich in vitamins and minerals – and low CV mortality[201] and lower risk for myocardial infarction.[202] Given this strong evidence, numerous intervention studies have tested the impact of supplementation with micronutrients (vitamins) and certain fatty acids (omega-3 series) on primary and secondary prevention of CV events. From a practical point of view, most of these studies showed no clinical benefit related to supplementation in the doses studied and in the face of the drug therapies used to prevent CV. Tables 6.1. to 6.3 summarize the recommendations for and against the use of these supplements.

6.2. Carotenoids

Carotenoids are a class with over 600 compounds, responsible for the yellow, red, and orange pigments in plants, with α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin being the most commonly found in food. Known primarily as precursors of vitamin A, carotenoids are also essential suppressors of free radicals and act as potent antioxidants.[203] The evidence for the role of carotenoids in CVD originated from studies showing that increased consumption of fruits and vegetables was associated with a lower risk for CVD.[204] A series of retrospective and prospective longitudinal studies identified an inverse association between carotenoid intake and risk for CVD.[204] However, the effect of carotenoids is complex and probably does not result from a single isolated compound. In contrast, prospective randomized studies showed no benefit of carotenoid supplementation for CVD.[204,205] Corroborating this information, a cross-sectional analysis, consisting of 894 members of the cohort study Kardiovize, revealed that the consumption of foods containing vitamins (carotene, zinc, selenium, and vitamins A and C) was associated with a reduction in the intimal thickening of the

Table 6.1 – Summary of the recommendations for the non-consumption of vitamin supplements to prevent cardiovascular diseases

Recommendations	Description	Recommendation grade	Level of evidence	References
Vitamin A or beta-carotene	There is no evidence of the benefit of vitamin A or beta-carotene supplementation for primary or secondary prevention of CVD	III	A	204,205
Vitamin B and folic acid supplements	They are not effective in preventing primary or secondary CVD	III	A	164,208
Vitamin D	Vitamin D supplementation is not recommended to prevent CVD in people with normal blood levels for this vitamin. Similarly, there is no evidence that its supplementation in individuals with deficiency will prevent CVD	III	A	215,216,217
Vitamin E	Vitamin E supplementation is not recommended to prevent CVD	III	A	205,208
Vitamin K	In the same way, there is no evidence that vitamin K supplementation, in its different forms, can prevent CVD	IIa	C	219,220

CVD: cardiovascular disease.

Table 6.2 – Recommendations for the consumption of and/or supplementation with products rich in omega-3 fatty acids

Recommendation	Recommendation grade	Level of evidence	References
Supplementation with 2-4 grams of marine omega-3 per day or even higher doses should be recommended for severe hypertriglyceridemia (>500 mg/dL in the absence of familial chylomicronemia), with risk for pancreatitis, refractory to non-pharmacological measures and drug treatment	I	A	235
At least two fish meals per week should be recommended as part of a healthy diet to decrease the CV risk. This recommendation is particularly aimed at individuals at high risk, such as those who already had myocardial infarction	I	B	32
Omega-3 supplementation (EPA) at a dose of 4 g per day can be administered to patients in secondary prevention who use statins and have TG between 150-499 mg/dL	II	B	227
Omega-3 supplementation at a dose of 1 g/day (EPA+DHA) can be administered to patients with HF functional class II to IV	II	B	235
Supplementation with EPA+DHA is not recommended for individuals in primary prevention, whether or not they are on preventive treatments based on evidence	III	A	231

CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; HF: heart failure; TG: triglycerides.

Table 6.3 – Recommendation for the consumption of foods rich in omega-3 fatty acids of plant origin

Indication	Class	Level of evidence	References
Stimulating the consumption of omega-3 polyunsaturated fatty acids of plant origin as part of a healthy diet can be recommended to reduce the CV risk, although the real benefit of this recommendation is debatable, and the evidence is inconclusive	IIb	B	238
ALA supplementation is not recommended to prevent CVD	III	B	

ALA: alpha-linolenic acid; CV: cardiovascular; CVD: cardiovascular disease.

carotids in women.[206] In this research, the authors developed a "dietary antioxidant index" to categorize the foods, excluding individuals who used antioxidant supplements. Therefore, the use of supplements only with carotenoids, β-carotene, or similar compounds is not recommended. Instead, efforts should be directed toward increasing the consumption of fruits and vegetables rich in these nutrients.

6.3. Vitamin E

Vitamin E is the main fat-soluble antioxidant in the human body and is present in a complex of four isomers (α-, β-, γ-, and δ-tocopherol). The interest in the potential benefit of vitamin E for risk of CVD was related to its antioxidant capacity and the possibility of modifying oxidized low-density lipoprotein (Ox-LDL), particularly involved in atherogenesis.[207] However, prospective randomized studies, such as the ATBC, CHAOS, GISSI, and HOPE, showed no benefit of vitamin E supplementation for CVD.[205,208] The effect of supplementation with vitamin E and vitamin C on alternate days for eight years on 14,641 individuals did not reduce the incidence of myocardial infarction, CVA, and CV mortality, in addition to being associated with an increased incidence of hemorrhagic CVA.[209] Despite the solid molecular basis theory of oxidative stress and its role in atherosclerosis, these clinical trials do not corroborate the use of vitamin E supplementation to prevent CVD. On the other hand, consuming foods containing vitamins E, A, and C was associated with a lower risk for adverse CV outcomes, as demonstrated in the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS), a longitudinal study comprising 875 participants.[210] Thus, the consumption of foods with vitamin E has proven to be more effective and safe, and vitamin E supplementation is not recommended to prevent CVD.

6.4. Vitamin D

Vitamin D is an important precursor of the steroid hormone calcitriol, which is crucial for mineral and bone metabolism. In addition, it has other functions and supplementation with this vitamin to prevent and treat a wide range of diseases has increased considerably in the past decade.[211] Its two main forms are vitamin D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 can be synthesized by human skin cells after exposure to UV-B radiation from sunlight. In the absence of sunlight, the intake of vitamin D is crucial. Vitamin D and dietary supplements are absorbed by the intestine and then converted into 25-hydroxyvitamin D3 [25(OH)D] in the liver, and 1.25 dihydroxyvitamin D3 [1.25(OH)2D3], the active form of vitamin D, in the kidney. Zittermann et al.[212] summarized the underlying mechanisms for the potential role of vitamin D in preventing coronary disease. They include inhibiting the proliferation of vascular smooth muscle, suppressing vascular calcification, down-regulating pro-inflammatory cytokines, up-regulating anti-inflammatory cytokines, and acting as a negative

endocrine regulator of the renin-angiotensin system. Low concentrations of circulating vitamin D were associated with AH, obesity, DM, and MS; furthermore, observational studies associated the deficiency of this vitamin with the risk for CVD.[212,213] Some ecological studies suggest that vitamin D has a role in CVD, showing an increase in cardiac disease events according to the geographical latitude, that is, associated with lower exposure to solar radiation, with the concentration of vitamin D decreasing with latitude. Several prospective studies have investigated the association between plasma concentration of 25-hydroxyvitamin D and CVD, indicating an inverse relationship between the concentrations of this vitamin in the blood and the risk for CVD.[213,214] Despite this evidence, data from a systematic review conducted by Beveridge et al.[215] showed a lack of consistent benefit of vitamin D supplementation for the main markers of endothelial and vascular function.[215] A randomized, controlled, double-blind study that lasted 5.3 years tested the efficiency of daily supplementation with 2,000 IU of vitamin D3 (cholecalciferol) in 25,871 participants.[216] The primary outcomes assessed were myocardial infarction, CVA, and mortality from all CV causes, in addition to secondary outcomes of CV events. Vitamin D supplementation did not result in a lower incidence of CV events compared to placebo. The ViDA (Vitamin D Assessment) trial involved 5,108 participants in New Zealand aged 50-84 years. In the treatment group, participants received an initial dose of 200,000 IU followed a month later by 100,000 IU or placebo for an average of 3.3 years. The study found no significant reduction in CVD and mortality in the group that received vitamin D in comparison with the placebo group.[217]

Although observational studies demonstrate a positive association between low concentrations of 25hydroxyvitamin D and the risk for CV events, its supplementation is not indicated to prevent CV at the moment. However, studies with an adequate design still need to prospectively investigate populations with prominent deficiencies, especially patients with CKD, and other doses of this vitamin.[218]

6.5. Vitamin K

The review prepared by the Cochrane Library could not assess the effectiveness of vitamin K supplementation in decreasing all-cause mortality, including CV and non-fatal outcomes (myocardial infarction, CVA, and angina), in depth because only one study met the pre-established inclusion criteria.[219] This study comprised 60 individuals aged 40-65 years investigated for three months and revealed that vitamin K2 did not change their BP and concentration of plasma lipids. The very limited results of this review highlight the lack of robust data about the efficiency of vitamin K in the primary prevention of CVD. However, the authors declared that the evidence for this assertion was minimal.

A recent systematic review and meta-analysis, registered as the PROSPERO study, analyzed the results of 13 clinical trials that evaluated the effects of vitamin K supplementation on cardiometabolic risk factors in healthy individuals or a population at high risk for CVD. The study found no benefit for plasma lipids, inflammatory cytokines – such as CRP and interleukin-6 – SBP, and DBP, both in healthy individuals and among those at CV risk.[220] Therefore, the literature has no evidence to recommend vitamin K for CV prevention.

6.6. Vitamin C

Vitamin C or ascorbic acid is soluble in water and a very effective antioxidant since it loses electrons easily. The free radical theory of the aging process clarifies its role in the progression of chronic diseases.[207] The Japan Collaborative Cohort Study (JACC)[221] assessed food intake in 23,119 men and 35,611 women aged 40 to 79 years without a history of CVD, and showed that the consumption of foods rich in vitamin C was inversely associated with mortality from CVD in Japanese women. Despite the beneficial effects of consuming foods rich in vitamin C shown in observational studies, RCTs do not confirm the efficiency of its supplementation in primary or secondary prevention of CVD.[222] Consequently, vitamin C supplementation is not recommended to prevent CVD.

6.7. B Vitamins and Folate

Evidence of a connection between vitamin B and CVD was demonstrated by the effect of these vitamins on the reduction of homocysteine.[223,224] Homocysteine, an amino acid containing sulfur, is a metabolite produced indirectly in the demethylation of methionine. Prospective studies have shown an independent but modest association between plasma concentrations of homocysteine and the risk for CVD.[223] Some factors identified as associated with high concentrations of homocysteine are: inadequate intake of folic acid and vitamins B6 and/or B12; for this reason, the growth in plasma concentrations of homocysteine can only be one follow-up marker of an inadequate diet. Other factors that might be associated with increased homocysteine include: preexisting atherosclerotic disease, consumption of coffee and alcohol, smoking, DM, use of antiepileptic drugs or methotrexate, renal failure, rheumatoid arthritis (RA), hypothyroidism, and cystathionine beta-synthase and methylenetetrahydrofolate reductase mutations. Prospective randomized studies with a large number of CV events failed to show any benefit of folate and B complex supplementation in reducing homocysteine and preventing CVD.[208] The disagreement between the results of epidemiological studies and clinical trials might be partially due to the inclusion of different populations and the use of folic acid-fortified foods in some countries. Folic acid or B complex supplementation is not recommended to prevent CVD.[224]

A recent observational study conducted in 195 countries reiterated the efficiency of consuming foods containing vitamins to prevent CV risk and mortality, associating the mortality rate of CVD attributed to diet with low intake of fruits, grains, and vegetables.[164] In conclusion, based on current evidence, a diet rich in vitamins must be encouraged; however, there is no indication that supplementation with these compounds can prevent CV events.

6.8. Omega-3 Polyunsaturated Fatty Acids of Marine Origin (Docosahexaenoic Acid and Eicosapentaenoic Acid)

Omega-3 fatty acids of marine origin – docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) – produce numerous effects on different physiological and metabolic

aspects that can influence the chance of developing CVD.[225,226] Despite the general agreement that regular consumption of fish rich in omega-3 fatty acids is part of a healthy diet, recommending dietary supplementation with fish oil capsules is controversial, fostered by conflicting results of clinical studies.[32,227-229]

6.9. Effects of Omega-3 on the Lipid Profile

Clinical studies show that 2 to 4 grams of EPA/DHA supplementation per day can reduce TG levels by up to 25 to 30%, slightly increase HDL-c (1 to 3%), and raise LDL-c by 5-10%.[32] The ability to decrease TG levels depends on the dose, with a reduction of approximately 5 to 10% for each 1 g of EPA/DHA consumed per day, which can be higher in individuals with greater baseline TG concentrations. These data show that high doses of omega-3 supplementation can be used to treat hypertriglyceridemia.

6.10. Omega-3 and Cardiovascular Outcomes

In a meta-analysis of 36 RCT, supplementation with fish oil (median dose of 3.7 g/day) reduced SBP by 3.5 mmHg and DBP by 2.4 mmHg.[230] The decrease in adrenergic tonus and systemic vascular resistance is a proposed mechanism. Although several old pieces of evidence suggest a protective effect of fish and omega-3 fatty acids of marine origin on CV events,[230] particularly in individuals with established CVD, more recent studies, showed no benefit of omega-3 supplementation for subjects who had or had not presented manifestations of atherosclerotic disease.[227,228] In fact, a meta-analysis of 10 studies involving 77,917 individuals both in secondary (64% with prior coronary disease, 28% with prior CVA) and primary prevention (37% of diabetic individuals) failed to show any benefit of omega-3 supplementation (EPA doses ranging from 226 to 1,800 mg/day and DHA from 0 to 1,700 mg/d) after a mean follow-up of 4.4 years, presenting 6,273 coronary events (2,695 coronary deaths).[231] These results were confirmed in an extensive systematic review and meta-analysis by the Cochrane group, with more than 119,000 individuals from 79 randomized studies.[232] Also, the same meta-analysis did not find the benefit of supplementation with alpha-linolenic acid (ALA), the plant omega-3. Possible reasons for the divergent results between old and contemporary studies concern the profile of the population studied, mainly regarding the more frequent use of medicines known as protectors (e.g., statins, beta-blockers, ACEI), the more aggressive control of traditional risk factors, and the higher number of myocardial revascularization procedures in more recent studies. Another difficulty in analyzing studies with omega-3 supplementation is the diversity in its composition and the lack of control regarding the intake of omega-3 in the diet.

More recently, two published clinical trials used low doses (up to 1 g/day of EPA + DHA) of omega-3 in primary prevention of CVD. One of them has assessed the role of omega-3 in the primary prevention of CVD and cancer among men over 50 years of age and women over 55 years of age (VITAL study).[233] Using a formulation containing 460 mg of EPA and 380 mg of DHA, the study included 25,871 patients with a median follow-up of 5.3 years and found no benefit of omega-3 in reducing major CV event or invasive cancer.[233] Another study on primary prevention, but in diabetic patients, also examined the combination of EPA/DHA in the same composition of the VITAL study. It included 15,480 diabetic patients followed for an average of 7.4 years and found no benefit of omega-3 in reducing major vascular event.[234] Thus, the role of omega-3 fatty acids in the doses used with respect to the primary prevention of CV events is questionable.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)[33] tested omega-3 in the reduction of CV outcomes among patients with hypertriglyceridemia and established CVD or diabetic patients with an additional risk factor. The patients received highly purified EPA (icosapent ethyl) at a dose of 4 g/day. The study included 8,179 patients who used statins and had TG ranging from 135 to 499 mg/dL (median of 216 mg/dL) and a median LDL-c of 74 mg/dL. The median reduction was 18% for TG and 6.6% for LDL-c in the EPA group. REDUCE-IT showed a relative decrease of 25% in composite CV outcomes among patients who received EPA and an absolute risk reduction of 4.8%, NNT of 22 patients to prevent an event. The hierarchical analysis demonstrated a significant decrease of 20% in CV mortality. On the other hand, the risk of hospitalization for atrial flutter or fibrillation presented a relative increase of 67% (1% absolute) with the treatment. The reduction of events in the REDUCE-IT study is similar to the results of the Japan EPA Lipid Intervention Study (JELIS), in which 1.8 g/day of EPA also led to a significant decrease in CV events among individuals who already used low doses of statins.[227] However, the results of this last study are limited by their open design and lack of a placebo group.

Data from these studies suggest that high doses of EPA (4 g) can be used in patients with prior CVD and who remain with elevated TG levels, despite taking statins to prevent CVD. However, there is no evidence for the use of lower doses and other formulations of omega-3 for CV prevention, both primary and secondary. We emphasize, however, that several studies are still testing moderate to high doses of EPA and EPA + DHA in individuals at high risk for CVD who present persistent moderately high TG.

6.11. Omega-3 in Heart Failure

The GISSI-Heart Failure (GISSI-HF) trial evaluated the role of omega-3 in HF.[235] This study randomized patients with chronic HF functional class II-IV of different etiologies to receive 1 g of omega-3 (EPA + DHA) (n = 3,494) or placebo (n = 3,481) per day.[235] The primary outcome was time to death and time to death or hospitalization for CV causes. During a median follow-up of 3.9 years, the omega-3 group presented lower mortality rate (27 versus 29%, HR 0.91, 95% confidence interval 0.83–0.99, p = 0.041, with NNT = 56) and lower incidence of primary outcome (57 versus 59%, HR 0.92, 95% confidence interval 0.84–0.99, p = 0.009, with NNT = 44).[235] Data from this study, however, need to be confirmed.

6.12. Omega-3 Polyunsaturated Fatty Acids of Plant Origin

ALA has shown inconsistent effects on lipid levels.[236,237] A systematic review and meta-analysis of 14 randomized controlled trials with ALA supplementation found no significant influence on TC, LDL-c, or TG and only a minimal effect on HDL-c (a 0.4 mg/dL reduction).[238]

Specifically, the effects of linseed on experimental animals range from zero to a slight lipid decrease, and a review suggested a reducing impact on TG due to humans consuming large amounts of linseed oil.[238] Observational studies indicate a modest reduction in the risk for CVD with the consumption of ALA.[238] Data from the Alpha-omega study showed no benefits of ALA supplementation in preventing CVD among individuals who had a prior CVD. More recent data from the Cochrane group meta-analysis suggest that increasing the intake of ALA probably makes little or no difference in all-cause mortality, CV mortality, and coronary events.[232] Its effects on CVA are unclear. However, the authors recognize the low quality of most studies; therefore, further studies on ALA supplementation are necessary to prove or refute its effectiveness in preventing CVD. We can conclude that, at the moment, there is no evidence to recommend ALA supplementation to prevent CVD. Table 3.3 presents the recommendations for ALA consumption and supplementation.

7. Smoking

7.1. Introduction

Smoking control in Brazil has been considered as a model, not only for its programming, but for the results, with tobacco use being reduced by at least half when compared to the last decades of the 1900s. Increased cost-effective taxes, a ban on advertising, a ban on indoor use (smoke-free laws), the sale of tobacco products to minors, discussion of the subject in the school curriculum, and warnings and information about Harmful effects of smoking on schools, universities, the media, and on cigarette packs themselves were effective measures to reduce smoking. There are currently over one billion smokers in the world. Brazil is considered one of the countries in the world that has most reduced the prevalence of smokers in the last thirty years. In 1989, about 32% of the population over the age of 15 were smokers, according to the National Health and Nutrition Survey of the Brazilian Institute of Geography and Statistics (IBGE). In 2018, the VIGITEL Survey of the Ministry of Health, through a telephone survey in 27 Brazilian cities, found a frequency of adult smokers over 18 years of age of 10.1%, being higher in males (13.2%) and lower in females (7.5%). The highest frequencies were found in men between the cities of Curitiba and Porto Alegre (17.3%) and São Paulo (15.6%).[239] For the CV system, continued long-term use of tobacco and its derivatives leads to the onset of chronic diseases, which will manifest around 30 years after the start of regular smoking. As most smokers become addicted to nicotine before age 18, the health consequences are disastrous given the long exposure of the body to the harmful components contained in cigarettes. Therefore, prevention is the key to this health catastrophe.

Smoking Prevention: Despite worldwide tobacco control efforts, the number of nicotine addicts is still substantial. Effective public policies against the sale, advertising and use of cigarettes in public areas are important tools in primary prevention, as they prevent non-smokers, especially children and adolescents, from being exposed to nicotine. Therefore, the experimentation rate should be reduced in young people under 15 years of age. This initiative will surely reduce the number of potential tobacco users.

Primordial prevention of smoking: "Primordial prevention of smoking" is understood to be established before the initiation of smoking. It first identifies the risk factors for smoking, with a wide range from the individual's own vulnerability, such as the surrounding social determinants. Providing a personalized and continuing education and enabling information exchange requires the formation of a multidisciplinary team.[240] The aim of this team is to work with individuals and their families on the risks of smoking, to outline strategies to prevent them from smoking and to promote health.[241,242]

Factors that contribute to starting smoking:

1. ***Attitudes and beliefs:*** a study of adolescents[243] showed that 40% of those who had never smoked became experimenters and that 8% had a smoking habit for 4 consecutive years.[244] The lack of a firm decision not to smoke was the strongest predictor of experimenting;
2. ***Influence of friends and family:*** the presence of smokers among family and friends is an important predictor of tobacco initiation during adolescence; refusing a cigarette in the face of social pressure is a challenge for most teenagers, and only 44% of them can refuse a cigarette at a party;[245]
3. ***Age:*** both positive and negative attitudes towards smoking are more pronounced in adolescence;[246]
4. ***False conception:*** adolescents tend to overestimate the frequency of smoking among adults[247] and to underestimate their own;[248]
5. ***Advertinsing:*** magazines and movies are main advertising sources promoting adolescent smoking;
6. ***Nicotine dependence:*** nicotine is a highly addictive substance, and many individuals develop dependence after a few days or weeks of exposure.[249] Young people are more vulnerable than adullts to nicotine dependence;[250]
7. ***Other risk factors:***

- *Depression:* the majority of studies show a relation between the presence of depression and the initiation of smoking, allthough it is not clear if the association is causal;
- *Poor school performance:* missing classes and poor school performance are associated with initiation and continuation of smoking;[251,252,253]
- *Adverse experiences:* separation of parents or divorce, physical emotions; emotional physical, or sexual abuse; growing up among family members who are addicted, mentally ill or imprisoned;[254,255]
- *Substance abuse:* there is a high frequency of smokers among adolescents who use illicit drugs,[256] so every

adolescent who smokes should be considered potentially engaged in other risky behaviors.

7.2. Strategies in Combating Smoking Initiation[257,258]

One way to approach primordial prevention is by age groups, observing for each group five main items (5 As):

Group 0 to 4 years: Ask parents and other family members about their smoking habits; advise to keep the environment free of cigarette smoke; the message should include information about the risks to parents and children, as well as the importance of the parental model; assess willingness to cooperate between parents and other family members; assist parents with trying to quit by informing them about self-help material and/or referring them to their own doctors; make an appointment with clinic within 3 months if a relative is a smoker; check parental progress at each subsequent pediatric visit.

5 to 12 years old group: Ask children about how they feel when someone is smoking nearby and what they do about it if they think it is dangerous to try smoking and if they think they will smoke when they are older, if they have tried smoking or if they have friends who smoke; advise children not to try smoking, praise them for remaining a non-smoker and/or staying away from cigarette smoke; remind children about the short-term negative effects of tobacco, such as reduced ability to smell and athletic capacity, as well as personal health risks (e,g., asthma exacerbation); advise parents to quit smoking and to give clear anti-smoking information to their children; assess the risk factors of smoking initiation or regular smoking progression, including level of experimentation, smoking among friends, depressive symptoms, school performance and adverse experiences; help parents in trying to quit smoking; assist children with developing skills to refuse smoking and exposure to it; assist parents in efforts to prevent tobacco use by their children through parenting and firm anti-smoking messages; make an appointment with clinic within 1-2 months for any child who is smoking or has worrisome risk factors for smoking, refer as necessary cases of social or learning difficulties and mental disorders as well.

Group of adolescents and young adults: ask adolescents about smoking behavior, confidentially about friends who smoke and about light cigarettes; advise adolescents to stop smoking, reinforcing personal health risks and danger of addiction; commend adolescents who are not smoking and remind them about the health risks; assess the motivation and symptoms of tobacco dependence among adolescents who are smoking; assess risk factors for smoking initiation among non-smokers; assist adolescents who are smoking with trying to quit, including nicotine replacement and referring if necessary; help parents with their efforts to prevent smoking initiation among their children through parenting and firm anti-smoking information; make an appointment with clinic within one month for each teenager who is smoking, supporting attempts to quit or assessing motivation and barriers to quitting; refer as necessary if risk factors are identified, such as social or learning difficulties, or findings of mental disorders.

Primordial Prevention of CVD, in its broadest context, it involves avoiding the establishment of modifiable CVD risk factors, including smoking, and effective strategies for promoting CV health of the individual and the population. Therefore, the joint action of interdiscipline teams (doctors, nurses, psychologists, physical educators, educators, nutritionists, social workers, communicators, managers) and intersectoral (family, school, government, society specialists, university) teams is necessary in a continuous and simultaneous way.

7.3. How to Treat Smoker's Psychological Dependence

Nicotine addiction is a highly complex process that should be addressed by all health professionals. Every healthcare professional, especially the doctor during consultations, as well as the multidisciplinary team, should ask if the patient is a smoker. This question is essential. If the patient is a smoker, two types of approach can be used.

Basic approach where the goal is to ask if you smoke, to evaluate the smoker's profile, to advise to quit smoking, to prepare for cessation and to accompany the smoker to the cessation of smoking. This approach should always be performed by the physician during the routine consultation, with an average duration of 3 (minimum) to 5 (maximum) minutes with each contact the patient makes. The patient should be questioned and asked systematically at each consultation and feedback on the evolution of the cessation process. Suitable for all smokers. Meta-analysis involving 29 studies showed that cessation rates were 19.9% for those who underwent medical intervention.[259]

Specific Intensive Approach: performed by health professionals available and trained to make a more in-depth follow-up with the patient, including the doctor. In this case, the professional should have a structured program available to the patient with scheduled sessions (8 group/individual sessions), and will use national reference medication for treatment of smoking, as well as the cognitive behavioral approach. If possible, the patient should be followed up to 1 year of treatment. The cognitive behavioral approach is a psychological approach that is based on working out the automatic thoughts that the smoker has and that lead him/her to get a cigarette. These thoughts are often accompanied by emotion and behaviors associated with smoking. It is important for the patient to feel welcomed by the doctor, to show empathy, not to judge or condemn because of difficulties in smoking cessation. Another aspect is that the better the smoker knows his/her addiction profile, the easier it is to work on ways to control smoking addiction.[259,260]

In the cognitive-behavioral approach it is necessary to: distinguish the patient's automatic (dysfunctional) thoughts - example: "if I do not smoke I cannot think" - helping him to seek coping strategies for situations other than getting a cigarette. Behavioral techniques most commonly used: self-observation, control of stimuli or triggers that lead to smoking (telephone, computer, alcohol, bathroom, car), identification and learning of functional thinking patterns, relaxation techniques, deep breathing, postponement and breaking of conditioning, assertiveness training (so that one can face situations where there is the temptation to smoke), self-instruction (situations in which patients are taught to argue

with themselves about the situation that tries to induce them to smoke) and problem-solving so that patients are taught about appropriate ways to solve a problem situation.[260-262]

Instruments that help in assessing and understanding the patient profile:

- ***Prochaska and Di Clemente Scale for Behavior Change:*** This scale provides a model that allows one to clearly and objectively evaluate which phase of behavior change the patient is in. Quitting smoking is a dynamic process that repeats over time and has different stages. At each stage, the individual uses different cognitive and behavioral processes.[263] The authors propose five different stages in this process. Pre-contemplation is characterized by the absence of intention to change behavior. The individual does not perceive, in this case, the act of smoking as a problem. Contemplation implies some awareness of the problem. It is perceived, and there is an intention to change, but there is no notion of when, so there is no commitment. Preparation is the pre-action stage. There is a clear intention to change, the individual already has some initiatives regarding change, but the action is not yet effective. Action is already a behavior change to try to solve the problem. The individual spends time looking for treatments and promotes changes that must be sustainable. Maintenance is the stage at which such changes must be consolidated, encompassing all that has been achieved at the action stage. The problem is that these stages do not occur sequentially in the process of change, but rather in a spiral way; that is, the individual may be at an earlier stage, and at some point, for some reason, regresses to an earlier stage. and then evolves again. When he returns to an early stage of pre-contemplation, he may relapse back to his previous smoking pattern. The individual can start the whole process again, and be able to abstain once again. Basic signs that indicate that the smoker is ready for change: has less resistance, asks fewer questions about the problem (addiction), asks more questions about change (what and how to do it), takes a resolving attitude (feels decided), makes more self-motivational claims, talks about life after change (difficulties and benefits), begins to experience some changes (decreased smoking).
- ***Motivational Interviewing:*** It is a viable alternative in the treatment of dependent behaviors within brief interventions, as the initial impact seems to influence the motivation for behavior change. Motivational interviewing employs a particular way of assisting in recognizing present or potential problems as well as in behavioral change aimed at solving such problems. Motivational Interviewing Strategies: Providing Guidance, Removing Barriers/ Assisting Obstacles, Providing Alternative Smoking Options, Decreasing Undesirable Aspects of Behavior, Practicing Empathy, Giving *Feedback*, Clarifying Objectives, and Actively Assisting and Taking Care of Relapse Prevention - Coping With Abstinence.[264]
- ***Fagerström Scale:*** This is an evaluation scale that allows us to determine the degree of physical dependence on nicotine. It should be used in the initial assessment of the smoker on arriving for treatment. If medication is needed, it helps to determine which medication is best and how much to take.[265,266] In this case, it is noteworthy that the use of medication should not be considered only in cases where Fagerström is ≥ 5. It is known today that a very low Fargeström means that psychological dependence is very high and in this case the medication helps in reducing withdrawal symptoms.[260]
- ***Reason for smoking scale:*** This is a rating scale that allows us to check in which situations the smoker uses the cigarette. It has to do with physical, psychological dependence and conditioning and helps to clarify to smokers the risk situations of their daily life. This scale assesses: stimulation, ritual handling, pleasure in smoking, tension reduction/relaxation, physical dependence, habit/automatism, and social smoking. These items should be worked through throughout the smoker's intensive approach process.[267]

7.4. Pharmacological Treatment of Smoking

7.4.1. Secondary Intervention Smoking

The CV effects of smoking are harmful, so CVD is the leading cause of death among smokers.[268] Smokers with CVD should stop smoking.[269]

The safety of first-line anti-smoking drugs such as varenicline, bupropion and nicotine replacement has been reiterated by clinical studies designed[270] to answer publication questions that suggested there may be CV risk with the use of anti-smoking medication.[271] The CATS study,[270] among others, proved that there is no such risk. Thus, respecting the contraindications of each product, the use of these drugs should be encouraged so that the patient can really quit smoking, as the drugs increase cessation success rates.[272]

The prescription of anti-smoking drugs is essential for improving the effectiveness of smoking treatment, as well as conducting follow-up appointments and encouraging changes in patients' habits and behavior.[273,274]

The main features of first-line anti-smoking drugs are:

1. Nicotine Replacers (Chart 7.1)

Nicotine is primarily responsible for cigarette addiction and nicotine replacement therapies (NRT) have been used since 1984 to help smoking cessation. The forms of NRT currently used and available in Brazil are transdermal and oral (lozenges and chewing gums). Both are effective in smoking cessation and are often used in combination and can double the rate of smoking cessation compared with placebo.[268,275]

2. Transdermal Nicotine

Effectiveness - compared to placebo - RR = 1.9 (95% CI 1.7-2.2).

6-Month abstinence rate - RR= 23.4 (95% CI 21.3-25.8).

- Doses: 21 mg; 14 mg; 7 mg.
- Presentation: patches for transdermal application.
- Route(s) of administration: transdermal application with daily replacement.
- Dose schedule: use of each presentation for 4 weeks on average, with gradual dose reduction. e.g.: (21, then 14, then 7 mg/day).

Chart 7.1 – Initial evaluation in approach to smoking[300]

Anamnesis
• Scales: Fagerström (for nicotine dependence)[265] – Table 7.2
• Prochaska and DiClementi (for motivation)[263] - check the patient's counseling techniques - Table 7.3
• Clinical and/or psychiatric comorbidites (diabetes, hypertension, depression, alcoholism, stroke, convulsion, cancer)
• Continuous use medications
• Risk factors for CVD (dyslipidemia, uso of oral contraceptives or estrogen)
• Pregnancy or breastfeeding
• Questions about smoking:
- How long have you been smoking
- How many cigarettes do you smoke per day
- Have you tried to quit smoking and what was the result
- Are you interested (or thinking) about quitting smoking?
• Questions about smoking cessation:
- Are you considering a date to quit smoking and would you like help
- If you have tried to quit, if you have succeeded, if you have taken any medication and how long you have been without smoking
Physical examination
• Monitor BP, especially during bupropion use
• Monitor weight: weight gain can be a barrier to starting smoking cessation and a predictor of relapse
Complementary examinations
• Complete blood count, liver function tests, blood glucose, lipid profile and serum biochemistry
• Chest X-ray
• Electrocardiogram
• Spirometry (not always readily available)
• Measurement of COex, if possible. This parameter is directly related to carboxyhemoglobin and cigarettes smoked per day. The cutoff point is 6 ppm

COex: carbon monoxide; CVD: cardiovascular disease; BP: blood pressure.

- Care in administration: application to upper chest, anterior and posterior region, and upper lateral region of arm.
- Adverse reactions: itching and redness at the application site, nausea, feeling sick, tachycardia with overdose.
- Contraindications: Dermatological disorders that prevent the application of the patch, 15 days after episode of acute myocardial infarction (AMI), pregnancy and breastfeeding.
- Overdose (toxicity): nausea, feeling sick, tachycardia, hypertensive crisis.

3. Nicotine for oral use - nicotine gum or lozenge

Effectiveness - compared to placebo RR = 2.2 (95% CI 1.5-3.2).

6-Month abstinence rate - RR= 26.1 (95% CI 19.7-33.6).

- Doses: 2 and 4 mg.
- Presentation: chewing gum or lozenge.
- Route(s) of administration: oral.
- Dose schedule: use at times of craving, intense desire to smoke, instead of cigarettes (1 to 15 gums/day).
- Care in administration: Swallow with a glass of water before use to neutralize oral pH, which may be altered by food intake and food residue removal, which may decrease absorption by the oral mucosa.
- Adverse reactions: nicotine gum - temporomandibular joint pain when chewed quickly and incessantly; oropharyngeal irritation and nausea when chewed quickly and frequently.
- Adverse reactions: nicotine lozenge - oropharyngeal irritation and nausea when chewed rather than allowed to dissolve in the mouth or overuse.
- Contraindications:

Nicotine gum - Inability to chew, active peptic ulcer, 15 days after AMI.

Nicotine lozenge - active peptic ulcer, 15 days after AMI.

- Overdose (toxicity): nausea, feeling sick, tachyhardia, hypertensive crisis.

4. Bupropion hydrochloride (Chart 7.2)

Bupropion is a dopamine and norepinephrine reuptake inhibitor that is effective in smoking cessation,[268,276] decreasing nicotine withdrawal symptoms. Because it is an antidepressant, it can help control depressive symptoms that may arise during the smoking cessation process.

Effectiveness - placebo compared - RR = 2.0 (95% CI 1.8-2.2).

6-Month abstinence rate - RR = 24.2 (95% CI 22.2-26.4).

- Presentation: 150-mg prolonged-release lozenges.
- Route of administration: oral.
- Dose schedule: 1 tablet daily for 4 days, then increase to 1 tablet twice daily with a minimum interval of 8 hours.
- Care in administration: Avoid night administration to minimize the risk of insomnia.
- Adverse reactions: dry mouth, insomnia (interrupted sleep), constipation, epigastric pain, dizziness.
- Contraindications: Absolute: risk of seizure (history of seizure, epilepsy, childhood febrile seizure, known electroencephalogram abnormalities); alcoholism; use of monoamine oxidase inhibitors (MAOI) in the last 14 days; cerebrovascular disease; central nervous system tumor, head trauma.
- Warnings/precautions: The combination of bupropion with nicotine replacement, especially patches, may increase BP; for this reason, it should be evaluated at all doctor visits. Alcohol use may predispose to seizure, so patient should be advised to restrict alcohol consumption during use.
- Overdose (toxicity): convulsions.

5. Varenicline tartrate (Chart 7.2)

Varenicline[268,277] it is a partial nicotinic receptor agonist in the central nervous system. The substance is the most effective medication among the first-line drugs in treating smoking.[278,279]

Effectiveness - compared to placebo - RR = 3.1 (95% CI 2.5-3.8).

6-Month abstinence rate - RR = 33.2 (95% CI 28.9-37.8).

- Doses: 0.5- and 1-mg varenicline tartrate tablets.
- Route of administration: Oral use.
- Dose schedule: Start with 0.5 mg once a day. On the 4th day, prescribe 0.5 mg twice a day. On the 7th day, prescribe 1 mg 2 times a day. Prescribe for 12 to 24 weeks. Varenicline therapy does not require immediate cessation of smoking. It is recommended to stop smoking from the 14th day after starting the medication.
- Care in administration: take after meal with water (between 150 and 250 ml to reduce nausea).
- Adverse reactions: The most expected side effect with this substance is nausea (30% of patients). This effect is minimized by taking the medication after meals and with a glass of water. Less than 6% of patients discontinue medication because of this effect. Other effects reported to a lesser extent are insomnia (14%), headache (10%), constipation (6%), abnormal dreams (dream recall and actual content) and flatulence, which in some circumstances require dose reduction (1 mg/day), but rarely cause discontinuation of medication.
- Contraindications: Absolute - terminal renal failure, pregnancy and breastfeeding. Dose adjustment in patients with severe renal failure (see adjustment table).
- Precaution for use: Caution should be exercised when using in patients with a history of psychiatric illness such as severe depression, bipolar disorder and panic syndrome. Although the causal connection has not been demonstrated, and considering that smokers have a higher risk of depression and suicidal ideation,[280] the US Food and Drug Administration (FDA) in 2009,[281] warned about the possibility of mood swings, restlessness and suicidal ideation among users of varenicline, and is therefore not recommended in patients with non-stabilized psychiatric disorders.

In 2011, Singh et al.[271] conducted a meta-analysis with some varenicline studies warning of possible risks of CV events among users. After careful analysis of the study, it was concluded that a significant number of patients who used varenicline in randomized trials were not included in the meta-analysis and did not present with any CV event.[282] Prochaska and Hilton[283] performed a more comprehensive meta-analysis, including all varenicline studies, and found no risk of increased CV event in the varenicline versus placebo group. The safety of varenicline was assessed by Rigotti et al.,[284] when they analyzed, in a randomized, placebo-controlled manner, the efficacy and safety of varenicline in patients with CVD. The authors found no additional CV risk in the varenicline group.

- Overdose (toxicity): nausea, feeling sick, vomiting.

Second line medicine:

1. Nortriptyline

Nortriptyline is a tricyclic antidepressant that blocks the reuptake of norepinephrine into the central nervous system. It is a 2nd line drug in the treatment of smoking. The FDA has not yet approved its use for treatment because, although its efficacy is similar to that obtained with NRT or bupropion, there is a greater risk of side effects from the medication.[268,281] The recommended dose is 25 mg/day, as a single dose, gradually increasing to 75 to 100 mg per day. Use is not recommended in patients with structural heart disease of any nature because of the risk of inducing conduction disorders and arrhythmia.

7.5. Anti-Smoking Drug Combinations

The effectiveness of first-line anti-smoking drugs is between 20 and 25% for nicotine replacement and bupoprione, and does not exceed 35% with varenicline.[268] Thus, we can imagine that out of 10 patients treated, about 3 will quit and 7 will not.

The combination of anti-smoking drugs seems to be a reasonable application option to improve success rates. Despite the increase in cost, it should be considered that quitting smoking has an substantial cost-benefit ratio, so the proposal is perfectly viable, leaving the perspective of dealing with the possible increase in side effects as the main factor to be managed.

Some studies with the combination of patches and oral nicotine have shown improved results. Meta-analysis of 9 studies[277] that combined a nicotine patch with a nicotine rapid-release drug (gum, spray, lozenge) proved to be more effective than a single type of NRT (RR 1.34, 95% confidence interval 1.18 to 1.51).

The combination of NRT and bupropion was more effective than bupropion alone in the meta-analysis of 4 studies.[277] (RR 1,24; 95% confidence interval 1.06 to1.45).

Chart 7.2 – Non-nicotine therapy[300]

Bupropion hydrochloride
• Simulates some of the effects of nicotine on the brain by blocking the neuronal uptake of dopamine and norepinephrine. It may be used in combination with nicotine replacement therapy with patch
• Excellent option for subgroups of relapse-prone smokers with depression after smoking cessation, and for women and those with a high degree of dependence. Success rates for smoking cessation range 30 to 36%
• Therapeutic scheme: Start treatment 8 days before smoking cessation
– 150 mg in the morning for three days, followed by 150 mg in the morning and afternoon at 8-hour intervals for 3 months, which may be extended for up to 6 months. Control blood pressure and, if elevated, the dose may be reduced to 150 mg/day before stopping in refractory cases. Reduce doses in renal and hepatic impairment to 150 mg/day. Monoamine oxidase inhibitors should be discontinued for up to 15 days before starting bupropion. Use with caution or avoid in patients on antipsychotics, theophylline and systemic steroids, as it favors the onset of seizures
• Contraindications:
– Absolute: history of convulssions (even febrile), epilepsy, brain injury, electroencephalogram abnormalities, brain tumor, severe alcoholism, anorexia nervosa and bulimia, pregnancy and breasfeeding
– Relatives: Combined use of barbiturate, benzodiazepines, cimetidine, pseudoehedrine, phenytoin, oral hyproglycemic agents or insulin
Varenicline tartarate
• α4β2 nicotinic acetylcholine receptor partial agonist, which mediates the release of dopamine in the brain
• Has double effect: reduces withdrawal symptoms and the desire to smoke
• Therapeutic schedule: start 1 week before the cessation date, with 0.5 mg for 3 days in the morning, followed by 0.5 mg from the 4th to 7th morning (7 h) and in the afternoon (19 h) and 1 mg/day for 3 months in the morning (7 h) and in the afternoon (19 h), which may be extended to 6 months in cases without complete cessation of smoking or risk of relapse. Varenicline is administered orally and does not undergo hepatic metabolism, and it isrenally excreted practically unchanged
• Adverse effects: nausea (20%), headache, vivid dreams and weight gain. Rarely, mood changes, agitation, restlessness, and aggressiveness
• Because it is not metabolized by the liver, varenicline does not interfere with concomitant use of digoxin, metformin or warfarin. Cimetidine may increase varenicline bioavailability
• It should be used with caution in patients with renal failure
• Contraindication: pregnancy, breastfeeding, less than 18 years old, bipolar disorder, schizophrenia or epilepsy

The combination of varenicline and bupropion appears to be the most effective of all (Evidence B);[285] however, randomized studies[286] of greater consistency need to be performed.

7.6. Future Proposals

The use of serotonin reuptake inhibitors has not proven to be an option for treatment of withdrawal symptoms,[281] but considering how often depressive symptoms manifest during smoking cessation,[285] with or without drugs,[286] randomized trials to test concomitant use of this drug should be conducted to assess whether results are improving, as nicotine has an action on monoaminoxidase A, which is responsible for serotonin degradation, among many other neurotransmitters, which would explain the high frequency of this condition. smoking cessation, with or without anti-smoking medication. Bupropion and varenicline have no action on serotonin, explaining the higher frequency of mood disorders in drug users compared to those on nicotine replacement.

We believe that this event is more likely to occur in varenicline users due to the high antagonist potency in the α4 β2 receptor, thus preventing nicotinic action, even if the patient smokes. From this perspective, the longitudinal, observational study that evaluated the effectiveness of the combination of varenicline, bupropion and sertraline[287] had a better success rate among those that used all three drugs. These findings warrant corroboration through a randomized, placebo-controlled study, so that there is indeed robust evidence of the benefit of these combinations, as well as testing whether the use of serotonin reuptake inhibitors is confirmed as an ancillary strategy in anti-smoking treatment in patients who manifest depressive symptoms during smoking treatment.[288,289]

Nicotine vaccines,[290] long awaited to comprise the therapeutic arsenal, are still under study. They act by stimulating the immune system to produce specific antibodies that bind with great affinity to nicotine in plasma and extracellular fluids.Nicotine bound to antibodies cannot cross the blood-brain barrier because of its size, the vicious circle of gratification for brain receptor activation is broken. The main brands under study are: Nic-VAX®, TA-Nic® and Nic-Qb®.

7.7. Nicotine Electronic Devices (Electronic Cigarette, Heated Cigarette, Pen Drives)

These devices were launched in 2006 and have since been refined by their manufacturers to replace the

conventional cigarette. The industry of these products insists on seeing them as "smoking cessation treatment," arguing that smokers, by replacing the use of ordinary cigarettes with these devices, would reduce the risk of disease by consuming a product with less toxic substances. With this argument, they are investing heavily in marketing, and Phillips Morris, one of the largest conventional cigarette manufacturers in the world, is widely publicizing its strategy to stop producing ordinary cigarettes and replace it with heated cigarettes, also an electronic nicotine-release device, without combustion.[291]

The marketing, importation and advertising of any electronic smoking device, including electronic cigarette and heated cigarette, have been banned by Anvisa (National Health Surveillance Agency) since 2009 in Brazil (RDC 46). The agency considers that there is no scientific evidence to aid smoking cessation - meaning cessation as a treatment process for nicotine addiction - or scientific arguments that actually prove reduced morbidity and mortality by tobacco-related diseases in populations that have replaced tobacco use. Although they contain less toxic substances than conventional non-combustion cigarettes, those present are not harmless, and nicotine is a substance known to have CV effects, and perpetuates the addiction condition.[292]

The impact of the use of these products on people's health is not yet known, and although manufacturers are betting on their use as a harm reduction policy, the concern is that there is an epidemic of consumption and a setback in encouraging smoking cessation worldwide. Therefore, WHO does not recognize these devices as a treatment for smoking and warns that they cause nicotine addiction just as much as regular cigarettes, and looks forward to studies evaluating the impact of these products on morbidity and mortality.[293]

7.8. Hookah

Contrary to popular belief that hookah is less harmful and less addictive than cigarettes, research shows that both carry significant health risks, and may induce nicotine addiction.[294,295]

The world panorama shows that the trends of hookah use are alarming and have shifted from being a social phenomenon among young people in some regions to becoming the beginning of a global epidemic.[296]

In Brazil, the frequency of hookah use in the Brazilian adult population aged 18 to 59 years was determined in a population-based cross-sectional study using the 2013 National Health Survey (PNS). Of the 60,225 adults interviewed, 15% reported using any tobacco use, with the frequency of hookah use being 1.2% (95% confidence interval 0.8 – 1.6), higher in the male, white and younger age groups, with medium to high schooling, and urban and southern and midwestern residents; Among those who tried hookah, 50% used it sporadically, 12.8% monthly, 27.3% weekly and 6.8% daily. These results point to the need for supervision and educational campaigns on the risks of hookah use.[297]

7.9. Conclusion

Pharmacological treatment of smoking should be considered as a secondary prevention strategy, mainly aimed at reducing CV injury. Smoking is a chronic degenerative disease, and should be viewed by the cardiologist like the other common illnesses in their care routine, such as hypertension and DM.

Defining criteria for choosing which anti-smoking drug will initially be used for patient treatment is still a challenge for treatment guides and guidelines because of the lack of systematization of models to be tested. In clinical practice, the choice of drugs is made on the basis of contraindications, drug availability and price, among other criteria. Therefore, systematically discussing criterion models for this choice becomes relevant and necessary for increasing the efficacy of anti-smoking treatment.

The high degree of nicotine dependence[298] could be a factor in decision making, as well as factors that identify subpopulations that benefit from any particular drug, considering gender, age, pharmacogenetics[299] (genetic polymorphism of nicotinic, dopamine and hepatic receptors) among others. These factors are not yet known at this time.

Recommendations for addressing adult smokers can be found in Table 7.1 and Charts 7.1, 7.2, 7.3 and 7.4.

Table 7.1 – Recomendations for approach for adult smokers

Recomendation	Recommendation class	Level of evidence	Reference
Routine assessment of smoking for adults at all health professional appointments, recorded in medical records	I	A	2,10,300
Systematic counseling for all adults on smoking cessatio	I	A	2,10,300
A combination of behavioral and pharmacological interventions is recommended for all adults to minimize dropout rates	I	A	2,10,300
Smoking cessation is recommended for all adults to reduce cardiovascular risk	I	B	2,10,300
A multidisciplinary team should be allocated to facilitate smoking cessation in all health systems	IIa	B	2,10,300

Chart 7.3 – Nicotine Replacement Therapy[300]

Rapid Nicotine Replacement: chewing gum and lozenge
• Used when craving (imperative need to smoke) or at 1- to 2-hour intervals
• Promotes faster release of nicotine. It can be combined with nicotine patch or combined with bupropion and varenicline
• The approximate time for nicotine release is 5 minutes with the lozenge and 10 minutes with the gum
• The maximum tolerated dose is around 10 gums or lozenges per day
• Patients should chew/suck the gum/lozenge until it tastes spicy. At this point, they should stop for 2 minutes (time to absorb nicotine) until the taste disappears and then chew/suck again by repeating the cycle within 20 minutes for a second nicotine release. They should drink a glass of water before use to neutralize oral pH, which changes with food intake, and to remove food residues, which may decrease absorption by the oral mucosa
• Side effects: hypersalivation, nausea, hiccups, gingival ulceration (which may lead to tooth softening) and temporomandibular joint (TMJ) pain
• Contraindication: inability to chew/suck, oral mucosa lesions, peptic ulcer, TMJ subluxation and use of mobile dental prostheses
Slow Replenishment: Nicotine Patch
• The patches are provided in boxes of seven units each, in doses ranging from 7 to 25 mg
• They are indicated to maintain a continuous level of circulating nicotine for 24 hours, in a process of gradual smoking cessation
• They may be indicated as pre-cessation therapy for 2 to 4 weeks in smokers who have a hard time reducing the number of cigarettes and setting a date to quit
• The patches should be applied in the morning to covered areas on the upper chest or anterior, posterior and upper lateral regions of the arm, rotating between these sites and changing at the same time of day. Sun exposure should be avoided at site
• They may be used in combination with bupropion or varenicline
• Therapeutic scheme:
– Smoker of 20 cigarettes/day and/or with Fagerström score of 8-10 points: A patch of 21 to 25 mg/day from the 1st to 4th week; 14 to 15 mg/day from 5th to 8th week; 7 mg/day from 9th to 10th week. It is suggested to put the patch on in the morning just after waking up. In cases of insomnia, it should be removed after 16 hours of use. In special cases of high dependence and in the absence of contraindication, up to two 21-mg patches may be used
– Smoker of 10-20 cigarettes/day and/or with Fagerström score of 8-10 points: A patch of 14-15 mg/day in the first 4 weeks followed by 7 mg/day from the 5th to 8th week
• Side effects: pruritis, rash, erythema, headache, nausea dyspepsia, myalgia and tachycardia with overdose
• Contraindications: history of recent myocardial infarction (in last 15 days), severe cardiac arrhythmias, unstable angina pectoris, peripheral vascular disease, peptic ulcer, skin diseases, pregnancy and breastfeeding

Chart 7.4 – Standard pharmacological treatment for smoking[300]

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

Table 7.2 – Fagerström test for nicotine dependence[265]

1. How long after waking up do you smoke the first cigarette?
[3] Within 5 minutes [2] Within 6-30 minutes
[1] Within 31-60 minutes [0] After 60 minutes
2. Is is hard for you not to smoke in forbidden places?
[1] Yes [0] No
3. Which of the cigarettes that you smoke during the day give you the most satisfaction?
[1] The first in the morning [0] Others
4. How many cigarettes do you smoke per day?
[0] Less than 10 [1] 11-20 [2] 21-30 [3] More than 31
5. Do you smoke more often in the morning?
[1] Yes [0] No
6. Do you smoke even when sick, when bedridden most of the time?
[1] Yes [0] No

→Total: [0-2] very low; [3-4] low; [5] moderate; [6-7] high; [8-10] very high.

Table 7.3 – Stages of motivation and counseling techniques[263]

• Precontemplative: not yet concerned; not ready for behavior change → briefly report risks of continuing to smoke and encourage patient to think ↓
• Contemplative: recognizes that you need and want to change, but still want to smoke (ambivalence) → ponder the pros and cons of cessation and remain available to talk ↓
• Determined: Wants to quit smoking and ready to take the necessary action → choose a date to quit smoking ↓
• Action: engage in attitudes intended to bring about change and abstain → follow-up to prevent relapse and relieve withdrawal symptoms ↓
• Maintenance: Keeps the behavior change achieved and remains abstinent → reinforce the benefits gained from quitting, identify risk situations for relapse and the skills to cope with them ↓
• Relapse: unable to maintain achieved abstinence and returns to smoker behavior → offer support, review and resume the whole process

8. Physical Activity, Physical Exercise and Sport

8.1. Introduction

Physical inactivity is one of the major public health problems, and physical inactivity, which is strongly related to all-cause and CVD mortality, is highly prevalent in Brazil and worldwide.[301,302] Increased physical activity is related to health gain, better quality of life and greater life expectancy.[303-307] Therefore, both in an individual and population-based CVD prevention strategy, it is of utmost importance to prioritize a strong fight against sedentarism, and requiring the questioning of PA habits and encouragement of adopting a more active lifestyle should be routinely done at medical office visits.[308]

8.2. Relevant Concepts and Expressions in Physical Activity

PA is used as a broad term that includes both structured and unstructured forms of leisure, sports, transportation, and domestic and work-related activities. physical activity involves body movement, with increased energy expenditure in relation to rest, and can be classified in terms of intensity as mild, moderate or high. Physical exercise is defined as a subset of structured activities aimed at improving cardiorespiratory fitness, balance, flexibility, strength and/or power and even cognitive function, particularly important in the elderly.[309]

Thus, physical activity, physical exercise and sports are related but distinct terms, and Table 8.1 defines some concepts and expressions.

There is a strong association of different levels of physical fitness components with all-cause mortality and the occurrence of unfavorable CV events, with inverse association, i.e., the lower the physical fitness, the higher the mortality,[310-317] requiring preventive action, focusing on combating physical inactivity as of childhood. WHO recently presented specific recommendations for children 0 to 5 years of age related to daily physical activity/exercise and sleep times, which considerably limits or restricts sitting time in front of screens.[318] Table 8.2 presents a classification of the profile of children and adolescents according to physical exercise.[319]

8.3. Main Acute and Chronic Effects of Exercise

The effects of exercise can be divided into acute and chronic.[320] The acute effect is that which dissipates rapidly and may be immediate after a single session or last for up to 24 hours (subacute or late acute effect). Improvement in flow-mediated response with respect to endothelial function is an example of the acute effect of a single exercise session. The chronic effect is achieved by repeated acute/subacute effects and can be evaluated at rest, even if long after the last exercise session. Resting bradycardia observed in athletes of predominantly aerobic modalities is an example of chronic effect. Repetition of responses can produce a chronic effect, as in the case of decreased blood pressure. Some of the main effects of exercise are listed in Chart 8.1.

8.4. Epidemiological Rationale of the Benefits of Physical Exercise

In addition to aerobic fitness,[312-315,321,322] other components of physical fitness are associated with prognosis, with higher mortality associated with poor fitness. proven as a predictor of mortality in middle-aged and elderly men and women.[311,323] Other studies on muscle strength and power have also shown associations with mortality.[316,317]

Scientific findings support the previous recommendations of national[324,328] and international guidelines[329] that recommend the regular and combined practice of aerobic and resistance exercises. Flexibility and balance exercises should be part of an exercise program, especially aimed at the elderly.

Regarding PE, the greatest benefit is when comparing sedentary individuals and those who engage in very little or no exercise, since the positive impact of abandoning a sedentary lifestyle is very significant. However, comparing the varying degrees of aerobic fitness on an increasing scale, we realize that there is a continuous decrease in the risk of cardiac death

Table 8.1 – Main concepts and terms in the subject: exercise, sedentarism and health

Concepts and terms	Significance
Physical aptitude	Ability to perform activities and physical exercises expected for their age group, gender and body, which promote health, survival and adequate functionality in the environment in which they live. It is divided into aerobic and non-aerobic components (muscle strength/power, flexibility, balance and body composition).
Physical activity	Any body movement produced by skeletal muscles that results in energy expenditure.
Physical exercise	Structured and repetitive physical activity, for the purpose of maintaining or optimizing physical fitness, body aesthetics and health.
Sport	Physical exercises with variable energy demand, involving rules and competitions and aimed at individual or collective winning.
Sedentarism	It is a condition in which there is no regular exercise or frequent physical activity involving energy expenditure > 2 to 3 times that at rest, at work, personal transportation or leisure.
Exerciser	One who works out regularly.
Athlete	One who simultaneously meets the following criteria: a) training in sports to improve performance, b) actively participating in sports competitions, c) being formally registered in sports organizations, and d) having sports training and competition as their focus of interest or way of life.

Table 8.2 – Childhood and adolescence profile according to physical exercise (adapted from Balassiano et al.)[319]

Score	Definition	Childhood/Adolescence
0	Sedentary or very inactive	Sometimes riding a bicycle, often dismissed from physical education at school.
1	Little active	Normal frequency in school physical education and short and intermittent periods of sports or dancing.
2	Moderately active	Regular participation most of the time in physical activity classes or sports activities or dance or fighting academies.
3	Very active	Regular and frequent participation in various sports activities on most days of the week.
4	Very active and competitive	Participation most of the time in training and/or sports competition or regular and frequent practice of predominantly aerobic exercise.

and all-cause death. The higher aerobic fitness, the lower the risk is of total morbidity and mortality and CVD both in healthy individuals and in CVD patients.[312-315,321,322]

Greater physical fitness and amount of physical activity are associated with lower risk of developing hypertension.[330] In already hypertensive individuals, PE reduces BP, and better results have been found with aerobic exercise (mean SBP reduction of 8.3 mmHg and DBP 5.2 mmHg). Smaller but significant reductions also occur with dynamic resistance training.[150] Another useful and clinically safe strategy for BP reduction is based on manual isometric training.[150,331] In patients with resistant hypertension - those with over-target BP despite the use of three or more antihypertensive medications, exercise in warm water (30 to 32°C) resulted in a more marked reduction in BP, and should be considered when available.[332-334]

The effects of reducing blood pressure levels during exercise occur immediately after the end of exercise and last up to 24 to 48 hours. Thus, as with drugs, this action in the CV system needs to be repeated periodically for the benefit to be chronically maintained. Regular PE exerts a hypotensive action, which adds to the effects of pharmacotherapy[335] and may, in some cases, require reduction of medication doses.

It has also been suggested that dyslipidemic individuals with higher cardiorespiratory fitness, even without statin use, have a lower CVD risk than those with poor fitness using medication. Those with higher aerobic fitness and statin use have lower all-cause mortality, which reinforces the importance of physical exercise and greater physical fitness, even in patients with optimized drug treatment.[336,337]

8.5. Risks of Physical Activity, Physical Exercise and Sport

Healthy individuals have an extremely low risk of events due to regular exercise. A study of more than 20,000 physicians with an average follow-up of 12 years found that the risk was approximately one out of every 1.5 million hours of exercise exposure (during and within the first 30 minutes post-exercise).[338] Thus, the recommendation to be physically active is quite safe and the fear of exercise-related problems should not be a barrier or justification for maintaining a sedentary lifestyle. This message needs to be widely disseminated to the population because the percentage of physically active individuals is very low in our country.[339]

For further information regarding sport and pre-participation assessment, it is recommended to read the recent update of the Brazilian Society of Cardiology Guidelines for Cardiology of Sport and Exercise.[328]

8.6. Recommendations for Exercise and Physical Activity

Although a meta-analysis has shown that simply stimulating the adoption of a more active lifestyle can increase physical activity levels,[340,341] the physician's guidance should be for physical exercise to be in an organized and structured manner.

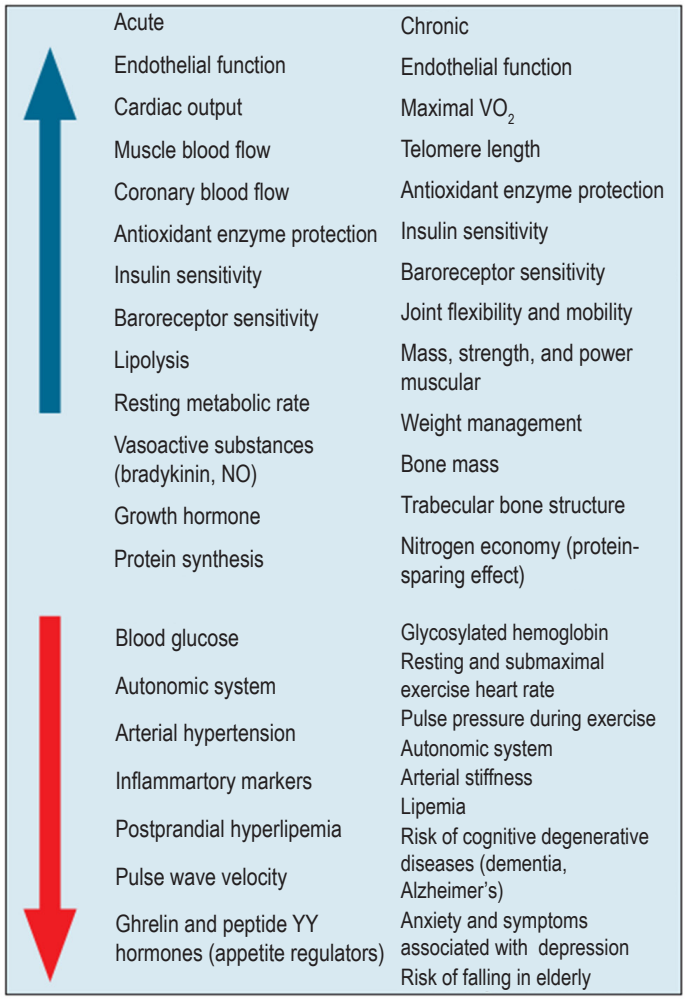

Chart 8.1 – *Main acute and chronic effects of exercise. NO: nitric oxide; VO_2: oxygen consumption.*

A good weekly goal for CVD health promotion and prevention is physical activity/exercise/sport for at least 150 minutes of moderate intensity or 75 minutes of high intensity.[10,342,347] Getting more than 300 minutes per week of moderate to high intensity exercise may provide additional benefit. However, there is no scientific evidence for a clear delineation of an upper limit from which there would be a greater possibility of harm to a healthy individual.[303]

More recent studies have associated sedentary time, such as watching television, with higher all-cause mortality, CV mortality, and the risk of developing DM.[348]

8.7. Prescription for Exercises

Exercises may be prescribed for their characteristics, such as type (aerobic, muscle endurance, flexibility), modality (walking, running, cycling, dancing), duration (running time), weekly frequency and its intensity (Tables 8.4 and 8.5).

Previously sedentary patients may begin exercise at the lower end of the prescription and progress to higher intensities gradually over the following weeks. The progression should initially be made in the duration of the session and later in the intensity of the exercises. Already physically active patients, according to individual assessment, can perform exercises at more intense levels, aiming at a minimum of 75 minutes, ideally divided into two or more weekly sessions.

Localized muscular endurance and strengthening or power exercises have been shown to be very beneficial for general health and for CV and musculoskeletal systems, being of fundamental importance in patients with sarcopenia and/or osteopenia. They should be performed at least twice a week, favoring large muscle groups of the upper and lower limbs and trunk. They can be made using one's own body or using attachments such as free weights, shin guards, elastic bands and weight machines. The load or weight for each exercise or movement must be individually adjusted. Due attention

Table 8.3 – Recommended levels of physical exercise to reduce cardiovascular risk

Recommendation	Recommendation class	Level of evidence	Reference
During consultations, doctors should advise their patients about PA	I	B	341
Weekly PA of ≥ 150 minutes of moderate intensity exercise or 75 minutes of more intense exercise reduces CV risk	I	A	341
Weekly PA of < 150 minutes of moderate intensity exercise or <75 minutes of more intense exercise reduces CV risk	IIa	B	341

CV: cardiovascular; PA: physical activity.

Table 8.4 – Classification of physical exercise

Denomination	Characteristic
By the predominant metabolic pathway	
Alactic anaerobic	High intensity and very short duration
Lactic Anaerobic	High intensity and short duration
Aerobic	Low or medium intensity and long duration
By pace	
Fixed or constant	No change in pace over time
Variable or intermittent	With change in pace over time
By relative intensity *	
Low or light	Quiet breathing, very little panting. (Borg < 4)
Medium or moderade	Rapid breathing, panting but controlled. Can say a sentence. (Borg 4 to 7)
High or heavy	Very rapid breathing, a lot of panting. Speech difficult. (Borg > 7)
By muscle mechanics	
Static	No movement occurs and mechanical work is zero
Dynamic	There is movement and positive or negatice work

** For exercises with implements or weights that use localized muscle groups, the relative intensity can be expressed according to the maximum load possible to perform a maximum repetition (MR). For example, light intensity - up to 30% of 1 MR; medium intensity - 30 to 60 or 70% of 1 MR. Another alternative is to use Borg's psychophysiological scales. For the above classification, the scale version ranging from 0 to 10 was used.*

Table 8.5 – Prescribed methods for moderate intensity aerobic exercise

Method	Description
Subjective Sensation of Exertion (Borg)	Exercises with self-perceived exertion as moderate, medium or heavy, ranging 2 to 4 on the Borg scale 0-10 and 10 to 13 on the 6-20 scale
Speech Test	Performing intense exercises with heavy breathing but controlled so that a complete sentence can be said without pauses
HR Peak Percentages	Exercises at intensity between 70 and 90% of peak HR* Target HR = peak HR* x percentage
Reserve HR (Karvonen)	Exercises at intensity between 50 and 80% of reserve HR (peak HR* - resting HR). Target HR = resting HR + (peak HR* - resting HR) x percentage
Cardiopulmonary Test Thresholds	Performing exercises at iintensity between ventilatory thresholds 1 and 2 (anaerobic threshold and respiratory compensation point)

** Peak HR obtained in a maximum exercise test is preferred, since there are individual variations that cause errors in the prediction of HR by age, especially in patients using medications with negative chronotropic effects.*

should be given to the execution of the movements so that technique and posture are correct.

There are different protocols for resistance exercise, from the number of exercises used per session from 6 to 15 (when done daily, there is a tendency to work a muscle group on alternate days), ranging from one to three sets for each exercise and also in the number of repetitions from 6 to 15. When training muscle power, the speed of execution should be as fast as possible in the concentric phase of the movement. In this case, only 6 to 8 repetitions per exercise are used, requiring only 20 to 30 second interval between each series to allow replenishment of the adenosine triphosphate (ATP) and phosphocreatine stocks needed to perform the next series. This strategy also has the advantage of greatly reducing the time dedicated to resistance exercises, which in many situations may represent the difference between adhering to the prescribed exercise program and not.

Flexibility exercises can offer osteomyoarticular benefits, health-related quality of life and prevention of falling in the elderly. By contributing to easier and more efficient joint movement, they ultimately reduce the demand for oxygen in moving situations and thus benefit the CV system. In these exercises, we seek to reach the maximum range of motion, reaching the point of slight discomfort and statically held position for 10 to 30 seconds. Flexibility exercises should ideally be individualized from specific assessments, such as the.[349] In general, women tend to be more flexible than men, and there is a tendency for a progressive loss of flexibility with aging. tends to be proportionally larger in shoulder and trunk movements.

Depending on the age range, clinical conditions and objectives of the exercise program for a given patient, other forms of

exercise may be included in the prescription, such as motor coordination and balance exercises, not to mention the numerous opportunities generated by more playful forms and exercise socializers such as ballroom dancing and Tai-Chi-Chuan.[351,352]

Performing assessments of aerobic and non-aerobic fitness allows a more individualized prescription of physical exercise, aiming to obtain the best results and, through risk stratification and search for hidden abnormalities, minimize the risks of exercise of any kind or intensity.

The initial evaluation consists of anamnesis, physical examination and ECG. More detailed assessments should be individualized, with exercise testing or maximal exercise cardiopulmonary testing, anthropometric assessment, muscle strength/power and flexibility. In the initial evaluation, we can quantify the functional deficit against the desirable, as well as set goals to be achieved. It is important to emphasize that even those with low initial levels of physical fitness can benefit from and become adherent to a supervised exercise program.[353] It is also possible to obtain clinical and functional support for appropriate counseling on sexual activity based on the KiTOMI model proposed by Brazilian authors in 2016.[354] It is essential for commitment to be encouraged in the patient on reevaluation, while measuring his/her evolution and benefits obtained.

8.8. Formal and Informal Physical Activity: Encouraging Referral, Implementation and Adherence

Although health benefits occur with relatively low intensity activities resulting from informal daily actions such as walking, climbing stairs, cycling and dancing, it is ideal that regular exercise (formal activities) also occur, which provides greater gains.

Patients with heart disease also benefit from regular physical exercise, ideally in the context of a formal CV rehabilitation program (or supervised physical exercise). CV rehabilitation acts on major disease outcomes, with proven effects by meta-analyses of randomized trials, reducing CV mortality, reducing hospitalizations[355,356] and improving quality of life. In addition, CV rehabilitation is a cost-effective treatment.[357,358]

A possible way to improve exercise counseling by health professionals would be to combat their physical inactivity, as it has been shown that physically active people have greater knowledge about recommendations on prescribed exercises and can motivate more.[359]

In addition to direct medical practice, there is a need for changes in public and private policies, with the need for comprehensive strategies established through simultaneous actions, such as increasing physical activity in school programs; transport policies and systems that favor commuting through walking, cycling and public transportation; public education, including public awareness campaigns; sports organization at various levels (school, work, community etc.), with proposals that encourage and enable lifelong sports, from childhood to old age.

8.9. Final Messages

Physical inactivity should be combated by increasing physical activity in its various forms, both structured, physical and unstructured, favoring urban mobility with bicycle paths and facilitating travel through walking.

There is a consensus that a good and plausible weekly goal for health promotion and CVD prevention is to engage in physical activity/exercise/sport for at least 150 minutes of moderate intensity or 75 minutes of high intensity.

Given the current stage of knowledge, it can be said that:

- any amount of physical activity is better than none, and sedentarism is a worse possible situation;
- the benefits of exercise seem to be greater with more exercise, up to 5 times the minimum recommendation;
- there is no consistent scientific evidence that more than 10 times the minimum recommended exercise is harmful to health;
- there are no longitudinal studies relating heart disease to severe physical exercise, when performed regularly in healthy individuals.[303,360]

9. Spirituality and Psychosocial Factors in Cardiovascular Medicine

9.1. Concepts, Definitions and Rationale

9.1.1. Introduction

There are lines of evidence that demonstrate a strong relationship between spirituality, religion and religiosity and the processes of health, illness and healing, composing together the physical, psychological and social aspects of the integral vision of the human being. In contrast to the easy conceptual assimilation, obstacles are observed, mainly due to lack of knowledge of the concept and scientific outdating, regarding the operationalization of the spirituality construct and the understanding of how to measure and evaluate its influence on health outcomes.[361]

Spirituality and religiosity are valuable resources used by patients to cope with illness and suffering. The process of understanding relevance, identifying demands, and providing adequate spiritual and religious support benefits both patients, the multidisciplinary team, and the health system itself. About 80% of the world's population have some religious affiliation, and faith has been identified as a powerful mobilizing force in the lives of individuals and communities.[362,363]

9.1.2. Concepts and Definitions

Definitions of spirituality typically merge with other constructs such as religiosity and the dimensions of psychological well-being, especially positive relationships with other people, purpose in life, and sometimes paranormal beliefs. Conceptual heterogeneity has been widely recognized and, for some authors, spirituality has no clear definition, the term being used inaccurately and inconsistently, varying according to religion, culture and time and therefore difficult to gauge.[364]

The meaning of the word religion has Latin derivations that refer to rereading (from scripture), to (re) binding or even to

reelection (back to a god), inferring connections to deity, other people, or their beliefs and values. Although the term religion in the past (and in current theological erudition) has been used to grasp the institutional and individual dimensions of experience, contemporary references to religion increasingly imply institutional, social, doctrinal, and denominational characteristics of lived experiences.[361]

According to Koenig, religion is "an organized system of beliefs, practices and symbols designed to facilitate closeness with the transcendent or the Divine and foster understanding of one's relationship and responsibilities with others living in the community".[361,363-365] Religion is a multidimensional construct that includes beliefs, behaviors, dogmas, rituals and ceremonies that can be practiced in private or public contexts, but are somehow derived from established traditions that have developed over time within a community. Religion is also designed to facilitate closeness with the transcendent and promote an understanding of one's relationship and responsibility to others when living in a community.[365] Religiosity is how much an individual believes, follows and practices a religion. It can be organizational (church, temple, or religious services) or non-organizational such as praying, reading books, or attending religious programs.

Historically, spirituality was considered a process that unfolded within a religious context, with institutions designed to facilitate the spiritualization of the practitioner. Only recently has spirituality been separated from religion as a distinct construct, in part because of the distancing from the authority of religious institutions in modern social life and the increasing emphasis of individualism on Western cultures.[361]

More recently, faced with the need to standardize a definition for spirituality in palliative care, a group of interprofessional specialists in palliative and spiritual care has defined spirituality as "a dynamic and intrinsic aspect of humanity, through which people seek meaning, purpose and transcendence and experience relationship with self, family, others, community, society, nature and the meaningful or sacred. Spirituality is expressed through beliefs, values, traditions and practices."[366]

According to the Study Group on Spirituality and Cardiovascular Medicine (GEMCA) of the Brazilian Society of Cardiology, "spirituality is a set of moral, mental and emotional values that guide thoughts, behaviors and attitudes in the circumstances of intra- and interpersonal relationship life." One can also add the aspect of being motivated or not by the will and be subject to observation and measurement (http://departamentos.cardiol.br/gemca). We consider it important that spirituality be valued measurable in all individuals, regardless of religious affiliation, including atheists, agnostics, or even those with religious affiliation but without observing and practicing it. For some, both atheists and agnostics, while not believing or uncertain about God's existence, still have a form of spirituality based on existential philosophy, finding meaning, purpose, and fulfillment in their own lives. Spirituality evokes concerns, compassion, and a sense of connection with something greater than us.[367]

Thus, spirituality may include religion and other universal views, but it encompasses much more general ways in which these experiences are expressed, including through the arts, relationships with nature and others, and for some through the concept of "secular humanism." This emphasizing reason, scientific inquiry, individual freedom and responsibility, human values, compassion and the needs for tolerance and cooperation.

9.1.3. Rationale and Mechanisms

A significant and growing body of evidence demonstrates an association between spirituality and religiosity and mortality indices, quality of life, with supposed mechanisms based on a huge range of biological and mediating variables, varying according to the model of healthy populations (or not). -healthy), forms of expression of spirituality and religiosity, research development scenario etc.[365,368,369]

In an American cohort predominantly composed of Christians > 40 years of age and followed for an average of 8.5 years, a lower risk of death was observed, regardless of confounding factors among those who reported religious services at least once a week compared to no presence. The association was substantially mediated by health behaviors and other risk factors.[370]

In a 2009 systematic review, spirituality/religiosity was associated with reduced mortality in studies involving healthy populations, but not in trials of the sick population. The protective effect of spirituality and religiosity was independent of behavioral factors such as smoking, alcohol, exercise, socioeconomic status, negative affect, and social support. When compared to organizational but not non-organizational religious activities, it was associated with longer survival.[371]

In the Women's Health Initiative study involving more than 43,000 menopausal women, CV risk was highest in patients with private spiritual activity such as prayer, Bible reading, and meditation. Subgroup analysis suggests that this association may be determined by the presence of severe chronic diseases.[372]

It is possible that spirituality and religiosity will have little impact on outcomes once disease is established, identified and treated, and is more important in promoting resistance to health problems before they reach an advanced stage. It should also be noted that religious coping is often used but may have positive or negative connotations. Negative religious coping (such as passive acceptance of fatality and requests for direct intercession) can be detrimental in contrast to other beneficial effects.[371]

More recently, new cohort studies have made important contributions from the perspective of epidemiology and the associations between religious service, mortality and quality of life. In the Nurses' Health Study cohort of over 74,000 nurses followed for up to 8 years, both all-cause mortality and CVD or cancer mortality were reduced by about 30% in women who attended religious services at least once a week compared to those without any participation.[373] In this same population, attendance at religious services was significantly associated with lower suicide rate.[374]

Similarly, the follow-up of a large cohort of black American women showed a significant 46% reduction in mortality rate, comparing attendance at religious services several times a

week with no frequency. On the other hand, involvement in prayer several times a day, religious confrontation or self-identification as a very religious/spiritual person did not correlate with mortality.[375]

This interface between spirituality and religiosity and health and illness processes is multifactorial and can, in part, be attributed to a behavioral self-regulation determined by religious affiliation and participation, with reduced consumption of alcohol, tobacco and drugs, reduction in the number of partners, better transport, food and access to health care. Emotionally, religious communion brings better positive psychology and social support, and positive spiritual coping can provide more hope, forgiveness, comfort, love, and other benefits.

In addition to behavioral aspects, most studies demonstrate the beneficial relationship between spirituality and religiosity and the physiological and pathophysiological variables of many clinical entities, including CVD. Despite the great heterogeneity between studies, better BP levels, neurohormones and autonomic nervous system activation, HR variability, dyslipidemia, CV risk, atherosclerotic disease, DM, CRP and other markers of inflammation and immunity have been observed.[365,368] Another way of understanding the scope spirituality and religiosity may have on clinically relevant outcomes, including greater longevity, is expressed in the direct relationship with telomere size in leukocytes.[376,377]

9.2. Spiritual History and Scales for Measuring Religiosity and Spirituality

The degree of spirituality and religiosity of patients can be assessed in spiritual history or anamnesis, understood as "the set of questions asked to the patient to share their spiritual and religious values, to identify possible spiritual issues that may contribute to or undermine the therapy, as well as feelings that are used in daily life, in the life of relationship, whether positive (edifying) or negative (not edifying)." It should always be patient-centered and guided by what it expresses about its spirituality.[378] At first, spiritual anamnesis as an integral part of clinical history should be obtained from all patients seeking medical attention, but especially those hospitalized with serious, chronic, progressive or debilitating illness.

9.2.1. Why Address Spirituality and Religiosity

The approach to the subject is very important because many patients are religious or spiritual, and their beliefs influence how to cope with adverse situations in life and may help to cope with the disease. During periods of hospitalization or chronic illness, they are often removed from their communities and prevented from practicing their religious beliefs. In addition, personal beliefs may affect health-related decisions that may be conflicting with treatment.[379,380]

Many health professionals do not know if patients wish, agree with, or are open to this approach. Studies show that most patients would like their doctors to ask about spirituality and religiosity, generating more empathy and trust in the doctor and thus rescuing the doctor-patient relationship, with a more humane care.[381,382]

9.2.2. Objectives of Spirituality and Religiosity Assessment

It is essential to seek to understand the patients' beliefs, identify aspects that interfere with health care, evaluate the individual, family or social spiritual strength that will allow them to cope with the disease, offer empathy and support, help them to find acceptance of the disease and identify situations of conflict or spiritual suffering that will require evaluation by a skilled professional.[383,384] In this evaluation, it is essential to detect negative feelings that may contribute to the illness or aggravation of the condition, such as hurt, resentment, unforgiveness, ingratitude, among others.

9.2.3. How to Address Patient Spirituality and Religiosity

There are several ways to approach this issue, and most importantly it should be done sensitively without promoting religion or prescribing prayers or religious practices. Nor should the individual be coerced into adopting specific beliefs or practices.

Most of the time, the approach can be taken naturally, during the interview, as the doctor assesses psychosocial aspects.[365] Patients should be asked about the importance of spirituality, religiosity, and religion to them, if this helps to cope with illness, generates stress or negative feelings (guilt, punishment etc.), or influences treatment adherence or decisions, and if there are any unmet spiritual needs.

The health professional should be sensitive and welcoming to religious beliefs and practices. If there are negative feelings, conflicts, or spiritual needs, the provider should solicit the participation of a trained individual or member of the patient's community to properly address these issues. In the case of nonreligious patients or those who refuse to talk about the subject, the doctor may inquire about the ways in which individuals live with the disease, what promotes purpose and meaning for their life (family, friends, hobby etc.) and what beliefs may have an impact on their treatment.

For this approach to be non-conflictive, preparation and acceptance by both health professionals and patients is required.

9.2.4. Scales and Instruments for Evaluating Spirituality and Religiosity

Measuring spirituality and religiosity in clinical practice and research is challenging, given the complexity of the elements and definitions involved in denomination, beliefs, religious/spiritual practices, participation in religious communities, support in dealing with illness, forgiveness, gratitude, altruism, spiritual well-being, pain or suffering and others.

The various psychometric instruments can be divided into tools for spiritual tracking or for spiritual history collection.[386,387]

1. Spiritual Tracking – Evaluate the presence of spiritual needs that indicate deeper assessment. They are brief and easy to apply. Some of the instruments for spiritual tracking are listed in Chart 9.1.

Spiritual tracking provides important information and may indicate the need for further evaluation, although aspects remain to be studied (better time to apply in different stages of the disease and differences in cultural context, among others).

Chart 9.1 – Instruments spiritual tracking

Tracking tools	Spiritual domains evaluated
"Rush" protocol for tracking religiosity/spirituality[388]	Importance of religiosity/spirituality in dealing with disease. Spiritual strength or comfort
"Are you at peace?"[389]	Inner peace
"Do you feel spiritual pain or suffering?"[390]	Spiritual pain/suffering
Spiritual injury scale[391]	Guilt, anger, sadness, feeling of injustice, fear of death

2. Collection of spiritual history – They allow a broader evaluation of the different domains of patients' spirituality and religiosity that may affect clinical evolution, their attitude towards CVD, self-care and their physical, mental and spiritual well-being during the disease.

They are well-structured instruments, addressing the different domains, but they should be applied informally from memory throughout the conversation with the patient, which serve as a tool or guide and should not be viewed rigidly, but as continuous learning and consequent familiarization with the task of completing the anamnesis. There are several validated instruments for collecting spiritual history, whether to evaluate spirituality and religiosity more broadly or for research purposes.

2. a. Religiosity scales – The religiosity index DUREL (Duke University Religion Index) is a scale of five items that measure three dimensions of religious involvement:

(1) assesses organizational religiosity (OR);

(2) assesses non-organizational religiosity (NOR); and

(3, 4 and 5) consider the assessment of intrinsic religiosity (IR) (Chart 9.2).

Validated in Brazil,[392] DUREL is succinct and easy to apply, addresses the main domains of religiosity and has been used in various cultures. It has shown good psychometric characteristics, face and competitor validity, and good test-retest reliability, but does not evaluate spirituality. The dimensions of religiosity measured by DUREL have been related to several indicators of social support and health.[39]

2. b. Assessment of spiritual history – The assessment of spirituality involves a set of questions about its different domains that are associated with health outcomes, based on previously validated scales. Known by acronyms, some of the main instruments are FICA,[393] HOPE,[394] FAITH[380] and SPIRIT.[395]

Among these, the FICA questionnaire has shown the best psychometric characteristics (Chart 9.3). It was created by doctors based on clinical experience and can be used in different clinical situations. It analyzes four dimensions (Faith or Belief, Importance and Influence, Community and Action in treatment), has easy application, fast execution and good memorization[383] Similarly, HOPE has shown good performance in spiritual assessment (Chart 9.3).

Studies evaluating the association of spirituality and religiosity with CV outcomes have been criticized for the difficulty in adjusting for multiple comparisons, certain seemingly contradictory findings, and too many instruments. Measuring spirituality is complex because of the many aspects involved in defining it and the multiple domains it encompasses.

Systematic reviews[386,396,397] broadly discuss the tools available for assessing spirituality and religiosity, showing that the different instruments measure a wide range of spiritual dimensions, including religious denomination, attendance at religious ceremonies, OR, NOR and IR, religious/spiritual coping, religious and spiritual beliefs, practices and values, well-being and inner peace, stress generated by religion ("struggle"), a tendency towards forgiveness and gratitude.

The scale called Brief Multidimensional Measure of Religiousness and Spirituality, validated in Brazil,[392] considers in its analyses the frequency of spiritual experiences, values/beliefs, propensity for forgiveness, personal religious practices, religious and spiritual overcoming, religious support and commitment.

The WHO Quality of Life instrument in the Spirituality, Religiosity and Personal Beliefs module (WHOQOL-SRPB) comprises 32 items, distributed in 8 facets involving connection to being or spiritual strength, meaning in life, wonder, wholeness and integration, spiritual strength, inner peace, hope, optimism and faith.[398]

In a systematic review, Lucchetti et al.,[386] selected and evaluated instruments for clinical research validated in Portuguese.

9.2.5. Attitudes and Behaviors after Spiritual Anamnesis

With information on the spiritual dimension of patients, it is possible to establish new possibilities for understanding the pathophysiology illness and consequent medical intervention. Some general lines can be established:

1. Take no action: religious issues are delicate and not always objective to the point of plausible resolution, even though they may be of great importance to the patient. Often, the best course is simply to offer your empathy and understanding;
2. Incorporate spirituality in preventive health: the physician can encourage the patient to use his/her spirituality as a disease prevention tool by engaging in activities such as prayer and meditation;
3. Include spirituality in adjuvant treatment: the physician can help the patient identify spiritual aspects that, along with standard treatment, may help with the outcome of the disease; in the case of serious illness, the physician can collect the spiritual history and help the patient find meaning, accept the illness, and cope with the situation using his/her spiritual resources in the best way;
4. Modify the treatment plan: it is up to the physician to understand that the patient has the freedom to be able to modify the therapeutic plan on the basis of religious beliefs and thus to propose modifications in the course of the treatment. For example, the patient may opt for meditation as an option for chronic pain, change chemotherapy plans, and seek community support.

Chart 9.2 – *Duke University Religion Index (DUREL).*

1) How ofern do you go to church, temple, mosque, worship service, prayer group, spirit session, or other regious gathering?
   1. ( ) Never
   2. ( ) Once a year or less
   3. ( ) A few times a year
   4. ( ) Two or three times a month
   5. ( ) Once a week
   6. ( ) More than once a week

2) How often do you devote your time to individual religious activities, such as prayers, meditations, Bible readings, or other religious texts?
   1. ( ) Never
   2. ( ) A few times a month
   3. ( ) Once a week
   4. ( ) Two or more times a week
   5. ( ) Daily
   6. ( ) More than once a day

The next section contains 3 sentences with respect to beliefs or religious experiences. Please indicate how much each sentence applies to you.

3) In my life, I feel the presence of God (or the Holy Spirit).
   1. ( ) Certainly not true
   2. ( ) Usually not true
   3. ( ) Not sure
   4. ( ) Usually true
   5. ( ) Totally true

4) My religious beliefs are truly behind my way of living.
   1. ( ) Certainly not true
   2. ( ) Usually not true
   3. ( ) Not sure
   4. ( ) Usually true
   5. ( ) Totally true

5) I strive hard to live my religion in all aspects of life.
   1. ( ) Certainly not true
   2. ( ) Usually not true
   3. ( ) Not sure
   4. ( ) Usually true
   5. ( ) Totally true

Chart 9.3 – FICA and HOPE questionnaires for spiritual history

FICA questionnaire	HOPE questionnaire
F – Faith/beliefs Do you consider yourself religious or spiritual? Do you have beliefs that help you deal with problems? If not, what gives life meaning?	H – Are there sources of hope? What are your sources of hope, comfort and peace? What do you cling to in hard times? What gives you support and makes you move forward?
I – Importance/influence What importance do you give to faith and religious beliefs in your life? Has faith or beliefs helped you cope with stress or health problems? Do you have any beliefs that may affect medical decisions or your treatment?	O – Religious organization Do you consider yourself part of an organized religion? Is this important? Are you part of a community? Does it help? In what ways does your religion help you? Are you part of a religious community?
C – Community Are you part of any religious or spiritual community? Does it support you? How? Are there any groups of people you really love or are important to you? Is there any community (church, temple, support group) that supports you?	P – Personal spiritual practices Do you have any spiritual beliefs that are independent of your organized religion? Do you believe in God? What is your relationship with God? What aspects of your spirituality or spiritual practice help you the most? (prayer, meditation, readings, attending religious services?)
A – Action in treatment How would you like your doctor to consider the religiosity/spirituality question in your treatment? Name any religious/spiritual leaders in your community.	E – Effects on treatment Are there any spiritual resources you are missing? Are there any restrictions on your treatment generated by your beliefs?

9.3. Primary Prevention

Available scientific evidence describes that high levels of spirituality and religiosity are associated with lower prevalence of smoking, alcohol consumption, sedentarism/PA, better nutritional and pharmacological adherence in dyslipidemia, hypertension, obesity and DM.[365,399-401]

Alcohol: In many studies that examined the relationship between spirituality and religiosity with alcohol use, an inverse relationship was found; that is, there were higher rates of spirituality or frequency of religious activity, with lower alcohol consumption. According to the same authors, several studies have shown that more religious individuals are more physically active. There is also a positive relationship between spirituality and religiosity and PA.[365] Among Brazilian university students, a higher prevalence of alcohol consumption, smoking and use of at least one illicit drug in the last 30 days among those who had less frequent religious involvement.[399]

Smoking: In the CARDIA cohort study, it was observed that religiosity was related to lower risk of subclinical carotid atherosclerosis and had a positive association with higher consumption of fiber, vegetables and fruits, and lower consumption of processed foods.[401,402]

Obesity: In both the MESA and CARDIA studies, a higher association was observed between extent of religious involvement and higher propensity for obesity.[401,402] Compared to those who did not participate in any religious activity, individuals with different frequencies of religious involvement were significantly more prone to obesity even after adjusting for demographic and smoking characteristics.

Diabetes mellitus: Regarding diabetes, although they are more prone to obesity, patients with greater religiosity had no higher risk of being diabetic. This may be explained by better diet or better treatment adherence.[366] In contrast, in the Third National Health and Nutrition Examination Survey (NHANES III) study, there was no association between diabetes and attendance at religious services.[370]

Hypertension: Regarding hypertension, the results are contradictory. In the Chicago Community Adult Health Study, it was found that higher religiosity indicators were not associated with hypertension.[403] In the prospective Black Women's Health Study, after an 8-year follow-up, the greater involvement with spirituality and religiosity employed in coping with stressful events was associated with a lower risk of developing hypertension, especially in women with higher stress.[404] A national study involving a highly religious community found that the prevalence of hypertension among these individuals was lower than the national prevalence.[405]

Meditation is one of the most studied interventions among practices related to spirituality and religiosity and the repercussions on BP levels. In these studies, the magnitude of BP reduction varies significantly. Studies have methodological limitations with data bias, high dropout rates, and different populations studied.

In a systematic literature review, transcendental meditation reduced SBP by ~4 mmHg and DBP by ~2 mmHg, effects comparable to other lifestyle interventions such as weight loss and exercise.[407] The mechanisms by which meditation reduces PA have not yet been fully elucidated. Possibly, the long-term neurophysiological changes that occur with meditation may lead to changes mediated by the autonomic nervous system in BP. The impact of stress reduction on BP remains to be better defined.[406]

9.4. Secondary Prevention

As with primary prevention, secondary prevention should be viewed as comprehensive and taking into account psychosocial factors such as socioeconomic status, depression, anxiety, hostility/anger, and type D personality that may aggravate CVD.[2] In this context, some of these factors should be highlighted, as well as the results obtained with new proposals for intervention in the field of spirituality, religiosity and related areas.

Forgiveness: Evaluated by various scales as tendency and attitude, forgiveness determines multiple effects, generating states more favorable to homeostasis in the emotional, cognitive, physiological, psychological, and spiritual aspects. Forgiveness broadens the possibilities for behavior by building better adaptive strategies and counteracting the feelings of anxiety, anger, and hostility that are potent CV risk factors. It also reduces stress, drug addiction and rumination; improves social support, interpersonal relationships, and health self-care.[409-413]

One study analyzed the effect of forgiveness on myocardial ischemia, ischemia generated by stress and measured by scintigraphy techniques. Patients were randomized to receive or not a series of psychotherapy sessions to develop interpersonal forgiveness. After 10 weeks of follow-up, the forgiveness intervention was able to reduce the burden of anger-induced myocardial ischemia in patients with CAD.[414]

Gratitude: In clinical practice, gratitude can be assessed by specific questionnaires such as the Gratitude Questionnaire – 6 (GQ-6),[415] allowing the analysis of behavioral interactions and physiological, pathophysiological and clinical outcomes. Individuals with greater gratitude have a better CV health profile, similarly to those with higher spirituality and religiosity indices.

In asymptomatic HF patients assessed by the gratitude, depression, sleep, gratitude, and spiritual well-being questionnaires, the latter two correlated with better inflammatory profile and better mood and sleep quality, less fatigue, and greater self-efficacy.[416] Psychological strategies that may increase feelings of gratitude such as regular journaling, thoughts, meditation, and fact-checking, or grateful people have been studied, demonstrating increased feelings of gratitude and reduced inflammatory markers.[417]

Depression and Resilience: Depression is significantly more common in patients with CVD than in the general community. This higher prevalence is often secondary to the disease as an adaptation disorder, with symptoms disappearing spontaneously in most patients. However, approximately 15% of them develop a major depressive disorder, which is an independent risk marker of increased morbidity and mortality.[418,419]

In a cross-sectional study including 133 patients diagnosed with ischemic heart disease assessed by the Wagnild & Young Resilience Scale, 81% were classified as

resilient, suggesting that disease may act as a facilitator for the presence of this feeling.[420]

Resilience is a behavior that greatly improves treatment adherence as well as quality of life and can be acquired at any stage of life, regardless of age and disease state. Spirituality and religiosity are associated with higher levels of resilience.[420,421]

In another series, elderly patients (≥ 65 years) were significantly more resilient than younger patients. Resilience correlated negatively with depression and inversely with affective, cognitive, and somatic symptoms of depression and was responsible for greater variation in the affective characteristics of depression than in the somatic characteristics.[419]

In a long-term cohort, patients were analyzed for functional social support, BMI, recent history of major depression, coronary artery disease, hypertension, and diabetes. After 13 years, it was observed that social support was responsible for reducing the relationship between depression and the occurrence of coronary artery disease. Specifically, depression was prospectively associated with coronary artery disease among individuals with low social support but not those with high support, suggesting that it may function as a resilience factor against CV risk associated with depression.[422]

The Palliative Care in Heart Failure study was the first randomized controlled trial involving palliative care to demonstrate the significant clinical benefit of incorporating interdisciplinary interventions in the management of patients with advanced HF. The addition of palliative care improved physical and psychosocial condition (anxiety/depression), and spiritual quality of life.[423]

Relaxation and Meditation: Relaxation and meditation are well-established mind/body approaches to improving stress, and their benefit has been demonstrated in many populations, including heart disease.[344,424-426] Easy to learn and practical, they are inexpensive and widely accessible techniques.

In an observational study in patients with coronary artery disease, the cardiac rehabilitation strategy associated with a 13-week program was analyzed using self-relaxation, spiritual well-being and psychological stress control techniques. There were significant increases in relaxation practice time and spiritual well-being scores, as well as improvement in depression, anxiety, hostility, and overall severity scores. A greater increase in relaxation practice time was associated with spiritual well-being, which in turn was associated with improved psychological outcomes.[424]

Patients with coronary artery disease were enrolled in a transcendental meditation or health education program with an average follow-up of 5.4 years. Transcendental meditation significantly reduced the risk of mortality, myocardial infarction, and stroke, these changes being associated with lower BP levels and psychosocial stressors.

Additionally, a national study randomized patients with chronic HF to do meditation or not, demonstrating a reduction in serum norepinephrine and VE/VCO_2 slope in the cardiopulmonary test and improved quality of life assessed by the Minnesota Living with Heart Failure questionnaire.[426]

A recent paper by the American Heart Association reviews various forms of meditation and highlights the prolonged effects observed on brain physiology and anatomy, possibly responsible for better systemic physiological status and reduced cardiovascular risk. Meditation shows a better physiological response to stress, smoking cessation, reduced BP, insulin resistance and metabolic syndrome, endothelial function, inducible myocardial ischemia, and primary and secondary prevention of CVD. Although some data on CVD risk reduction are limited, meditation can be considered as a complement to risk reduction and lifestyle modification.[344]

In a robust study involving 1,120 meditators, other complex domains have been identified that may be crucial to people's psychological and spiritual development by acting as mediators and/or mechanisms responsible for the effects of meditation. Of difficult measurement, relational and transpersonal aspects, mystics, and anomalous or extraordinary phenomena linked to meditation deserve further study.

The extent of the possible effects to be obtained with each form of meditation remains open. Transcendental meditation has been shown to reduce anxiety, improve mood, and to double the acute pain tolerance time when compared to secular forms of meditation.[428]

Medication adherence: In a cohort of 130 HF patients, adequate adherence score was observed in only 38.5% of patients. Spirituality, religiosity, and personal beliefs were the only variables consistently associated with adherence. It is noteworthy that depression or religiosity were not correlated with adherence when evaluated separately. When spirituality was assessed by both, it was positively correlated with adherence, adjusted for demographic and clinical characteristics and psychosocial instruments.[429]

Cardiac Rehabilitation: Several studies report improvement in psychological stress in patients with coronary artery disease undergoing CV rehabilitation. In addition, a meta-analysis of 23 randomized controlled trials involving 3,180 coronary artery disease patients seeking to assess the impact of adding psychosocial interventions to standard rehabilitation exercise reported greater reduction in psychological distress and improvements in SBP and serum cholesterol.[430] The scope of cardiac rehabilitation can be amplified by positive psychology techniques. In patients undergoing coronary angioplasty, these explanatory techniques, with telephone contacts and inductive correspondence, resulted in better physical performance (caloric expenditure), with a reduction in medical events, as opposed to the effects observed by stress.[431]

In another meta-analysis, the influence of rehabilitation associated with psychosocial and/or educational interventions in 14,486 individuals with pre-established coronary artery disease with a median follow-up of 12 months was evaluated. In general, rehabilitation led to a reduction in CVD mortality and the risk of hospitalizations and a better quality of life.[354]

9.5. Recommendations for Clinical Practice

Most patients and their families, guardians or caregivers have varying degrees of religiosity and spiritual needs and, importantly, expect health professionals to know their beliefs and to be part of the decision-making process, reinforcing the concept of integrality.

Health professionals involved should keep in mind that spirituality and religiosity favorably influence ability to cope with the disease, but the isolation imposed by hospitalization may be negative as it removes patients from their religious meetings or practices, from religious leaders and of dedicated communities.

These beliefs and practices can impact and often antagonize proposed medical strategies. It is worth noting that health professionals also present their own profiles of spirituality and religiosity, influencing their practice, especially in severe, critical or limiting situations.

Every professional should be aware of the relevance of screening involving spirituality, and those focused on direct care such as doctors, nurses, and chaplains should have an anamnesis of spirituality and religiosity, viewed not only as part of identifying where professed religion is concerned, but how a broader construction obtained by structured or unstructured questionnaires, allowing to penetrate and understand the true identity of spirituality and religiosity in patients and relatives.[387,432,433] Most professionals are sensitive to the demand of patients only when informed, but the contemporary view is to actively search for this information and demands, because the patient often does not feel comfortable discussing it.[432]

In a holistic view of a human being, the anamnesis of spirituality and religiosity should be remembered in each care interaction and by all health professionals.[366,433] Naturally, this approach may be unimportant or difficult to use in many situations, such as in major emergencies, but it is of enormous relevance in critical, terminal, chronic degenerative diseases or palliative care.

Critically ill patients have high rates of not only pain, dyspnea, anorexia, and fatigue, but also of anxiety, nervousness, sadness and depression. For this patient profile, Cicely Saunders' concept of "total pain," understood as a sum of physical, psychological, social, emotional and spiritual elements, must be valued and addressed in a systematic and structured manner, even in the first days of hospitalization.[434,435]

Patient-centered approaches with a greater focus on spirituality make it easy to understand and value the motivations for consultation, understand the patient's universe (including emotional and existential issues), and strengthen the relationship between practitioners and patients, shared decision making, and prevention and promotion of health.[433,436]

It is essential for professionals to be technically prepared and the patient to agree on addressing issues related to spirituality and religiosity so that the interaction is constructive and without conflict. In the absence of technical training or resistance to the subject by the patient, the spiritual history should be postponed to a more opportune time or even canceled. When these alignments do not occur, serious conflicts can develop and sometimes very deleterious to medical management.

To avoid conflicts in the doctor-patient relationship, it should always be borne in mind that this area is deeply personal as well as intensely emotional, and therefore, the physician should not address emotional issues without proper approximation of spiritual and/or religious aspects. The physician should be sure of the patient's agreement to address the issue.

Health professionals, especially those involved in critical or terminal patient care or palliative care, are subject to a significant burden of professional stress. This work involves a lot of compassion, understood as an attitude of addressing the needs of others and helping those in distress, which can be viewed as a spiritual practice. Training and practice strategies on spirituality and religiosity in this setting can contribute to a better sense of meaning and purpose at work, spiritual well-being, less fatigue and reduced burnout.[366]

The reasons for professionals not addressing spirituality and religiosity are diverse, such as feeling uncertain about initiating spiritual discussions, being misunderstood as imposing religion, invasion of privacy, causing discomfort, difficulties with the language of spirituality.[436] These justifications have also been identified in Brazilian medical students[437] and represent weaknesses in medical education and practice, with specific ignorance or inadequate dimensioning, lack of mastery of specific tools and training.

The solution to these limitations lies in the development of hospital spirituality support and training programs. These programs contribute to well-being and health improvement, assist with misunderstanding in conducts, and meet patients' expectations, and they are part of accreditation processes and prospects for reducing hospitalization costs.[438] For the development of these programs, there should be deep institutional involvement, formal training of the teams most directly connected to care, availability of infrastructure and resources, adjustments to care routines, and alignment with the various religious communities.

Health teams, especially when acting in scenarios where there is a higher demand for spirituality and religiosity, should be structured with systematic training and clear definition of responsibilities, such as obtaining and recording anamnesis in medical records, clarifying the observed demands and the implemented clinical course, as well as the observed outcomes. At initial contact, spiritual history can be obtained through open and brief questions by the doctor, nurse or chaplain, thus tracking needs and anticipating conflicts. For the spiritual approach, no professional is expected to be able to do so, but a certified chaplain or a spiritual care professional with equivalent technical training and structured standards and concepts to develop a spiritual care plan.[387]

Religion should never be prescribed, forced or even encouraged, at the risk of adding guilt to the burden of disease. Identifying the right time for spirituality and religiosity approaches is important to avoid any kind of misunderstanding, always under the rule of common sense. We emphasize that the evaluation of spirituality is always desirable, enabling the search for information in all patients regardless of religion or religiosity, but the approach in extreme situations can lead to stress and even worsen patient evolution.

Respect for spirituality, religiosity and individual beliefs is essential and should match the therapeutic plan if it is not harmful. If necessary and at the patient's wishes and in the face of risk or harm or in conflict situations, the presence of religious

representatives or leaders can bring comfort, balance and better management and can contribute to a desired consensus.

The approach of spirituality and religiosity topics in medical consultation in an area such as cardiology, where the patient is generally in a situation of fragility, and more sensitive and stressful, increases the complexity of the multiple variables already mentioned and may generate some conflicts. The misunderstanding or intolerance of the parties involved are major factors and can generate conflicts of various kinds and at all interfaces involving the patients, their families and their relationships, within the multidisciplinary team itself and between the team and the patient. All these problems can be prevented by good management of the doctor-patient relationship which, once consolidated, will make all other situations less influential.

Conflicts can be avoided even for untrained professionals, as long as some important steps are followed: conduct spiritual anamnesis without prejudice, showing deep interest and respect for the patient, seeking to understand their religion, beliefs, and practices,[363] encourage questions to help patients clarify their feelings and thoughts about the spiritual perspective of what is going on or even their possible spiritual problems.[393] In questions related to spirituality and religiosity, it should be kept in mind that it is always better to understand than to advise.

Concepts involving evidence-based medicine have also been applied in the realm of spirituality, but the available evidence is not always ideal and definitive. In these scenarios, available evidence should be used to improve this practice, also contributing to the revision of old concepts, the development of new research and the advancement of science in the field of spirituality. In Chart 9.4, GEMCA gathers recommendations that may be useful for improving cardiology practice in our country.

10. Associated Diseases, Socioeconomic and Environmental Factors in Cardiovascular Prevention

10.1. Introduction

In the last century, humanity has undergone an epidemiological transition in relation to the causes of death; infectious diseases are no longer the leading cause of death while chronic degenerative diseases, especially CVD now take the lead. Although they are still the leading causes of mortality worldwide, from the late 1950s, a decline in CVD mortality began in industrialized countries. In Brazil, this decrease in CVD mortality began to be observed in the late 1970s, with a significant reduction in these rates, despite significant regional differences.[2,440,441]

It is not possible to only associate the reduction in mortality due to CVD to the better control of classic CV risk factors such as diabetes, hypertension, obesity, dyslipidemia and smoking, since all of these, except smoking, have increased in prevalence in recent decades. This led to new concepts about occupational, behavioral and environmental risk factors, which are directly influenced by the socioeconomic conditions of the populations and have an important relationship with the causes of mortality.

In this chapter, we describe important conditions associated with increased CV risk that require concomitant assessment with classic CV risk factors when addressing CVD as a complex relationship between patients and the context in which they live.

10.2. Socioeconomic Factors and Cardiovascular Risk

The health conditions of populations are influenced in a complex way by social determinants such as income

Chart 9.4 – Practices in spirituality and health. Recommendation class and level of evidence

Recommendation	Recommendation class	Level of evidence	References
Brief tracking of spirituality and religiosity.	I	B	388-391,429
Spiritual anamnesis of patients with chronic diseases or with poor prognosis.	I	B	386,387,393,429,432
Respect and support the patient's religions, beliefs and personal rituals that are not harmful to treatment.	I	C	361,365,366, 384
Support from trained professional for patients suffering or with spiritual demands.	I	C	361,365,366,393
Organizational religiosity is associated with reduced mortality	I	B	370,371,373,375
Hospital program for training in spirituality and religiosity.	IIa	C	365,438
Spiritual anamnesis of stable individuals or outpatients.	IIa	B	384,386,387
DUREL, FICA, HOPE, or FAITH questionnaire to assess spirituality.	IIa	B	380,386,393,394
Meditation, relaxation techniques and stress management.	IIa	B	406,424-426
Spirituality and religiosity potentially increase survival.	IIa	B	370,371,373,375
Spiritual empowerment techniques such as forgiveness, gratitude and resilience.	IIb	C	412,413,417-420
Evaluate spirituality and religiosity in patients in acute and unstable situations.	III	C	384,387,439
Prescribe prayers, religious practices or specific religion.	III	C	365,381,382

distribution, wealth and education. These indicators act as interdependent risk factors for disease occurrence. Relationships between mortality rates and socioeconomic level have already been evidenced in Brazil and other countries, showing an inverse relationship, i.e., low socioeconomic levels are related to high mortality rates. These relationships between reductions in mortality rates, in particular deaths from diseases of the circulatory system (DCS), and improvement in socioeconomic indicators are highly correlated. Several prospective studies have shown that low socioeconomic status, defined as low educational level, low income, low status employment, or living in poorer residential areas, have contributed to the increase in all causes of death, as well as the risk of death from CVD.[9,442-446]

Low socioeconomic status, when defined as an independent CV risk factor, has been shown to confer an increased risk for CVD; with RR mortality between 1.3 and 2.0.[445,447] The time periods in which there was a reduction in mortality rates due to diseases of the circulatory system were preceded by periods with improvement in socioeconomic indicators. In Brazil, between the 1930s and 1980s, there was great economic growth that, despite the concentration of income, enabled educational, sanitary, economic and infrastructure improvements, reducing infectious diseases and inflammatory processes. In developed countries, the decline in CVD mortality began a little over a decade after the end of World War II, which followed the great depression of the early 1930s and the 1918 influenza pandemic. The same decline began just over 40 years after the beginning of the period of economic growth. Exposure to infectious agents and other unhealthy conditions in the early years of life may make individuals more susceptible to the development of atherothrombogenesis. It is also possible that the reduction in exposure to infectious diseases in the early stages of life is related to the observed decline in adult CV mortality.[442,446,448-452]

Strong correlations have been shown between the Human Development Index, falling child mortality, rising per capita gross domestic product (GDP) and the increasing education levels; with the reduction in mortality from diseases of the circulatory system in adults, from 1980, in some Brazilian states and municipalities, showing that the improvement in socioeconomic indicators preceded the reduction of CV deaths. The great increase in education over the last decades, which practically doubled in the states of Rio de Janeiro, São Paulo and Rio Grande do Sul, had a great impact on mortality, and is related to the reduction of more than 100 deaths from CVD with a one-year increase in average years of study in adults. Comprehensive measures to improve socioeconomic indicators should be part of the paradigm for CV disease control. These relationships show the importance of improving the living conditions of the population in order to reduce CV mortality.[442,446,448,449,453,454] The assessment of social factors in patients and people with CV risk factors is essential as a means to stratify future preventive efforts with individual's risk profile.

Recommendations for socioeconomic indicators and CV risk are listed in Table 10.1.

10.3. Environmental Factors and Cardiovascular Risk

Atherosclerosis has a complex and multifactorial pathophysiology, depending on the integration of several factors inherent to the individual, acquired or not, with the environment in which he is inserted. The impact of environmental factors on the epidemiology of CV disease has been increasingly studied and recognized, especially in relation to the possibility of adopting preventive strategies. In this context, in addition to the influence of socioeconomic factors such as income and education, the characteristics of the individual's own habitat and lifestyle are also considered. Thus, the natural and social environments are two different types that potentially influence CV disease.[455]

The natural environment is determined by specificites of the place where the individual resides such as altitude and latitude, density of wooded areas, seasons, exposure to sunlight and atmospheric temperature. A study by Massa et al.,[456] in the city of São Paulo in 2010, suggested an inverse relationship between green area density and CV risk, regardless of income.[456] In addition, CVD lethality appears to be higher in winter months, while in some places there is an increase of up to 53% in the incidence of AMI.[457] This increase occurs similarly in young adults (< 55 years) and in elderly (> 75 years) individuals, and may be a consequence of both hemodynamic variations. (e.g., elevated BP), as well as the higher incidence of respiratory infections at this time (e.g., influenza), which are known to increase the risk of heart attack.[455] However, elevated temperatures are also associated with a higher CVD risk, especially when there is an abrupt variation in temperature.[458]

The social environment is related to the artificial forms of housing and the characteristic of daily life in modern society, especially in the urban environment. Population, noise level, violence, access to clean water, sanitation and air pollution may limit health promotion and promote the development of infectious and chronic diseases. In this context, air pollution was established as the most important modifiable environmental determinant of CVD risk, consisting of a complex mixture of gaseous particles and components.[459]

Among such pollutants, particulate matter (PM) is the element that is most relevant to health, which is formed by substances whose size and types of particles vary over

Table 10.1 – Socioeconomic indicators and cardiovascular risk

Recommendation	Recommendation Class	Level of Evidence	References
Socioeconomic indicators should be investigated in the clinical assessment and considered in the patient approach to improve the quality of life and prognosis of circulatory system diseases.	IIb	B	483,484,486,488

time in the same region. The main sources of PM are motor vehicle emissions, tire fragmentation and reuse in asphalt production, energy industry-related combustion, ore processing, agriculture, construction and demolition activities, forest burning and volcanic eruptions, among others.[460] Thus, because of the complexity related to their composition, the particles are identified according to their diameter: coarse PM or PM10 (< 10 and ≥ 2.5 μm); Fine PM or PM2.5 (< 2.5 and ≥ 0.1 μm); Ultrathin PM or PM0.1 (< 0.1 μm).[459]

Current evidence suggests that PM2.5 is the major pollutant associated with increased CVD risk for both fatal and nonfatal events. The central justification for this relationship is the increased oxidative stress and systemic inflammation promoted by the particles. These effects result in the amplification of other traditional risk factors already present and in the potential instability of coronary plaques.[461] According to the WHO, the mean daily PM2.5 concentration should be < 20 μm/m^3, and the annual < 10 μm/m^3. With each 10μm/m^3 increase in short-term exposure, there is a 2.5, 1 and 2.1% increase in the risks of admission or death from AMI, stroke and HF, respectively. However, as exposure tends to occur over several years, atherosclerosis becomes progressive and cumulative, and also affects regional CV mortality. Thus, recurrent events may occur even with average annual PM2.5 concentrations below the WHO targets. Other consequences possibly associated with short- and long-term pollution are venous thromboembolism, acute atrial fibrillation, hypertension, and insulin resistance.[459]

The recommendations for environmental indicators and CVD risk can be seen in Table 10.2.

10.4. Vaccination for People with Heart Disease

In most clinical situations, vaccination is identified as a primary prevention action. When it is transposed to heart disease, it is usually secondary prevention for decompensations that aggravate pre-existing CV disease. Several vaccines are indicated for adults, with priority to patients with NCD, such as heart disease. We will list those prescribed for adults with heart disease. There is a specific guideline published by the Brazilian Society of Cardiology regarding indications and doses of vaccines indicated for children and adolescents with heart disease.

10.4.1. Prevention of Respiratory Tract Infections in People with Heart Disease

Historical reports evidence the seasonal relationship of influenza epidemics with higher mortality among the elderly and patients with NCD. Observational trials, reports, population studies and meta-analyzes have proven the benefits of vaccination against respiratory infections in the elderly and in patients with NCD, with a marked reduction in overall mortality, hospitalizations, myocardial infarction and stroke rates.[463-471] Venous congestion and immunosuppression present in patients with NCD who are predisposed to infections are highlighted among the pathophysiological explanations. In contrast, infections cause changes in coagulation factors, platelet aggregation, inflammatory response proteins, tumor necrosis factor and cytokines, and thus may be triggers for acute CV events. Infections also play a chronic role in decreasing cardiomyocyte contraction strength, inflammation, thrombosis, fibrin deposition, and acceleration of the atherosclerosis process and cardiac remodeling.[463,468,471] Despite all the evidence and guidelines, the rate of vaccination against respiratory infections – Influenza and pneumococcal pneumonia – are low in Brazil and worldwide.[472-474]

The overall consensus is for all patients with heart disease and NCDs to be vaccinated, regardless of age; they are summarized in Chart 10.1 and Table 10.3. If the patient is over 60, the patient will be included in government campaigns according to age group. If the patient is under 60 years of age, a referral form is required along with a declaration that there is a clinical indication for vaccination.

10.4.2. Which Vaccines?

Influenza Vaccine: In Brazil, it is up to the Ministry of Health to determine the composition of the vaccine according to the prevalence of circulating types and strains in recent epidemics. It is an inactivated, trivalent or tetravalent vaccine, with the latter having a greater immunization spectrum. Indications, characteristics and restrictions are common to trivalent and tetravalent. Vaccination should occur annually in the national campaign, which takes place between April and May.[475-477]

Pneumococcal Vaccine: There are two types of vaccine: conjugate and polysaccharide. Among the conjugates is "Pneumo 10" which is intended to prevent serious infections in children under 2 years of age; therefore outside the scope of NCDs, with the exception of congenital heart disease. The other available type which is widely used is the "Pneumo 23". This vaccine contains 23 pneumococcal serotypes and is indicated for those older than 60 years and those with clinical conditions which put them at risk for pneumonia, including those with NCD. Conjugate vaccines have shown better performance in clinical work, but are not always available in the public network. Referral for vaccination after confirmation of diagnosis. Recommended revaccination time is five years.[475-478]

Table 10.2 – Environmental indicators and cardiovascular risk

Recommendation	Recommendation class	Level of evidence	References
Restrict exposure to air pollution as a non-pharmacological measure for primary and secondary prevention of cardiovascular events	I	B	459-461

Table 10.3 – Indication of vaccination in heart disease

Recommendation	Recommendation class	Level of evidence	References
Vaccine heart disease patients against influenza to reduce morbidity and mortality	I	B	463-471
Vaccine heart disease patients against pneumococcus to reduce morbidity and mortality	I	C	475,476,478
Vaccine heart disease patients with other vaccines recommended for adults (Hepatitis, Triple Viral, Diphtheria and Tetanus)	I	C	475-477
Yellow fever vaccine for people over 60 years old, with or without heart disease, at high risk of exposure to the disease against Yellow Fever	IIa	C	475-477,479
Yellow fever vaccine for people older than 60 years, with or without heart against at low risk of exposure to the disease	III	C	475-477,479

Chart 10.1 – Main priority indications for influenza vaccination and pneumococcal vaccine

System	Syndromes, diseases or clinical situations
Cardiovascular	Stroke
	Congenital heart disease
	Valvular heart disease
	Coronary Artery Disease (Angina pectoris, Myocardial Infarction)
	Pulmonary hypertension
	Systemic hypertension if target organ injury
	Heart failure and cardiomyopathies
Respiratory	Asthma
	Bronchiectasis
	Bronchopulmonary dysplasia
	Interstitial lung disease
	Chronic Obstructive Pulmonary Disease (COPD)
	Cystic fibrosis
Endocrine	Diabetes mellitus
	Grade 3 Obesity
Gastrointestinal	Cirrhotics
	Chronic liver disease
	Chronic kidney disease (stages 3,4 and 5)
Other	Down Syndrome
	Solid organ transplant
	Over 60 years old, even if healthy

Source: Martins WA.[477]

Other vaccines indicated for adolescents and adults with NCDs: The other vaccines indicated for adults should not be neglected for those with heart disease. Among them is the Hepatitis B vaccine, for which three doses are recommended in patients up to 49 years of age, depending on the previous vaccination situation. Regarding the triple virus, two doses up to 29 years of age and one dose over 30 years are indicated, with an age limit of 49 years. Older people and patients with heart disease are susceptible to falls and injuries, and therefore the double vaccine is recommended, DT (Diphtheria and Tetanus), with a booster vaccine every 10 years.[475-477]

Yellow Fever: There is limited evidence regarding the safety of the yellow fever vaccination in heart disease patients and those over 60 years of age. There are two prospective studies and one report suggesting that serious adverse effects are rare in this age group, but much more frequent than in young people. There is limited data available on the relationship between the risk of adverse effects and the presence of previous CVD disease; interaction with CVD drugs; and the use of the fractional doses currently adopted in Brazil. Therefore, vaccination is recommended for those at risk of exposure to the disease, such as the elderly and heart disease patients. The vaccine should be given as a single dose without the need for a booster vaccine.[475-477,479]

Vaccination Precautions: The use of platelet antiaggregants is not an impediment to the use of intramuscular vaccines, thus there is no need for suspension. Subcutaneous vaccination can be performed in patients taking warfarin anticoagulation or direct anticoagulants. There are no reports of clinically significant interactions of vaccination in patients using antihypertensives, anti-ischemics, statins, fibrate, warfarin or digoxin.[475,476,480,481]

10.5. Lower Extremity Peripheral Artery Disease

10.5.1. Context

The evolution of atheromatous plaque and its association with the various CVD risk factors is widely described in the literature. It is also recognized that the atherosclerotic phenomenon can occur in different vascular beds, of larger or smaller caliber. The term peripheral arterial disease (PAD) has been used to characterize atherosclerotic disease that affects several peripheral (non-coronary) vascular beds. In this context, the current PAD guidelines deal with the theme in different ways. While the European directive,[482] has chosen to analyze PAD in various vascular territories (i.e., carotid, subclavian, mesenteric, renal, and lower limb arteries), the current American document,[483] as well as the Society for Vascular directive Surgery,[484] deals exclusively with lower extremity PAD.

More than 200 million people worldwide are estimated to have diverse stages of PAD, ranging from the asymptomatic phase of the disease to intermittent claudication (IC) and the more severe late stages of the disease.[485] Prevalence increases with aging, rising by more than 10% in patients aged 60 to 70 years; and over 20% in patients over 80 years of age. Although the prevalence of symptomatic and more severe forms of PAD is higher in men, a recent study of 3.6 million individuals in the US has shown that women may be worsening the odds of developing the disease compared to men (odds ratio [OR] of 1.62, 95% confidence interval between 1.60-1.64). Inversely, women were less prone to carotid stenosis or abdominal aortic aneurysm (AAA) than men.[485,486] Publications of previous decades already evidenced that the simultaneous presence of PAD and CVD or cerebrovascular is frequent, especially at older ages. Likewise, the anatomopathological characteristics and clinical manifestations of CVD in patients with PAD are usually more severe, with a higher occurrence of multivessel coronary branch injury and a higher prevalence of left coronary trunk injury.[487,488]

10.5.2. Interrelationship between the Various Cardiovascular Risk Factors and Lower Extremity Peripheral Artery Disease

In most studies, the proportion of symptomatic patients ranges from 20 to 33%, among all patients with PAD. In the Swedish population aged 60-90 years, the prevalence of lower extremity PAD was 18% and intermittent claudication 7%.[489] In Brazil, a multicenter cross-sectional study evaluated 1,170 individuals in 72 urban centers. The prevalence of intermittent claudication was 9% among those with ABI below the cutoff point of 0.9. In this analysis, women with coronary artery disease were 4.9 times more at risk for lower extremity PAD.[490]

Arterial Hypertension: Hypertension increases the chance of lower extremity PAD by 32% up to 2.2 times in various epidemiological studies. Although the risk of hypertension causing lower extremity PAD has been modest in some studies, the high prevalence of this risk factor among the elderly reinforces the epidemiological burden of lower limb arteriopathy.[489] A comprehensive study of more than 4.2 million individuals in primary health care in the UK, investigated the association between hypertension and the risk of lower extremity PAD. In this study, with each 20 mmHg increase in systolic blood pressure in hypertensive men aged 40-79 years, the risk of lower extremity PAD increased by 63%. Lower extremity PAD was associated with an increased risk of ischemic heart disease, CKD, HF, aortic aneurysm and atrial fibrillation; however, it was not associated with hemorrhagic stroke.[491]

The Harmonica Project, a Finnish community-based report, showed that the prevalence of asymptomatic (without claudication) lower extremity PAD, by means of ABI, was 7.3% in 532 hypertensive subjects, compared with 2.3% in 440 normotensive individuals. By adjusting multiple variables, hypertension continued to be an independent risk factor associated with lower extremity PAD, more than tripling the occurrence of lower limb arterial involvement (OR: 3.20). Hypertensive patients with borderline and altered ABI represented one third of all participants with hypertension in the average age range of 60 ± 7 years.[492]

Smoking: This is a particularly prominent risk factor in atherosclerotic disease of the lower extremities. The prospective Health Professionals Follow-up Study (HPFS) investigated 44,985 men with lower extremity PAD aged 40 to 75 years with a history of limb amputation, need for revascularization, arterial angiographic injury > 50% occlusion, and ABI below 0, 90. The authors followed the attributable risk of four of the most traditional risk factors, diabetes, hypertension, hypercholesterolemia, and smoking, by a median follow-up of 24.2 years. Active smoking significantly increased the adjusted risk of lower extremity PAD by 12.89-fold (95% confidence interval between 8.59 and 19.34), compared with individuals who had never smoked. Also, in participants who stopped smoking for more than 20 years, the risk of lower extremity PAD remained 39% higher than in those who had never smoked.[493] The Guangzhou Biobank Cohort Study (GBCS) evaluated the association between second-hand smoke exposure and lower extremity PAD in non-smokers. By adjusting for confounding variables, exposure to residential passive smoke for 25 hours / week or more was significantly associated lower extremity PAD (OR = 7.86; p = 0.003).[494]

Diabetes: The presence of diabetes increases the risk of lower extremity PAD by 1.9 to 4 times compared to non-diabetics.[489] In our country, the risk of diabetic men developing lower extremity PAD was 6.6 times higher than that of non-diabetics.[490] A case-control trial in patients with diabetic foot investigated ulcers that progressed to amputation. After adjusting several variables, at least three widely known risk factors were predictors of amputation risk:

i. HbA1c level > 8% (p = 0.002);

ii. hypertriglyceridemia (p = 0.004); and

iii. hypertension (p = 0.028).495

The risk of lower extremity PAD tends to increase with the duration and evolution of both metabolic factors, diabetes (p < 0.001) and hypercholesterolemia (p = 0.05) over time.[493]

Dyslipidemia: Hypercholesterolaemia increases the risk of developing lower extremity PAD by 90% (p = 0.05).[493] FH is an autosomal dominant condition associated with mutations in the LDL receptor-encoding gene or ApoB and PCSK-C coding genes.[9] In a Brazilian cross-sectional study, 202 patients with heterozygous FH were compared to 524 normolipidemic controls. The prevalence of lower extremity PAD in the FH group went from 17.3 to 2.3% in the group with appropriate lipid profile (p < 0.001).[496]

Classic risk factors continue to play a relevant role when lower extremity PAD progresses to more severe forms of vascular impairment, such as critical lower limb ischemia (CLI) or acute limb ischemia. Such presentations of lower extremity PAD have a poor prognosis in terms of disability and death. The UK-based prospective population-based Oxford Vascular Study (OXVASC) analyzed the incidence of severe peripheral ischemic outcomes in 92,728 patients. Compared with the control population, the occurrence of unstable events was associated with risk factors:

i. hypertension: adjusted risk of 2.75 times;

ii. smoking: adjusted risk of 2.14;

iii. diabetes: adjusted risk of 3.01; and

iv. CLI: adjusted risk of 5.96.[497]

10.5.3. Summary of Anatomical Location of Atherosclerotic Lesions of Lower Extremity Peripheral Artery Disease

The classic document from the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) has been updated to include infrapopliteal segment lesions in the anatomical classification of lower extremity PAD.[498,499] The location of lower extremity PAD according to the affected arterial territory has been harmonized by the recent Peripheral Academic Research Consortium (PARC) document (Chart 10.2).[500]

10.5.4. Preventive Management of Lower Extremity Peripheral Artery Disease

Several aspects of the preventive approach to lower extremity PAD risk factors are equally applicable, both regarding the asymptomatic and symptomatic (intermittent claudication) form of the disease.[484] The items listed below and, in particular, Chart 10.3 summarize the risk factors and proposed treatment approaches (including recommendation class / level of evidence) according to the latest international guidelines for lower extremity PAD:

i. Smoking cessation is recommended for people with lower extremity PAD.[482-484]

ii. Physical Exercise: In patients with claudication due to lower extremity PAD, a supervised exercise program is recommended to improve functional performance and quality of life.[482-484] The comprehensive review by Olin et al.,[501] highlights that the methodology of supervised exercise, either home or community-based, has improved considerably over the past decade.

iii. Antiplatelet: Despite the small sample size (n = 366), the CLIPS study showed the benefit of ASA in preventing 52% of vascular events such as AMI, stroke, pulmonary embolism, and CLI.[502] The CAPRIE lower extremity PAD subgroup analysis, which compared clopidogrel 75mg / day and acetylsalicylic acid in the secondary prevention, showed positive results in reducing CVD death, AMI and stroke by 24% in symptomatic lower extremity PAD.[502] The EUCLID study compared ticagrelor and clopidogrel in 13,885 symptomatic lower extremity PAD patients. There was no significant difference between drugs in preventing CVD, AMI, or stroke.[502] The presence of increased bleeding (TIMI score) was infrequent (0.94/100-patient years) and similar in randomized patients on ticagrelor and clopidogrel (p = 0.49) .[503]

iv. Anticoagulants: The recent COMPASS study evaluated the cumulative risk of new outcomes one year after the occurrence of a major lower limb adverse event (MALE). The cumulative incidence 1 year after hospitalization due to MALE was 95.4%, vascular amputation was 22.9%, the risk of death was 8.7% and major CV events reached 3.8%. In this study, rivaroxaban (direct selective coagulation factor Xa inhibitor) at a dose of 2.5 mg twice daily associated with ASA reduced the incidence of MALE by 43% (p = 0.01), decreased vascular amputations by 58 % (p = 0.01), restricted peripheral vascular interventions by 24% (p = 0.03) and decreased all peripheral vascular outcomes by 24% (p = 0.02) compared to AAS monotherapy.[504]

v. At present, this analysis of patients with lower extremity PAD from the COMPASS study is not characterized as a recommended treatment, but it has been relevant as a hypothesis and has reinforced the importance of further investigation on the possible role of new oral anticoagulants in the prevention of vascular events in symptomatic lower extremity PAD.

vi. Antihypertensives: In hypertensive patients with lower extremity PAD, strict BP control below 140/90 mmHg with first-choice drugs is recommended.

vii. Renin-angiotensin inhibitor drugs, such as ACE inhibitors or ARBs, when tolerated, are recommended to control BP in lower extremity PAD.[482,483]

viii. Hypolipidemics: Management of hypercholesterolaemia in patients with lower extremity PAD aims to keep LDL-cholesterol below 70 mg/dL or reduce it by 50% if baseline levels are between 70-135 mg / dL.[482] Statin prescription is broadly recommended in current international guidelines.[482-484] Statins reduce the risk of CVD and lower limb ischemic events in patients with lower extremity PAD.[482,483]

ix. The FOURIER study tested evolocumab (PCSK-9 inhibitor monoclonal antibody) in patients aged 40 to 85 years with a history of clinically evident atherosclerotic CVD disease. In this trial, 13.5% of patients in the evolocumab group and 12.9% in the placebo group had symptomatic lower extremity PAD (13.2% of all participants).[98] In the subgroup analysis of patients with lower extremity PAD claudication, evolocumab reduced the primary combination of outcomes by 21% (p = 0.0098).[505] Additional information on

Chart 10.2 – Lower extremity PAD location according to PARC[500]

Aortoiliac segment: infrarenal abdominal aorta; common iliac arteries; internal iliac artery, external iliac artery. Distal limit is the pelvic ring or inguinal ligament.

Femoropopliteal: common femoral artery; deep femoral artery; superficial femoral artery; segment 1 - above the knee popliteal artery, from the Hunter canal to the proximal edge of the patella; segment 2 - from the proximal portion of the patella to the center of the knee joint space; segment 3 - below the popliteal knee artery, from the center of the knee joint space to the origin of the anterior tibial artery (distal limit).

Tibiopedal: tibioperoneal trunk (origin of the anterior and below tibial artery until the bifurcation of the posterior and peroneal tibial arteries); anterior tibial, posterior tibial, peroneal, dorsalis pedis, arterial plantar arch and minor arteries of the feet.

cholesterol-lowering drugs in lower extremity PAD will be available in the future.

x. Glycemic Control: Optimized glycemic control is indicated in all diabetics with lower extremity PAD, especially those with greater severity, such as critical lower limb ischemia.[482,483,484] The objective is to reduce ischemic events in the lower extremities.[483]

In addition to their efficacy in glycemic control, new hypoglycemic drugs have been required to demonstrate CV safety. In the EMPA-REG study, the SGLT-2 inhibitor empagliflozin reduced the risk of CV death by 38%. A recent subanalysis of this study showed that in patients with lower extremity PAD at the start of the trial, the risk of lower limb amputation in the empagliflozin group was not significantly different from placebo (HR = 0.84; 95% confidence interval 0.54 and 1.32).506 However, the CANVAS study with canagliflozin, despite a 14% reduction in the risk of the primary combined outcome (CV death, AMI and nonfatal stroke), showed almost doubling of amputations, predominantly at the toe or metatarsal level. (6.3 [canagliflozin] compared with 3.4 / 1000 patient years [placebo]; hazard ratio = 1.97; 95% confidence interval between 1.41 and 2.75).[57] Inversely, the recent DECLARE study TIMI507, with dapagliflozin, in addition to showing reduced CVD death or hospitalizations for heart failure, did not significantly increase the risk of amputations (1.4% in the dapagliflozin group versus 1.3% in placebo; p = 0.53).[507] While further analysis is awaited, it is important that patients using SGLT-2 inhibitors maintain routine preventive foot care and adequate hydration. Monitoring the patient with lower extremity PAD at risk of foot infections, ulcer, gangrene or osteomyelitis is critical.

Risk Factors/Therapeutic Conduct and their Recommendation Classes/ Lower extremity PAD Evidence Levels, according to the latest international Peripheral Artery Disease guidelines, are listed in Chart 10.3.

10.6. Autoimmune Diseases and Cardiovascular Risk

Several autoimmune diseases can affect the heart through various manifestations including arrhythmias, pericardial, myocardial and coronary artery diseases. In relation to this last complication, advances and research in the field of atherosclerosis have increasingly reinforced the participation of the immune system in its pathophysiology. The presence of lymphocytes and macrophages within atheromatous plaques suggests that inflammation is a major factor in the disease evolution cascade. This hypothesis even motivated a recent clinical trial that evaluated the effect of low dose methotrexate on the reduction of CV events in patients without autoimmune diseases but with previous infarction. Although the reduction in the primary outcome was not achieved in this study, further work in this area is still ongoing.

However, in patients with rheumatic diseases, the systemic inflammatory process is amplified and which may result in the occurrence of accelerated atherosclerosis.[509] This condition may be the main explanation for the high percentages of morbidity and mortality in these patients.[510] In addition, the use of certain immunosuppressive medications, such as corticosteroids, may also contribute to the worsening of the CV risk profile. It is worth mentioning RA and systemic lupus erythematosus (SLE) among the diseases that may have this pathophysiological feature, although other conditions such as scleroderma, inflammatory bowel diseases, psoriasis and certain primary vasculitis such as polyangeitis granulomatosis, are also relevant.[509-511]

RA is associated with a 3-fold reduction in survival, with ischemic heart disease accounting for about 40% of deaths.[512] In addition, the risk of AMI is about 2 times higher than in the general population, and the prognosis after the event tends to be worse. This scenario begins to develop at the onset of the disease and independently of other factors classically associated with atherosclerosis. Vascular inflammation caused by autoimmunity seems to play a more important role in this context. Some population studies even suggest a recent reduction in CV lethality in these patients, perhaps due to the greater availability of disease-specific treatments.[513] Nevertheless, functional limitation and consequent physical inactivity imposed by RA may also increase the likelihood of developing other risk factors, such as obesity, hypertension and diabetes. On the other hand, it is noteworthy that systemic inflammation in individuals with RA can reduce serum levels of total cholesterol and LDL, promoting what is known as the "lipid paradox", since the risk of events remains high even with this metabolic profile.[513,514] Nevertheless, control of traditional risk factors remains the main strategy for preventing CV events in these patients. Like RA, SLE also behaves as an independent risk factor for CV disease, with a coronary disease prevalence of up to 10% and a risk of events up to 8 times higher than the general population. Some studies suggest that AMI may be the cause of death in up to 25% of cases, especially in patients who have the disease for longer.[509] At the same time, the prevalence of major CV risk factors such as hypertension, diabetes, obesity, physical inactivity and dyslipidemia is also higher in individuals with SLE. Frequent use of corticosteroids for disease management is another condition that worsens the metabolic profile, although daily doses of prednisone below 10 mg appear to be safe in this respect, as do antimalarial drugs.[515] Nevertheless, risk calculators using traditional factors often underestimate the incidence of events in these patients. Other markers associated with atherosclerosis that are more relevant in individuals with SLE, such as osteoprotegerin and osteopontin, are promising predictors that could refine this estimate. The fact that disease-associated coronary artery disease is more often associated with atherosclerosis than vasculitis corroborates this expectation.[516]

As most autoimmune diseases are more common among women, a thorough stratification of CV risk in females is essential in the presence of these conditions, despite the limitations already mentioned. Even so, the fundamental issue is the absence of clinical studies demonstrating a benefit in treating this group of patients more aggressively. To date, there is no evidence that therapeutic targets for blood pressure, blood glucose, LDL cholesterol, or any other risk factor should be modified due to the presence of an autoimmune disease. The relatively low prevalence of these diseases in the population is the main factor limiting good quality studies to answer these questions. Therefore, each case needs to

Updated

Chart 10.3 – Risk Factors / Therapeutic Conduct and their Recommendation Classes / Levels of Evidence at DAPEI according to the latest international Peripheral Artery Disease guidelines

Risk Factor / Therapeutic Management	Society for Vascular Medicine Guidelines (2015)[484]	AHA / ACC Guidelines (2016)[483]	European Society of Cardiology (ESC) Guidelines (2018)[482]
Smoking	Comprehensive preventive interventions aimed at smoking cessation in asymptomatic Lower extremity PAD, intermittent claudication and after open endovascular or surgical procedure I-A	Lower extremity PAD smoking cessation programs, including pharmacotherapy I-A	Smoking cessation is recommended in all patients with Lower extremity PAD I-B
Statins	In Lower extremity PAD with intermittent claudication I-A Optimized statin therapy is recommended for all patients with claudication and after endovascular or open surgical procedure I-A	Suitable for all patients with Lower extremity PAD I-A	Recommended statins for all patients with Lower extremity PAD I-A In patients with Lower extremity PAD it is recommended to lower LDL-c below 70 mg/dL or to decrease it by > 50% if baseline values are between 70-135 mg/dL I-C
Physical exercise	Supervised Exercises I-A Residential exercises I-B Post limb revascularization exercises for claudication I-B At least annual follow-up of claudication to check the results from exercise I-C	Treadmill test may help in functional evaluation in Lower extremity PAD IIa-B Supervised exercises in patients with claudication I-A Residential or community exercises with behavioral change techniques may be beneficial in functional improvement IIa-A In lameness patients, alternative exercises such as low intensity, painless walking may be beneficial in functional improvement IIa-A	Supervised exercises are recommended in patients with lameness. I-A Unsupervised exercise in patients with claudication I-C Healthy diet and physical activity are recommended in patients with Lower extremity PAD I-C
Antiplatelets	Use of aspirin 75-325 mg/day in claudication I-A In claudication, use of clopidogrel (75 mg/day) as an effective alternative to aspirin IIb Optimized antiplatelet therapy is recommended for all patients with claudication and after endovascular or open surgical procedure I-A Improves patency of venous and artificial lower limb vascular grafts II-B In infrainguinal endovascular intervention for lower limb claudication, aspirin with clopidogrel for at least 30 days is suggested IIb	Use of aspirin monotherapy (75-325 mg/day) or clopidogrel monotherapy in claudication (75 mg/day) reduces AMI, stroke and vascular death I-A In asymptomatic Lower extremity PAD, antiplatelet use is reasonable to prevent risk of AMI, stroke and vascular death IIa-C In asymptomatic borderline ABI Lower extremity PAD, the advantage of antiplatelets is uncertain to prevent risk of AMI, stroke and vascular death IIb-B The efficacy of dual antiplatelet therapy (aspirin + clopidogrel) in reducing risk of CV events in symptomatic Lower extremity PAD is not well established IIb-B Dual antiplatelet therapy (aspirin + clopidogrel) may be reasonable to reduce risk of lower limb events in symptomatic Lower extremity PAD following limb revascularization IIb-C	In patients with symptomatic Lower extremity PAD, antiplatelet monotherapy is indicated I-A In all patients with revascularized Lower extremity PAD, antiplatelet monotherapy is indicated I-C In infrared revascularized Lower extremity PAD, antiplatelet monotherapy is indicated I-A In patients with Lower extremity PAD requiring antiplatelet agents, clopidogrel may be preferable to aspirin IIb-B Following infrainguinal endovascular intervention with stenting for lower limb claudication, aspirin + clopidogrel for at least 30 days is suggested IIa-C After prosthetic bypass graft in infrapopliteal PAD (below the knee), the use of aspirin + clopidogrel IIb-B
Anticoagulants	They reduce the risk of limb loss and increase graft patency, but double the risk of bleeding compared with antiplatelet agents B-C Suggests against warfarin use only to reduce risk of CV events or vascular occlusions I-C	The usefulness of oral anticoagulants in maintaining patency of vascular grafts is uncertain IIb-B Anticoagulation should not be used to reduce risk of CV events in Lower extremity PAD III-A	Vitamin K antagonist may be considered after revascularization with infra-inguinal autologous venous graft. IIb-B

Antihypertensives	Optimized antihypertensive therapy is recommended for all patients with claudication and after endovascular or open surgical procedure I-A	Antihypertensive therapy recommended in hypertensive patients to reduce the risk of AMI, stroke, heart failure and CV death inLower extremity PAD I-A Use of ACE inhibitors or ARB may be effective in reducing risk of CV events in Lower extremity PAD IIa	In hypertensive patients with Lower extremity PAD it is recommended to maintain BP < 140/90 mmHg I-A The use of ACE inhibitors or ARB is considered a drug of choice in patients with Lower extremity PAD and hypertension IIa-B
Diabetes, glycemic control and hypoglycemic drugs	Hemoglobin A1C target < 7.0% in lameness if it can be achieved without hypoglycaemia I-B Recommended optimized glycemic control for all patients with claudication and after endovascular or open surgical procedure I-A	Optimized glycemic control may be beneficial in patients with critical lower extremity ischemia to reduce limb outcomes IIa-B	Strict glycemic control in diabetic patients with Lower extremity PAD I-C

ABI: Ankle-Brachial Index; ACEI: angiotensin-converting enzyme inhibitors; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; CV: cardiovascular; CVI: Stroke; Lower extremity PAD: lower extremity peripheral arterial disease.*

be individualized, with constant reassessments throughout the disease evolution of the potential risks and benefits of treatment.

Recommendations for autoimmune diseases and CV risk are shown in Table 10.4.

10.7. Chronic Kidney Disease

The overall prevalence of CKD is estimated at 11-13%,[517] and in Brazil, despite inconsistent data, it is estimated that between three and six million people have the disease.[518] The relationship between CKD and CVD is complex, dynamic and multifactorial. In addition to both sharing risk factors such as systemic arterial hypertension, diabetes and advanced age, there is a higher prevalence of traditional CVD risk factors in patients with CKD.[519,520] In a study by Foley et al.,[519] with more than 15,000 patients, 83.6% of those with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and 100% of those with GFR-e < 30 ml/min/1.73 m^2 had at least two risk factors for CVD.[519] Furthermore, the loss of renal function itself causes changes that can accelerate CVD, such as arterial stiffness and anemia contributing to left ventricular hypertrophy, endothelial dysfunction disease, chronic inflammation, vitamin D deficiency, oxidative stress, and activation of the renin-angiotensin system.[520-523]

The result of this interaction is that CVD is the leading cause of death in patients with CKD.[521] In a meta-analysis by van der Velde et al.,[524] evaluating cohorts of patients with hypertension, diabetes or CV disease, they observed an increase in all causes of mortality with eGFR reduction, and rates of 60, 45 and 15 ml/min/1.73m^2 presented a hazard ratio of 1.03, 1.38 and 3.11, respectively, when compared to patients with eGFR 95 ml/min/1.73 m^2. In addition, the presence of albuminuria, even when borderline, was also associated with higher mortality in this same study, and urinary albumin-creatinine ratios of 10 mg/g, 30 mg/g and 300 mg/g presented a hazard ratio of 1.08, 1.38 and 2.16 when compared to the ratio of 5 mg/g.[524]

Currently, CKD[525] and albuminuria are considered independent predictors of CV[522-526] events and thus, CV prevention plays a key role in the management of CKD patients. Overall, the risk assessment should be individualized and CKD should be interpreted in the context of the overall risk assessment according to each clinical setting, and is considered a high risk CV marker.[7,525] Given the various clinical scenarios related to CKD, it is worth mentioning systemic arterial hypertension, dyslipidemia and the use of antiplatelet agents in primary prevention.

With regard to systemic arterial hypertension, risk stratification and treatment to prevent events and additional loss of renal function should follow the guidelines published by this Society.[146] It is noteworthy that in this case, CKD is used in the additional risk stratification according to eGFR and urinary albumin-creatinine ratio, and can be interpreted as target organ damage (eGFR 30-60 ml/min/1.73 m^2 or urinary albumin-creatinine 30-300 mg/g) or as an established disease (eGFR < 30 ml/min / 1.73 m^2 or urinary albumin-creatinine > 300 mg/g). Similarly, the approach to dyslipidemia in CKD patients should follow the stratification and treatment model proposed in this Society's specific guideline.[7] In this case, CKD (eGFR < 60 ml/min/1.73 m^2) is considered as a high-risk CV marker for proposed goals and treatments.[7]

Table 10.4 – Autoimmune Diseases and Cardiovascular Risk

Recommendation	Recommendation Class	Level of evidence	References
In the context of preventing cardiovascular events, the benefit of using stricter therapeutic targets specifically due to the presence of autoimmune diseases is uncertain	IIb	C	513,514,516

Finally, regarding the use of antiplatelet agents in primary prevention, the evidence regarding its benefit is not robust enough to indicate its routine use considering CKD alone. In a meta-analysis of more than 50 studies and more than 27,000 patients, the use of ASA reduced the risk of infarction without, however, reducing overall mortality, CV mortality or stroke, with increased numbers of major and minor bleeds.[527] Thus, the use of antiplatelet agents should be assessed according to the overall risk and decision-making should be made on an individual basis when considering their use solely for CKD.

Recommendations for CKD and CV risk can be seen in Table 10.5.

10.8. Obstructive Sleep Apnea

In recent years, much has been debated about obstructive sleep apnea (OSA) as a CV risk factor and, in 2018, the Brazilian Society of Cardiology published a position on this clinical condition and its implications on CV risk.[528] OSA is characterized by the temporary narrowing or occlusion of the upper airway during sleep,[529] which in turn activates the sympathetic nervous system and triggers a chain of events involving elevation of blood pressure, release of inflammatory mediators, oxidative stress, endothelial dysfunction, reduced insulin sensitivity and activation of the renin-angiotensin-aldosterone system.[528-530] Despite the short duration of events, prolonged repetitive exposure to periods of hypoventilation and hypoxemia can lead to chronic changes in metabolism and circulatory system leading to consequences such as systemic arterial hypertension, pulmonary hypertension, arrhythmias, coronary disease, stroke, heart failure, diabetes, dyslipidemia, and increased mortality CV.[528-533]

The prevalence of OSA has increased in recent years[528,529] and some series have reported apnea-hypopnea index equal to or greater than 5 events per hour in 34% of men and 17% of women aged 30 to 70.[534] In CVD patients The prevalence of OSA is higher when compared to patients of the same age and sex in the general population, regardless of body mass index.[529] Among CVD, hypertension, coronary artery disease, stroke and heart failure with reduced ejection fraction, with reports of associated prevalence of OSA of up to 83%, 58%, 91% and 53%, respectively.[528,529]

The treatment of OSA is mainly based on the use of continuous positive airway pressure (CPAP). There is evidence that this treatment modality has beneficial effects on blood pressure control,[535] but evidence regarding rigid outcomes such as total and CV mortality is not as robust,[528-530] with data on primary prevention from observational studies.[531,536] In a recent systematic and meta-analysis review, no reduction in major CV events including vascular death or all-cause death was observed.[537] It is worth mentioning that in 60% of the studies evaluated CV disease (secondary prevention) was documented and in such cases, with patients undergoing optimal clinical treatment, CPAP treatment may have little additional effect than current treatment when assessing total mortality and CV outcomes,[530,537] despite the benefits of blood pressure control and improvement of extra-cardiac symptoms.[530]

Finally, CV prevention strategies in OSA patients should consider the higher morbidity and mortality attributed to this condition, emphasizing the control of other associated risk factors and respecting specific treatment indications according to this Society's position on group 11 of AOS.[528]

Recommendations for obstructive sleep apnea (OSA) and CV risk are shown in Table 10.6.

10.9. Erectile Dysfunction

Erectile dysfunction (ED) is the recurrent inability to obtain and maintain an erection that allows for satisfactory sexual activity. ED is not a disease but a symptomatic manifestation of isolated or associated pathologies.[538] It has a prevalence of just over 50% in men over 40 years of age in the USA and Brazil. Studies have shown a prevalence between 43 and 46% in the same age range.[538-541] The causes of ED can be classified as psychological, organic or a combination of both. Organic factors include vascular, endocrine, neurological, drug-related causes, and urological interventions. Vascular etiology is the most common cause of erectile dysfunction. Arterial traumatic disease, atherosclerosis and SAH are among the main causes of vascular ED. Increasing the prevalence in patients with

Table 10.5 – Chronic Kidney Disease (CKD) and cardiovascular risk

Recommendation	Recommended class	Level of evidence	Reference
Cardiovascular prevention measures in patients with CKD should be individualized and consider the eGFR, the presence of other associated diseases and the overall cardiovascular risk	I	C	525-527

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Table 10.6 – Obstructive sleep apnea and cardiovascular risk

Recommendation	Recommended class	Level of evidence	References
Measures for cardiovascular prevention in patients with obstructive sleep apnea should be individualized and consider the presence of other associated diseases, the overall cardiovascular risk and indications for treating the disease itself	I	C	528,530,537

hypertension and / or diabetes and also with aging, it may reach a prevalence of over 68% in these populations and also be related to therapy with CV action drugs that contribute to the occurrence of ED.[542-544]

ED is currently recognized as being of vascular etiology in most men, with endothelial dysfunction as the common denominator. ED often precedes CVD and is often present in men with known CVD, leading to the concept that a man with ED and no CVD symptoms is a patient with CVD until proven otherwise, and a man with known CVD should be routinely asked about your erectile dysfunction. ED also has a significant negative impact on the patient and partner (one man's problem but a couple's concern), thus emphasizing the need to approach ED as early as possible.[545]

A meta-analysis of 20 prospective cohort studies involving 36,744 participants suggested that erectile dysfunction significantly increases the risk of ischemic heart disease, stroke and all-cause mortality and concluded that it could play a role in quantifying CV risk based on traditional risk factors.[546] Another population-based study of 95,038 men aged 45 and over showed that CVD risk is related to the severity of erectile dysfunction in men with and without established CVD, with a relative risk (respectively) of 1.6 and 1.7 for the development of ischemic heart disease.[547] All men with erectile dysfunction should be considered potential candidates for primary prevention, CV risk stratification and treated according to their risk estimates.

Recommendations for autoimmune diseases and CV risk are listed in Table 10.7.

10.10. Prevention of Rheumatic Heart Disease

Rheumatic heart disease (RHD) is the cardiac consequence of acute rheumatic fever (ARF), an inflammatory disease caused by streptococcal pharyngitis. Its prevalence is closely related to unfavorable sanitary conditions, agglomerations and inadequate access to health systems.[548] Over the last decades there has been a significant reduction in prevalence and mortality from RHD worldwide (with a reduction in standardized global mortality of 47, 8% from 1990 to 2015[2]), markedly in developed countries, and even near eradication in some regions. However, the burden of disease remains high in underdeveloped countries and even in poor regions of developed countries.[548] In 2015, the highest age-standardized mortality rates for RHD prevalence were observed in Oceania, South Asia, and central sub-Saharan Africa, but there is clearly an underestimation of data from Brazil and Latin America, partly due to the scarcity of primary data. It is estimated that in 2015 there were 33.4 million cases and approximately 10.5 million disability-adjusted life years (DALY) attributable to RHD worldwide.[549]

The principal determinant of RF is the admittedly repeated infection with group A beta-hemolytic streptococci (GAS), and some theories attempt to explain the pathophysiology involved in susceptibility to damage, which affects only 6% of individuals exposed to GAS: a) an antigenic similarity between agent structures (M protein surface and GlcNAc epitope) and molecules in host tissues, triggering an exaggerated immune response, and b) generation of a "neo-antigen" through contact between GAS and collagen matrix subendothelial, with consequent binding between M proteins and CB3 region of collagen type IV, inducing an autoimmune response against collagen.[548]

Thus, primary prevention of RF requires early identification and appropriate therapy for GAS pharyngitis. When selecting a treatment regimen, consideration should be given to the bacteriological and clinical efficacy, ease of adherence to the recommended regimen (ie: dosing frequency, duration of therapy and acceptability), cost, spectrum of activity of the selected agent and potential adverse effects. In this context, intramuscular benzathine penicillin G, oral potassium penicillin V and oral amoxicillin are the recommended antimicrobial agents for the treatment of GAS pharyngitis in people without penicillin allergy (Table 10.8). GAS resistance to penicillin has never been documented, and penicillin potentially prevents primary attacks of RF even when started nine days after the onset of infection.[550,551]

In recent decades, the long asymptomatic period of RHD and the possibility of early interventions in the subclinical phase have led to the increased role of echocardiography in disease management, with the development of population screening studies and the publication of the 2015 revised Jones criteria.[552] In addition to the incorporation of detected subclinical carditis on echocardiography, patients were stratified according to population risk for RHD,[552-554] with different criteria for endemic and non-endemic regions (Chart 10.4).

Once RHD is diagnosed, prevention strategies should focus on preventing recurrences that are associated with worsening or developing RHD. A GAS infection does not necessarily have to be symptomatic to trigger a recurrence, and RHD can recur even when a symptomatic infection is correctly treated. Therefore, prevention requires continuous antimicrobial prophylaxis rather than simply recognizing and treating acute episodes of pharyngitis.[548] Therefore, continuous prophylaxis is recommended in patients with well-documented history of RHD and in those with evidence of RHD. Prophylaxis should be started as soon as RHD or RF is diagnosed. In order to eradicate GAS in the oropharynx, a complete penicillin cycle should be given to patients with RHD, even for those with a negative oropharyngeal culture.[548,550,551]

Table 10.7 – Autoimmune Diseases and Cardiovascular Risk

Recommendation	Class	Level of evidence	Reference
All men with erectile dysfunction should be submitted to cardiovascular risk stratification and treated according to the observed risk estimate	IIa	C	9,546,547

Table 10.8 – Primary and secondary prophylaxis regimens for acute rheumatic fever and rheumatic heart disease

Recommendation	Recommendation level	Level of evidence	Reference
Primary prophylaxis			
Penicillins:			
Amoxicillin 50 mg/kg (maximum 1 g) VO 1x/day for 10 days **Penicillin G Benzatin** Patients up to 27 kg: 600,000 IU IM in single dose; patients > 27kg: 1,200,000 IU IM in single dose **Penicillin V Potassium** Patients up to 27 kg: 250 mg OR 2 or 3x/day for 10 days; patients > 27 kg: 500 mg OR 2 or 3x/day for 10 days	I	B	549,550
Allergic to Penicillin:			
Low Spectrum Cephalosporins (Cephalexin, Cefadroxil) Variable	IB	B	549,550
Azithromycin 12 mg/kg (maximum 500 mg) OR 1x/day for 10 days	IIa	B	
Clarithromycin 15 mg/kg OR per day, divided into 2 doses (maximum 250 mg 2x/day) for 10 days	IIa	B	
Clindamycin 20 mg/kg OR/day (maximum 1.8 g per day) divided into 3 doses for 10 days	IIa	B	
Secondary Prophylaxis:			
Penicillin G Benzatin Patients up to 27 kg: 600,000 IU IM every 3 to 4 weeks †; patients > 27 kg: 1,200,000 IU IM every 3 to 4 weeks †	1	A	549,550
Penicillin V Potassium 250 mg OR 2x/day	1	B	
Sulfadiazine Patients up to 27 kg: 0.5 g OR 1x/day; patients > 27 kg: 1 g OR 1x/day	1	B	
Macrolide or azalide (for penicillin and sulfadiazine allergic patients) ‡ Variable	1	C	

† Administration every 3 weeks is recommended in certain high risk situations. ‡ Macrolide antibiotics should not be prescribed to patients using other cytochrome P450 3A inhibiting drugs such as azole antifungals, human immunodeficiency virus protease inhibitors, and some selective serotonin reuptake inhibitors. IM: intramuscular; IU: international units; OR: orally.

Chart 10.4 – Summary of Jones Criteria for Acute Rheumatic Fever (2015 Review), highlighting major changes from 1992 review

Jones criteria revised for diagnosis of ARF[6]		
ARF Risk	Low risk population: Incidence of ARF ≤ 2 per 100,000 school-age children or prevalence at all ages ≤ 1 per 1000 per year	Moderate to high risk population: Children not included in low risk populations
Major criteria:		
Carditis	Clinical and/or subclinical*	Clinical and/or subclinical*
Arthritis	Polyarthritis	Monoartrite, poliartrite e/ou poliartralgia
	Korea Marked Erythema Subcutaneous nodules	Korea Marked Erythema Subcutaneous nodules
Minor criteria:		
Carditis Arthralgia Fever Inflammatory markers	Extended PR Range† Polyarthralgia ≥ 38.5°C ESR peak ≥ 60 mm in 1 hr and / or CRP ≥ 3.0 mg/dL	Extended PR Range† Monoarthralgia ≥ 38°C ESR peak ≥ 30 mm in 1hr and/or CRP ≥ 3.0 mg/dL

*Changes from the 1992 revision are highlighted in bold. * Subclinical carditis: seen only on echocardiography, without auscultatory findings. † Considering variability by age and only if carditis is NOT counted as a major criterion. ARF: acute rheumatic fever; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.*

Patients diagnosed with rheumatic carditis with or without valvular disease are at high risk for recurrence and presumably a progressive risk of more severe cardiac involvement at each episode.[555] These patients should receive long-term antibiotic prophylaxis until adulthood and, in selected cases, for life. Patients with persistent valvular disease should receive prophylaxis for 10 years after the last episode of RHD or until the age of 40, whichever one is longer. The severity of valvular disease and the potential for day-to-day GAS exposure should be determined, and lifetime prophylaxis should be considered in those at high risk (e.g, permanent contact with children in schools and day care centers, care for institutionalized patients, work in health facilities etc.).[550,551] In non-endemic regions, administration of benzathine penicillin G every 4 weeks is the recommended regimen for secondary prophylaxis in most situations. In higher-risk populations, administration every 3 weeks is warranted because serum antimicrobial levels may fall below protection levels before 4 weeks after the initial dose (Table 10.9).

Regarding echocardiographic screening studies in high-risk populations have shown that its accuracy is arguably higher than auscultation for detection of subclinical RF,[554] and its application at the research level has grown exponentially in the last decade. Based on screening programs involving more than 100,000 patients, in 2012, the World Heart Federation (WHF) published the first evidence-based consensus standardizing the criteria for echocardiographic diagnosis of RF (borderline and definitive).[555] The concepts of subclinical (echocardiographic findings without alterations on clinical examination) and latent (a broader spectrum encompassing RHD present on echocardiography, with no known prior history of RF or RHD) were defined.[555]

The population echocardiographic screening strategy has already been tested in Brazil, and its implementation has proved feasible in schools – especially the public schools in regions with low socioeconomic indices – and primary health care, with diagnostic support by telemedicine.[556,557] In addition, non-physician imaging using the WHF simplified protocol was effective, including the basic identification of changes related to RHD.[558] There was a high prevalence of subclinical RHD in low-income regions of 4.5% (4.0% borderline and 0.5% definitive).[556,557]

However, despite the various cohorts involving these patients, the clinical significance and prognostic implication of these findings has not been well established so far. Recently, a score derived from large population studies in Brazil and Uganda has been proposed to stratify patients according to the risk of RHD progression, based on weights attributed to the echocardiographic variables in the WHF criteria.[559] However, it has also been shown that giving a child a diagnosis of latent RHD can potentially worsen their quality of life and create stigmas,[560] which raises important questions about the risk-benefit ratio of large screening programs. For these reasons, there is no indication for the use of echocardiographic screening outside the research field until further studies on its impact on disease progression are completed.

11. Child and Adolescence

11.1. Introduction

Childhood and adolescence are the phases with the most potential for the prevention of atherosclerosis. There is robust evidence, based on analyzes of the aortas and coronary arteries, that atherosclerosis begins at fetal age. However, more recent studies show that atherosclerosis may regress in children more easily than in adults, since their lesions are less complex and fixed. CVD risk factors respect the tracking phenomenon, i.e., a child who has some risk factor will probably have the same factor in adulthood, with similar intensity. Coupled with the fact that health habits are formed in childhood and adolescence, there is a clear need and possibility to prevent atherosclerosis from an early age.[561] Therefore, we will present strategies to control the main habits and risk factors that can be controlled in this age group. (Recommendation Level IIa; level of evidence B).

11.2. Childhood and Adolescent Nutrition

Nutrition is the basis of health promotion in childhood and adolescence. In addition, eating habits are mainly formed by 7 years of age, reinforcing the importance of food education from an early age. Population studies show that almost all children ingest larger amounts of poor quality fat and added sugar or lower amounts of fiber than recommended for their age. The following principles are recommended for good child growth and development to prevent atherosclerosis from childhood:[562-564] (Recommendation Level IIa; level of evidence C).

1. Exclusive breast milk up to 6 months, and introducing other foods up to 2 years old.
2. Eating fresh and whole foods from 6 months of age, starting with pureed foods and then eating the family diet, which should be as healthy as possible.

Table 10.9 – Duration of secondary prophylaxis regimens for acute rheumatic fever and rheumatic heart disease

Type	Duration after last episode	Class	Level of evidence	Reference
ARF with carditis and residual heart disease (persistent valve disease)†	10 years or up to 40 years old (whichever is longer); Lifelong prophylaxis may be required	I	C	549,550
ARF with carditis but no residual heart disease (absence of persistent valve disease)†	10 years or up to 21 years old (whichever is longer)	I	C	549,550
FRA without carditis	5 years or up to 21 years old (whichever is longer)	I	C	549,550

ARF: acute rheumatic fever. † Clinical or echocardiographic evidence.

3. Age-appropriate caloric intake, taking into account their basal metabolic rate, as well as growth and exercise needs, except in children with special conditions, or inadequate growth and body composition.
4. Offer the child the most varied and colorful food possible, respecting the proportionality between protein (10 to 20% of total daily caloric volume), fat (30 to 40%) and carbohydrates (30 to 50%) in each age, provided there are not any risk factors that require different proportions.
5. Encourage the daily intake of fruits and vegetables by offering this type of food at every meal. The child should eat the equivalent of his age + 5 in grams of fiber.
6. Avoid sugar (ideally less than 5% of total daily calories), coffee, canned goods,fried foods, soft drinks, candies, snacks and other treats throughout development, these foods should be banned in infants. Replace, whenever possible, processed and ultra-processed foods with fresh or minimally processed foods, regardless of age and body composition.
7. Use salt sparingly. Children's food must have a less spice and salt than an adult's; 1.2 to 1.5 g/day of salt for children up to preschool age and up to 2 g/day in school children and adolescents.
8. Associate proteins of animal and vegetal origin, eat whole grains and vegetables at least 5 times a week, in the ratio of 3:1. Animal proteins should be of varied origins, encouraging the consumption of fish.
9. Frequent water intake throughout the day, limiting the intake of juices, even if natural and without added sugar: Ideally, only provide juices from 1 year of age, and at most 120 mL, 180 mL and 240 mL, for infants, preschoolers and schoolchildren, respectively.
10. Offer high nutritional value fats, such as nuts (nuts, almonds, walnuts, among others) and vegetable oils, as long as they are safe (avoid fresh nuts in children under 3 years due to the risk of aspiration) and according to age-appropriate amount. Avoid the intake of trans fats as much as possible.

For children with dyslipidemia, fat intake should be limited to about 25-30% of their total daily calories, while maintaining a proportion of < 7 to 10% saturated fat and 20% mono and polyunsaturated fat, similar to recommendations for adults. The addition of sugar should be avoided and the intake of omega-3 in the form of fish rich in these fatty acids ideally 2 or 3 times a week should be encouraged. Follow-up with a nutritionist or nutrologist is recommended when there is a risk of malnutrition or impaired growth and development.[565] (Recommendation Level IIa, evidence level A).

For children with SAH, the DASH diet should be used, as in adults, which includes increasing the proportion of fresh foods, especially fruits and vegetables, and reducing salt intake.[566] (Recommendation Level IIa, level of evidence B).

Control of the food environment is of utmost importance in childhood and adolescence, especially the school environment, which should be protected by public policies that encourage the supply of foods with high nutritional value and restrict ultra-processed, high-calorie or high-density foods with added sugar and trans fats.[567] (Recommendation Level I, level of evidence C).

11.3. Physical Activity in Childhood and Adolescence

Physical activity is considered an independent protective factor in the primary prevention of coronary artery disease since childhood, because of its effect on modulating traditional risk factors and promoting normal endothelial function. Higher levels of physical activity are associated with improved bone health, nutritional status, cardiometabolic health, cognitive function, and reduced risk of depression.[568] Intervention programs to increase physical activity in children are associated with improved blood pressure and lipid profile.[569]

Physical activity is considered any body movement that results in energy expenditure. Physical exercise consists of planned, structured and repetitive physical activity.

In Brazil, the prevalence of physical inactivity was assessed in a sample of 74,589 adolescents in the Study of Cardiovascular Risks in Adolescents (ERICA). The prevalence of leisure-time physical inactivity reached 54.3%, being especially worrying in female adolescents (70.7%). More than a quarter of adolescents reported no leisure-time physical activity.[570]

The discussion about childhood physical activity has two important aspects for cardiovascular prevention. The first is the tracking phenomenon described above, highlighting the importance of establishing healthy habits at a time when the child is developing, which is much easier to intervene than after the sedentary lifestyle has been established and excessive screen time (more than 2 hours/day). The second aspect is the accumulation of risk or protective factors over the course of life, which can determine different levels of risk over many years of exposure.

Regarding these concepts, in 2016, the American Heart Association published the Cardiovascular Health Promotion in Children document: Challenges and Opportunities for 2020 and Beyond The Scientific Statement From the American Heart Association, stating that maintaining optimal CV health from birth to young adulthood is critical part of reducing CVD disease in adulthood.[571]

The physical activity level considered ideal for children and adolescents aged 6 to 17 years is 60 minutes or more per day of intense to vigorous aerobic activity. The document also recommends performing muscle strength activity and muscle-strengthening and bone-loading1 at least three times a week (Recommendation Level IIa, Evidence Level B).[568,571]

Preschoolers (3-5 years old) should remain active throughout the day to encourage growth, development and to acquire a repertoire of motor skills. Caregivers should aim to achieve a total of at least 3 active hours per day, diversifying from mild to vigorous intensities (Recommendation Level IIa, level of evidence B).

Although there is no consensus on the amount of activity or exercise needed to treat CV risk factors such as dyslipidemia, hypertension or obesity in childhood, it is known that even without effective control of their CV risk, physical activity is one of the most important pillars in the prevention of

atherosclerosis, with improvement of endothelial function and even regression of intimal thickening, markers of subclinical atherosclerosis.[571,572] (Recommendation Level IIa, level of evidence B).

Current evidence for adults shows that total activity volume is more important than the duration of each individual session.[573]

Recommendations for all age groups emphasize increasing overall physical activity (moving more) and reducing sedentary activity (avoiding long sitting periods) whenever possible. For children, this means encouraging outdoor play whenever possible, activities with different levels of intensity, such as walking the dog, storing toys, walking to school, among others. It also means, from a public policy point of view, ensuring safe spaces for children and adolescents to play sports or jogging, an urban layout that encourages walking or cycling, and the structure and availability of qualified physical exercise teachers, schools and other community locations such as parks and gyms.[568,573] (Recommendation Level I, level of evidence C).

11.4. Smoking in children and Adolescence

About 18.5% of Brazilian adolescents have tried cigarette smoking. Smoking increases CV risk in childhood, even when it is passive: low birth weight, higher risk of childhood obesity; it also determines endothelial dysfunction as early as childhood, in addition to all pulmonary neurological risks.[574,575] Childhood is the most important phase for smoking prevention, as about 90% of people start smoking by age 18. In addition, it is an ideal moment for parental smoking cessation, as they may change their habits if the harmful effects of secondhand smoke are shown to their children. This intervention should occur in different environments, 2 of which may be directly addressed by the physician:[576] (Recommendation level I, level of evidence C).

At the pediatrician clinic:

1. Ask about your child's passive exposure to smoking during childcare consultations and in consultations regarding potentially smoking-related illnesses. Ask about caregiver and environment smoking, electronic cigarettes and cannabis use.
2. Include smoking prevention in your childcare agenda. Clarification about the harms of smoking in consultations from 5 years of age. For teens, talk about the effects on appearance, sports performance and costs. Discuss electronic cigarette.
3. Recommend treatment for caregivers who smoke. Refer to specialized smoking cessation services.
4. Offer treatment to adolescent smokers users who want to quit smoking. Moderate or severe adolescent users may benefit from drug treatment. Periodic follow-up should occur due to the high chance of relapse.
5. Closely assess the risk of psychiatric symptoms during treatment. Suicidal ideation and suicide may occur, which must be monitored and treated.
6. Do not recommend the use of electronic cigarettes. The harmful effects are similar.
7. If second-hand smoke cannot be eliminated, agree on measures that minimize exposure.

In medical schools:

At all levels of teaching and learning and for all health professionals, smoking cessation training should be provided. The prevention of active and passive smoking, as well as forms of intervention in smoking cessation should be part of the curriculum of pediatric and family medicine residency programs, due to the great importance of abuse in the general population. (Recommendation Level I, level of evidence C).

11.5. Obesity in Childhood and Adolescence

Between 1975 and 2016 the prevalence of obesity between 5 and 19 years increased on average from 0.7% to 5.6% in girls and from 0.8% to 7.8% in boys in all geographic regions of the world. The study estimated that in 2016 there were 50 million obese girls and 74 million obese boys worldwide.[577] In Brazil, the 2015 National School Health Survey identified a prevalence of overweight and obesity in 23.3 % and 8.5% in students from 13 to 17 years old, respectively.[578]

11.5.1. Diagnosis

BMI is used as the standard measure of overweight and obesity in children from two years of age,[579] using World Health Organization reference curves. (https://www.who.int/childgrowth/standards/bmi_for_age/en/). Overweight is defined as between the 85th and 94th BMI percentile; obesity above the 95th percentile; severe obesity, when BMI is greater than or equal to 120% of the 95th percentile or BMI equal to or above 35 kg/m^2. (Recommendation Level IIa, level of evidence C).

11.5.2. Consequences

Childhood obesity is associated with dyslipidemia (high triglyceride levels and low HDL-cholesterol), hypertension, hyperglycemia, hyperinsulinemia, inflammation and oxidative stress, favoring the evolution of fatty striae in the aorta and coronary arteries, as well as other atherosclerotic lesions.[580]

About 50% of obese children aged 6 years and one obese parent will have obesity in adulthood; 80% of obese adolescents in this condition, will be an obese adult.[580]

11.5.3. Etiology

It is the result of the interaction between genetic factors and environmental factors; sedentary lifestyle and excessive calorie consumption, the focus of treatment strategies, are among the latter.[580,581] The secondary causes of childhood obesity are described in Chart 11.1.

11.5.4. Treatment

The therapeutic approach for overweight in children and adolescents should be multiple and gradual, with progressive evaluation of the results obtained and involve better diet quality, reduced calorie intake, increased physical activity and meal replacements. Pharmacotherapy (Orlistat is currently the only one approved for use in adolescents) and bariatric

Chart 11.1 – Causes of secondary obesity in childhood and adolescence

Cause Type	Examples
Medicines	Psychoactive drugs (olanzapine, risperidone), antiepileptic drugs, corticosteroids
Endocrine Diseases	Cortisol excess, hypothyroidism, growth hormone deficiency, pseudohypoparathyroidism, hypothalamic obesity
Genetic syndromes	Prader-Willi, Bardet-Biedl, melanocortin or leptin receptor mutation
Programming	Epigenetic changes in vulnerable phases of pregnancy and childhood
Other	Intestinal microbiome, individual response to viruses and toxins

surgery has only been used in severely obese adolescents when dietary and physical activity strategies are not effective in weight control.[580,581] (Recommendation Level IIa, level of evidence B).

11.6. Systemic Arterial Hypertension in Childhood and Adolescence

BP screening data in childhood and adolescence show a prevalence of SAH of up to 8.2%,[582,583] which decreases to approximately 3.5% when measurements are repeated at clinical follow-up. Prehypertension is observed in approximately 2.2 to 3.5% of the population; in overweight and obese adolescents, it can reach 24.8%. It is also associated with sleep disorders (3.6 to 14%), chronic kidney disease (up to 50%), diabetes mellitus (9.5%); aorta narrowing (17 to 77%), endocrine alterations (0.05 to 6%) and prematurity 7.3%.[584] Although hypertension in children is more often due to a secondary cause, with a defined etiology, there has been an increase in the diagnoses of primary hypertension, especially in older children and adolescents, when other risk factors are associated, such as overweight and obesity. Blood pressure measurement is considered mandatory from the age of three, on an annual basis, or before this age when the child has a neonatal history, history of prematurity, history of aortic narrowing, kidney disease, diabetes mellitus or is using medication that can increase blood pressure. SAH is defined by the blood pressure percentile in relation to age, sex and height. The tables with gender, age and height percentiles (https://pediatrics.aappublications.org/content/pediatrics/140/3/e2017) have been redefined in the American Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, facilitating the adoption of a single table containing the three parameters used and the assigned percentile. As we do not have specific tables for the Brazilian population, this criterion is used for our population. The first blood pressure measurement can be performed by the oscillometric method on the right arm using an appropriate cuff. If the result of this measurement is greater than or equal to the 90th percentile, another measurement must be taken; If the mean of these two measurements is still ≥ 90th percentile, two measurements by auscultatory method should be performed. Table 11.1 shows blood pressure levels in normal and hypertensive children and adolescents. (Recommendation Level I; level of evidence B).

In children and adolescents > 13 years of age, blood pressure is considered normal when: < 120/80 mmHg; elevated when between 120/< 80 and 129/< 80 mmHg, HAS stage 1 when between 130/80 and 139/89 mmHg and stage 2 when ≥ 140/90 mmHg. (Recommendation Level I; level of evidence B).

When BP remains persistently at or above the 90th percentile, measured 6 and 12 months after initial diagnosis, the initial assessment should attempt to identify the etiology, if any, based on information on sleep habits, family history, and risk factors, diet, smoking and alcohol intake. It is important that BP is measured in both upper limbs and one lower limb. The initial complementary exams should include: blood count, urea dosage, creatinine, sodium, potassium, calcium, uric acid, lipid profile, urine summary, renal ultrasound when < 6 years of age or with impaired renal function. For children with a BMI percentile greater than the 95th percentile, glycosylated hemoglobin, liver enzymes, blood glucose and fasting lipid profile should also be ordered.[584,585] (Recommendation Level IIa; level of evidence C).

When BP indicates stage 1 or 2 hypertension in asymptomatic children, it should be confirmed by three measurements and ABPM. Non-pharmacological measures should be initiated and, only if necessary, drug treatment should be started. If the child is symptomatic or the BP is 30 mm Hg above the 95th percentile or > 180 x 120 mmHg in adolescents, the patient should be referred to an emergency room service.[584.585] (Recommendation level IIa; Level of Evidence B).

ABPM is indicated in children above 5 years of age when the diagnosis of elevated BP continues after one year from the initial diagnosis or after three measurements in patients with stage 1 hypertension, it is very important to investigate

Table 11.1 – Blood pressure classification in children and adolescents[563]

Up to 13 years old	Systolic or diastolic blood pressure percentile
Normal (1-13 years old)	< 90
High blood pressure	≥ 90 to <95 or PA 120 x 80 mmHg at < 95 (whichever is lower)
SAH stage 1	≥ 95 to < 95 + 12 mmHg or 130 x 80 mmHg to 139 x 89 mmHg (whichever is lower)
SAH stage 2	≥ 95 + 12 mmHg or ≥ 140 x 90 mmHg (whichever is lower)

white coat and masked hypertension as well as for diagnosis in obese patients. Additional tests are needed when there is a suspected disease with elevated BP, these include: polysomnography, renin dosage or plasma renin activity; renal scintigraphy with captopril administration; dosage of plasma and urinary catecholamines; dosage of steroids in plasma and urine; nuclear magnetic resonance; digital angiography and renal arteriography. Echocardiography should be performed when drug treatment is indicated for target organ injury evaluation.[586] (Recommendation level IIa; Level of Evidence B).

The drug treatment for hypertension in childhood and adolescence is similar to that of adults. Due to the ease of supply in SUS in Brazil, the most used drugs among these groups are described in Chart 11.2. Treatment should be initiated on its own with one of the above drugs and when necessary a second drug, with hydrochlorothiazide bring the prefered choice.[586] (Recommendation Level I; Level of Evidence B).

11.7. Dyslipidemia in Childhood and Adolescence

Dyslipidemia is known to be one of the CV risk factors with the greatest impact on accelerating the progression of atherosclerosis. Considering all lipid fractions, the prevalence of dyslipidemia in childhood and adolescence has remained between 30-40%.[587] According to the ERICA study, which evaluated 38,000 adolescents in Brazil, the prevalence of dyslipidemia in this group was as follows: 46% had HDL-cholesterol concentrations below 45 mg/dL, 20.1% had total cholesterol concentrations greater than 170 mg/dL, 7.8% had triglyceride concentrations greater than 130 mg/dL, and 3.5% LDL-cholesterol concentrations greater than 130 mg/dL.[588]

Chart 11.2 – Antihypertensive drugs most frequently used in the treatment of hypertension in children and adolescents in Brazil

Medicine	Dose
Captopril	0,5-6 mg/kg/day
Enalapril	0,08-0,6 mg/kg/day
Losartan (> 6 years old)	0,7-1,4 mg/kg/day (max 100 mg/day)
Amlodipine (1-5 years old) (> 6 years old)	0,1-0,6 mg/kg/dia (max 5 mg/day) 2,5-10 mg/day
Hydrochlorothiazide	1-2 mg/kg/day (max 37,5 mg/day)

11.7.1. Causes

The causes of primary or secondary dyslipidemia are similar in adults and children. It is worth mentioning some specificities in childhood, such as the higher prevalence of more severe primary types that do not allow survival until adulthood if not treated intensively and early, such as familial hypercholesterolaemia (heterozygous or homozygous), and lipoprotein lipase deficiency (monogenic hypertriglyceridemia). Among the secondary causes, ketogenic diet, used in refractory epilepsy, has been identified more frequently, in addition to obesity, physical inactivity and inadequate diet, considered at epidemic levels in the country.[589]

11.7.2. Normal Values

The lipid profile should be measured between 9 and 11 years of age. At the population level, fasting-free dosing can be of great value, due to its practicality and cost, especially in these cases measuring HDL and non-HDL levels. In younger children, it should be done in children 2 years and older when there is an early family history of atherosclerosis, any CV risk factor or habits (Table 11.2) or clinical signs compatible with monogenic severe primary dyslipidemia. Normal values are described in Table 11.3.[590,591]

11.7.3. Treatment

The treatment is initially based on intensive lifestyle modification for at least 6 months, with weight control, diet and physical activity, as already described.[7]

The goal of LDL-cholesterol for drug use varies according to the risk profile of the child or adolescent following unsuccessful lifestyle changes (Table 11.4). The drug arsenal is similar to that of adults by age group as described in Table 11.5.[7,592]

There is no robust evidence on the use of medications in cases of hypertriglyceridemia. However, those of the fibrate class can be used in children older than 12 years, similarly to adults, when triglyceride levels reach concentrations of 700 mg/dL or persistently above 500 mg/dL even with all conventional control measures.[593] Table 11.6 shows the recommendations for approaching children and adolescents.

Table 11.2 – Cardiovascular diseases and risk factors, according to risk intensity, in children and adolescents

Type and intensity of injuries	Health problems
High risk diseases	*Diabetes mellitus, renal failure, heart or kidney transplantation, Kawasaki disease with aneurysm*
Moderate risk diseases	Chronic inflammatory diseases, HIV infection, Early coronary insufficiency in the family
High risk factors	Blood pressure above the 99th percentile medicated, smoking, body mass index above the 97th percentile
Moderate risk factors	Hypertension without indication for drug treatment, obesity between 95 and 97 percentile, HDL < 40 mg/dL

Updated

Table 11.3 – Reference values for lipids and lipoproteins in children and adolescents

Lipids	Fasting (mg/dL)	Not fasting (mg/dL)
Total cholesterol	< 170	< 170
HDL-cholesterol	> 45	> 45
Triglycerides (0-9 years old) (10-19 years old)	< 75 < 90	< 85 < 100
LDL-cholesterol	< 110	< 110
Non-HDL-cholesterol	> 145	> 145

Adapted from "Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report".

Table 11.4 – LDL-cholesterol targets in children and adolescents, according to cardiovascular risk profile

LDL-cholesterol levels	Risk
< 190 mg/dL	Without another risk factor
< 160 mg/dL	Early coronary insufficiency in the family Or other risk factor
< 130 mg/dL	Established coronary insufficiency OR 2 diseases or high risk factors OR 1 disease OR high risk factor AND 2 diseases or moderate risk factors (Table 11.3)

Table 11.5 – Medicines used to treat dyslipidemia in childhood and adolescence

Medicine	Dose	Observations
Lovastatin, pravastatin, simvastatin and atorvastatin	10-40 mg/day	Pravastatin for HIV and atorvastatin for HF (> 7years)
Rosuvastatin	5-20 mg/day	Mainly in HF (> 7 years)
Cholestyramine	4-16 g/day	Any age
Ezetimibe	10 mg/day	> 4 years old
Bezafibrate, fenofibrate	200-600 mg/day	TG persistently > 500 mg/dL
Omega 3	2-4 g/day	Variable effect
Phytosterols	1,2-1,5 g/day	Variable effect

Table 11.6 – Recommendations for approaching children and adolescents

Recommendation	Recommendation class	Level of evidence	Reference
Blood pressure classification in children and adolescents	I	B	590-593
Antihypertensives most frequently used in the treatment of hypertension in children and adolescents in Brazil: captopril, enalapril, hydrochlorothizide, amlodipine and losartan in children over 6 years old	I	A	590-593
Reference values for lipids and lipoproteins in children and adolescents	IIa	C	590-593
LDL-cholesterol targets in children and adolescents according to cardiovascular risk profile	IIa	C	590-593
Drugs used to treat dyslipidemia in childhood and adolescence	IIa	A	590-593

Up to 13 years old	Systolic or diastolic blood pressure percentile
Normal (1-13 years old)	< 90
High blood pressure	≥ 90 to < 95 or PA 120 x 80 mmHg at < 95 (whichever is lower)
SAH stage 1	≥ 95 to < 95 + 12 mmHg or 130 x 80 mmHg to 139 x 89 mmHg (whichever is lower)
SAH stage 2	≥ 95 + 12 mmHg or ≥ 140 x 90 mmHg (whichever is lower)

Lipids	Fasting (mg/dL)	Not fasting (mg/dL)
Total cholesterol	< 170	< 170
HDL-cholesterol	> 45	> 45
Triglycerides (0-9 years old)	< 75	< 85
(10-19 years old)	< 90	< 100
LDL-cholesterol	< 110	< 110
Non-HDL-cholesterol	> 145	> 145

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Omega 3	2-4 g/day	Variable effect
Phytosterols	1,2-1,5 g/day	Variable effect

LDL-a: low-density lipoprotein cholesterol; SAH: systemic arterial hypertension.

12. Populational Approach to Risk Factors for Cardiovascular Diseases

12.1. Introduction

The population is aging, in Brazil and in the world. The Brazilian population has maintained an aging trend in recent years and has gained 4.8 million elderly people since 2012, surpassing the 30.2 million mark in 2017, according to the National Household Sample Survey – PNAD.[594]

In 2012, there were 25.4 million people aged 60 and over. The 4.8 million new elderly in five years correspond to an 18% growth in this age group, which has become increasingly representative in Brazil. Women are the majority in this group, with 16.9 million (56% of the elderly), while elderly men are 13.3 million (44% of the group).[594]

Between 2012 and 2017, the number of elderly grew in all units of the federation, with Rio de Janeiro and Rio Grande do Sul being the states with the highest proportion of elderly, both with 18.6% of their populations within this age group. Amapá, in turn, is the state with the lowest percentage of the elderly, with only 7.2% of the population (Figure 12.1).[594]

According to the WHO, the world's population of elderly people is increasing, and in the coming decades the world's population of people over 60 years of age will grow from the current 841 million to 2 billion by 2050, making chronic diseases and well-being new global public health challenges.[595]

"By 2020 we will have for the first time in history more people over 60 than children under five," reported the WHO in a health and aging series in The Lancet medical journal, noting that 80% of older people will live in low- and middle-income countries.[595]

The WHO also states that the increase in longevity, especially in high-income countries, is mainly due to the decline in CVD deaths - such as stroke and ischemic heart disease, through simple and cost-effective interventions to reduce smoking and high BP.[595]

Old people or very old people (aged 85 and over) will increase by 351% between 2010 and 2050, compared with an increase of 188% for the population aged 65 and over and an increase of 22% for the 65-year-old population (Figure 12.2).[596]

Over the next 10 to 15 years, people in every region of the world will suffer more deaths and disabilities from noncommunicable diseases such as heart disease, cancer, and diabetes.[596]

These data are directly linked to inadequate lifestyles of the population, such as physical inactivity, obesity and stress, leading to an increased prevalence of risk factors such as hypertension, smoking, diabetes and dyslipidemia, with consequent increase in mortality and CV morbidity.

AH is the leading risk factor for death and CVD worldwide[597,598] Figure 12.3.[597-599] The deaths attributable to CV risk factors can be seen in Figure 12.3.

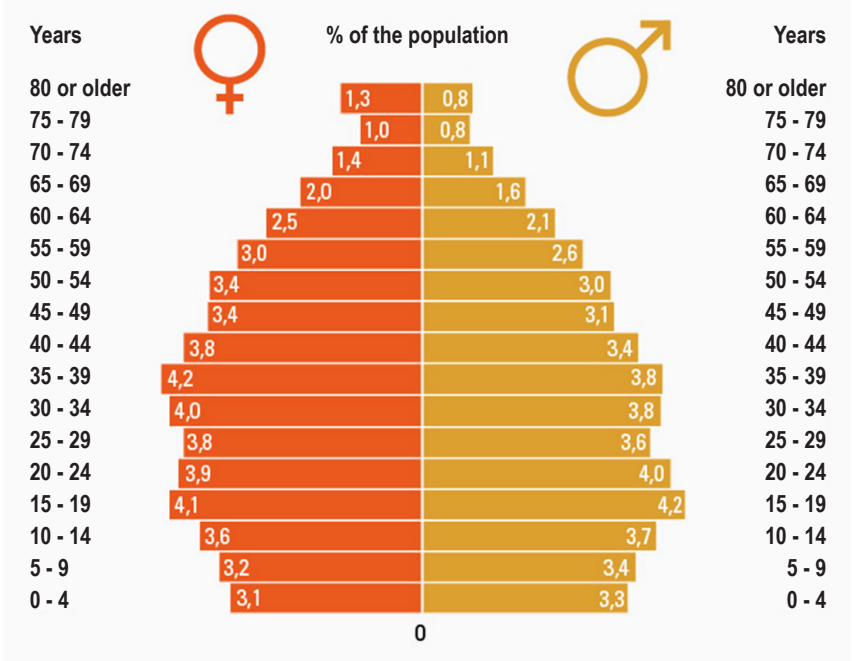

Figure 12.1 – *Population distribution by sex and age group - 2017. Source: Number of elderly grows 18% in 5 years and exceeds 30 million in 2017. IBGE.[1] https://agenciadenoticias.ibge.gov.br/agencia-noticias/2012-agencia-de-noticias/noticias/20980-numero-de-idosos-cresce-18-em-5-anos-e-ultrapassa-30-milhoes-em-2017.html*

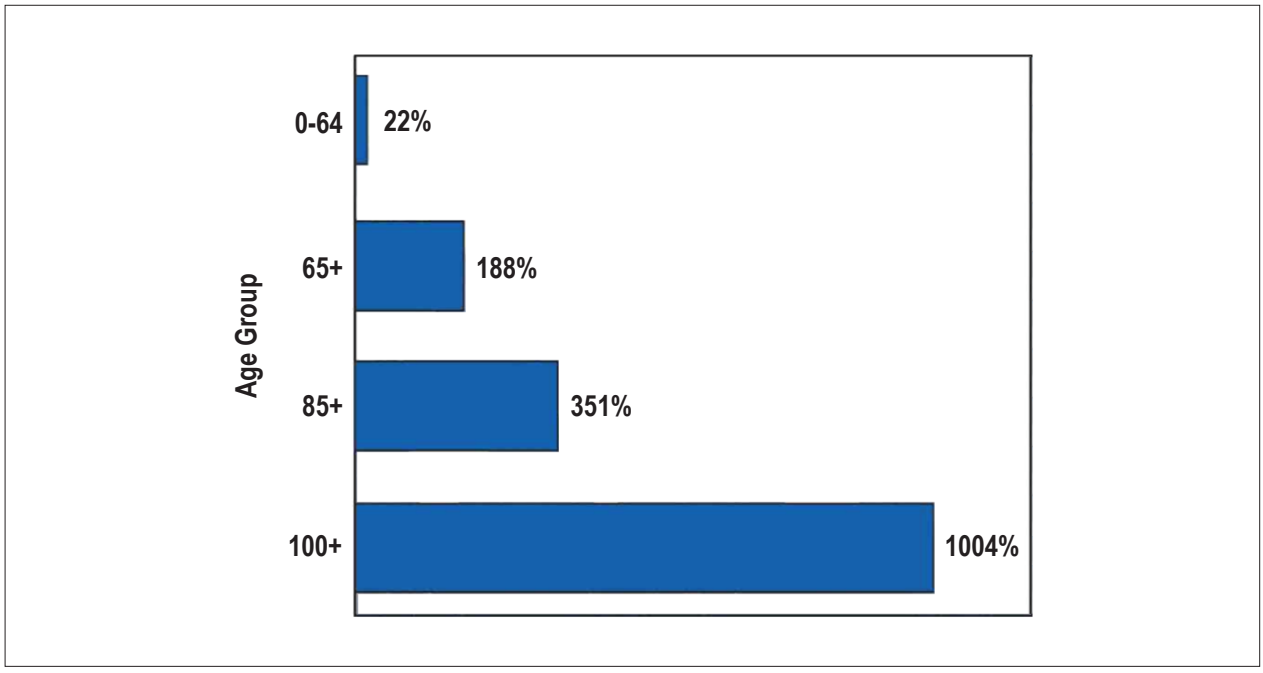

Figure 12.2 – *Percentage of change in world population according to age: 2010-2050.[596] Adapted from United Nations, World Population Prospects: The 2010 Revision.*

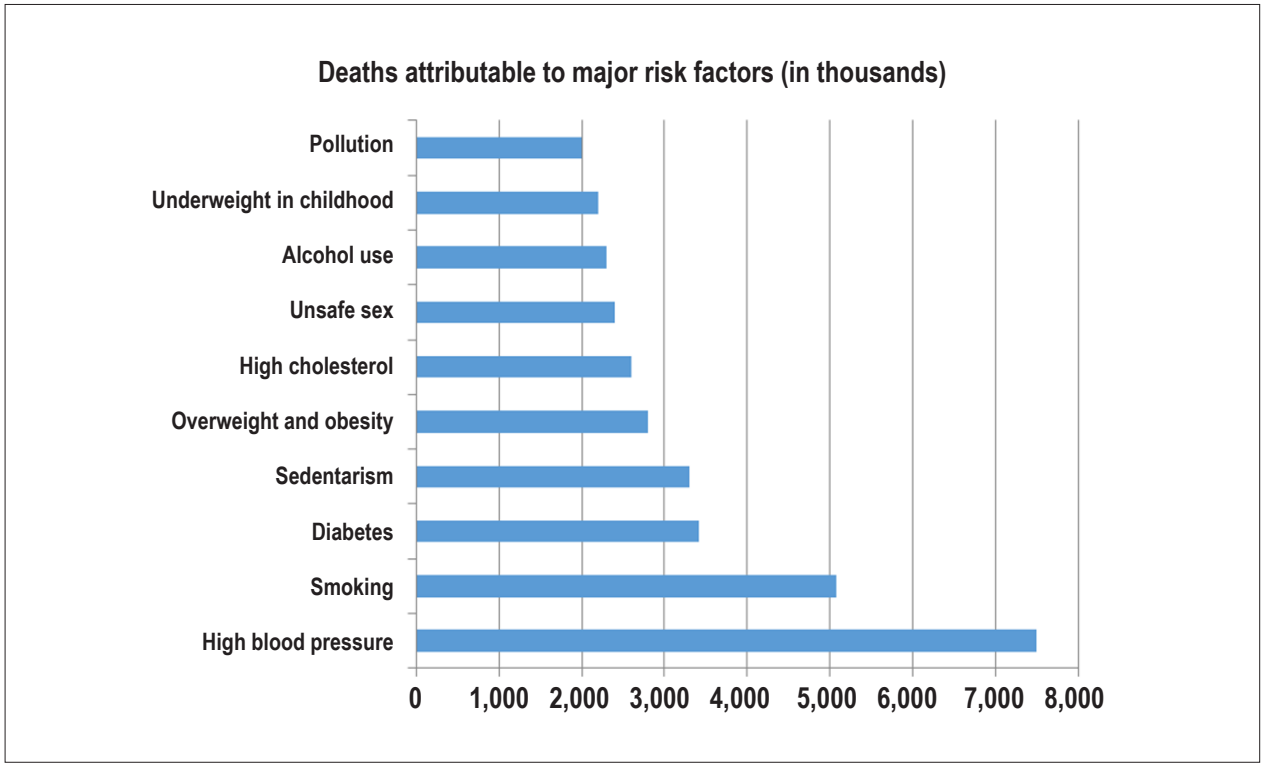

Figure 12.3 – *Deaths attributable to major risk factors.[597-599]*

Based on the above data, strategies to address these risk factors, as well as disease prevention and health promotion actions for at-risk populations should be implemented as soon as possible, and start as early as possible.

Some considerations related to the population aspects of risk factors will be discussed specifically in this chapter and others.

12.2. Population Aspect of Smoking

Cigarette smoking is one of the leading and preventable causes of mortality in the world. This habit accounts for 12% of adult mortality worldwide, which corresponds to 5 million people; if this persists, 10 million people per year will die and 70% of these deaths will occur in developing countries.

Specifically in Brazil, the National Congress approved the text of the Global Framework Convention on Tobacco Use (FCTC) through Legislative Decree 1012 of October 28, 2005, and the Brazilian government ratified the 2005 Convention which entered into force on February 1, 2006.

The primary goal of the FCTC is to preserve present and future generations from the devastating health, social, environmental and economic consequences of smoking and exposure to tobacco smoke. It establishes some of its obligations to draft and update smoking control policy, establish an international coordination and cooperation mechanism with other States Parties, and protect national policies against the interests of the tobacco industry.

World No Tobacco Day was created in 1987 by the member states of the World Health Organization to draw the world's attention to the epidemic of smoking and preventable tobacco-related diseases and deaths; there are over 1 billion smokers in the world and 80% of them are in low- and middle-income countries where the effects of smoking-related illnesses and deaths is highest; current smokers are presumed to consume around 6 trillion cigarettes every year.

12.3. May 31st - World No Tobacco Day

Federal Law 12546/2011 in force since December 2014 was published and must be known and respected by all, as well as be adequately enforced the Health Surveillance Sectors in particular.[601] Data on VIGITEL released in April 2012 revealed a 14.8% drop in smokers in Brazil in people over 18 years.

Among men, the percentage of smokers was 18.1% and in women 12%. The capitals with the most smokers are: Porto Alegre 23%, Curitiba 20% and São Paulo 19%; and Maceió 8%, João Pessoa, Aracaju and Salvador are the capitals with the lowest incidence of smoking in the Northeast with 9%.[602]

There are strategies for tobacco control:

a) Prevention

It is essential to prevent young people from trying cigarettes, because if they do, there is a 50% chance that they will become addicted.

Hence the importance of education from family and schools.

Enforcement of the Anti-smoking Act which bans the advertisement of tobacco products and other actions directed at underage young people.[603]

b) Protection

Protect the population from the effects of environmental tobacco smoke and the influences that lead to smoking, particularly those related to the social group.

Strictly enforce the anti-smoking law, which among other rules, prohibited smoking in public environments.[603]

12.4. Population Aspects of Obesity and Overweight

Relationships between sociodemographic characteristics and lifestyle habits such as income, socioeconomic status, nutritional status, and physical inactivity with weight gain have been established.[604-610] In addition, especially in the last two decades, international authorities have strongly recommended the implementation of effective obesity prevention policies. However, no country in the world has succeeded in reversing the obesity epidemic.[611,612]

A number of factors may explain the failure to combat obesity, but perhaps the most important is the way it is still understood by most people. Instead of being perceived as a chronic, complex disease, the result of the interaction of genetic and environmental variables, strongly influenced by socio-economic and cultural factors with a highly obesogenic environment, obesity is seen as a personal failure. Obese people are often blamed for their disease, being judged lazy, undisciplined, unmotivated and negligent.[611,612]

From a population standpoint several measures have already been tested and found to be successful locally or for a predetermined period of time. The great challenge is to institute these measures in a more comprehensive and lasting way, and to identify cultural and regional particularities that allow adaptations of these policies to each of the realities.[613,614]

Interventions in schools are the most common and most promising, precisely because of their educational and anti-obesity character in the early stages of life. Modifications in school lunches, sedentary lifestyle, health education are examples of measures that have been beneficial not only for the children and adolescents involved, but also for adults in the same circle.

Fighting physical inactivity in an organized way, with mass campaigns, in addition to more regionalized actions, focused on a particular exercise practice has also been shown to be beneficial for reducing obesity. There is also a lot of research focused on reducing the amount of physical activity required to achieve the weight reduction benefit. Such studies arise precisely from the lack of time to devote to exercise, which ends up being the justification for the sedentary lifestyle of most people.[615] Finally, there are still population actions aimed at improving people's diets. Such measures are extremely varied, but ultimately use mostly financial interventions to target dietary choices and habits that are associated with overweight/obesity. There are examples of taxing sweetened beverages, financial incentives to purchase healthy foods, types of financial penalties for buying unhealthy foods, reductions in health-care-related health insurance costs, and maintaining healthy diets.[618]

A concern that should be highlighted in view of population aging is the high prevalence of obesity in older populations.

Such individuals should be evaluated very carefully, since the identification of obesity is not so simple, but mainly because of its association with musculoskeletal diseases, diabetes and AMI.[619]

12.5. Population Aspects of Hypertension

The treatment of hypertension is known to be effective in relation to the individual, but from the population point of view, it has been frustrating for many reasons.[620-624] These begin with the lack of education in general and particularly in health, which prevents knowledge about the disease and its importance as one of the main CV risk factors.[594-599] They go through the difficulty of accessing health services for the correct diagnosis, proper treatment with guidance on lifestyle and medication use and end with the great challenge of treatment compliance.[620-624] These assumptions alone are sufficient to definitively indicate the actions that can effectively modify the natural history of hypertension and interfere with the equation CV risk, morbidity and mortality. These actions, at the collective level and focusing on primary and primordial prevention, will have a great interface with other CVD risk factors.[10,620-626]

Primordial (prevention of risk factors) and primary (actions on installed risk factors) prevention actions, although presenting much better cost effective results, demand more time for their appearance. For this reason, huge amounts are spent on secondary or even primary prevention measures, but with a focus on medicalization which, in an misleading way, shows favorable changes in short-term statistics and may even give political results with immediatist benefits.[10,620-626]

It is evident that population intervention must involve the involvement of society as a whole. It should be part of a government policy, and linked in a partnership with organized civil society, non-governmental organizations, and industries in general, especially food producers and beneficiaries. Every action will only achieve the expected objectives if it is developed collectively, with multidimensional action.[10,620-626]

It must be highlighted, particularly for hypertension, but has a strong interface with other CV risk factors:

- Education as a whole and, in particular, health education for the dissemination of knowledge about CV risk factors and the understanding of the importance of healthy lifestyles;[10,620-626]
- Legislation enforcement which encourages the production of healthy foods, and discourages and foods harmful to health;[10,624,625]
- The encouragement of families to have healthy lifestyles, with the possibility of monetary benefits in case of lifestyle changes (maintenance of ideal weight, decreased sodium intake, regular physical activity, increased fruit intake, vegetables and cereals, smoking cessation);
- The provision of safe areas for the practice of regular physical activity;
- Provision of a simplified means for basic assessment of key CV risk factors (BP, body mass index, blood glucose, cholesterol and smoking status);[2,620]
- Access to basic medicines when preventive measures fail and the use of drugs to prevent disease is needed.[10,620]

12.6. Population Aspects of Dyslipidemia

Scientific knowledge leaves no doubt about the relevance of dyslipidemias as an important risk CV factor.[2,628] There is also a general recognition that individual or even collective actions aimed at treatment, although useful and beneficial, are very expensive and much lower cost effective, even in developed countries.[2,627-631]

From these premises we have opened a huge door of opportunity. It is unthinkable to admit that the health system, especially in developing countries, such as Brazil, can adequately afford the high costs of treating established diseases.[2,629,630,632]

Thus, population-based primary prevention becomes a cost-effective and absolutely sustainable long-term alternative.[633-636]

This must be the fundamental mission of any government.

Public policies for food quality control, health education at all levels, with priority for young people and, finally, a health system that allows universal access to care and when necessary, drugs as the last option.[633,637,638]

It should be noted that small reductions in each of the risk factors may promote large reductions in CV events. Additional benefit can be obtained through the adoption of healthy lifestyles in society that will bring benefits to all risk factors that are completely interconnected (smoking, poor diet, overweight, dyslipidemia, AH and physical inactivity).[632,634,636]

Thus the entire population, with an initial focus on children and adolescents, should be encouraged to adopt healthy diets, maintain adequate weight or decrease weight for this purpose, practice regular physical activity with at least moderate intensity and smoking cessation.

The government should offer political, legal and financial conditions for the implementation of these actions in the educational field for the entire population.[2,627,628,636]

12.6.1. General Practice Measures[639]

- Encourage exclusive breastfeeding up to at least 6 months;
- Decrease salt content in the preparation of processed and industrialized foods;
- Encourage the consumption of fruit and vegetables, as well great supply and accessibility;
- Decrease intake of saturated and trans fats, replacing with unsaturated fats;
- Decrease sugar content in industrialized beverages;
- Reduce food portion sizes and limit excessive caloric intake;
- Healthy food supply in all public institutions;
- Incentive and collaboration policies with producers for the production and commercialization of healthy foods;
- Incentives and continuous health education policy for the population as a whole (with emphasis on children and adolescents;
  - Improved labeling of processed and industrialized foods.

12.7. Population Aspects of Physical Activity

Physical activity includes all forms of human movement and active life, including walking, exercise, as well as sports, and is a natural behavior that confers many benefits.[648,649]

The urgency of addressing NCD, including CVD, which contribute to a significant burden of premature death, disease, disability, and economic burden for all countries is emphasized.[648,649] To reaffirm that physical inactivity is a major factor in modifiable risks to NCD. As an important point of the strategy to reduce the burden of NCD, as articulated in the WHO Global Action Plan for NCD prevention and control, 2013-2020.[627,648,649]

Recognizing this strong link between physical activity and major noncommunicable diseases, WHO member states agreed on a relative 10% reduction in the prevalence of physical inactivity by 2025 as one of nine global targets for improving the prevention and treatment of noncommunicable diseases.

In Brazil, according to VIGITEL 2017, physical activities practiced in four domains (leisure, occupational activity, commuting and domestic activities), which allow building multiple indicators of physical activity standard.[650]

In addition, the frequency of adults who, in their free time spend: a) three or more hours of the day watching television; b) three or more hours of the day using computer, mobile or tablet; and c) three or more hours of the day watching television or using a computer, mobile phone or tablet.

The frequency of adults practicing leisure time physical activity equivalent to at least 150 minutes of moderate physical activity per week ranged from 29.9% in São Paulo to 49.6% in the Federal District. Among men, the highest frequencies were found in Macapá (57.1%), São Luís (54.1%) and Distrito Federal (53.8%) and the lowest in São Paulo (36.0%), João Pessoa. (39.5%) and Fortaleza (42.1%). Among women, the highest frequencies were observed in the Federal District (45.9%), Palmas (41.9%) and Curitiba (37.7%). The smallest were in São Paulo (24.8%), Porto Alegre (26.7%) and Recife (28.1%), 650 showing a high prevalence of sedentary individuals.

Physical activity in leisure time is increasing. In 2009, the indicator was 30.3%, and in 2016, 37.6%. Prevalence decreases with age, being more common among young people from 18 to 24 years old.[650]

The situation is not different from other countries, whether developed or developing. Prevalence in 2016 was more than twice as high in high-income countries (36.8%, 35.0–38.3%) than in low-income countries (16.2%, 14.9–9.9) and physical inactivity increased in high-income countries over time (31.6%, 27.1–37.2 in 2001). If current trends continue, the global physical activity target for 2025 (a relative 10% reduction in physical inactivity) will not be met. Policies to increase population levels of physical activity need to be prioritized and expanded urgently.[649]

Physical inactivity is one of the top 10 risk factors for global mortality, causing about 3.2 million deaths each year.[651,652] Sedentary adults have a 20-30% increase in risk of all mortality causes compared with those who do at least 150 minutes of moderate physical activity per week, or equivalent, as recommended by WHO. Regular physical activity reduces the risk of ischemic heart disease, stroke, diabetes, and breast and colon cancer. In addition, regular physical activity is a major determinant of energy expenditure and is therefore critical to energy balance, weight control and obesity prevention.[651,652]

12.8. Population Approach to Increased Physical Activity

The proposed policy options aim to promote the implementation of the global strategy regarding diet, physical activity and health and other relevant strategies, and to promote the additional benefits of increasing physical activity levels in population, such as improved educational performance and social and mental health benefits , coupled with cleaner air, reduced traffic, less congestion and links to healthy child development and sustainable development.[654,655]

In addition, interventions to increase participation in physical activity throughout the population for which favorable cost-effectiveness data are emerging and should be promoted. The objective is to contribute to achieving the voluntary global goals listed below:[654,655]

A relative 10% reduction in the prevalence of physical inactivity.

- It can stop the rise of diabetes and obesity.
- Lead to a 25% relative reduction in the prevalence of hypertension or contain the prevalence of increased BP according to national realities.

Proposed policy options include:

- Adopt and implement national guidelines on physical activity for health.
- Consider establishing a multisectoral committee or similar body to provide strategic leadership and coordination.
- Develop appropriate partnerships and involve all segments of society concerned, levels of government, non-governmental organizations (NGO), civil society, scientific societies and economic operators, in the active and appropriate implementation of actions aimed at increasing physical activity at all ages.
- Develop policy measures in cooperation with relevant sectors to promote physical activity through activities of daily living, including through "active transport", recreation, leisure and sport, for example: National, state and municipal urban planning and transport policies to improve accessibility, acceptability and safety of support infrastructure for walking and cycling.
- Improvement in the provision of quality physical education in educational settings (for elementary and high school students) including opportunities for physical activity before, during and after the formal school day.

Actions to support and encourage "physical activity for all" initiatives.

- Creation and preservation of natural environments that facilitate physical activity in schools, universities, workplaces, clinics and hospitals, and in the wider community, with a particular focus on providing infrastructure to support active transportation such as walking and cycling, recreation and active play and participation in all types of sports.

- Promote community involvement in implementing local actions to increase physical activity.
- Conduct evidence-based public campaigns through mass media, social media, and community and social marketing initiatives to inform and motivate adults and youth about the benefits of physical activity and facilitate healthy behaviors. Campaigns should be linked to supportive actions across the community for maximum benefit and impact.

Encourage the evaluation of actions aimed at increasing physical activity to contribute to the development of an evidence base for effective and cost-effective actions.[654,655]

12.9. Socioeconomic and Environmental Factors and Associated Diseases in Cardiovascular Prevention

The main determinants of population health are multiple and classifiable in the fields of biology, environment (physical, social and economic), behaviors (lifestyle) and health care.[656] It is estimated that major, socioeconomic determinants , represent 75%, while genetic, biological and behavioral factors together account for approximately 25% of the population's health[657,658] (Chart 12.1).

The literature reports different models that intend to describe the complex relationship between the multiple factors that influence the socioeconomic determinants of health, one of the most mentioned is the Dahlgren and Whitehead[659] model (Figure 12.4).

According to Rose,[660] the socioeconomic determinants underlie the pyramid of health inequalities and, consequently, the right to health cannot be guaranteed only by the health sector, requiring economic and social public policies.[660] Prospective studies have shown that in Brazil and in developed countries, low socioeconomic status defined as low status employment, low educational and income levels, and living in poorer residential areas contribute to increased CV mortality and all-cause death.[664-668]

Through a macroeconomic indicator, represented by the Gross Domestic Product per capita (GDPpc) from 1979 to 2010 of municipalities of the State of Rio de Janeiro, the relationship between this indicator and the reduction in

Chart 12.1 – Examples of health determinants divided by socioeconomic and environmental categories[596]

Environmental determinates	Water and air pollution, biodiversity, global warming, ozone depletion, housing conditions, transport quality, food safety, waste management, energy policy, urban environment
Economic determinates	Country economic performance, per capita income, access to health services, employment conditions, housing, security, transportation
Social determinates	Culture, lifestyles, gender, ethnicity, degree of social inclusion, age, health-related behaviors, living conditions, working conditions, education

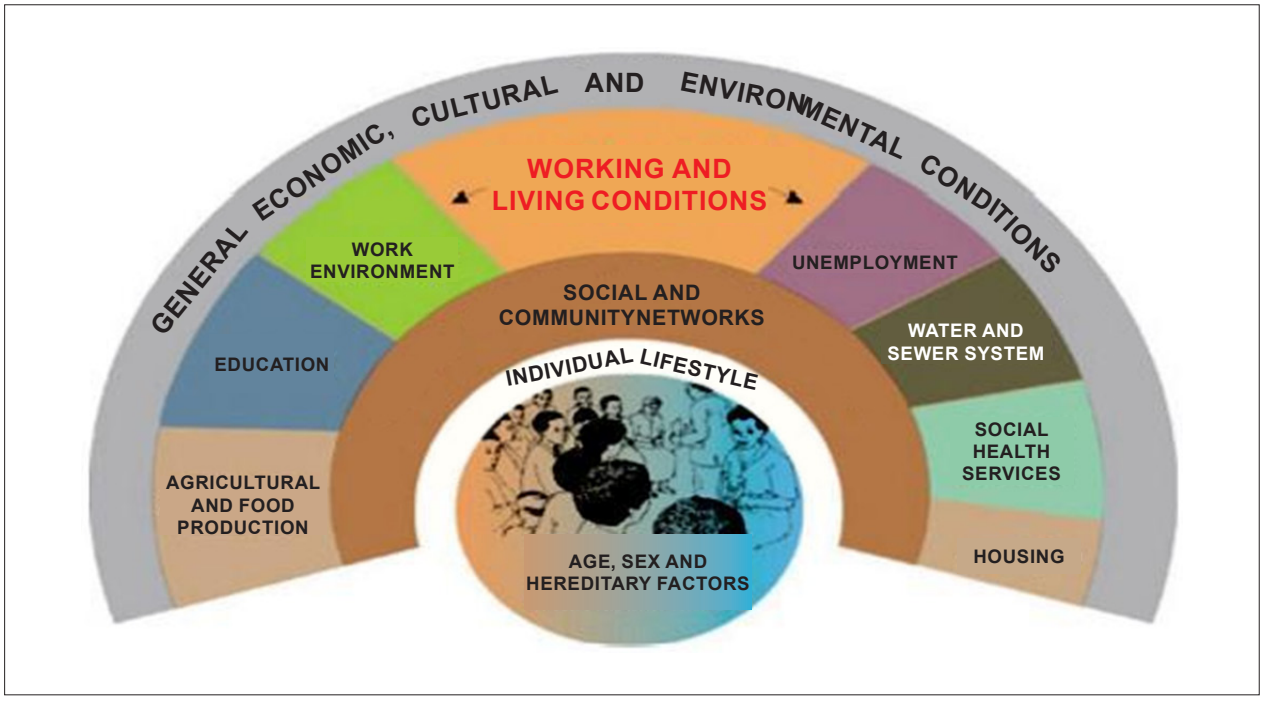

Figure 12.4 – *Socioeconomic and environmental determinants: Dahlgren and Whitehead model. Source: Carvalho A.[659]*

mortality from circulatory system diseases was analyzed. The decrease in mortality was preceded by an increase in GDPpc, with a strong association between the indicator and mortality rates, showing the importance of improving the living conditions of the population in the reduction of CV mortality.[664] The American Heart Association Document , on the influence of social factors on CVD, revealed that populations with lower educational levels have a higher prevalence of CV risk factors, a higher incidence of CV events, and a higher CV mortality rate, regardless of other demographic factors.[665]

12.10. Health and Sustainable Development

Health is a timeless value. Good health is a precondition for work and a measure of sustainable development.[666] The WHO created the "Commission of Social Determinants of Health" in 2005 to define health promotion directed at "health equity" in populations, and a global movement to reach it. In an extensive evidence-based publication, WHO prioritized the following actions: early childhood education, healthy housing, urban and rural infrastructure, universal access to health and other services, employment, quality social protection, inclusion social, gender equality. Regardless of policy options, it advocated health equity in all Policies, Systems and Programs through fair financing and "Good Global Governance".

It recommended, as an example, the United Nations (UN) Millennium Project, prepared in 2000 during the Millennium Summit, the largest meeting of world leaders, aimed at establishing a global partnership to reduce extreme poverty.[667,668] The 2015 goals, known as the "Millennium Development Goals (MDG)", represented a paradigm shift to improve the health of vulnerable and disadvantaged groups. They are: eradicate extreme poverty and hunger; implement a universal basic education; promote gender equality and empower women; reduce child mortality; improve maternal health; combat AIDS, malaria and other infectious diseases; ensure environmental sustainability and develop a global partnership for development.

Subsequently, in 2015 the WHO Health report "Health in 2015: from MGDs to SDGs" highlighted health progress on the MDG and redefined priority actions to achieve the new "Goals for Sustainable Development" (SDG).[668] The SDG, which make up Agenda-2030, contain more numerous and ambitious actions (17 goals, 169 goals) than the MDG (8 goals, 21 goals).[668] It recognizes that improving the health of people depends on social justice, environmental protection (climate change, heat waves, droughts, fires, storms, floods), polluting energies, antibiotic resistant agents, aging, migrations, increased global burden of NCD, indivisible pillars of sustainable development.[669] (Chart 12.2).

In this context, Brazil launched the "Strategic Action Plan for Coping with NCD in Brazil, 2011-2022" at the UN assembly and implemented a CNCD Surveillance System (VIGITEL) over the last decade that allows the national and global monitoring of NCD targets, representing a breakthrough in NCD Surveillance in the country.[670] Between 2000 and 2011, Brazil recorded an average decline of 2.5% per annum in all major NCD, with a significant decrease of 3.3% in CVD, observed in both sexes and in all regions of the country.[671] However, between 2015 and 2016 there was a trend of stability in mortality rates due to NCD, which may be a consequence of the change in risk factor behavior and worsening of risk factors, living conditions (access to services, unemployment) caused by the economic and the social crisis.[672,673] If these trends are maintained, Brazil may not meet the WHO-UN target set for the reduction in premature mortality from NCD in Agenda – 2030.

Chart 12.2 – Sustainable Development Goals, WHO 2015[669]

Sustainable development goals
1. Eradicate poverty
2. End hunger
3. Promote health and well-being
4. Quality and inclusive education
5. Gender equality
6. Clean water and sanitation
7. Clean, renewable energy
8. Employment, decent work and economic growth
9. Innovation in Resilient Infrastructure
10. Reduce inequalities within and between countries
11. Sustainable cities and communities
12. Sustainable production and consumption
13. Tackle climate change
14. Use the seas and marine resources sustainably
15. Promote sustainable use of terrestrial ecosystems;
16. Peace, justice and sound institutions
17. Implement global partnership

12.11. Cardiovascular Prevention, Environment, Sustainability and Associated Diseases

Hippocrates, the author of "Airs, Waters, and Places" (400 BC) was probably the first to recognize a relationship between disease and the environment, including the effects of climate and lifestyle.[674] Numerous aspects regardinf the quality of the physical environment (air pollution, cycle paths, green areas, parks) and behavioral factors (smoking, high-fat diets, physical inactivity) are determining factors for increasing or decreasing risks for CVD.[675] Since 2004, the American Heart Association has recognized exposure to air pollution as an important modifiable risk factor for CVD morbidity and mortality in populations, with a higher risk attributable to particulate matter (PM) over gaseous components.[676] Particulate matter $< 2.5\ \mu m$ (PM2.5) is the most important environmental risk factor, with higher risk than gaseous components, posing a major threat to public health.[677] Short-term PM2.5 elevations increase the relative risk of acute CV events by 1% to 3% within a few days. Long-term exposures (years) increase the risk by ± 10%, which is partly attributable to the development of cardiometabolic disorders such as high blood pressure, diabetes mellitus, among others.[677]

The pathophysiological mechanisms of changes caused by PM include: increased blood viscosity, vascular reactivity, induction of a systemic inflammatory state (thrombosis), changes in cardiac autonomic control (arrhythmia, hypertension), development and progression of atherosclerosis (acute myocardial infarction) heart failure and other CVD.[676]

The finer particles are more harmful to CV health given their greater ability to penetrate the airways. When inhaled, they penetrate deep into the lung tissue, inducing oxidative stress and inflammation through the release of IL-6, IL-1β, TNF-α by macrophages. Parallel to the intense oxidative stress that begins in the lung tissue, trophic effects on vascular and cardiac cells occur, increased generation of reactive oxygen species, impairment of nitric oxide-mediated vasodilation, endothelial dysfunction and, consequently, development and/or progression of atherosclerosis.[678]

The Harvard Six Cities study, involving populations from six US cities, revealed that the risk of myocardial infarction in a city with polluted air increases by 5% compared with that of clean air.[679] In the city of São Paulo it was observed that pollution is so high that it would be the equivalent to smoking two cigarettes a day.[677] In the Brazilian Amazon, burning biomass (bush) increased mortality from CV and respiratory events among the elderly, especially from acute myocardial infarction.[680]

Particles and gases released at high altitudes circulate throughout the troposphere and can be transported over long distances, with impacts on a global scale.[680] After forest fires in Canada, high concentrations (up to 30 times higher) of mostly fine PM have been recorded in the city of Baltimore, in the United States. Thus, environmental threats are not limited only to industrial gases and lead particles from motor vehicles in urban areas, but also to the PM generated by biomass burning in rural areas, and it is estimated that air pollution, a growing public health problem, will double CVD mortality by 2050.[680]

The Expert Position Paper on Air Pollution and Cardiovascular Disease of the European Society of Cardiology revealed that in 2010, air pollution accounted for 3.1 million of the 52.8 million deaths, for all causes and ages. The American Heart Association reports that 60,000 Americans and 6,000 Canadians die each year from short- or long-term exposure to airborne pollutants.681 Study shows that living near (50 m) high-traffic roads can increase risk sudden death.[682]

Other factors related to lifestyle, eating habits, and socioeconomic variables may exacerbate the effects of exposure to pollution, such as smoking, a diet high in fats and sugars, physical inactivity, and the use of licit (alcohol) and illicit (marijuana) drugs.

The key recommendations of the Environment & the Heart Campaign campaign, organized in 2015 by the European Society of Cardiology and the European Heart Network (EHN), to European policy makers to promote a healthy environment for a healthy heart were: 1) Include the air and noise pollution in the group of modifiable risk factors for CVD; 2) Include clean air and noise reduction in all areas of health policy; 3) Adopt WHO air quality limits; 4) Intensely reduce the emission of automotive gases; 5) Promote green urban planning to reduce pollution and promote physical activity; 6) Promote clean forms of energy (low emission vehicles and non-combustion renewable energy sources); 7) Guarantee funds for studies on the effects of environmental stress on the CV system; 8) Support events addressing NCD, social, economic and environmental inequalities regarding access to health.[683,684] Brian Garvey[685] from the University of Strathclyde, Scotland, in the preface to Larissa Bombardi's study "Geography of Pesticides in Brazil and Connections with the European Union", stated that "every sick community, every poisoned field, every polluted watercourse threatens to extinguish an alternative variety of life".

The major steps in developing an action plan for addressing CV disease risk factors,[686] are described in Figure 12.5.

12.12. Conclusion

Commitment from universities, scientific societies, organized civil society, state and municipal health secretariats, state and municipal education secretariats, the ministry of health, and federal, state and municipal governments is necessary to implement population-based approaches to address CV disease risk factors. These actions should be state policies aimed at impacting the various related morbidity and mortality indicators, as well as improving the population's quality of life.

Updated

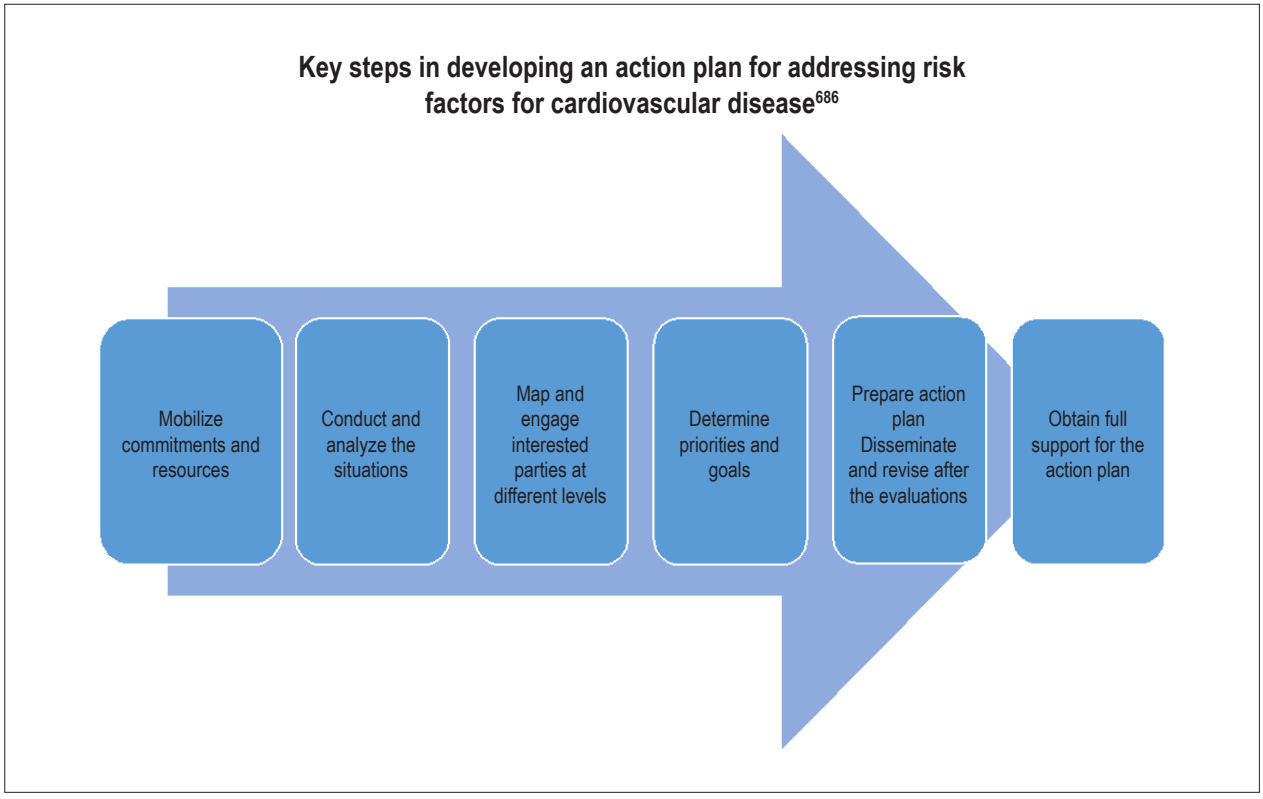

Figure 12.5 – *Key steps in developing an action plan for addressing risk factors for cardiovascular disease.[685] Adapted from Global status report on NCDs 2014.*

Erratum

In the "Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019", with DOI: https://doi.org/10.5935/abc.20190204, published in the journal Arquivos Brasileiros de Cardiologia, on page 862, correct item "Non-HDL-cholesterol" in table 11.3, "> 145" to "<145", in columns 1 and 2; on page 863, correct the item "Non-HDL-cholesterol", in Lipids, from table 11.6, "> 145" to "< 145", in columns 1 and 2.

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