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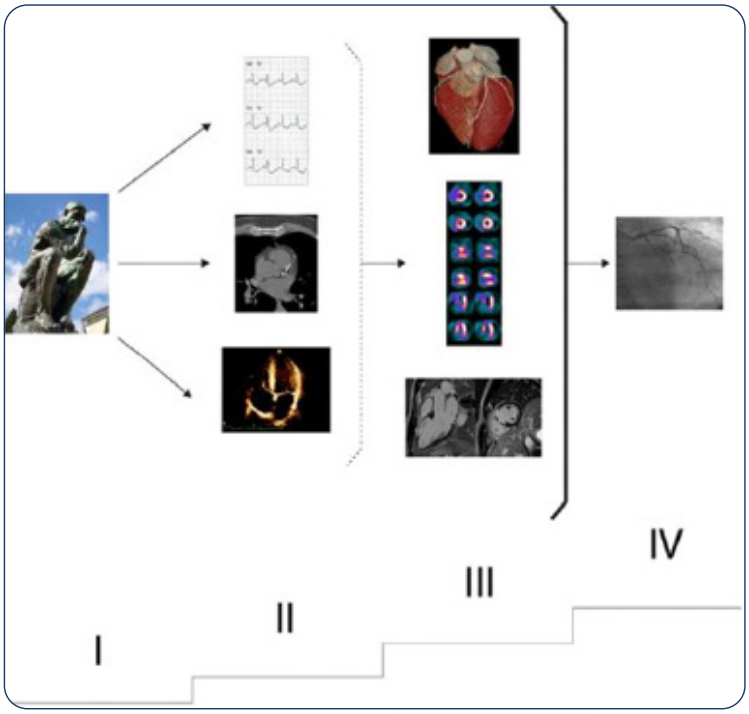

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ABC Cardiol
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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Nuclear Cardiology in 2020 – Perspectives of the New SBC Guideline

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To get to know, to discover, to communicate
François Arago

French physicist François Arago's quote is one of the most powerful summaries of scientific activity, starting with the search for existing knowledge, followed by the discovery of new information and culminating in their prompt communication. This flow is essential for scientific progress to reach and transform society. Thus, in the medical area, guidelines are considered to be essential for the organization and guidance of conducts and knowledge in a structured manner and within a pre-established method. The development of consistent and up-to-date guidelines is one of the most important tasks of a medical specialty society and involves the considerable effort of multiple specialists in the field of knowledge, reviewers, layout editors, among others. In addition to the arduous and complex task, the preparation of recommendations has against it the uninterrupted flow of publications that appear every day and that can change the current state of knowledge. We should highlight the amplitude, up-to-date status, and extensive applicability of this Nuclear Cardiology Guideline[1] jointly developed by the Nuclear Cardiology Area of the Department of Ergometry, Exercise, Nuclear Cardiology and Cardiovascular Rehabilitation (DERC), by the Department of Cardiovascular Imaging (DIC) of the Brazilian Society of Cardiology (SBC) and the Brazilian Society of Nuclear Medicine (SBMN).

In little over a decade, the management of chronic coronary artery disease (CAD) has undergone a paradigmatic shift towards an optimized clinical treatment, which consistently reduces the progression of atherosclerosis and prevents thrombosis and acute coronary syndrome.[2] Myocardial revascularization is indicated in acute cases, in higher risk cases and in those whose symptoms are progressive or refractory to drug treatment.[3,4] The SBC Nuclear Cardiology Guideline joins the Chronic Coronary Syndrome Guideline, reinforcing the importance of functional methods in the diagnosis of the etiology of symptoms in patients with suspected CAD, identifying the most at-risk patients, in therapeutic decision-making and in the follow-up of treatment response.[4] The question whether myocardial revascularization should be the initial management strategy in patients with chronic CAD and moderate to severe ischemia[5] seems to have been answered with the presentation of the ISCHEMIA Study, which showed no benefit from routine revascularization when added to optimized drug treatment.[6] However, we highlight the role of revascularization in improving symptoms and quality of life, reinforcing the importance of shared and individualized decision-making in patients who remain symptomatic despite optimized clinical treatment. Notably, several situations that were excluded from the ISCHEMIA study are covered in detail in the text of the Nuclear Cardiology Guideline,[1] such as patients with coronary trunk injury, recent acute coronary syndrome, angioplasty in the last 12 months, ejection fraction < 35% and those with progressive or unstable symptoms.

It is important to emphasize that Nuclear Cardiology is not restricted to the study of coronary disease only, but has undergone a revolution in recent years, with advances in equipment, software and tracers that make it important in the management of several conditions, for which the cardiologist previously had no tools to meet their needs. The Nuclear Cardiology Guideline[1] takes a comprehensive and practical approach to this new application for the cardiologist. In Figure 1 we show some of the new applications in which nuclear cardiology has important practical significance.

Among the new applications of nuclear cardiology, we highlight the use of 18F-FDG PET-CT and labeled leukocyte scintigraphy, as they were the nuclear medicine techniques included in the international algorithms and consensuses of investigation of infectious endocarditis in valve prostheses and in cases of suspected infection in implantable devices, such as pacemakers and defibrillators.[7] The SBC Nuclear Cardiology Guideline addresses in detail the basis of the use of these techniques in modern cardiology practice.

Another important new recommendation for the use of 18-FDG PET-CT included in the guideline is cardiac sarcoidosis. In addition to a vital contribution to the diagnosis of cardiac sarcoidosis,[8] PET-CT is crucial for monitoring treatment response, and its serial use is recommended to guide the use of immunosuppressants and anti-inflammatory drugs.[9]

Nuclear cardiology has become important in the diagnosis of cardiac amyloidosis caused by transthyretin deposits. A positive result in a scintigraphy with bone tracers, such as 99m-Technetium pyrophosphate, in the absence of light

Keywords

Coronary Artery Disease/diagnostic imaging; Myocardial Perfusion Imaging/methods; Prognosis; Biomedical Technology/trends; Positron Emission Tomography Computed Tomography/trends; Tomography Emission-Computed, Single/methods.

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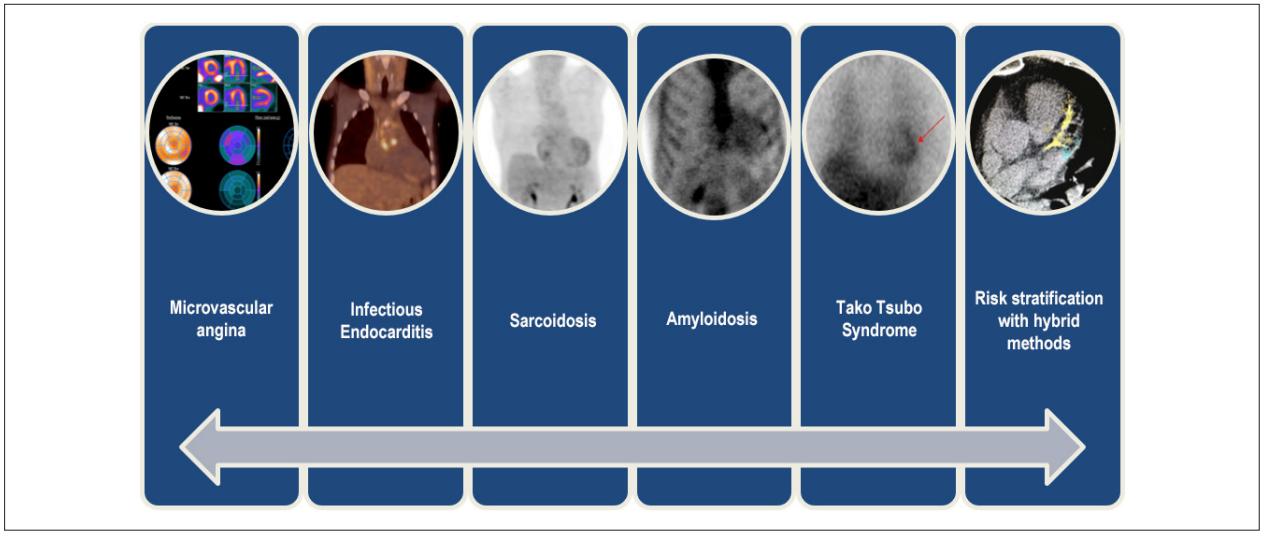

Figure 1 – *New applications of nuclear medicine in Cardiology where the use of the technique provides diagnostic, prognostic or guiding therapeutic decision-making information.*

chain screening in blood and urine, allows the diagnosis of cardiac amyloidosis by transthyretin and correlates with the cardiac biopsy, which may prevent the latter. With the development of treatments that delay the deposition of transthyretin protein in the heart and reduce mortality and morbidity, myocardial pyrophosphate scintigraphy has gained additional relevance.[10,11]

The use of 123I-MIBG cardiac scintigraphy is based on the unique opportunity to evaluate the autonomous sympathetic component of cardiac innervation. The adrenergic impairment identified with this technique allows early detection of cardiotoxicity related to cancer treatment, stratifying the risk of sudden death in patients with heart failure[12] and assisting in the diagnosis of Tako-Tsubo Syndrome.[13]

A modern and evolving chapter of Nuclear Cardiology, which is addressed in the SBC Guideline, is the assessment of microcirculation. Data from the Core 320 study and the ISCHEMIA study itself confirmed that a significant number of patients have angina and ischemia in the absence of coronary obstruction.[14] The evaluation of these patients using PET-CT techniques allowed us to identify the presence of microvascular ischemia as responsible for most cases, which implies an adverse prognosis and specific treatment.[15] The flow reserve assessment through PET-CT is the most appropriate technique to investigate these cases and is recommended in international guidelines and in the SBC Guideline. With the rapid advancement of high-performance machines with solid CZT detectors and improved software, the new SPECT chambers allow high-quality images with low radiation exposure and will contribute to the evaluation of these cases with studies demonstrating their validation, in comparison to the PET-CT equipment.[16] The recognition of microvascular angina reinforces the importance of functional techniques and that a CAD assessment focused on the anatomy of CAD may lead to the underdiagnosis in cases of microvascular angina and overtreatment in cases where anatomic lesions do not have a functional significance.

One last part to be highlighted is the intersection between the several imaging modalities with hybrid equipment and software that allow the collection and analysis of nuclear cardiology data concomitantly with computed tomography or magnetic resonance imaging. The integration of exam information from different modalities into SPECT-CT, PET-CT and PET-MR equipment enhances the amount and quality of available information for cardiologists to make decisions in patient management. Even the integration of information from exams acquired from separate equipment can increase the potential for risk stratification and improve patient management.[17] Ongoing studies will allow better definition of which patient groups will routinely benefit from these strategies.

In conclusion, cardiology has come a long way in recent years and so has nuclear cardiology. The new nuclear cardiology guideline by SBC enables us to learn about the most significant findings and publications through structured recommendations that impact the practice of modern cardiology.

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Trends in Mortality Rates from Cardiovascular Disease and Cancer between 2000 and 2015 in the Most Populous Capital Cities of the Five Regions of Brazil

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Abstract

Background: **In many cities around the world, the mortality rate from cancer (CA) has exceeded that from disease of the circulatory system (DCS).**

Objectives: **To compare the mortality curves from DCS and CA in the most populous capital cities of the five regions of Brazil.**

Methods: **Data of mortality rates from DCS and CA between 2000 and 2015 were collected from the Mortality Information System of Manaus, Salvador, Goiania, Sao Paulo and Curitiba, and categorized by age range into early (30-69 years) and late (≥ 70 years), and by gender of the individuals. Chapters II and IX of the International Classification of Diseases-10 were used for the analysis of causes of deaths. The Joinpoint regression model was used to assess the tendency of the estimated annual percentage change of mortality rate, and the Monte Carlo permutation test was used to detect when changes occurred. Statistical significance was set at 5%.**

Results: **There was a consistent decrease in early and late mortality from DCS in both genders in the cities studied, except for late mortality in men in Manaus. There was a tendency of decrease of mortality rates from CA in São Paulo and Curitiba, and of increase in the rates from CA in Goiania. In Salvador, there was a decrease in early mortality from CA in men and women and an increase in late mortality in both genders.**

Conclusion: **There was a progressive and marked decrease in the mortality rate from DCS and a maintenance or slight increase in CA mortality in the five capital cities studied. These phenomena may lead to the intersection of the curves, with predominance of mortality from CA (old and new cases). (Arq Bras Cardiol. 2020; 114(2):199-206)**

Keywords: **Cardiovascular Diseases/mortality; Coronary Artery Diseases/physiopathology; Neoplasms/mortality; Epidemiology.**

Introduction

Cardio-oncology has emerged as a new area of study and practice, resulting from numerous epidemiological and clinical interactions between diseases of the circulatory system (DCS) and cancer (CA). This interrelationship is supported by the prevalence of common risk factors, population aging, advances in diagnostic and treatment techniques, and cardiovascular injuries secondary to CA treatment.

One of the common questions in cardio-oncology is where the intersection point between the curves of mortality for DCS and CA will be, i.e., when DCS will become the leading cause of mortality thereafter.[1] Circulatory diseases have become the most prevalent causes of death in Brazil, followed by CA, since the decrease in the prevalence of infectious diseases.[2,3] In developed countries, there has been a fall in the mortality from DCS since the mid-1960s,[4,5] and deaths from CA outweigh deaths from DCS.[6] In Brazil, there has been a reduction in the rate of mortality from DCS since the 1980s, for both sexes, especially in the South and Southeast regions.[7] Concomitantly with this trend, the number of deaths due to CA in Brazil has grown; it went from the fifth to the third cause of death from 1980 to 2000, and today, CA is the second cause of mortality.[8]

Cancer is the leading cause of death in half of the United States of America (USA) and in some Western European countries. It has a close relationship with population aging. The drop in mortality from DCS is partly attributed to improved diagnosis and treatment.[9-11] However, both DCS and CA have a complex relationship mediated by several risk factors common to both, like smoking and alcoholism, overweight and obesity, eating pattern, sedentary lifestyle; hypertension, and diabetes mellitus.[12,13]

There are few studies that seek to understand the relationship between CA and DCS in the Brazilian population. Patterns of morbidity and mortality in Brazil have changed

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over the years. Demographic and epidemiological transitions, differences in access to health care, genetic peculiarities, among other factors, have resulted in the formation of regional population groups with particular characteristics.[14] Analysis of temporal trends in mortality based on population data could further clarify the scenario.

This study aimed to compare early and late mortality, by gender, from CAD and CA between 2000 and 2015 in the most populous capital cities of each Brazilian region and in the country as a whole.

Methods

It was decided to study the mortality rates from DCS and CA in the most populous capital cities, one of each of the five federated states of Brazil. The Federal District was not included. Demographic and mortality data were obtained from the Brazilian Institute of Geography and Statistics (IBGE). The following cities were included: Manaus (Northern region), São Paulo (Southeast), Goiania (Central west), Curitiba (South), and Salvador (Northeast).

Early and late mortality was defined using the age ranges of 30-69 years and ≥70 years, according to the definition of early mortality from non-communicable diseases, stratified by gender, adopted by the Brazilian Ministry of Health, and in line with the recommendations published in the United Nations' World Population Prospects.[14]

Data of mortality from 2000 to 2015 were obtained from the Department of Informatics of the Brazilian Unified Health System (DATASUS), and following the International Classification of Diseases (ICD)-10 as follows: mortality from DCS (chapter IX of ICD-10) and specific causes – acute rheumatic fever and chronic rheumatic heart diseases (066), hypertensive diseases (067), ischemic heart diseases (068), acute myocardial infarction (068.1), other forms of heart diseases (069), cerebrovascular diseases (070), atherosclerosis (071), and other and unspecified disorders of the circulatory system (072), and mortality from neoplasms (chapter II of ICD-10) and specific causes: malignant neoplasms, lip, oral cavity and pharynx (032), malignant neoplasms of esophagus (033), malignant neoplasms of stomach (034), malignant neoplasms of colon, rectum and anus (035), malignant neoplasms of liver and intrahepatic bile ducts (036), malignant neoplasms of pancreas (037), malignant neoplasms of larynx (038), malignant neoplasms of trachea, bronchi and lungs (039), malignant neoplasms, skin (040), malignant neoplasm of breast (041), malignant neoplasm of cervix uteri (042), malignant neoplasm of corpus uteri and uterus, part unspecified (043), malignant neoplasm of ovary (044), malignant neoplasm of prostate (045), malignant neoplasm of bladder (046), malignant neoplasm of meninges, brain and other parts of the central nervous system (047), non-Hodgkin's lymphoma (048), multiple myeloma and malignant plasma cell neoplasms (049), leukemia (050), in situ neoplasms, benign neoplasms and neoplasms of uncertain behavior (051), and other malignant neoplasms (052).

The data were obtained from the computerized databases of the death certificate records of the Brazilian Mortality Information System (Vital Statistics System) and "Population estimates: city, gender and age 2000-2015 RIPSA IBGE" (division of Demographic and Socioeconomic sector). All the information was collected from the DATASUS website.[15]

Statistical analysis

To assess the tendency of the estimated annual percentage change (EAPC) of the mortality rate from DCS and CA during the study period, the Joinpoint regression model (joinpoint software version 4.6.0.0 National Cancer Institute, Bethesda, Maryland, EUA)[16] was used. The Monte Carlo permutation test was used to detect the years when significant changes in the trends occurred.[17,18] Also, the Poisson distribution was used with the JoinPoint regression model. Assuming such distribution, a maximum of two joinpoints were selected. The software calculates the annual percentage change by the parametric method, with a 95% confidence interval for each segment of trend. The program calculated adjusted mortality rates for sex and age using the standard population based on WHO 2000-2025. Statistical significance was set at 5%.

Results

Figure 1 shows the curves of mortality from DCS and CA in the five capitals studied. For all groups and age ranges, there was a decrease in DCS, more pronounced in early mortality, especially in women, among whom CA is already the leading cause of mortality. A stability trend or a slight increase in mortality rate was found in the CA curves. In late mortality, there was a striking difference between the rates of mortality from DCS and CA, with higher rates of deaths from DCS compared with deaths from CA. Thus, the intersection point of these curves occurs later as compared with early mortality.

Table 1 shows the EAPCs in mortality from DCS and CA in the most populous capital cities of the five regions of Brazil between 2000 and 2015. Between 2000 and 2015, there was a consistent decrease in early and late mortality from DCS, in both sexes, in the most populous capitals, except for late mortality in men in the city of Manaus. The EAPC for mortality from DCS ranged from -6.5% for early mortality in women in São Paulo, to 0.3%, for early mortality among men in Curitiba. This variation, however, was not statistically significant, probably resulted from an inversion of the trend, with increased mortality in the last two years analyzed, i.e., 2014 and 2015. The reductions were comparable between genders and more pronounced in early mortality. Interestingly, the coefficients of late mortality from DCS were at least ten times the coefficients of early mortality.

Differently from DCS, the coefficients of mortality from CA showed different behaviors by regions, time periods and genders. In general, there was a decreasing trend in the rates of mortality from CA in São Paulo and Curitiba in all time periods and sexes. In contrast, there was an increase in the rates of mortality from CA in all periods in Goiania. In Salvador, there was a mixed behavior, characterized by a drop in early mortality in men and women and increment in late mortality in both genders.

Manaus was a major exception in terms of mortality rate behavior; mortality from DCS decreased in all time periods except for the late mortality in men. On the other hand, early mortality from CA exceeded that from DCS in both men and women.

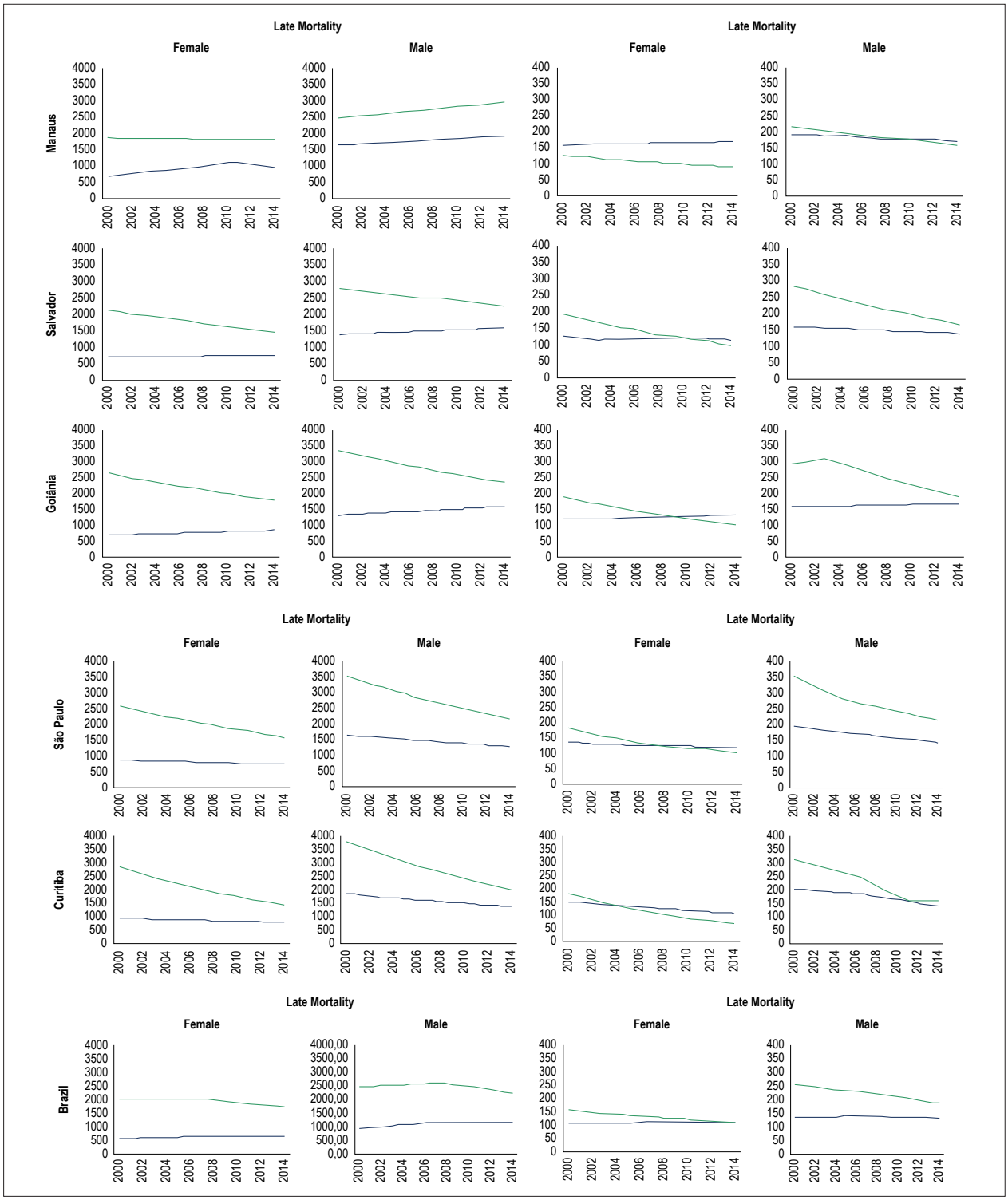

Figure 1 – *Trends in mortality rates from cardiovascular disease and cancer in the most populated capital cities of five Brazilian regions, stratified by gender and age group, 2000-2015. Source: DATASUS. Green curve represents cardiovascular diseases and blue curve represents cancer*

Therefore, the determinant of the convergence of the mortality curves seems to be the greater decrease in mortality from CD.

Table 2 shows the intersection points (years), real or presumed, of the mortality curves from CA and DCS. Regarding early mortality, CA ranks first in males in Goiania, and in women in all the studied cities. In late mortality, however, the intersection of the curves has not occurred in any of the cities yet, and may occur, it he trends continue, from 2026 on.

Table 1 – Trends in estimated annual percentage change of mortality from diseases of the circulatory system and cancer in the most populated capital cities of the five geographic regions of Brazil, 2015

Capitals		Early mortality				Late mortality			
		Male		Female		Male		Female	
		CA	DCS	CA	DCS	CA	DCS	CA	DCS
Manaus	APC 95%CI	-0.8* (-1.5;0)	-2.0* (-2.9;-1.1)	0.5 (-0.4;1.3)	-2.3* (-2.8;-1.7)	1.1* (0.5;1.7)	1.1* (0.5;1.7)	-3.0 (-6.6;0.8)	-0.3 (-0.9;0.3)
Salvador	APC 95%CI	-0.9* (-1.4;-0.4)	-3.4* (-4.1;-2.7)	-1.7 (-4.4;1.1)	-4.3* (-4.9;-3.6)	0.9* (0.3;1.5)	-1.4* (-2.1;-0.8)	0.5 (0;1)	-2.4* (-2.9;-1.9)
Goiania	APC 95%CI	0.4 (-0.4;1.2)	-4.0* (-4.5;-3.4)	0.7* (0.1;1.4)	-4.0* (-4.8;-3.2)	1.2* (0.4;2)	-2.3* (-3;-1.7)	1.4* (0.7-2.1)	-2.5* (-3;-2)
São Paulo	APC 95%CI	-1.9* (-2.1;-1.7)	-2.6* (-3.1;-2.2)	-0.9* (-1.1;-0.8)	-2.9* (-3.5;-2.3)	-1.5* (-1.7;-1.3)	-3.1* (-3.3;-2.8)	-1.0* (-1.3;-0.8)	-3.1* (-3.4;-2.8)
Curitiba	APC 95%CI	-3.4* (-4.2;-2.7)	0.3 (-6.8;7.8)	-2.2* (-2.8;-1.5)	-6.5* (-7.1;-5.9)	-1.9* (-2.3;-1.4)	-4.1* (-4.5;-3.6)	-1.1* (-1.9;-0.3)	-4.4* (-4.8;-3.9)
Brazil	APC 95%CI	-0.9* (-1.1;-0.7)	-2.7* (-3.5;-1.9)	0.1 (-0.1;0.4)	-2.4* (-2.6;-2.2)	0.1 (-0.1;0.3)	-2.1* (-2.5;-1.6)	0.2 (-0.1;0.4)	-2.1* (-2.6;-1.7)

**indicates statistically significant association (p < 0.05); CA: cancer; DCS: diseases of the circulatory system; EAPC: estimated annual percentage change; CI: confidence interval*

Table 2 – Estimated intersection point (year) of the mortality curves from diseases of the circulatory system and cancer in the most populated capital cities of the five geographic regions of Brazil

Locality	Age range of early mortality		Age range of late mortality	
	Male	Female	Male	Female
	Year of intersection			
Manaus	2009	1992	-	-
Salvador	2023	-	2031	2038
Goiania	2018	2000	2026	2034
São Paulo	2071	2009	2047	2051
Curitiba	-	2004	2032	2033
Brazil	2035	2015	2045	2057

Source: DATASUS, according to chapters II and IX from International Classification of Diseases-10; age of early mortality: between 30 and 60 years old; age of late mortality: older than 70 years

Table 3 shows the three main causes of mortality, stratified by early and late, and by gender, in the most populous capital cities of the five regions. There were differences between the cities, the age ranges and the genders.

Discussion

Mortality from DCS and CA in Brazil compared with the world

In Brazil, the discussion about the increase in cancer mortality is more recent than in European countries and USA, where the epidemiological transition occurred earlier than in Brazil. In Brazil in 2005, 32% of deaths were caused by DCS, followed by cancer (15%). At that time, Rosa et al.[19] drew attention to a probable intersection of the curves of mortality from DCS and CA. In the United Kingdom, in 2011, the DCS passed from the first cause of mortality to second position for the first time since the middle of the 20th century;[20] 29% of the deaths were caused by CA, while 28% by DCS.[21] The reduction of mortality from DCS in the United Kingdom was explained by a decrease in the mortality from myocardial infarction, increase of pharmacological and surgical treatments, and decrease of risk factors like smoking.[21-23] Similar situation to Brazil was observed in the USA, where mortality from DCS decreased more than from CA. If this tendency continues, CA will be the leading cause of deaths in 2020.[24]

The different stages of growth and development of the Brazilian regions made us make a particularized analysis, since it is difficult to draw a reliable picture of Brazil as a whole. The choice of the most populous capitals came from the assumption of a higher degree of urbanization and its influence on the health of the inhabitants. In general, in the western world, the interception of the mortality curves is caused by a marked decrease of mortality from DCS, especially in more developed countries in terms of socioeconomic development.

Table 3 – Three main causes of specific deaths (according to the International Classification of Diseases-10) in the most populated capital cities of the five geographic regions of Brazil, 2015

Gender/ Age range	Manaus		Salvador		Goiania		São Paulo		Curitiba	
	Cancer	DCS	Cancer	DCS	Cancer	DCS	Cancer	DCS	Cancer	DCS
	Cervix	CVD	Breast	CVD	Breast	IHD	Breast	IHD	Breast	IHD
Female 30-69 years	Breast	IHD	Colon	IHD	Lung	CVD	Lung	CVD	Lung	CVD
	Lung	MI	Lung	MI	Cervix	MI	Colon	MI	Colon	MI
	Lung	CVD	Breast	CVD	Breast	CVD	Breast	IHD	Breast	CVD
Female ≥ 70 years	Cervix	IHD	Colon	IHD	Colon	IHD	Colon	CVD	Colon	IHD
	Breast	MI	Lung	MI	Lung	HD	Lung	MI	Lung	MI
	Stomach	IHD	Lung	IHD	Lung	IHD	Lung	IHD	Lung	IHD
Male 30-69 years	Lung	CVD	Prostate	CVD	Colon	MI	Colon	MI	Colon	MI
	Larynx	MI	Pharynx	MI	Pharynx	CVD	Stomach	CVD	Stomach	CVD
	Prostate	CVD	Prostate	CVD	Prostate	CVD	Prostate	IHD	Prostate	CVD
Male ≥ 70 years	Lung	IHD	Lung	IHD	Lung	IHD	Lung	MI	Colon	IHD
	Stomach	MI	Colon	MI	Colon	MI	Colon	CVD	Lung	MI

Source: DATASUS. DCS: diseases of the circulatory system; CVD: cerebrovascular disease; IHD: ischemic heart diseases; MI: myocardial infarction; HD: hypertensive diseases; for the analysis, MI was considered a separate cause (from ischemic diseases) of death, and the sections 069 (chapter about DCS) and section 052 (chapter about cancer) of the International Classification of Diseases-10 were not included in the ranking of diseases

General trend of the curves of mortality from DCS and CA in Brazil

Analysis of the historical trend of the curves of mortality from DCS and CA reveled an important and sustained decrease of deaths from DCS in the most populous capital cities of each of the five Brazilian regions, except for Manaus. In this city, late mortality from DCS increased in men. Data from Brazil showed that DCS continue the main cause of mortality. However, an analysis of the cities revealed that CA already surpassed DCS as the leading cause of deaths in nearly 10% of the Brazilian cities.[25]

The results of the present work suggest two patterns of trends that led to the grouping of the five capitals into two subgroups: in the first subgroup, São Paulo and Curitiba, whose pattern is more similar to that of developed countries, i.e., with a significant fall in mortality from DCS, plus maintenance or slight decrease of mortality from CA. In this pattern, convergence of the curves results from the decrease in deaths from DCS. In the second pattern, Goiania, Salvador and Manaus, where there was also a decrease in mortality due to DCS, but less significant, in contrast to a modest increase in mortality from CA. In this second group, the convergence of the curves takes longer to occur. Manaus showed a singular behavior, with increase of late mortality from DCS in males.

In the Brazilian cities studied, data of 2015 showed that ischemic heart disease and cerebrovascular disease were the main causes of DCS. While individuals in the early age group die more from ischemic heart disease, at late age, mortality from cerebrovascular disease is higher. Between 1996 and 2011, in Brazil, there was a consistent decrease in mortality rate due to cerebrovascular disease in both genders, with differences in the magnitude of decrease between the regions.[26] In addition to socioeconomic development, the control of cardiovascular risk factors and a considerable increase (450%) in the access to primary care services, may have contributed to the decrease.[27] As observed in developed countries, efforts to diagnosis and treatment of risk factors and comorbidities have probably contributed to the decrease of stroke mortality,[28] and hence to the decrease of mortality from DCS.

Regional trends in the curves of mortality from DCS and CA

São Paulo and Curitiba presented a decrease in early and late mortality in both genders. It could be partly explained by the greater access to the diagnosis and treatment of CA. Chemotherapy and radiotherapy services are more concentrated in the Southern and Southeastern regions of Brazil.[29]

In Salvador, it was observed a decrease in early mortality from CA in men. Lung cancer has a high lethality and is the main type of cancer in this population. It is currently the main cause of death among men in North America and Europe and its mortality has significantly increased in Asia, Latin America and Africa.[30] In Brazil, adenocarcinoma is the main cause of early mortality among men and is related to the high prevalence of smoking in male sex.[15,31] The decrease in CA mortality in Salvador can be attributed to the public policies for CA prevention during the last decades, and in 2004, Salvador presented the lowest smoking rate in Brazil.[32] On the other hand, late mortality from CA has increased among men and women. One hypothesis for such increase among women is the high mortality rates from breast cancer, which represents the leading cause of late mortality in women.[15] Mortality rates from breast cancer in the Brazilian population have shown geographic variations, with a trend to stabilization in the southeast, decline in the south and increase in the north, northeast and central-west regions.

In the northeast region, between 2000 and 2010, CA mortality increased by 100% in white women, a population subgroup that increased by only 10% in size in the period. In contrast, there was a 183% increase in mortality among black women, with a respective population growth by 58%.[33] A possible explanation for the increase in late mortality rates from CA among men in Salvador is the high percentage of Afro-Brazilians living in this city. Prostate cancer is the leading cause of late mortality among men in Brazil[15] and a black man has 1.6 of being diagnosed and 2.4 higher odds of dying from prostate cancer than a white man.[34]

Manaus greatly differs from the other capital cities regarding the pattern of the mortality curves from DCS and CA. Early mortality from CA significantly increased among women. Cervical cancer is the main type of cancer,[15] whose mortality rates increased in the north and northeast regions.[35-37] In Manaus, early mortality decreased whereas late mortality increased among men. The main causes of early death from CA was gastric cancer followed by lung cancer. In Brazil, mortality rates from gastric cancer significantly increased in individuals older than 59 years. In the north region, mortality rates have increased in individuals of both sexes older than 75 years.[37] Prostate cancer mortality continues to increase in Brazil, with a vast number of under-reported or late-diagnosed cases.

In Goiania, early mortality and late mortality from CA increased in both men and women. Early death from CA was mainly caused by breast CA in women. This may be explained by the difficult access to appropriate diagnosis, since only 18% of the mammography machines available in the whole State of Goias belong to the Unified Health System, and 80% of the population living in the state are users of the public health system.[38,39] Another possible reason is the fact that mammograms is performed at relatively late age in Goiania, 49 years old.[40]

Differences between sexes in the trends of mortality from DCS and CA

Early and late mortality rates from DCS were lower in women than in men in all studied capitals and showed a more marked decrease over the years among women than men. One hypothesis for these findings is the fact that women are more adherent to primary healthcare programs for the screening and prevention of diseases.

With respect to CA, regional differences were found in the incidence of different tumors of varying mortality rates. For example, in Sao Paulo, colon CA ranks the second in incidence and cervical CA is in the fourth position, whereas in Manaus, cervical cancer ranks the first.[37]

Breast CA is the most prevalent cancer among women in Brazil and in most of the studied capitals. The treatment may include surgery, chemotherapy, radiotherapy, and hormonal therapy. Despite many advances in the treatment of breast CA, such as the use of immunohistochemical tests and anti-HER-2 agents, the access to these therapies by users of the health public system occurred later, and probably had no effect on the outcome of the patients included in this research.

Some limitations need to be considered when analyzing the results of this study. Data analyzed in this study were obtained from death certificates, and hence subject to inaccuracy. The diagnosis of CA is confirmed by imaging tests and/or anatomopathological examination, which confer greater reliability. The diagnoses of DCS are essentially established by clinical examination. Also, it is worth mentioning that the results were obtained from populations living in large urban centers; extrapolations to medium- and small-sized cities may not be appropriate, as reproducibility of these data is not necessarily guaranteed. Finally, determinants of mortality and estimates of trends can be influenced by public polices.

Conclusion

In general, and considering specific regional exceptions, there was a gradual and marked decrease in mortality rates from DCS in the five Brazilian capital cities studied, whereas mortality rates from CA remained unchanged or showed a slight increase from 2000 to 2015. Such events will lead to the intersection of the mortality curves, with perspective of a predominance of CA (old and new cases) mortality.

Author contributions

Conception and design of the research: Martins WA; Acquisition of data: Matos RCC, Silva WDS, Souza Filho EM; Analysis and interpretation of the data: Martins WA, Matos RCC, Silva WDS, Souza Filho EM; Statistical analysis: Rosa MLG, Matos RCC, Silva WDS, Souza Filho EM; Obtaining financing: Martins WA, Matos RCC; Writing of the manuscript: Martins WA, Rosa MLG, Matos RCC, Silva WDS, Souza Filho EM; Critical revision of the manuscript for intellectual content: Martins WA, Rosa MLG, Jorge AJL, Ribeiro ML, Silva EM.

Potential Conflict of Interest

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Death from Cancer and Cardiovascular Disease between Two Brazils

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Short Editorial related to the article: Trends in Mortality Rates from Cardiovascular Disease and Cancer between 2000 and 2015 in the Most Populous Capital Cities of the Five Regions of Brazil

Introduction

Population aging has been represented as one of the main global trends in future prospects, and Brazil is increasingly becoming established within this scenario. While life expectancy is estimated to be over 83 years in countries like Japan, Switzerland, and Spain, in others such as Nigeria and Somalia individuals reach an average age of 55. In 2018, life expectancy was estimated at 71 years in Brazil.[1] The relationship between health and development is quite complex, and it presents countless interactions. Both life expectancy and main causes of death appear as indicators of a region or a country's quality of life. They are signs of lifestyle (and advice regarding adequate change), preventative healthcare services provided to the community and advances in diagnostic techniques.[2] Health conditions are influenced by the socio-economic environment, given that higher indicators of income and educational level manifest as adoption of healthier lifestyle habits and, naturally, access to more effective treatment.[3]

In the past, communicable diseases represented the leading cause of death. In low-income countries, 52% of deaths were caused by communicable diseases, conditions resulting from pregnancy and childbirth, and other issues related to nutritional deficiencies. In contrast, in high-income countries, these causes accounted for at most 7% of deaths.[4] It is estimated that, by 2030, most countries will have made the much acclaimed epidemiological transition and have profiles with a higher prevalence of non-communicable diseases.

Relationship between economic development and cardiovascular mortality

In 2016, of the 56.9 million deaths that occurred worldwide, ischemic heart disease and stroke were the two leading causes, and they have remained the main causes of global death over the past 15 years. It is, nonetheless, worth emphasizing that causes of mortality vary according to countries' wealth patterns.[4]

Keywords

Cardiovascular Diseases/mortality; Coronary Artery Disease/physiopathology; Neoplasms/mortality; Epidemiology.

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A recent publication presents data from a prospective, multicenter study involving 155,722 participants from 21 different countries, which evaluated risk factors and mortality from cardiovascular diseases (CVD).

Countries were stratified according to level of economic development. It was observed that the majority of diseases and deaths related to the cardiovascular system could be attributed to a small number of modifiable risk factors, some with important effects, others varying by the countries' economic levels. The study emphasizes, moreover, that health policies should concentrate on specific risk factors. For example, low educational level's association with CVD and death was strongly identified in countries with low to medium economic development. In developed countries, 70% of CVD were attributed to modifiable risk factors (with the exception of environmental pollution), with the important contribution of metabolic risk factors and tobacco use. In undeveloped countries, 80% of diseases and deaths due to cardiovascular etiology were attributed to modifiable risk factors, with the important contribution of metabolic factors, environmental pollution, and poor diet. Level of education's association with death is even stronger than its association with wealth. From early childhood onward, education affects multiple living conditions, including living and working in healthier environments and greater access to health services. It is worth reiterating that improvements in education will likely decrease the number of deaths from different conditions, indicating that investments in this area could bring wide reaching benefits to health.[5]

Socioeconomic aspects of the incidence of malignant neoplasms

The prevalence of cancer is relevant worldwide. In 2018, on the global level, one in every six deaths was related to this group of diseases. Malignant neoplasms are also responsible for approximately 70% of deaths in low- and middle-income countries.[6]

Some Western countries have managed to control the incidence of determined types of cancer by reducing the prevalence of classic risk factors, as well as by early detection and appropriate treatment. However, lung, breast, and cervical neoplasms continue to increase significantly, due to risk factors typical in Western countries, such as tobacco use, obesity, sedentarism, and changing reproductive patterns. Organs such as the stomach, liver, and cervix also continue to present high morbidity related to infection.

Countries with high economic development continue to present high incidences of lung, colorectal, breast, and prostate cancer. What are distinct, however, are the mortality rates; while there is a reduction in the number of deaths

from cancer in developed countries, this figure increases in undeveloped countries. Mortality rates due to malignant neoplasms have been increasing in countries with low levels of development, as a consequence of increased prevalence of risk factors, such as increased tobacco use, excess body weight, physical inactivity, and better treatment.[7]

The article "Trends in Mortality Rates from Cardiovascular Disease and Cancer between 2000 and 2015 in the Most Populous Capital Cities of the Five Regions of Brazil"[8] presents important conclusions regarding the incidence of cancer and CVD in relation to a country's level of development. In England, for instance, the rate of mortality from CVD decreased more than the rate from cancer. In individuals over the age of 75, in particular, the impact of advances made in diagnosis and treatment on the mortality rate from cancer was even lower. In 2011, the age-standardized mortality rate from cancer exceeded that of CVD in both sexes, in the United Kingdom, long before this is observed in Brazil.[9]

In the USA, mortality rates from cancer in adults between the ages of 45 and 64 decreased by 19%, from 1999 to 2017, whereas rates of mortality from heart diseases decreased by 22%, from 1999 to 2011, and then increased by 4% from 2011 to 2017. The mortality rate from cancer has always been higher than that from heart diseases in that country.[10]

Final considerations

In this manner, Brazil continues with its demographic transformation and its epidemiological transition. Population aging, as previously observed, is a foreseeable trend, allowing society and individuals to plan for this new profile. As a national panorama, our demographic profile is already similar to that of large countries. The elderly group (individuals over the age of 60) is growing faster than any other age group in Brazil. Nevertheless, the epidemiological transition continues with inequality: The group of Brazilians who live with housing and income conditions similar to those in developed countries also demonstrate morbidity and mortality similar to those countries, whereas the rest of the population, which constitutes the majority of Brazilians, lives in poverty with scarce healthcare resources.

A correlation was recently demonstrated between the evolutionary variation of gross domestic product (GDP) per capita in the municipalities of the state of Rio de Janeiro and reduced mortality from coronary artery disease.[11] This once again emphasizes the importance of the need for better living conditions in order to reduce cardiovascular mortality. For this and other reasons, Martins et al.[8] draw attention to the need to fragment the discussion regarding death trends in Brazil, due to the distinct profiles the country presents, which correspond to different GDP and indicators of education.

The main challenge in Brazil will be that of recognizing this new profile that is being unveiled and designing targeted strategies according to the peculiarities found, leading to greater health promotion for the entire population in an equitable manner.

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Prognostic Prediction of Cardiopulmonary Exercise Test Parameters in Heart Failure Patients with Atrial Fibrillation

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Abstract

Background: **Atrial fibrillation (AF) is associated with increased mortality in heart failure (HF) patients.**

Objective: **To evaluate whether the risk of AF patients can be precisely stratified by relation with cardiopulmonary exercise test (CPET) cut-offs for heart transplantation (HT) selection.**

Methods: **Prospective evaluation of 274 consecutive HF patients with left ventricular ejection fraction ≤ 40%. The primary endpoint was a composite of cardiac death or urgent HT in 1-year follow-up. The primary endpoint was analysed by several CPET parameters for the highest area under the curve and for positive (PPV) and negative predictive value (NPV) in AF and sinus rhythm (SR) patients to detect if the current cut-offs for HT selection can precisely stratify the AF group. Statistical differences with a p-value <0.05 were considered significant.**

Results: **There were 51 patients in the AF group and 223 in the SR group. The primary outcome was higher in the AF group (17.6% vs 8.1%, p = 0.038). The cut-off value of pVO_2 for HT selection showed a PPV of 100% and an NPV of 95.5% for the primary outcome in the AF group, with a PPV of 38.5% and an NPV of 94.3% in the SR group. The cut-off value of VE/VCO_2 slope showed lower values of PPV (33.3%) and similar NPV (92.3%) to pVO_2 results in the AF group.**

Conclusion: **Despite the fact that AF carries a worse prognosis for HF patients, the current cut-off of pVO_2 for HT selection can precisely stratify this high-risk group. (Arq Bras Cardiol. 2020; 114(2):209-218)**

Keywords: **Atrial Fibrillation/mortality; Peak Expiratory Flow Rate; Exercise Test; Oxygen Consumption; Heart Failure; Prognosis.**

Introduction

Heart failure (HF) and atrial fibrillation (AF) often coexist,[1] with AF occurring in some reports in more than 50% of HF patients, and HF in more than one-third of AF patients.[2] Since the burden of each is growing, they have been called the two new epidemics of cardiovascular (CV) disease.[3]

The presence of AF in HF patients is associated with adverse hemodynamic consequences, which may exacerbate HF, increasing morbidity and mortality.[4-6]

The cardiopulmonary exercise test (CPET) is a powerful predictor of mortality in HF patients and is used as the criterion standard for the need for heart transplantation (HT),[7] with peak O_2 consumption (pVO_2) and the relation between ventilation and CO_2 production (VE/VCO_2 slope) as the most used risk assessment tools.[8] However, less information is known about whether HF patients with AF can be precisely stratified with the current CPET cut-offs for HT selection. Since the combination of HF and AF provide a worse prognosis, a timely referral for HT or mechanical circulatory support could be extraordinarily important to reduce the negative prognostic effect of AF in HF patients.

The present study seeks to compare the prognostic importance in HF patients of CPET parameters in AF versus sinus rhythm (SR) patients.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study protocol. All patients provided written informed consent.

Patient population and study protocol

The study included a single centre analysis of 274 consecutive HF patients referred to our institution with left ventricular ejection fraction (LVEF) ≤ 40% and New York Heart Association (NYHA) class II or III, from 2009 to 2016. All the patients were referred for evaluation with HF team and possible indication for HT or mechanical circulatory support. Patients with elective HT during the follow-up period (patients who had indication for HT and a heart become available in the first year of follow-up) were excluded from the analysis.

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Prospective follow-up included initial evaluation within a period of one month in each patient with:

- Clinical data including etiology of HF, implanted devices, medication, comorbidities, NYHA class and Heart Failure Survival Score (HFSS);[9]
- Laboratory data;
- Electrocardiographic data;
- Echocardiographic data;
- CPET data.

Patients were excluded if one of the following:

- Age < 18 years;
- Planned percutaneous coronary revascularization or cardiac surgery;
- Elective HT in the follow-up period;
- Exercise-limiting comorbidities (cerebrovascular disease, musculoskeletal impairment, or severe peripheral vascular disease);
- Previous HT.

Follow-up and endpoint

All patients were followed-up for 12 months from the date of completion of the aforementioned complementary exams.

The primary endpoint was a composite of cardiac death or urgent HT (occurring during an unplanned hospitalization with dependency of inotropes for worsening HF). Data were obtained from the outpatient clinic visits and medical charts review and was complemented with a standardized telephone interview to all patients at 12 months of follow-up. Secondary endpoints included all-cause mortality, sudden cardiac death and death for worsening HF.

Definition of atrial fibrillation

Only persistent or permanent AF was considered for the analysis. The diagnosis was made by electrocardiographic recording in the initial evaluation.

Cardiopulmonary exercise testing

A maximal symptom-limited treadmill CPET was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). Tha gas analysis was preceded by the calibration of the equipment. Minute ventilation, oxygen uptake and carbon dioxide production were acquired breath-by-breath, using a SensorMedics Vmax 229 gas analyser. The pVO_2 was defined as the highest 30-second average achieved during exercise and was normalized for body mass.[10] The anaerobic threshold was determined by combining the standard methods (V-slope preferentially and ventilatory equivalents). The VE/VCO_2 slope was calculated by least-squares linear regression, using data acquired throughout the whole exercise. Several composite parameters of CPET were also calculated. Patients were encouraged to perform exercise until the respiratory exchange ratio (RER) was ≥1.10.

Statistical analysis

All analyses compare AF patients with SR patients. Data were analysed using the software Statistical Package for the Social Science for Windows, version 24.0 (SPSS Inc, Chicago IL).

Baseline characteristics were summarized as frequencies (percentages) for categorical variables, as means and standard deviations for continuous variables when normality was verified and as median and interquartile range when normality was not verified by the Kolmogorov-Smirnov test. The Student's t-test for independent samples or the Mann-Whitney test when normality was not verified were used for the analysis of the variables.

Univariable and multivariable Cox proportional-hazards models were applied, with p values for time-to-event analyses being based on log-rank tests, and hazard ratios for treatment effects and 95% confidence intervals presented to study the combined endpoint considering the follow-up time of 12 months.

For selecting patients who would benefit from early selection for HT or mechanical circulatory support, the primary endpoint was analysed by several CPET parameters for the highest area under the curve (AUC) in the 12 months' follow-up. Hanley & McNeil test was used to compare two correlated receiver operating characteristics curves.[11]

The guideline recommended cut-off value of pVO_2 (pVO_2 ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without beta-blockers (BB)) and VE/VCO_2 slope (VE/VCO_2 slope > 35 with a RER < 1.05) for HT[7] selection were analysed (and compared for positive and negative predictive value (PPV and NPV, respectively) in our population of AF and SR patients.

Statistical differences with a p-value < 0.05 were considered significant.

Results

Overview of AF and SR groups

A total of 274 patients were enrolled in the study, with 51 patients in the AF group and 223 in the SR group. The baseline characteristics of SR and AF groups are presented and compared in Table 1.

In regard to clinical data, AF patients were older (57.96 ± 8.61 vs 52.61 ± 12.53, p < 0.001) and had a lower percentage of females. Medication with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, BB and mineralocorticoid receptor antagonists were similar and highly prevalent in both groups, and no differences were found regarding implantable cardioverter-defibrillator and cardiac resynchronization therapy between the two groups. There were no significant differences for sodium and NT-proBNP, but glomerular filtration rate (GFR) values were lower in the AF group (65.03 ± 29.05 vs 76.84 ± 30.20, p = 0.012).

Higher percentage of right ventricular dysfunction (40.0% vs 13.0%, p < 0.001) and lower values of LVEF (24.96 ± 7.44 vs 27.91 ± 7.23, p = 0.010), revealed a worse biventricular function in AF group.

CPET data showed no differences regarding heart rate parameters, but the AF group had lower baseline and maximal systolic blood pressure (SBP). Significant differences between

Table 1 – Baseline characteristics of AF and SR groups

	SR - n = 223	AF - n = 51	p for ≠ between groups
Clinical data – characteristics			
Age	52.61 ± 12.53	57.96 ± 8.61	< 0.001
Female (%)	61 (27.4%)	6 (11.8%)	0.019
BMI[1] (kg/m^2)	26.80 ± 4.07	27.47 ± 4.78	0.361
Ischemic etiology (%)	90 (40.4%)	14 (27.5%)	0.087
ACEi[2]/ARA[3] (%)	211 (96.3%)	50 (98.0%)	0.544
BB[4] (%)	179 (80.3%)	40 (78.4%)	0.768
MRA[5] (%)	184 (72.2%)	38 (74.5%)	0.677
Diabetes (%)	43 (21.4%)	10 (22.7%)	0.846
Baseline[6] ICD (%)	109 (49.8%)	27 (52.9%)	0.493
Baseline[7] CRT (%)	48 (21.5%)	12 (23.5%)	0.781
HFSS[8]	8.77 ± 0.95	8.22 ± 0.93	< 0.001
Laboratorial data			
Glomerular filtration rate (ml/min)	76.84 ± 30.20	65.03 ± 29.05	0.012
Sodium (mEq/L)	137.8 (135.7-139.3)	136.9 (133.6-139.3)	0.052
NT-proBNP (pg/ml)	2,046.79 ± 2,223.07	3,247.38 ± 4,578.571	0.097
Echocardiographic data			
LVEDD[9] (mm/m^2)	38 (35-43)	38 (35-43)	0.237
LVEF[10] (%)	29 (22-34)	26 (20-30)	0.010
MR III-IV[11] (%)	87 (39.0%)	12 (23.5%)	0.073
RV dysfunction (%)	29 (13.0%)	22 (40%)	< 0.001
CPET data			
Initial HR[13]	82 (72-92)	83 (70-100)	0.232
Maximal HR	137 (121-157)	130 (115-179)	0.747
Maximal HR predicted (%)	82.77 ± 12.86	86.88 ± 23.37	0.230
Delta HR during exercise	53 (39-71)	52 (34-64)	0.636
HHR1[14]	17 (12-26)	16 (10-25)	0.624
Initial SBP[15]	115 (110-125)	1,110 (100-120)	0.026
Maximal SBP	155.30 ± 26.83	145.92 ± 28.98	0.028
Duration of CPET[16] (min)	10.83 ± 3.99	8.53 ± 4.30	< 0.001
Peak RER[17]	1.10 ± 0.09	1.11 ± 0.09	0.340
pVO_2 (ml/kg/min)	20.27 ± 5.54	17.81 ± 5.55	0.005
pVO_2 predicted (%)	68.12 ± 17.65	63.12 ± 18.29	0.072
VE/VCO_2 slope	30.64 ± 6.78	34.33 ± 8.88	0.006
OUES	1.83 ± 0.58	1.64 ± 0.60	0.035
AT[18] time (minutes)	7.49 ± 3.44	5.49 ± 3.63	< 0.001
pVO_2 (ml/kg/min) at AT	16.35 ± 4.29	14.29 ± 4.32	0.002

Values are mean ± standard deviation or median (interquartile range); p values are calculated by Student´s T-test for independent samples or Mann-Whitney U test as appropriate. SR: sinus rhythm; AF: atrial fibrillation; BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitors; ARA: angiotensin receptor blockers; BB: beta-blockers; MRA: mineralocorticoid receptor antagonists; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; HFSS: Heart Failure Survival Score; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RV: right ventricular; HR: heart rate; HRR1: heart rate recovery in the first minute after finishing CPET; SBP: systolic blood pressure; CPET: cardiopulmonary exercise test; RER: respiratory exchange ratio; AT: anaerobic threshold.

the two groups were also observed with prognostic measures of CPET, with a worse status in AF group revealed by a lower CPET duration, pVO_2, oxygen uptake efficiency slope (OUES), time to anaerobic threshold (AT), pVO_2 at AT and a higher VE/VCO_2 slope (Table 1).

Primary and secondary endpoints

At 1 year, the primary endpoint (cardiac death or urgent HT) had occurred in 27 (9.9%) patients as represented in Table 2. There were no patients requiring mechanical circulatory support**.** The AF group had more events regarding the combined endpoint (17.6% vs 8.1%, p = 0.038), with cardiac mortality alone showing a trend for a worse prognosis in the AF group (11.8% vs 5.4%, p = 0.097), with no statistical difference regarding urgent HT (5.9% vs 2.7%, p = 0.249).

Table 2 – Adverse events at 12 months follow-up

Adverse events at 12 months follow-up	SR - n (%)	AF - n (%)	p
Combined endpoint	18 (8.1%)	9 (17.6%)	0.038
Total mortality	14 (6.3%)	9 (17.6%)	0.008
Cardiac mortality	12 (5.4%)	6 (11.8%)	0.097
Sudden cardiac death	5 (2.2%)	4 (7.8%)	0.043
Death for worsening HF	7 (3.1%)	2 (3.9%)	0.777
Urgent HT	6 (2.7%)	3 (5.9%)	0.249
Mechanical circulatory support	0 (0%)	0 (0%)	1.000

AF: atrial fibrillation; HF: heart failure: HT: transplantation; SR: sinus rhythm.

Secondary endpoints showed higher all-cause mortality (17.6% vs 6.3%, p = 0.008) and a higher sudden cardiac death (7.8% vs 2.2%, p = 0.043) in the AF group, with no difference regarding death for worsening HF (3.9% vs 3.1%, p = 0.777).

Complete data of univariable Cox analysis for prediction of the primary endpoint is presented in Table 3 and Table 4.

HFSS, Sodium, NT-proBNP, right ventricular dysfunction, LVEF, CPET duration, heart rate recovery in the first minute after finishing CPET (HHR1) and initial and maximal SBP during CPET were predictors of the primary endpoint in both groups.

With the exception of HHR1, heart rate (HR) parameters during CPET were only predictors of the primary endpoint in the AF group, as seen with lower values of maximal HR, lower values of maximal (%) predicted HR and a lower variation of the HR during exercise, for patients with AF for whom the primary endpoint occurred and for those for whom it did not, respectively (Table 4).

On the other hand, the use of BB was only a predictor of the primary endpoint in the SR group (Table 3).

Relationship between CPET prognostic parameters and primary outcome

The power to predict the primary outcome by CPET parameters is represented in the supplementary index. Univariate Cox analysis shows that pVO_2, pVO_2 (%) predicted, pVO_2 at AT, VE/VCO_2 slope and OUES are all predictors of the primary outcome in both groups (p < 0.05 for all).

In addition to the Cox analysis, these CPET parameters were analysed for the highest AUC in the 12 months' follow-up period. In the SR group, VE/VCO_2 slope had the highest

Table 3 – Univariate Cox proportional-hazards analysis (non-CPET parameters)

Characteristics	All				SR				AF			
	Wald	Hazard ratio	95% CI	p	Wald	Hazard ratio	95% CI	p	Wald	Hazard ratio	95% CI	p
Age	0.092	0.995	0.965-1.026	0.762	0.768	0.984	0.950-1.020	0.381	0.057	1.010	0.933-1.093	0.811
Gender	0.524	0.699	0.265-1.845	0.469	1.041	0.525	0.152-1.812	0.308	1.188	2.397	0.498-11.547	0.276
BMI	1.175	0.947	0.859-1.045	0.278	0.183	0.974	0.863-1.099	0.669	1.906	0.887	0.748-1.052	0.167
Beta-Blocker	5.139	2.469	1.130-5.393	0.023	4.259	2.713	1.051-6.998	0.039	0.877	1.941	0.484-7.779	0.349
Diabetes	0.130	1.197	0.451-3.174	0.718	0.027	0.910	0.297-2.792	0.869	0.691	2.416	0.302-19.326	0.406
Baseline CRT	1.614	1.995	0.687-5.790	0.204	1.047	2.160	0.494-9.446	0.306	1.807	2.940	0.610-14.167	0.179
HFSS	34.893	0.233	0.144-0.378	< 0.001	22.674	0.233	0.128-0.424	< 0.001	8.600	0.243	0.095-0.626	0.003
Glomerular filtration rate	3.520	0.586	0.971-1.101	0.061	2.578	0.985	0.967-1.003	0.108	0.205	0.994	0.969-1.020	0.650
Sodium	27.303	0.787	0.720-0.861	< 0.001	14.635	0.766	0.668-0.878	< 0.001	7.668	0.839	0.726-0.947	0.006
NT-proBNP	20.456	8.212	2.234-12.367	< 0.001	15.171	6.263	1.894-10.223	< 0.001	3.187	2.335	1.285-4.534	0.004
LVEDD	5.670	1.072	1.012-1.135	0.017	3.001	1.077	0.990-1.171	0.083	1.443	1.049	0.970-1.135	0.230
LVEF	18.934	0.887	0.840-0.936	< 0.001	13.810	0.884	0.828-0.943	< 0.001	3.351	0.912	0.826-0.998	0.049
RV dysfunction	21.377	3.758	2.144-6.588	< 0.001	6.160	2.846	1.246-6.499	0.013	8.346	4.267	1.594-11.419	0.004

SR: sinus rhythm; AF: atrial fibrillation; CI: confidence interval; BMI: body mass index; CRT: cardiac resynchronization therapy; HFSS: Heart Failure Survival Score; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; RV: right ventricular.

Table 4 – Univariate Cox proportional-hazards analysis (CPET parameters)

Characteristics	All				SR				AF			
	Wald	Hazard ratio	95% CI	p	Wald	Hazard ratio	95% CI	p	Wald	Hazard ratio	95% CI	p
Initial HR	0.220	1.006	0.983-1.029	0.639	2.265	1.024	0.993-1.056	0.132	1.414	0.977	0.940-1.015	0.234
Maximal HR	6.259	0.982	0.967-0.996	0.012	0.644	0.992	0.974-1.011	0.422	5.706	0.973	0.951-0.955	0.017
Maximal HR(%) predicted	8.343	0.962	0.937-0.968	0.004	1.864	0.975	0.941-1.011	0.172	5.590	0.958	0.924-0.993	0.018
Delta HR during exercise	10.141	0.969	0.951-0.988	0.001	3.324	0.979	0.956-1.002	0.068	6.527	0.960	0.930-0.991	0.011
HHR1	22.484	0.837	0.778-0.901	< 0.001	15.623	0.829	0.755-0.910	< 0.001	5.939	0.869	0.777-0.973	0.015
Initial SBP	13.913	0.946	0.919-0.974	< 0.001	8.317	0.951	0.919-0.984	0.004	4.346	0.939	0.885-0.996	0.037
Maximal SBP	21.896	0.959	0.943-0.976	< 0.001	12.029	0.964	0.945-0.984	0.001	7.205	0.954	0.922-0.987	0.007
Duration of CPET (min)	26.781	0.756	0.681-0.841	< 0.001	20.636	0.730	0.637-0.836	< 0.001	4.009	0.838	0.704-0.996	0.048

SR: sinus rhythm; AF: atrial fibrillation; CI: confidence interval; HR: heart rate; HHR1: heart rate recovery in the first minute after finishing CPET; SBP: systolic blood pressure; CPET: cardiopulmonary exercise test.

AUC value (0.906) followed by predicted pVO_2 (%) (0.903), with OUES with the lower AUC value (0.798). Despite these numerical differences, no statistically significant difference was found when the Hanley & McNeil test was applied to compare the different AUC values of the CPET parameters.

In the AF group, predicted pVO_2 (%) (0.878) and pVO_2 (0.869) had the highest AUC values. Similarly to the SR group, OUES had the lowest AUC value (0.833), but no statistically significant difference was found when the Hanley & McNeil test was applied to compare these parameters.

The Hanley & McNeil test was applied for comparing each CPET AUC parameter in the AF versus SR groups as well, with no statistically significant difference found.

Multivariate Cox analysis (Table 5) showed that when pVO_2 and the VE/VCO_2 slope are analysed together, significant differences were found between SR and AF groups. In the SR group, pVO_2 lost his predictive power ($p = 0.280$) while the VE/VCO_2 slope remained predictive of the primary outcome ($p = 0.001$). In the AF group, the VE/VCO_2 slope lost its predictive power ($p = 0.398$) and pVO_2 showed a trend towards the prediction of the primary outcome ($p = 0.091$).

Similar results were found in the multivariate Cox analysis of predicted pVO_2 (%) and the VE/VCO_2 slope in the AF group ($p = 0.094$ and $p = 0.145$, respectively), while in the SR group there was a difference, since predicted (%) pVO_2 ($p = 0.006$) and VE/VCO_2 slope ($p = 0.033$) kept their predictive power ($p = 0.006$), while pVO_2 had not ($p = 0.280$).

OUES lost its predictive power in the multivariate Cox analysis in both SR and AF groups when compared with pVO_2 ($p = 0.948$ and $p = 0.539$, for SR and AF group respectively)

Table 5 – Multivariate Cox analysis of CPET[1] prognostic parameters

Multivariate Cox analysis	SR			AF		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
1) pVO_2 vs VE/VCO_2 slope						
pVO_2	0.910	0.766-1.080	0.280	0.759	0.551-1.045	0.091
VE/VCO_2 slope	1.117	1.045-1.194	0.001	1.050	0.937-1.177	0.398
2) pVO_2 (%) predicted vs VE/VCO_2 slope						
pVO_2 (%)	0.933	0.888-0.981	0.006	0.942	0.879-1.010	0.094
VE/VCO_2 slope	1.070	1.005-1.139	0.033	1.078	0.974-1.193	0.145
3) OUES[5] vs VE/VCO_2 slope						
OUES	1.508	0.388-5.864	0.553	0.624	0.056-6.975	0.701
VE/VCO_2 slope	1.170	1.090-1.256	< 0.001	1.123	1.002-1.258	0.046
4) pVO_2 vs. OUES						
pVO_2	0.742	0.597-0.922	0.007	0.623	0.482-0.907	0.014
OUES	1.061	0.183-6.153	0.948	2.335	0.156-34.907	0.539

SR: sinus rhythm; AF: atrial fibrillation; CPET: cardiopulmonary exercise test; CI: confidence interval; pVO2: peak O2 consumption; OUES: oxygen uptake efficiency slope.

and when compared with the VE/VCO_2 slope (p = 0.503 and p = 0.701, for SR and AF group respectively).

Cut-off value for HT selection: PPV and NPV for the primary outcome

The univariate Cox analysis for the primary outcome of the two recommended CPET cut-offs for HT selection[7] (pVO_2 ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB and VE/VCO_2 slope ≤ 35) is represented in Table 6, showing that in the two groups, both cut-offs remained predictors of the outcome.

In pVO_2 ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB, the PPV for the primary outcome was 100% in the AF group and 38.5% in the SR group (Table 7), with a NPV of 95.5% and 94.3% in the AF and SR groups, respectively. Higher values were found when the analysis excluded patients not doing BB, with a PPV of 100% and 75%, and a NPV of 97.1% and 95.3% for the AF and RS groups respectively.

In VE/VCO_2 slope > 35 (Table 7), lower values of PPV were reported (33.3% and 29.8% for AF and SR groups, respectively), with similar NPV to pVO_2 (92.3% and 98.3% for AF and SR groups, respectively).

Discussion

The presence of AF is associated with a negative prognostic effect in HF, with 50-90% increased mortality and HF progression in the Framingham Heart Study.[12] Our population revealed some baseline differences between SR and AF groups, with some of that in previously described prognostic markers of HF, as AF patients were older,[13,14] with lower GFR,[15-17] with worse right ventricular function[18] and a lower LVEF.[19,20] In regard to CPET parameters, our AF patients revealed a lower exercise capacity than SR patients since they had a higher VE/VCO_2 slope and a lower CPET duration, pVO_2, OUES, time to AT and pVO_2 at AT. As expected, these differences converted in a worse prognosis in the AF group, with a 2-fold increase in the primary endpoint events (17.6% VS 8.1%, p = 0.038) and 3-fold increase in all-cause mortality (17.6% VS 6.3%, p = 0.008) in the 1-year follow-up.

The majority of the predictors of the primary endpoint were predictors for both SR and AF groups. The HFSS,[21] Sodium,[22] NT-proBNP,[23-25] right ventricular dysfunction,[18] lower LVEF,[19,20] CPET duration, HHR1,[26] and initial and maximal SBP during CPET[27] were included in this group, with all of them being formerly described as prognostic markers in HF patients.

Differences were found regarding maximal HR and variation of HR during the exercise, with lower values in AF patients predicting the primary outcome only in that group.

Patients not using BB were solely predictive of the primary outcome in the SR group, but not in the AF group. Whether this is in agreement with other studies that failed to reveal prognostic benefit from BB in the AF group of HF patients[28-30] or to a underpowered analysis since only 11 patients in the AF group were not doing BB cannot be guaranteed.

Cut-off value for HT selection: PPV and NPV for the primary outcome

Whether HF patients with AF can be precisely stratified with the current CPET cut-offs for HT selection have not been specifically studied before. The cut-off value for pVO_2 showed a PPV for the primary outcome of 100% in the AF group and 38.5% in the SR group, with a NPV of 95.5% and 94.3% in the AF and SR groups, respectively. Hence, despite AF carries a worse prognosis in HF patients, the current cut-off of pVO_2 for HT selection can precisely stratified these high-risk patients, with no patients under the cut-off misdiagnosed as high risk patients and less than 5% of patients above the cut-off having the primary outcome in the 1-year follow-up (Figure 1). These results suggest that patients under the cut-off of pVO_2 should be managed accordingly, considering quickly referring for HT or mechanical circulatory support, since medical treatment is associated with negative outcomes in a 1-year period, and that we can be relatively safe in regard to 1-year outcomes of patients above the cut-off.

Table 7 – Proportion of patients correctely classified at 12 months of follow up

	AF	SR
pVO_2 ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB2	7/7 - 100%	5/13 - 38.5%
pVO_2 > 12 ml/kg/min or > 14 ml/kg/min without BB	42/44 - 95.5%	198/210 - 94.3%
pVO_2 ≤ 12 ml/kg/min only in patients doing BB	5/5 - 100%	6/8 - 75%
pVO_2 > 12 ml/kg/min only in patients doing BB	34/35 - 97.1%	161/169 - 95.3%
VE/VCO_2 slope > 35	7/21 - 33.3%	14/47 - 29.8%
VE/VCO_2 slope ≤ 35	28/30 - 92.3%	173/176 - 98.3%

SR: sinus rhythm; AF: atrial fibrillation; pVO_2: peak O_2 consumption; BB: beta-blockers.

Table 6 – Univariate Cox analysis for the primary outcome of the two recommended cardiopulmonary exercise test cut-offs for Heart Transplantation selection

	SR			AF		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
pVO_2 ≤ 12 ml/kg/min	8.673	3.048-24.680	< 0.001	44.220	8.686-225.129	< 0.001
VE/VCO_2 slope > 35	20.858	5.985-72.696	< 0.001	5.613	1.164-27.059	0.032

SR: sinus rhythm; AF: atrial fibrillation; CI: confidence interval; pVO_2: peak O_2 consumption.

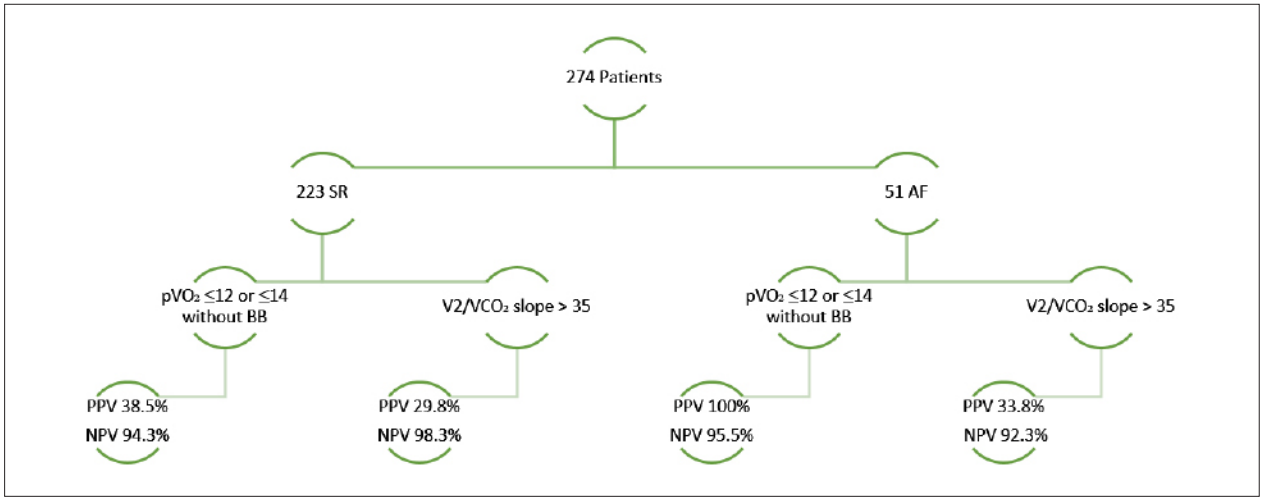

Figure 1 – *Positive (PPV) and negative predictive value (NPV) of pVO_2 and VE/VCO_2 slope.*

In regard to SR patients, the lower risks associated are responsible for a lower value of PPV above the pVO_2 cutoff. The PPV was raised from 38,5% to 75% when the analysis excluded patients not doing BB. The NPV remains high in this group (94,3%).

During exercise, both CO_2 output and ventilation increase steadily, but in patients with HF, the slope of the relationship is increased.[31] Previous studies have confirmed the prognostic impact of VE/VCO_2 in patients with HF, with higher values being associated with worse outcomes.[32-35] However, the value of VE/VCO_2 in AF patients with HF is not so well established, with differences in results in some trials.[36,37]

In our study, with a VE/VCO_2 slope > 35, lower values of PPV were reported (33.3% and 29.8% for AF and SR groups, respectively), with similar NPV compared to pVO_2 results (92.3% and 98.3% for AF and SR groups, respectively, figure 1). The power to predict the primary outcome by the VE/VCO_2 slope, revealed an AUC of 0.906 for the SR group (the highest of all the CPET parameters analysed) and 0.844 in the AF group, with no statistically significant difference found when comparing the different AUC values of the CPET parameters. These differences in PPV may suggest that despite the fact that VE/VCO_2 slope could be at least as good for prognostic assessment in HF patients as pVO_2, the cut-off to use with the VE/VCO_2 slope is not so well established as the cut-off for pVO_2 in AF patients.

One previous study has shown that in a multivariate Cox analysis, pVO_2 was identified as a sole significant predictor of cardiac events in HF patients in SR and the VE/VCO_2 slope in AF patients.[38] Our results, however, do not concur with the previous results. In fact, our multivariate Cox analysis (Table 5) showed that when pVO_2 and the VE/VCO_2 slope are analysed together, pVO_2 lost its predictive power ($p = 0.280$) while the VE/VCO_2 slope remained predictive of the primary outcome ($p = 0.001$) in the SR group. In the AF group, the VE/VCO_2 slope lost its predictive power ($p = 0.398$) while pVO_2 showed a trend for the prediction of the primary outcome ($p = 0.091$).

The predicted pVO_2 (%) has been demonstrated as a useful prognostic marker in previous HF studies.[39] In the multivariate Cox analysis of predicted pVO_2 (%) and the VE/VCO_2 slope, predicted pVO_2 (%) kept his predictive power in the SR group ($p = 0.006$) in contrast to pVO_2, while in the AF group, it showed a trend towards prediction of the primary outcome ($p = 0.094$) and had the highest AUC predictive value (0.878).

OUES is derived by plotting VO_2 as a function of log10VE, which is an approximately linear relation, indicating how effectively O_2 is extracted and taken into the body.[40] In HF patients, OUES is reduced in proportion to disease severity and linked to outcome.[41,42] In our population, OUES had the numerically lower AUC for predicting the primary outcome in both AF and SR groups and lost its predictive power in the multivariate Cox analysis when compared with pVO_2 and when compared with the VE/VCO_2 slope, which is in accordance with other previous study.[43]

Study limitations

There are limitations to our study that should be referenced. Even though data was obtained from the outpatient clinic visits, medical charts were reviewed and complemented with a standardized telephone interview to all patients at 12 months of follow-up to collect data for the primary and secondary outcomes. Information pertaining to the selection or not of rhythm control for the treatment of AF was not gathered. Despite this, the goal of the trial was to define, during the initial evaluation, which patients needed early indication for HT or mechanical circulatory support, reducing the importance of the aforementioned information.

Despite being a seven-year follow-up of patients evaluated for HT in one advanced HF centre, the analysed cohort was not larger than other studies of the relation between HF and AF.[2,36,38] However, the sample size is similar to other studies that highlighted the value of CPET parameters, including for the selection of patients for HT.[8,32,35,44,45]

Since patients were referred for a tertiary hospital for the purpose of evaluation with HF team and possible indication

for HT or mechanical circulatory support, these patients may not be representative of the older or with higher comorbidities HF community, who are not candidate for advanced HF treatment.

Conclusions

Despite AF carries a worse prognosis for the HF patients, the current cut-off of pVO_2 for HT selection can precisely stratify this group of high-risk patients. The findings from the present study suggest that HF patients with AF and a CPET under the current cut-off of pVO_2 for HT selection should be quickly referred for HT or mechanical circulatory support, since medical treatment is associated with negative outcomes in a 1-year period, with a higher PPV than patients in SR. In addition, pVO_2 cut-off seems to have higher PPV than VE/VCO_2 slope cut-off for the prediction of the primary outcome in HF patients with AF.

Author contributions

Conception and design of the research: Gonçalves AV, Pereira-da-Silva T, Soares R; Acquisition of data: Pereira-da-Silva T, Soares R, Feliciano J, Moreira RI, Rio P; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Gonçalves AV; Critical revision of the manuscript for intellectual content: Pereira-da-Silva T, Soares R, Abreu A, Ferreira RC.

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 *Centro Hospitalar Lisboa Central* under the protocol number CA2257. 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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Cardiopulmonary Exercise Test in the Evaluation of Heart Transplant Candidates with Atrial Fibrillation

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Short Editorial related to the article: Prognostic Prediction of Cardiopulmonary Exercise Test Parameters in Heart Failure Patients with Atrial Fibrillation

Antonio Valentim Gonçalves et al.,[1] authors of the original article "Prognostic Prediction of the Cardiopulmonary Exercise Test Parameters in Patients with Heart Failure and Atrial Fibrillation",[1] published in this issue of *Arquivos Brasileiros de Cardiologia*, intended to evaluate whether the cutoff points of two parameters of the cardiopulmonary exercise test (CPET), routinely used in the selection of patients for heart transplant (HT), would also be efficient in the presence of permanent or persistent atrial fibrillation (AF) in patients with heart failure with reduced ejection fraction (HFREF).

In their work, the authors assessed whether the study primary endpoint was reached in the presence of two recommendations of the International Society for Heart and Lung Transplantation (ISHLT) guideline:[2] 1) peak oxygen consumption (pVO_2) ≤ 12 (under betablocker therapy) - BB) or 14 mL/Kg/min (in the absence of BB) and, 2) slope of ventilation (VE) / carbon dioxide elimination (VCO_2) > 35, when the respiratory exchange ratio (RER) during the exercise is < 1.05.

This study included 274 consecutive patients with left ventricular ejection fraction (LVEF) < 40%, from a single center, assessed by CPET, of which 51 were in AF and 223 in sinus rhythm (SR). The primary endpoint [HT or cardiac death (CD)] was observed in 17.6% of patients with AF and 8.1% of patients in SR (p < 0.0038).

In the context of AF, the VO_2-related cutoff point (with or without BB) performed very well, with a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 95.5%. In contrast, the VE/VCO_2 slope cutoff point was found to have a PPV of 33.8% and a NPV of 92.3%.

In the group of patients in SR, the results of the cutoff point related to pVO_2 were lower, with a PPV of 38.5% and a NPV of 94.3%, similar to the cutoff point of the VE/VCO_2 slope, with a PPV of 29.8% and a NPV of 98.3%.

They concluded that the current cutoff points accurately stratify patients in AF, corroborating the initial hypothesis of their research.

To the best of my knowledge, this is the first study that specifically assessed the application of the ISHLT criteria for the selection of patients with AF and HFREF for HT. The study is valuable for having assessed the application of these criteria in this group that has a significant dimension in heart failure (HF) clinics.

Keywords

Heart Failure; Atrial Fibrillation; Heart Transplantation; Patient Selection; Oxygen Consumption; Exercise Test.

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Clinical application of the study findings

The main conclusions of the article are as follows:

1) The two ISHLT criteria were better suited to patients with AF than to those in SR.
2) In the context of AF, the performance of the peak VO_2 criterion ≤ 12 or 14 mL/Kg/min, depending on whether or not the patient was under betablocker medication, has a much higher value than the VE/VCO_2 slope.
3) In patients in SR, either of the two criteria (peak VO_2 and VE/VCO_2 slope > 35) have a low PPV (< 40%) and high NPV (> 90%); thus, they are more suitable to identify patients who do not need HT.

It seems logical that patients in AF, with LVEF < 40%, have a lower functional capacity than those in SR, because the AF reduces the maximum cardiac output by a percentage of not less than 25%. On the other hand, many of these patients have advanced HF,[3,4] with less capacity to extract oxygen at the muscle level, as a result of the muscular atrophy caused by inactivity and the myopathy inherent to HF. As pVO_2 is related not only to the cardiac output at the level of maximum effort, but also to the oxygen extraction capacity at the peripheral level, it is easy to understand why they have decreased pVO_2.

It would have been interesting also to evaluate the criterion of pVO_2 < 50% of the predicted maximum, in individuals under the age of 50 years or of the female gender, which was classified as class IIa, [level of evidence (LE) B], higher than the criterion VE/VCO_2 slope, which was rated as class IIb (LE C). The criterion VE/VCO_2 slope is indicated by the ISHLT for alternative use when a respiratory rate > 1.05 is not obtained during the exercise period.

The inefficient performance of the criteria used in the SR group, which obtained a PPV < 40%, is surprising. Part of the explanation may be related to the presence of 40% of women in the SR group, compared to 27.5% in the AF group (although with p < 0.087). Indeed, it has been shown that women have a better prognosis, despite having significantly lower pVO_2 values than men.[5]

The ISHLT criteria for risk stratification in HFREF

The 2016 ISHLT guideline[2] for placing patients on a HT list was conservative and generally maintained the recommendations of 2006. It included once more a recommendation (class I, LE B) confirming the suitability of the pVO_2 generic cutoff for patients with a cardiac

resynchronization device following the COMPANION study and recommended using the prognostic scores [Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM)] together with the CPET parameters (class IIb, LE B).

Regarding the pVO_2, it maintained the cutoff points $pVO_2 \leq 12$ (under BB therapy) and ≤ 14 mL/Kg/min (intolerant to BB therapy) as class I (LE B) recommendations. It considers reasonable to use as a cutoff point a pVO_2 value < 50% of the maximum predicted in patients under the age of 50 years and in females, assigning it a IIa classification, LE B.

It recommends using the criterion VE/VCO_2 slope > 35 only in cases of submaximal CPET, i.e., when the respiratory exchange ratio (RER) is < 1.05 at peak effort (class IIb, LE C).

Guazzi et al.[6] in 2012 considered that mortality would be > 50%, between 1 and 4 years, if the criteria VE/VCO_2 slope ≥ 45, pVO_2 < 10.0 mL/Kg/min, and ventilatory oscillations (VO),[7] the expired CO_2 pressure ($P_{ET}CO_2$) < 33 mmHg at rest and with an increase of less than 3 mmHg during exercise were present. In addition to the recommendation of using stricter criteria in pVO_2 and especially in the VE/VCO_2 slope, Guazzi et al.[6] introduced two new parameters in the assessment: the oscillatory breathing (OB) and $P_{ET}CO_2$. Before this publication, other authors, including Ferreira et al.,[8] defined higher cutoff points for the VE/VCO_2 slope. In this article, a cutoff point of 43 was defined, which is much stricter and more discriminative than the ISHLT criterion.

In 2016, Malhotra et al.[9] demonstrated that patients with HFREF with pVO_2 < 12 or 14 mL/Kg/min (with or without BB), VE/VCO_2 slope > 36, OB, oxygen uptake efficiency below 1.4, reaching systolic pressure value < 120 mmHg, with a heart rate decrease below 6 bpm from peak effort for the 1st minute of recovery, had a mortality rate > 20% at 1 year.

In line with these articles, Wagner et al.,[10] reviewed the recommendations in the light of current evidence and classified pVO_2, its percentage in relation to the maximum predicted pVO_2 and the VE/CO_2 slope as class I (LE A) recommendations, and the presence of OB as IIa (LE B) and OUES and $P_{ET}CO_2$ as IIb recommendations (LE B).

Cardiac transplant indication: based on CPET and risk scores

The final decision to place a patient without contraindications on the HT waiting list is based on a risk-benefit analysis of the different therapeutic options, based on a clinical, psychological and social assessment, and of parameters provided by the complementary tests.

The CPET parameters can be considered separately or incorporated to scores such as HFSS and MECKI. The HFSS has seven variables, including pVO_2. The MECKI, in turn, gives a higher weight to the CPET data when incorporated to the VE/VCO_2 slope and the percentage of the maximum expected VO_2 among its 5 variables.

Freitas et al.[11] recently published an article comparing the value of 4 scores – HFSS, MECKI and two scores that integrate clinical parameters data: SHFM (10 variables) and MAGGIC (13 variables) – and MECKI was the most discriminative for CD or HT in the first year, with an area under the curve of 0.87.

Conclusion

The CPET is indicated for risk stratification in HFREF, particularly in the assessment of candidates for HT and ventricular assistance, aiming to objectively quantify functional limitation and provide relevant clinical information on the etiology of functional limitations that may have a cardiac, pulmonary or mixed cause.[9]

It is not possible to perform CPET in patients in INTERMACS classes 1 to 3 (cardiogenic shock, receiving inotropic drugs or under circulatory assistance), in the presence of uncontrolled supraventricular or ventricular arrhythmias and in patients unable to exercise due to orthopedic pathology or extreme frailty.

However, in most patients in INTERMACS classes 4 to 7, provided that an exercise protocol adapted to the patient's functional capacity or an ergometer that allows minimizing their orthopedic limitations is selected, it is possible to perform a maximum CPET and obtain parameters with high prognostic value in most patients with HFREF.

Currently, pVO_2, maximum predicted pVO_2/VO_2, VE/VCO_2 slope and OB are considered as the parameters provided by the CPET with the highest prognostic value in HFREF.[9]

The CPET is still little used in Cardiology in the context of HF because its performance and interpretation involve some complexity, and because it has a higher cost than the conventional exercise test. However, it is of great interest as it allows an integrated assessment of the pathophysiology of the circulatory, respiratory and locomotor systems, making it possible to objectively identify the patients' limitations, their cause, and stratify them in terms of prognosis.

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A 10-Year Trend Analysis of Heart Failure in the Less Developed Brazil

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Abstract

Background: Data on heart failure (HF) epidemiology in less developed areas of Brazil are scarce.

Objective: Our aim was to determine the HF morbidity and mortality in Paraiba and Brazil and its 10-year trends.

Methods: A retrospective search was conducted from 2008 to 2017 using the DATASUS database and included patients ≥ 15 years old with a primary diagnosis of HF. Data on in-hospital and population morbidity and mortality were collected and stratified by year, gender and age. Pearson correlation and linear-by-linear association test for trends were calculated, with a level of significance of 5%.

Results: From 2008 to 2017, HF admissions decreased 62% (p = 0.004) in Paraiba and 34% (p = 0.004) in Brazil. The in-hospital mortality rate increased in Paraiba and Brazil [65.1% (p = 0.006) and 30.1% (p = 0.003), respectively], but the absolute in-hospital mortality had a significant decrease only in Paraiba [37.5% (p = 0.013)], which was maintained after age stratification, except for groups 15-19, 60-69 and > 80 years. It was observed an increase in the hospital stay [44% (p = 0.004) in Paraiba and 12.3% (p = 0.004) in Brazil]. From 2008 to 2015, mortality rate for HF in the population decreased 10.7% (p = 0.047) in Paraiba and 7.7% (p = 0.017) in Brazil.

Conclusions: Although HF mortality rate has been decreasing in Paraiba and Brazil, an increase in the in-hospital mortality rate and length of stay for HF has been observed. Hospital-based clinical studies should be performed to identify the causes for these trends of increase. (Arq Bras Cardiol. 2020; 114(2):222-231)

Keywords: Heart Failure/physiopathology; Heart Failure/mortality; Heart Failure/epidemiology; Comorbidity; Heart Failure/trends; Hospitalization.

Introduction

Heart Failure (HF) is the main cause of hospitalizations in the United States in patients older than 65 years old,[1,2] and is estimated to affect 26 million people worldwide.[3] Its prevalence has been increasing fast due to aging of the population.[1,4] A higher life expectancy has been achieved with adherence to medical therapy, ventricular assist devices (VADs) and increase in the number of heart transplants.[1]

Paraiba is one of the nine states of the Northeast region of Brazil and had an estimated population in 2017 of 4,025,558 inhabitants, corresponding to the 13th highest population among the 27 federative units of Brazil. The gross domestic product per capita of Paraiba was US$3,594.94 in 2010, corresponding to fourth poorest state in the country, and the human development index in 2014 was 0.701, the 6th lowest in the country.[5,6] Data regarding the epidemiology of HF in less developed countries are still limited and based mainly in cohorts of hospitalized patients or clinical trials.[2] In Brazil, there is no data about the epidemiology of HF in Paraiba, and only a few reports on HF statistics in the Northeast region of Brazil.[7,8]

A better understanding of the HF epidemiology in less developed areas of Brazil, as Paraiba, through a population-based study, could lead to a more effective and appropriate healthcare planning. The aim of this study was to describe and to perform a 10-year trend analysis of the HF morbidity and mortality in the state of Paraiba and in Brazil.

Methods

Study model

This is a population-based time series analysis using the Hospital Information System (SIH/SUS), available at DATASUS (Department of Informatics of the Brazilian Unified Health System– SUS) database.[6] DATASUS is responsible for the administration of health and financial information declared by all states and cities, and the federal district of Brazil. This database compiles information regarding health assistance, epidemiology, morbidity and demography.

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Study population

The population of interest was composed by Brazilians older than 15 years that used any healthcare services under the primary diagnosis of HF, represented by the code I50 of the International Classification of Diseases 10th Revision (ICD-10), between 2008 and 2017.

Variables

Epidemiological data on HF were extracted, including absolute and relative mortality of the population, in-hospital mortality (absolute numbers), in-hospital mortality rate, number of hospital admissions and length of hospitalization. Variables were stratified by year, gender and age groups (15-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years). In-hospital data from the period of 2008 to 2017, and population data from 2008 to 2015 were available. The last population census conducted by the Brazilian Institute of Geography and Statistics (IBGE)[5] in 2010 was also used.

Data analysis

Categorical variables were expressed as frequencies and continuous variables as mean ± standard deviation (SD).

In-hospital mortality rate from HF was obtained by dividing the number of all in-hospital HF deaths in Paraiba or Brazil by the number of hospitalizations for HF in the corresponding year. Population mortality rate from HF was calculated by dividing the number of all HF deaths in Paraiba or Brazil by the respective population in the corresponding year.

The Statistical Package for the Social Sciences (SPSS) version 21.0 (SPPS Inc., Chicago, USA) was used for the analysis. We used the Shapiro-Wilk's test to test the normality of data distribution for further analyses. The Pearson correlation was used to evaluate the correlation between numerical variables with normal distribution. The Chi-square test was performed using a contingency table and the linear-by-linear association test, also known as Mantel-Haenzsel test for trends, which is equivalent to the Cochran-Armitage test for trends available in other statistical packages.[9] The level of significance was set at 5%.

Results

Descriptive statistics of our variables are presented in Table 1.

Hospitalizations

The total number of HF admissions in Paraiba state between 2008 and 2017 was 51,172, representing the leading cause of hospitalizations due to cardiovascular diseases (29.4%), followed by other ischemic diseases of the heart (13%), stroke (11%), primary hypertension (10%) and acute myocardial infarction (5%). During the same period, HF was also the leading cardiovascular cause of hospitalization in Brazil, with 2,380,133 cases (21%). HF was responsible for 2.54% and 2.25% of all causes of hospitalization in Paraiba and in Brazil, respectively.

A downward trend in the absolute number of hospitalizations from HF in Paraiba and Brazil was observed between 2008 and 2017, corresponding to a decrease of 62% (R = -0.970; p = 0.004; Table 2; Figure 1A) and 34% (R = -0.964; p = 0.004; Table 3; Figure 1B), respectively. The frequency of males hospitalized for HF was 52% in Paraiba and 51% in Brazil.

When stratified by age, individuals older than 60 years old corresponded to 71% and 73% of all the cases of HF admissions in Paraiba and Brazil, respectively, with the highest frequency in the age range from 70 to 79 years old.

Absolute mortality of population

The absolute mortality from HF of the population showed a non-significant decline from 2008 to 2015 in Paraiba (R = -0.513; p = 0.175; Table 2) and Brazil (R = -0.412; p = 0.276; Table 3), with no difference by gender. Women represented 53% of deaths in Paraiba and 52% in Brazil. In Paraiba, the decrease in absolute deaths from HF in the population across all age categories was not statistically significant (Table 2).

Between 2008 and 2015, the highest proportion of deaths from HF occurred at the age group of ≥ 80 years old in both men and women in Paraiba (50% and 59%, respectively) and in Brazil (38% and 52%, respectively). The proportions of deaths from HF at the age ≥ 60 years old in Paraiba was 87% in men and 90% in women and, in Brazil, 83% in men and 89% in women.

Population mortality rate

The mean mortality rate from HF in the population was 19.2/100,000 (±1.09) in Paraiba and 14.0/100,000 (±0.53) in Brazil, with a significant decline of 10.7% (R = -0.751; p = 0.047; Table 2) in Paraiba and 7.7% (R = -0.905; p = 0.017; Table 3) in Brazil between 2008 and 2015, respectively (Figure 2).

Absolute in-hospital mortality

The absolute in-hospital HF mortality, between 2008 and 2017, showed a significant decrease of 37.5% in Paraiba (R = -0.824; p = 0.013; Table 2; Figure 3B) and a non-significant 14.6% decrease in Brazil (R = -0.504; p = 0.131; Table 3; Figure 3B). In the stratified analysis, a significant decrease in the absolute in-hospital deaths from HF was observed for both men and women in Paraiba (R = -0.837; p = 0.012 and R = -0.762; p = 0.022; Table 2); this statistically significant trend by sex was not observed in Brazil (Table 3).

Individuals older than 80 years old presented the highest proportion of absolute in-hospital HF deaths in Paraiba and Brazil, from 2008 to 2017, (37% and 32%, respectively) (Figure 4). In Paraiba, there was a statistically significant reduction in in-hospital deaths from HF for the age categories: 20-29 years (p = 0.010), 30-39 years (p = 0.008), 40-49 years (p = 0.029), 50-59 years (p = 0.025) and 70-79 years (p = 0.009) (Table 2).

Further data on the absolute number of in-hospital deaths from HF per age range in Brazil are specified in Table 3.

In-hospital mortality rate

The in-hospital HF mortality rate increased significantly by 65.1% in Paraiba (R = 0.917; p = 0.006; Table 2), from 6.6%

Table 1 – Descriptive statistics of Heart Failure epidemiology in Paraiba, from 2008 to 2017

Variables	Mean	Standard deviation	Shapiro-Wilk significance*
Deaths (population) †	739.88	32.92	0.385
Women	387.88	24.07	0.916
Men	349.63	17.71	0.099
Deaths (in-hospital)	474.50	95.52	0.324
Women	238.80	46.15	0.763
Men	234.70	52.04	0.161
Population mortality rate (per 100,000) †	19.16	1.09	0.775
In-hospital mortality rate (per 100)	9.76	1.84	0.659
Number of admissions	5117.20	1805.13	0.176
Mean duration of hospitalization (days)	5.92	0.80	0.121

**In the Shapiro-Wilk test, the null hypothesis is that the population follows a normal distribution; if p < 0.05, the data is not normally distributed; † Year interval: 2008-2015; Source of data: SUS Information System (DATASUS) and Brazilian Institute of Geography and Statistics (2010).*

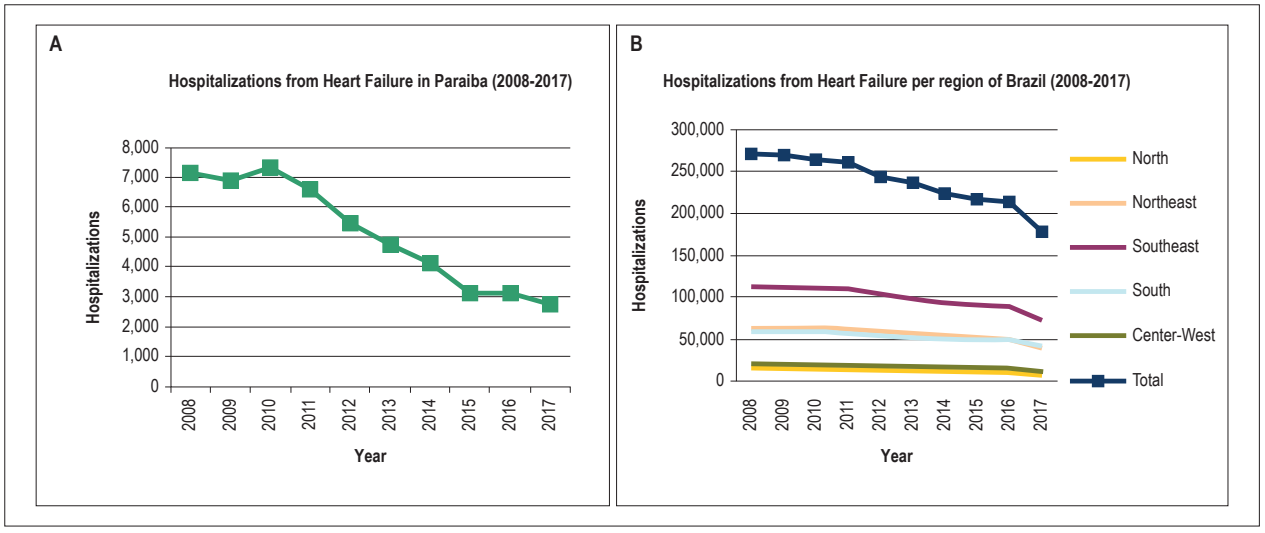

Figure 1 – *Trends in absolute number of hospitalizations from heart failure from 2008 to 2017 in Paraiba (A) and regions of Brazil (B).*

in 2008 to 10.9% in 2017, and by 30.1% in Brazil (R = 0.981; p = 0.003; Table 3), from 8.3% in 2008 to 10.8% in 2017 (Figure 3A). The increase in in-hospital mortality rate from HF by gender was also significant for both men and women in Paraiba (R = 0.828; p = 0.013 and R = 0.908; p = 0.006, respectively; Table 2). This trend was also observed for both sex in Brazil, in a similar magnitude of effect (R = 0.985; R = 0.980; p = 0.003; Table 3).

The in-hospital HF mortality rate per age range was highest in individuals older than 80 years old, with a mean of 14.7% in Paraiba and 14.5% in Brazil (Figure 5) from 2008 to 2017. In this age range, the in-hospital mortality rate from HF per gender in Paraiba was 12.4% in men and 15.2% in women, and in Brazil, 13.7% in men and 14.9% in women.

Length of hospital stay

The average length of hospital stay for HF was 5.9 days (±0.8) in Paraiba and 6.9 days (±0.4) in Brazil, with a significant increase of 44% (R = 0.953; p = 0.004; Table 2) and 12.3% (R = 0.960; p = 0.004; Table 3), respectively, between 2008 and 2017 (Figure 6). In Table 4, we present the duration of hospital stay per year, and the associated cost, both in Paraiba and Brazil.

Discussion

To our knowledge, this is the first study to describe the trends of HF epidemiology in a less developed region of Brazil. Information regarding the incidence, prevalence, morbidity

Table 2 – Heart failure trends in Paraiba, from 2008 to 2017

Variables	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P values for trends*†	Pearson (R)
Number of deaths (population)	722	777	772	753	719	768	725	683	------	------	0.175	-0.513
Women	365	398	390	413	386	421	383	347	------	------	0.665	-0.164
Men	351	374	379	337	332	347	341	336	------	------	0.130	-0.573
Number of deaths (in-hospital)	472	588	581	561	551	462	461	374	378	317	0.013*	-0.824
Women	220	310	294	282	265	235	224	207	188	173	0.022*	-0.762
Men	252	278	287	279	286	227	237	167	190	144	0.012*	-0.837
Mortality rate (population)	19,25	20.53	20.21	19.55	18.51	19.62	18.38	17.19	------	------	0.047*	-0.751
Mortality rate (in-hospital)	6.60	8.50	7.90	8.50	10.10	9.8	11.20	12.00	12.10	10.90	0.006*	0.917
Women	6.35	9.32	8.52	9.02	10.08	10.39	11.49	13.56	12.69	11.93	0.006*	0.908
Men	6.76	7.67	7.36	8.15	10.20	9.12	11.02	10.61	11.59	9.40	0.013*	0.828
Number of admissions	7143	6890	7331	6571	5450	4739	4102	3112	3115	2719	0.004*	-0.970
Deaths per age range (population)												
15-19 years	2	2	3	2	1	0	1	1	------	------	0.067	-0.693
20-29 years	3	8	8	5	5	6	2	6	------	------	0.588	-0.205
30-39 years	8	16	9	13	9	10	10	8	------	------	0.389	-0.326
40-49 years	21	22	29	23	25	23	24	13	------	------	0.292	-0.399
50-59 years	47	42	53	33	45	48	46	36	------	------	0.479	-0.267
60-69 years	84	88	92	75	92	101	82	93	------	------	0.457	0.281
70-79 years	164	172	152	172	147	179	174	154	------	------	0.979	-0.010
Older than 80 years	387	422	423	427	394	401	385	372	------	------	0.143	-0.553
Deaths per age range (in-hospital)												
15-19 years	3	2	3	3	2	2	2	2	4	2	0.815	-0.078
20-29 years	11	10	8	5	5	4	4	7	2	2	0.010*	-0.859
30-39 years	17	19	16	11	16	12	7	8	6	8	0.008*	-0.887
40-49 years	24	35	35	35	36	30	19	10	10	17	0.029*	-0.727
50-59 years	55	53	53	55	63	47	46	24	38	35	0.025*	-0.748
60-69 years	77	97	96	97	101	86	93	72	76	44	0.061	-0.625
70-79 years	129	150	136	142	131	119	129	96	89	75	0.009*	-0.865
Older than 80 years	149	213	227	211	194	157	156	153	148	129	0.052	-0.649
Mean duration of hospitalization (days)	5	5.2	5.3	5.5	5.6	5.6	6.1	6.5	7.2	7.2	0.004*	0.953

**p < 0.05; † P value for trends according to the linear-by-linear association; Source of data: SUS Information System (DATASUS) and Brazilian Institute of Geography and Statistics (count of 2010).*

and mortality of HF in Latin America and the Caribbean (LAC) are heterogeneous and scarce. Most of the data come from South America (92%), with 86% of the studies conducted in Brazil and Argentina.[10] In Brazil, most of the published data come from developed areas, the Southeast and South regions.

HF was the leading cause of hospitalizations among cardiovascular diseases in Paraiba and Brazil, and corresponded to 2.54% and 2.25% of all admissions, respectively. Similarly, in the U.S., HF was the cause of more than 1 million admissions per year from 2001 to 2009,[11] and represented 1-2% of all hospitalizations.[3]

Fang et al.[12] performed a study to determine the trends in HF in the U.S. using the National Hospital Discharge Survey data from 1979 to 2004, and observed an increase of 185% in the absolute number of HF admissions (from 409,000 to 1,166,000) and the HF hospitalization rates (per 100,000) increased from 219 to 390 during the same period. Other authors, however, have reported that the number of primary hospitalizations for HF have been decreasing in the U.S. between 1.0% to 4.3% per year since 2001.[11,13] In the LAC, Godoy et al.[14] showed a 32% decrease in HF admissions, between 1992-1993 and

Table 3 – Heart failure trends in Brazil, from 2008 to 2017

Variables	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P values for trends*†	Pearson (R)
Number of deaths (population)	27,567	27,314	27,544	27,818	26,694	27,290	26,783	27,434	------	------	0.276	-0.412
Women	13,990	14,136	14,236	14,525	13,824	14,014	13,846	14,435	------	------	0.929	0.034
Men	13,428	13,047	13,159	13,130	12,756	13,166	12,825	12,900	------	------	0.069	-0.689
Number of deaths (in-hospital)	22,513	23,043	23,667	24,451	23,071	22,858	22,031	22,756	23,519	19,209	0.131	-0.504
Women	11,021	11,356	11,740	12,099	11,426	11,305	10,963	11,450	11,738	10,509	0.401	-0.280
Men	11,198	11,395	11,676	12,092	11,408	11,301	10,823	11,097	11,577	10,213	0.119	-0.520
Mortality rate (population)	14.54	14.26	14.44	14.46	13.76	13.57	13.21	13.42	------	------	0.017*	-0.905
Mortality rate (in-hospital)	8.3	8.5	8.9	9.4	9.5	9.7	9.8	10.5	11.0	10.8	0.003*	0.981
Women	8.5	8.7	9.2	9.6	9.8	10.0	10.2	11.0	11.5	11.2	0.003*	0.980
Men	8.2	8.4	8.7	9.2	9.3	9.4	9.6	10.1	10.6	10.4	0.003*	0.985
Number of admissions	270,988	269,891	265,038	260,995	242,919	236,550	223,825	217,050	214,432	178,445	0.004*	-0.964
Deaths per age range (population)												
15-19 years	56	55	47	49	51	41	40	35	------	------	0.014*	-0.926
20-29 years	206	204	180	176	165	174	159	145	------	------	0.012*	-0.947
30-39 years	468	415	379	387	396	373	358	355	------	------	0.022*	-0.863
40-49 years	1,039	1,002	1,034	957	913	920	836	815	------	------	0.011*	-0.957
50-59 years	2,389	2,303	2,293	2,269	2,259	2,214	2,072	2,157	------	------	0.016*	-0.910
60-69 years	4,296	4,249	4,196	4,268	4,057	4,230	4,123	4,255	------	------	0.328	-0.370
70-79 years	7,178	7,027	7,062	7,013	6,727	6,969	6,707	6,845	------	------	0.037*	-0.788
Older than 80 years	11,788	11,928	12,206	12,539	12,012	12,259	12,383	12,733	------	------	0.039*	0.782
Deaths per age range (in-hospital)												
15-19 years	87	97	75	73	61	65	59	61	61	38	0.007*	-0.898
20-29 years	284	271	264	241	220	230	188	176	175	152	0.003*	-0.984
30-39 years	597	529	503	501	475	451	445	437	434	369	0.008*	-0.887
40-49 years	1,278	1,216	1,227	1,216	1,104	1,102	981	1,004	1,052	853	0.005*	-0.931
50-59 years	2,687	2,722	2,736	2,793	2,700	2,620	2,372	2,498	2,569	2,149	0.019*	-0.783
60-69 years	4,358	4,578	4,739	4,769	4,599	4,452	4,439	4,601	4,783	4,149	0.533	-0.208
70-79 years	6,337	6,371	6,583	6,820	6,237	6,343	5,984	6,174	6,496	5,706	0.101	-0.546
Older than 80 years	6,591	6,967	7,289	7,778	7,438	7,343	7,318	7,596	7,745	7,306	0.064	0.617
Mean duration of hospitalization (days)	6.5	6.4	6.5	6.6	6.7	6.9	7.1	7.3	7.4	7.3	0.004*	0.960

**p < 0.05;† P value for trends according to the linear-by-linear association; Source of data: SUS Information System (DATASUS) and Brazilian Institute of Geography and Statistics (count of 2010)*

2008-2009, which is consistent with our findings of a 34% decrease in the absolute number of hospitalizations for HF in Brazil, and 62% in Paraiba. This observed reduction can be a sign of improvement in the overall management of the risk factors for HF,[4] a decrease in the incidence of ischemic heart disease,[15] and an improvement in HF management.[16]

Hospitalizations for HF in Paraiba and Brazil were more common for individuals between the ages of 70 to 79 years old. Individuals older than 60 years old represented 71% and 73% of admissions for HF in Paraiba and Brazil, respectively; this is similar to the frequency (70%) reported in previous studies in LAC and U.S..[2,4] In Paraiba and in Brazil, the

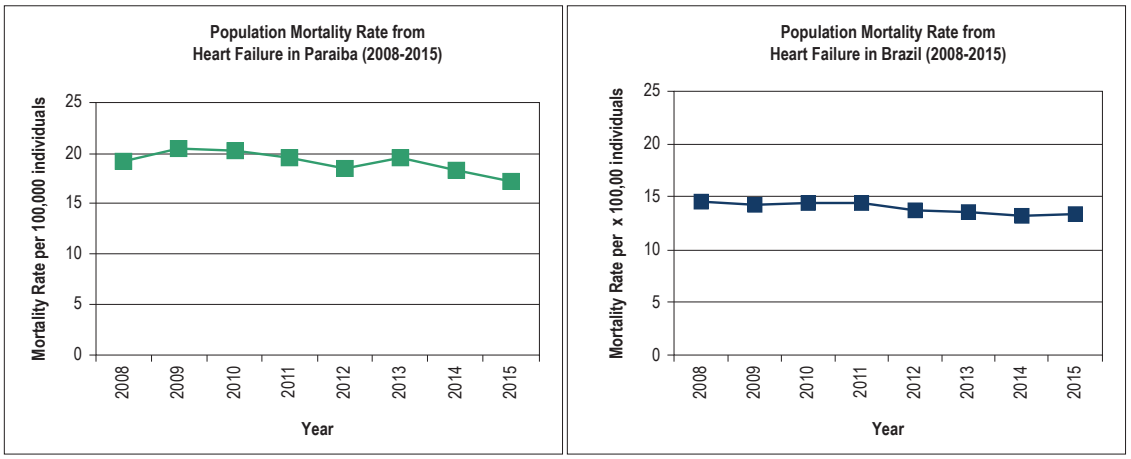

Figure 2 – *Trends in population mortality rate (per 100,000 inhabitants) from heart failure in Paraiba (green) and Brazil (blue) from 2008 to 2015.*

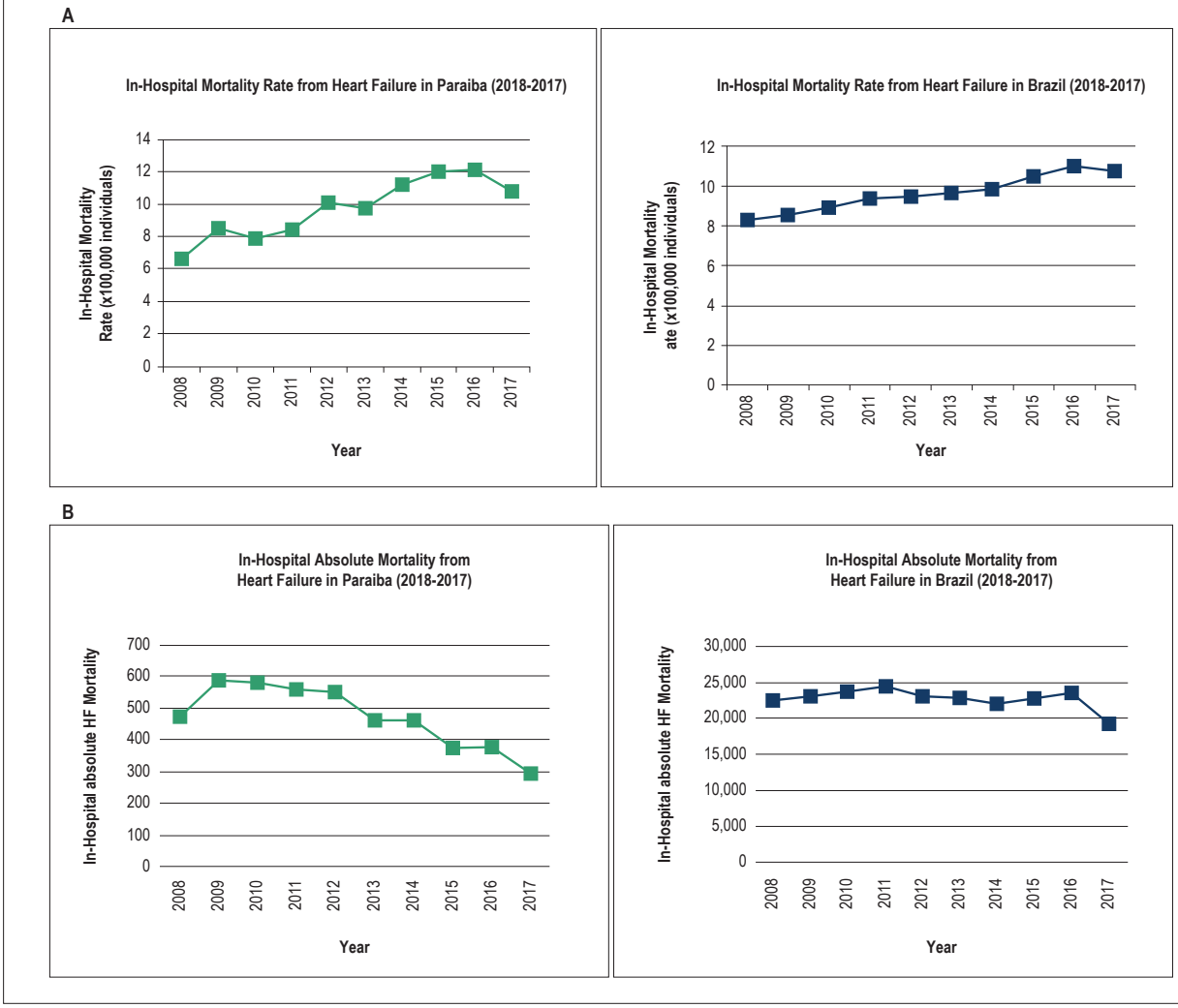

Figure 3 – *(A) Trend of the in-hospital mortality rate from heart failure in Paraiba (green) and Brazil (blue) from 2008 to 2017; (B) trend of the in-hospital absolute mortality from heart failure in Paraiba (green) and Brazil (blue) from 2008 to 2017.*

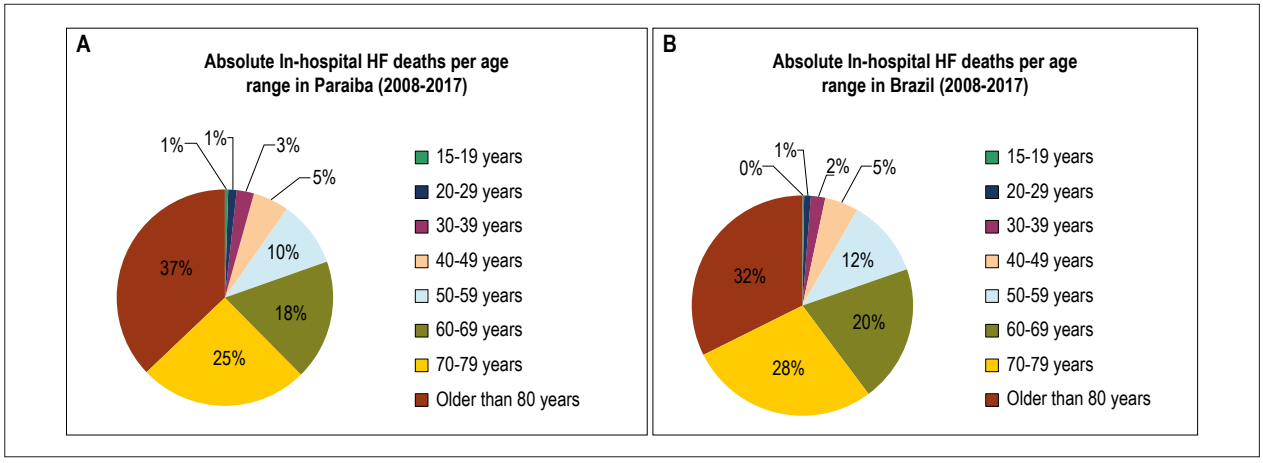

Figure 4 – *(A) Absolute in-hospital deaths from heart failure in Paraiba per age range, from 2008 to 2017. (B) Absolute in-hospital deaths from heart failure in Brazil per age range, from 2008 to 2017.*

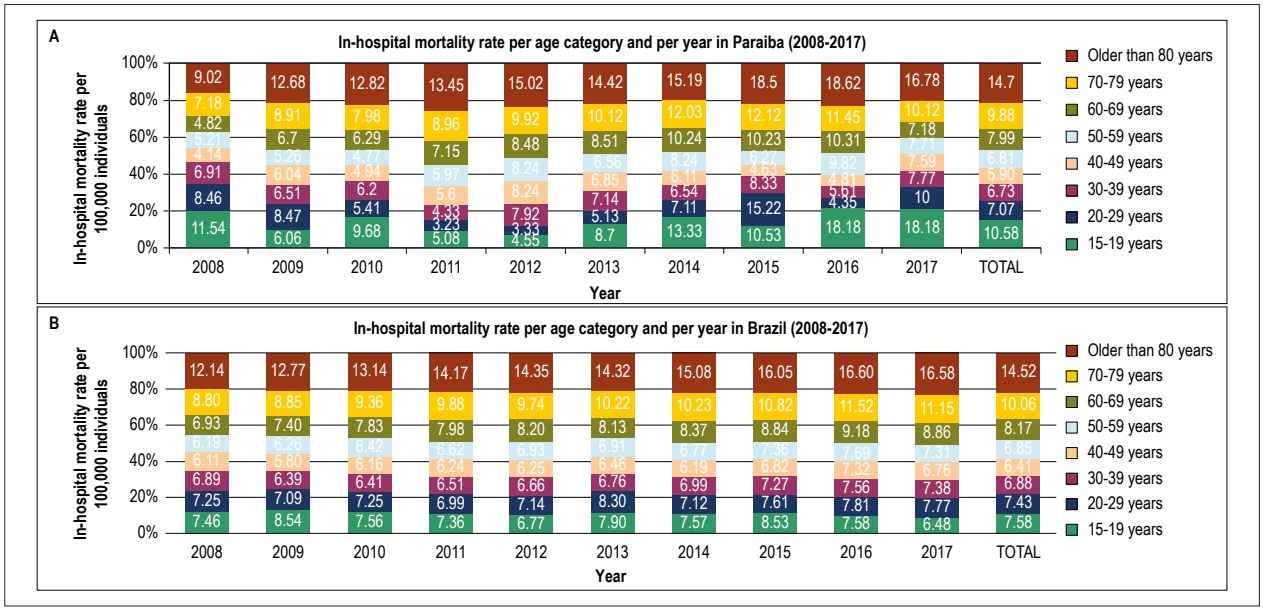

Figure 5 – *(A) Trend of the in-hospital mortality rate from heart failure in Paraiba per year and age range, from 2008 to 2017. (B) Trend of the in-hospital mortality rate from heart failure in Brazil per year and age range, from 2008 to 2017.*

proportion of women hospitalized for HF was 48% vs 49%, similar to studies in the U.S., with 40% to 50% of women.[3,17] A small study performed in a community in Brazil reported that 58% of hospitalized patients with HF were women.[18] Also, the I Brazilian Registry of Heart Failure (BREATHE registry)[8] describes that 60% of 1,263 admissions for HF in 51 centers of Brazil were women.

In our study, mean mortality rate for HF in the population between 2008 to 2015 was 19.2/100,000 (±1.09) cases in Paraiba and 14.0/100,000 (±0.53) cases in Brazil, with a decline of 10.7% and 7.7%, respectively. A decrease in the mortality rate for HF was also reported in Brazil and Argentina: in Sao Paulo, Brazil's largest city, there was a 29% decrease, from 19.1/100,000 (1992-1993) to 13.6/100,000 (2008-2009);[14] in Argentina, a nationwide study showed a reduction of 23% in the population HF mortality rate from 1995 to 2005.[10,19] In the U.S., Go et al.[20] compared the absolute number of HF deaths from 1995 to 2010, and found a decrease of 2.8% (287,000 vs 279,000), which potentially represents a significant decrease in the mortality rate, given the increase in the US population over 15 years.

Our study reports a mean in-hospital mortality rate for HF in Paraiba of 9.2% between 2008 and 2017. A prospective study performed in 51 centers from all the Brazilian regions, only with patients hospitalized due to acute HF, reported a total of 12.6% deaths in 1,263 hospitalized patients.[8] In the LAC, a meta-analysis of 37 studies revealed a similar in-hospital mortality of 11.7%.[10]

Our study demonstrated an increase in the in-hospital mortality rate for HF, both in Paraiba and in Brazil (65% and 30%, respectively), between 2008 and 2017. Godoy et al.,[14]

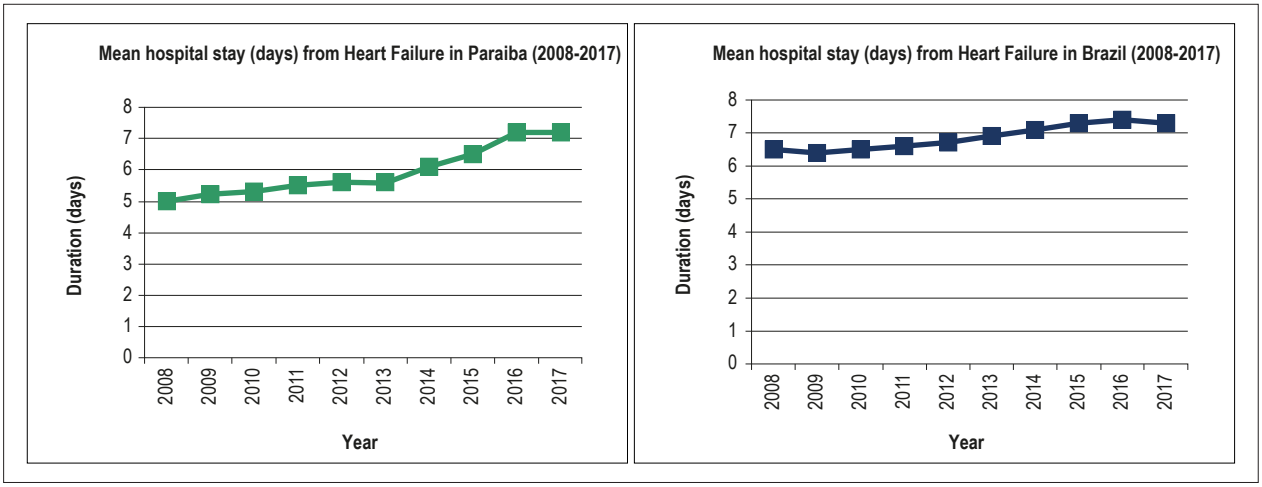

Figure 6 – *Trends in the mean length of stay (days) from heart failure hospitalizations in Paraiba (green) and Brazil (blue) from 2008 to 2017*

Table 4 – Total cost of HF hospitalizations (US$) and duration of HF admission (days) in Paraiba and Brazil, from 2008 to 2017

	PARAÍBA		BRAZIL	
Year	Total cost with hospitalizations (US$)	Duration of admission (days)	Total cost with hospitalizations (US$)	Duration of admission (days)
2008	1,762,825.91	5	77,940,473.93	6.5
2009	2,286,531.90	5.2	89,837,575.25	6.4
2010	2,541,429.71	5.3	92,835,802.31	6.5
2011	2,378,139.40	5.5	93,939,042.90	6.6
2012	1,939,284.53	5.6	91,509,632.22	6.7
2013	1,694,005.09	5.6	93,561,446.18	6.9
2014	1,578,506.24	6.1	96,199,113.56	7.1
2015	1,233,302.85	6.5	99,069,494.68	7.3
2016	1,249,580.27	7.2	102,181,019.88	7.4
2017	1,103,600.05	7.2	85,390,241.41	7.3
Total	17,767,205.95	5.9 ± 0.8 (mean ± SD)	922,463,842.32	6.9 ± 0.4 (mean ± SD)

SD: standard deviation; Source of data: SUS Information System (DATASUS) and Brazilian Institute of Geography and Statistics (count of 2010)

between 1992-1993 and 2008-2009, also reported a 15% increase in the previous 15% in-hospital mortality rate in Brazil. In the U.S., however, the in-hospital mortality rate decreased from 4.5% in 2001 to 2.9% in 2014 according to a study that included patients with a primary diagnosis of HF.[13] The decrease in the number of hospitalizations for HF during the study period, both in Paraiba and Brazil, is the most likely reason for the increased in-hospital mortality rate. Another plausible explanation could be the increased survival of HF patients, leading to a higher number of elderly patients, with more advanced HF and multiple comorbidities, and increased risk of death during hospitalization. Lastly, it is important to consider the lack of advanced therapies in less developed areas, as mechanical devices and heart transplantation, contributing to this trend of increased HF mortality rate in Paraiba, Brazil and LAC.

Although there was an increase in the in-hospital mortality rate, absolute in-hospital mortality showed a significant decrease of 37.5% in Paraiba and 14.6% in Brazil for the same period. In the U.S., Bueno et al.[21] also observed a 50% decrease in the in-hospital mortality for HF in a population of elderly Medicare patients, from 1993 to 2008, and Ni and Xu,[22] a 30% decrease.

Women represented 53% and 52% of the absolute mortality for HF in Paraiba and Brazil, respectively. The in-hospital mortality for HF in Paraiba had a similar proportion of women (50.5%). In the U.S., in 2010, 54.6% of all HF deaths happened in women.[20] Hsich et al.[23] observed no difference in the in-hospital mortality between women and men considering both the reduced and preserved ejection fraction groups.

Between 2008 and 2017, the mean duration of hospitalization for HF was 5.9 (±0.8) days in Paraiba and 6.8 (±0.4) days in Brazil, with an increase of 44% and 12.3%, respectively. In the LAC, Bocchi et al.[2, 24] found a mean hospital stay of 5.8 days between 1998 and 2012. Ciapponi et al.[10] reported an average of 7 days in 18 studies, and Godoy et al.[14] found an increase of 25% in the length of stay, from 8.8

(1992-1993) to 11.3 days (2008-2009) in Brazil. In the U.S., two authors reported a decrease in the length of stay due to HF, from 8.8 to 6.3 days (1993-2008)[21] and from 6.8 days (1999-2000) to 6.4 days (2007-2008).[4]

In the U.S., the per capita cost with healthcare was greater than the per capita gross domestic product of Paraiba (US$8,364.00 and US$3,594.94, respectively).[24] The lower socioeconomic status in Paraiba may represent a risk factor for the high morbidity and mortality observed in our study, because the population has limited access to effective HF treatment.[24] In the U.S., 52.5% of people with a household income less than US$10,000 suffer from a cardiovascular disease[20,25] and Eapen et al.[26] found that a higher income was associated with lower odds of 30-day mortality after a HF admission.

Limitations

This is a retrospective and observational study, and the lack of patient-level data limited our ability to establish relationship between variables. Since our data was derived from a national database, it is likely that underreporting and misreporting of data have occurred. Also, since readmissions are not considered in the total number of HF hospitalizations, in-hospital mortality rate may have been underestimated.

Conclusions

This is the first study to analyze the epidemiology of HF in Paraiba, a less developed state of Brazil, and to compare the results with national and international data. Over the last 10 years, the increase of the in-hospital mortality rate for HF in Paraiba and in Brazil followed the LAC trend, whereas the increase in the duration of hospitalization for HF is opposite to the decrease seen in the U.S.. In Paraiba and Brazil, we observed a decrease in admission for HF as primary diagnosis as well as in the absolute in-hospital deaths for HF, agreeing with the LAC and U.S.. More than 87% of the HF deaths in Paraiba and Brazil involved patients older than 60 years old. There was a higher frequency of woman admitted for HF, both in Paraiba and Brazil, with similar mortality rates when compared to men. Since women are generally underrepresented in clinical trials, there is a need for more studies focusing on that population. Hospital-based clinical studies should be performed to identify the causes for the trend of increase in in-hospital mortality rate for HF.

Author contributions

Conception and design of the research: Fernandes ADF; Acquisition of data: Fernandes ADF, Knijnik LM, Fernandes GS; Analysis and interpretation of the data: Fernandes ADF, Fernandes GC, Knijnik LM; Statistical analysis: Fernandes ADF, Fernandes GC, Mazza MR; Writing of the manuscript: Fernandes ADF, Fernandes GC, Mazza MR, Knijnik LM, Fernandes GS; Critical revision of the manuscript for intellectual content: Fernandes ADF, Fernandes GC, Mazza MR, Knijnik LM, Vilela AT, Badiye A, Chaparro SV.

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

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Heart Failure Trends in Paraíba: Earlier Diagnosis or Better Treatment? – That is One of the Questions

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Short Editorial related to the article: A 10-Year Trend Analysis of Heart Failure in the Less Developed Brazil

Heart Failure (HF) is a clinical syndrome with high prevalence, morbidity and mortality worldwide.[1-7] It is also one of the main causes for hospital admissions with elevated direct and indirect costs.[1-7] The prevalence of HF is expected to increase due to the increase in cardiovascular risk factors in the general population and to the increase in life expectancy. Elderly patients are more prone to the development of HF, as well as of admissions for HF. For that reason, an increase in the economic burden of HF is expected in the next decades.[1-7]

Previously published data showed, however, some epidemiological differences according to the world region, when comparing developing and developed countries. Recently published data from the European Society of cardiology Heart Failure Long-term Registry, a registry that included a wide spectrum of countries with very different socio-economic backgrounds, from Southern, Western, Northern and Eastern Europe, as well as Middle East and Northern Africa, showed significant between-region differences in baseline characteristics, clinical characteristics and also treatment and outcomes in patients with acute and chronic HF.[8]

Brazil is a very large country, with huge disparities between regions and thus, it was important to perform a regional study.

The article by Fernandes et al,[9] published in this journal, is a retrospective study on epidemiological data obtained between 2008 and 2017, based on DATASUS database, a population database.[9] They studied data specifically from the state of Paraíba, a region considered by the authors to be a developing state, compared to other parts of Brazil and they put the results into perspective by comparing with them with data from the entire country. Heart failure was the first cardiovascular cause of hospital admissions, both in Paraíba (29.4%) and Brazil (21%). There was a significant 62% decrease in hospital admissions and 37.5% in absolute numbers of hospital mortality due to heart failure in Paraíba, from 2008 to 2017. However, in-hospital mortality rates increased by 65.1%, from 6.6% to 10.9%. An increase in hospital length of stay of 44% was also observed. In absolute values, the authors found a non-significant reduction in death by heart failure, which was however significant when analyzing mortality rate, with a decline of 10.7%, being 14.0/100,000 inhabitants. The same trends were also observed in the general data from Brazil, but the magnitude of change was much higher in Paraíba.

This paper raises many important questions, which should be further addressed in subsequent studies. The reduction in hospital admissions might be the main explanation for the reduction in hospital mortality in absolute values. However, the increase in hospital mortality rate is an indirect sign that patients admitted were probably in worse clinical condition. The greatest improvement in this state, compared to Brazil, might be explained by a more sustained improvement in living conditions in Paraíba in the last decade, compared to others that are more developed and probably did not improve much in the last years, because the potential for improvements is higher in developing states. The authors did not show these specific data – was there a more significant increase in gross domestic product in Paraíba compared to other states?

The European study showed that in North Africa, the proportion of women is higher when compared to other groups, with younger patients, with less hypertension but more diabetes and smokers.[8] The ischemic etiology was much less frequent, ejection fraction was more preserved and patients were less treated.[8] In this registry, 1-year all-cause mortality was 23.6% for acute HF patients and 6.4% for chronic HF patients and 1-year hospitalization was 18.7% and 9.9% respectively. In North Africa, higher all-cause mortality was observed (15.6%) and lower hospitalization rates (10%) in the chronic HF group. Being from North Africa was an independent predictor of all-cause mortality in the acute HF group of up to 2.7 times compared to Southern Europe. The higher death rates observed were partially attributed to the much less frequent use of guideline-recommended medical therapies for HF with reduced ejection fraction, a problem shared by other low- and middle-income countries and regions, or by differences in the hospital admission criteria, also recently reported.[8,10,11] In Brazil, substantial between-region differences are expected regarding demographic characteristics, clinical characteristics and treatment, when we compare developed and developing regions, which can explain some of the results obtained in mortality and hospitalization rates.

For that reason, the results presented for the state of Paraíba require additional information for better interpretation, which in some cases contradict worldwide data projections.[1,2] Few studies have evaluated the different trends in HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), but HFpEF might be

Keywords

Heart Failure/physiopathology; Heart Failure/mortality; Heart Failure/epidemiology; Comorbidity; Heart Failure/trends; Hospitalization; Health Care Costs.

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dominant in the coming years, because in the past 20 years, trends have been reported on the increasing proportion of patients with HFpEF and relatively stable/decreasing rates of HFrEF[2]. In fact, the increase in HF prevalence might not be related to an increase in incidence. The aging of the population, together with improved HF survival, particularly in HFrEF, due to advancements in treatment is a likely explanation.[2] In addition, prevention programs might be reducing the incidence, with lower severity and better treatment of ischemic heart disease.[2] However, risk factors for coronary artery disease are still increasing. Thus, a reduction in HFrEF is expected, as well as an increase in HFpEF with consequent more cases of HF admissions due to HFpEF, with a lower mortality compared to HFrEF.[2]

The reduction in hospital admissions must also be clarified. Information regarding HF disease management program availability or the use of implantable devices (involving patient characteristics but also resource availability and reimbursement structure) can explain that reduction.[1,3] Another possible explanation is that HF patients might be detected earlier in the course of disease, and with that, premature hospital admissions can be avoided. If they are treated according to guidelines, this can also delay and reduce hospital admissions and mortality.[1]

Early diagnosis and optimal treatment are important quality indicators for the treatment of HF, and this is also a question to be addressed. Is the medical assistance in Paraíba significantly different from that in the rest of the country? Is it mostly private practice or a public system of health care? What is patient accessibility to healthcare like and what were the improvements obtained (if any) in the last years? If feasible, all those questions about socio-economic conditions and healthcare data should be analyzed from 2008 to 2017 to see what the trend is and to better identify the main specificities that require investment.

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Quantification of DNA Damage in Different Tissues in Rats with Heart Failure

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Abstract

Background: Chronic heart failure (CHF) is a complex syndrome which comprises structural and functional alterations in the heart in maintaining the adequate blood demand to all tissues. Few investigations sought to evaluate oxidative DNA damage in CHF.

Objective: To quantify the DNA damage using the comet assay in left ventricle (LV), lungs, diaphragm, gastrocnemius and soleus in rats with CHF.

Methods: Twelve male Wistar rats (300 to 330 g) were selected for the study: Sham (n = 6) and CHF (n = 6). The animals underwent myocardial infarction by the ligation of the left coronary artery. After six weeks, the animals were euthanized. It was performed a cell suspension of the tissues. The comet assay was performed to evaluate single and double strand breaks in DNA. Significance level (p) considered < 0.05.

Results: The CHF group showed higher values of left ventricle end-diastolic pressure (LVEDP), pulmonary congestion, cardiac hypertrophy and lower values of maximal positive and negative derivatives of LV pressure, LV systolic pressure (p < 0.05). CHF group showed higher DNA damage (% tail DNA, tail moment and Olive tail moment) compared to Sham (p < 0.001). The tissue with the highest damage was the soleus, compared to LV and gastrocnemius in CHF group (p < 0.05).

Conclusion: Our results indicates that the CHF affects all tissues, both centrally and peripherically, being more affected in skeletal muscle (soleus) and is positively correlated with LV dysfunction. (Arq Bras Cardiol. 2020; 114(2):234-242)

Keywords: Heart Failure; Rats; Rats Inbred Strains; Tissue Distribution; DNA Damage; Comet Assay.

Introduction

Heart failure is a complex syndrome which characterizes structural and functional abnormalities in the heart in maintaining adequate blood demand. Chronic heart failure (CHF) affects approximately 1 to 2% of the population in developed countries and its prevalence increases at least 10% in senior adults.[1] One of the most common causes to heart failure is myocardial infarction (MI), which induces pathologic cardiac remodeling.[2]

This syndrome does not affect only the heart, it also affects other organs, such as lungs and skeletal muscles.[3] CHF is characterized by changes in ventilatory mechanics which impair the uptake and supply of oxygen to the systems. Hypoperfusion, which is sustained with a ventricular dysfunction in a vicious cycle, induces oxidative stress in the majority of tissues.[4] Oxidative stress is a state in which the cell is in an oxidative imbalance, forming more reactive species than its neutralizing capacity.[5] It has been proposed elsewhere that oxidative stress biomarkers, such as concentration of malondialdehyde and uric acid, could enlighten the extent of oxidative damage and guide treatment in patients with CHF.[6]

Since reactive oxygen species (ROS) can damage different biomolecules, such as lipids, proteins and DNA, the damage in nucleic acids has not been consistently investigated in CHF. A biomarker that has already been a target of investigation is the concentration of 8-hydroxy-2'-deoxyguanosine (8-OHdG).[7] However, its measurement mirrors the oxidative damage in one type of DNA lesion, which does not reflect the total damage in the DNA helix. For that, toxicological assays, such as the comet assay, have never been tested in CHF, aiming to assess global DNA damage in different tissues. This technique is broadly used in toxicological studies and is considered to be consistent, sensitive and highly reproductive.[8]

The comet assay directly measures the extent of DNA damage, constituted by single and double DNA strand breaks.[9] This method allows its measurement in blood and all tissues of interest, expanding the analysis of local damage, and its correlation with physiological and functional parameters.[10] In heart failure, it is still not clear how the inability of the failing heart can affect different structures beyond the cardiovascular system, especially on DNA damage. Since in CHF there is a scenario of systemic oxidative damage as a function of the

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chronicity of the syndrome, the objective of this study was to evaluate DNA damage in different tissues, such as left ventricle, lungs and skeletal muscles (diaphragm, gastrocnemius and soleus) in rats affected by the condition.

Methods

Animals

There was a selection of 12 male Wistar rats (100 days old, from 300 to 330 g) from the Animal Breeding Unit of *Universidade Federal de Ciências da Saúde de Porto Alegre* (UFCSPA, Brazil). The animals were housed in groups of three animals per cage, which received food and water *ad libitum* in an specific room maintained at 22°C under a 12:12-hour light-dark cycle.

The handling of the animals obeyed Law No. 11.794 of 10/08/2008, Law No. 6.899 of 07/15/2009, and Resolution Nº. 879 of 02/15/2008 (CFMV), as well as other provisions applicable to the use of animals for research. The experiment complied with resolutions of the National Council on Animal Experimentation, the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy of Sciences, Washington, D.C., 1996), as well as of the Ethical Principles in Animal Experimentation of the National Animal Experimentation Control Council (CONCEA). This study was approved by CEUA/UFCSPA, under protocol number 114/13.

Induction of Myocardial Infarction (MI)

The animals were anesthetized with xylazine (12 mg/kg ip) and ketamine (90 mg/kg ip), intubated and artificially ventilated. The ligation of the left coronary artery was performed. Sham operations were performed as described elsewhere.[11] After the surgeries, the animals received one injection of cetoprophane (5.4 mg/kg ip) every 6 hours – completing 48 hours – and penicillin (70,000 units/ml ip). The surgeries were performed by one surgeon. Post-surgery mortality rate was 15%. After MI induction, 6 weeks of recovery were designated, which was necessary for the animals to develop CHF. In order to document the animals that developed heart failure, we used different variables to characterize this syndrome, such as the presence of left atrial trombi, thoracic effusions, pulmonary congestion, left and right ventricular hypertrophy to body weight.[12]

Heart Failure Condition

Those animals that presented left ventricular-end diastolic pressure (LVEDP) higher than 15.0 mmHg, as well as increased right ventricle weight to body weight ratio (> 0.8 mg/g) and the presence of pulmonary congestion were considered positive to CHF.[12–14]

Hemodynamic Evaluation

After the sixth week, the animals were anesthetized with xylazine (12 mg/kg i.p.) and ketamine (90 mg/kg i.p.). A polyethylene catheter (PE-50) was placed into the right carotid artery. Arterial pressure was recorded and the catheter was positioned into the left ventricle to perform ventricular pressure recording. Data were registered by a pressure transducer (strain-gauge, Narco Biosystem Miniature Pulse Transducer RP-155, Houston, Texas, USA), coupled to a pressure amplifier. Pressure analogical signals were digitalized by a data acquisiton system (CODAS-Data Acquisition System, Akron, Ohio, USA) with a sampling rate of 2,000 Hz. These data were used to determine diastolic blood pressure (DBP), systolic blood pressure (SBP), mean blood pressure (MBP), heart rate (HR), left ventricular systolic pressure (LVSP), LVEDP and left ventricular maximum positive and negative dP/dt (+dP/dt_{max}, -dP/dt_{max}), as previously described.[15] Animals that presented LVEDP higher than 15 mmHg in hemodynamic evaluation were considered with left ventricular dysfunction.[13]

Tissue Collection

The animals were euthanized through intravenous infusion overdose of the anesthetic pentobarbital (80 mg/kg i.p.).[16] After that, the lungs, the diaphragm, the right gastrocnemius, the right soleus and the heart were removed. The left ventricle was separated from the right one for the comet assay. All samples were stored at -80°C for posterior analysis.

Determination of Infarct Size, Cardiac Hypertrophy and Pulmonary and Hepatic Congestion

The hearts were removed and weighted, without blood within the chamber and without atria. The size of the infarct area was determined by planimetry.[17] To evaluate cardiac hypertrophy, organ mass was expressed as a proportion of body mass (tissue mass/body mass - mg/g).[18] Animals with right ventricle hypertrophy (i.e. right ventricle mass-to-body weight ratio > 0.80 mg/g) were considered as rats that developed heart failure.[12] To determine pulmonary and hepatic congestion, the lungs and liver of each animal were removed, weighted and dehydrated (80°C) for 48 hours, and then weighted again to evaluate water percentage.

Single Cell Gel Electrophoresis (SCGE)

Single Cell Gel Electrophoresis (SCGE) was performed in alkaline conditions (pH > 13.0).[19] All procedures were performed avoiding any direct incidence of light. For the assay, a cell suspension of the tissue (left ventricle, lungs, diaphragm, right gastrocnemius and right soleus) was primarily carried out in PBS buffer (pH = 7.40) with standard and gentle manual homogenization. This step required the observation of the density of cells that would be used in each slide. Neubauer's chamber was used to count approximately 7.3 x 10^5 cells/slide.

The suspension of cells (40 μl) was added to agarose of low melting point (90 μl). After gently mixed, this material was carefully superimposed over a slide previously covered with a thin agarose gel layer with a coverslip, and kept in a humid chamber at 4°C for 10 minutes, in order to further secure the suspension of tissue cells in the gel. Then, the coverslip was carefully removed and the slide was conditioned in a vertical cuvette containing lysis solution for at least 1 hour at 4°C.

The following step consisted in the unfolding of the cells, for 30 minutes in an alkaline buffer (pH > 10.0). Thereafter, it was followed by the process of electrophoresis, where lysed cells contained in the agarose gel were subjected to a voltage

of 25 mV and 300 mA for 15 minutes in alkaline buffer solution (pH > 10.0). Then the plate was neutralized, stained with silver nitrate, rinsed and kept at room temperature to dry for later analysis. The slides of each animal were made in duplicate and a positive control of DNA damage with hydrogen peroxide (30 μl/slide). The analysis was conducted under an optical microscope with a 20x increase by quantifying the size of the comet's tail in 50 to 100 cells, according to the lengths, diameters, radii and dimensions of individual comets. Percentages of tail DNA, tail moment and Olive tail moment were used as damage quantification parameters.

Quantification of DNA Damage

All the parameters presented in the results session regarding SCGE were calculated by the software CASP (CASP Labs®, Poland).[20] The percentage of DNA in the tail, tail moment and Olive tail moment formulas are available for consultation in the supplementary data. Tail moment is characterized as the product of tail length and the percentage of DNA in the tail. The Olive tail moment, which is another parameter for DNA damage, comprises the product of the distance (relative to the x-axis) between the center of gravity of the head with the center of gravity of the tail of the comet and the percentage of tail DNA.

Sample Size and Statistical Analysis

For a minimum difference of 23 arbitrary units of tail moment of ± 4 SD, it was possible to determine minimum statistical difference of two groups with three animals each.[21] In our investigation, we decided to use six animals in each group. Data are presented in mean ± SD. The normality test of Shapiro-Wilk was used to assess variables distribution. For comparisons between groups, an unpaired Student's t test and a two-way analysis of variance were performed among different tissues with a Tukey's post hoc test. A significance of 5%was considered. Statistical analysis was carried out by using SigmaPlot, version 12.0 for Windows, and graphics were created by GraphPad Prism, version 5.0 for Windows.

Results

Morphological Parameters

The animals showed no difference regarding neither initial nor final body mass. Animals submitted to MI showed mean infarction area of 36%. It was possible to observe higher ratio of myocardial mass, right ventricle and left ventricle-to-body mass compared to sham group, indicating cardiac remodeling in both ventricles. Regarding the congestion in the lungs and liver, higher rates of the former were only observed in the CHF group (Table 1).

Hemodynamic Parameters

When compared to the sham group, lower mean blood pressure was observed in the CHF group. SBP and DBP, as well as HR showed no difference in relation to the control group (Table 2). Regarding ventricular pressure variables, LVSP and higher LVEDP was observed in the CHF group, when compared to the sham one (Table 2).

The maximal positive derivative of ventricular pressure ($+dP/dt_{max}$) showed alterations in the CHF group, presenting lower values, as well as maximal negative derivative of ventricular pressure ($-dP/dt_{max}$), which showed lower values when compared to the control group (Table 2).

DNA Damage Parameters

Higher values of DNA damage were observed in all variables (% tail DNA, tail moment and Olive tail moment) in the CHF group, in all analyzed tissues (Table 3). DNA damage can be observed in the formation and frequency of comets in left ventricle, pulmonary, diaphragmatic, gastrocnemius and soleus cells (Figure 1).

Despite DNA damage being remarkably higher in CHF rats in all tissues when compared to other tissues in the same pathologic condition, it was observed higher damage in soleus compared to gastrocnemius and left ventricle in CHF group. The difference between tissue DNA damage in sham-operated animals and CHF ones can be observed in Figure 2.

Table 1 – Body mass, morphometric cardiac characteristics, infarcted area and pulmonary and hepatic congestion of sham-operated rats and rats with left ventricular dysfunction

Variables	Sham	CHF
Initial Body Mass (g)	330.25 ± 17.24	328.29 ± 18.12
Final Body Mass (g)	400.50 ± 29.61	356.38 ± 32.23
Infarcted Area (%)	---	36.39 ± 8.11
MM/BM (mg/g)	2.56 ± 0.08	3.29 ± 0.46*
LV/BM (mg/g)	1.88 ± 0.21	2.36 ± 0.47*
RV/BM (mg/g)	0.58 ± 0.12	1.40 ± 1.01*
Pulmonary Congestion (%)	65.67 ± 9.34	87.31 ± 3.36*
Hepatic Congestion (%)	70.46 ± 1.05	71.43 ± 1.07

*Values are presented in mean ± SD; n = 6 for all groups. Sham, sham-operated rats; CHF: Chronic heart failure rats; MM/BM: Myocardial mass-to-body mass ratio; LV/BM: left ventricle mass-to-body mass ratio; RV/BM: right ventricle mass-to-body mass ratio. * p < 0.05 compared to the Sham group.*

Table 2 – Mean, diastolic and systolic blood pressure, left ventricle end diastolic pressure, left ventricle systolic pressure and left ventricular maximum/minimum change over time of sham-operated rats and rats with left ventricular dysfunction

Variables	Sham	CHF
MBP (mmHg)	93.01 ± 14.70	76.78 ± 5.83*
DBP (mmHg)	73.54 ± 16.28	67.54 ± 7.15
SBP (mmHg)	99.75 ± 20.91	85.93 ± 5.51
Heart Rate (bpm)	253.56 ± 70.84	245.19 ± 57.69
LVEDP (mmHg)	5.40 ± 2.26	32.55 ± 5.32*
LVSP (mmHg)	104.24 ± 6.03	89.15 ± 3.15*
+ dP/dt_{max} (mmHg/s)	6,264.33 ± 1,566.47	4,281.63 ± 708.75*
- dP/dt_{max} (mmHg/s)	5,209.63 ± 1,274.09	2,823.80 ± 540.65*

*Values are presented in mean ± SD; n = 6 for all groups. Sham, sham-operated rats; CHF: Chronic heart failure rats; MBP: Mean blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; LVEDP: left ventricular end-diastolic pressure; LVSP: left ventricular systolic pressure; +dP/dt_{max}: Maximal positive derivative of ventricular pressure; -dP/dt_{max}: maximal negative derivative of ventricular pressure. * p < 0.05 compared to the Sham group.*

Table 3 – DNA quantification in different tissues of sham-operated animals and rats with chronic heart failure

	Sham			CHF		
	% Tail DNA	Tail Moment	Olive Tail Moment	% Tail DNA	Tail Moment	Olive Tail Moment
Left Ventricle	7.65 ± 3.35	0.77 ± 0.44	1.37 ± 0.59	33.29 ± 7.70*	10.51 ± 3.31*	7.04 ± 1.71*
Lungs	17.86 ± 3.93	6.76 ± 2.59	7.31 ± 2.15	36.20 ± 5.17*	23.30 ± 7.25*	19.10 ± 4.65*
Diaphragm	6.86 ± 2.63	1.40 ± 0.93	1.82 ± 0.79	41.23 ± 13.86*	14.06 ± 6.51*	9.82 ± 3.03*
Gastrocnemius	7.63 ± 4.66	1.04 ± 0.88	1.43 ± 0.70	28.07 ± 15.53*	8.69 ± 5.14*	6.17 ± 3.53*
Soleus	11.54 ± 2.46	1.53 ± 0.96	1.84 ± 0.76	55.79 ± 11.53*	20.90 ± 5.32*	12.83 ± 3.68*

*Values are presented in mean ± SD; n = 6 for all groups. Sham, sham-operated rats; CHF: Chronic heart failure rats. * = p < 0.01 versus Sham in relation to the variable and its corresponding tissue.*

Discussion

Although there are some investigations using the comet assay in CHF, to the best of our knowledge, this is the first study to report the total extent of DNA damage in different tissues in an experimental model of CHF. The major finding of this investigation is the reproducibility and applicability of SCGE in the MI experimental model. Animals with CHF demonstrated higher extent of DNA damage than the control group in heart, lungs, diaphragm and skeletal muscles. This finding supports the main hypothesis that CHF affects the stability of DNA not locally, but systemically.

Since CHF is a complex syndrome, it is essential to investigate the extent of damage that the hypoperfusion may promote. We showed an *in vivo* model of CHF whose damage was ranging from two- to six-fold higher than in the absence of heart failure. The animals of this study demonstrated traditional alterations observable in the ligation of the left coronary artery model of heart failure in rats.[22,23] Mean LVEDP above 30 mmHg was observed, which characterizes ventricular dysfunction.[14] Also, traditional hemodynamic alterations were observed in animals with CHF, such as lower LVSP, and maximum positive and negative derivatives of ventricular pressure. Morphological parameters also showed meaningful alterations in left and right ventricle hypertrophy, as well as pulmonary congestion. All these parameters (hemodynamic and morphological) characterize the presence of CHF.[12,24,25]

The SCGE method performed in alkaline conditions allows the evaluation of global DNA damage. The damage observed in the comets is formed by single and double strand breaks that are unattached from the chromatin, in DNA fragments.[10] The evaluation of 8-OHdG in patients with CHF has been recently proposed. The 8-OHdG is an oxidized purine base, one of the most frequent oxidative products of DNA.[26] Most of the lesions in DNA may be manifested in single and double strand breaks, not only in oxidative by-products. Reactive oxygen species may damage DNA and form oxidative bases, such as 8-OHdG, 5-hydroxyuracil, 2-hydroxyadenine and 4,6-diamino-5-formamidopyridine.

Some caveats should be made before comparing results measured by nuclear DNA damage, as in our study, to results obtained in concentrations of oxidized purine base. The DNA damage measured by the comet assay reflects the overall damage, other than the 8-OHdG measurement that cannot assert the same.[27]

A recent meta-analysis demonstrated that eight studies evaluated the oxidative DNA damage to the specific DNA lesion of 8-OHdG. All investigations demonstrated higher

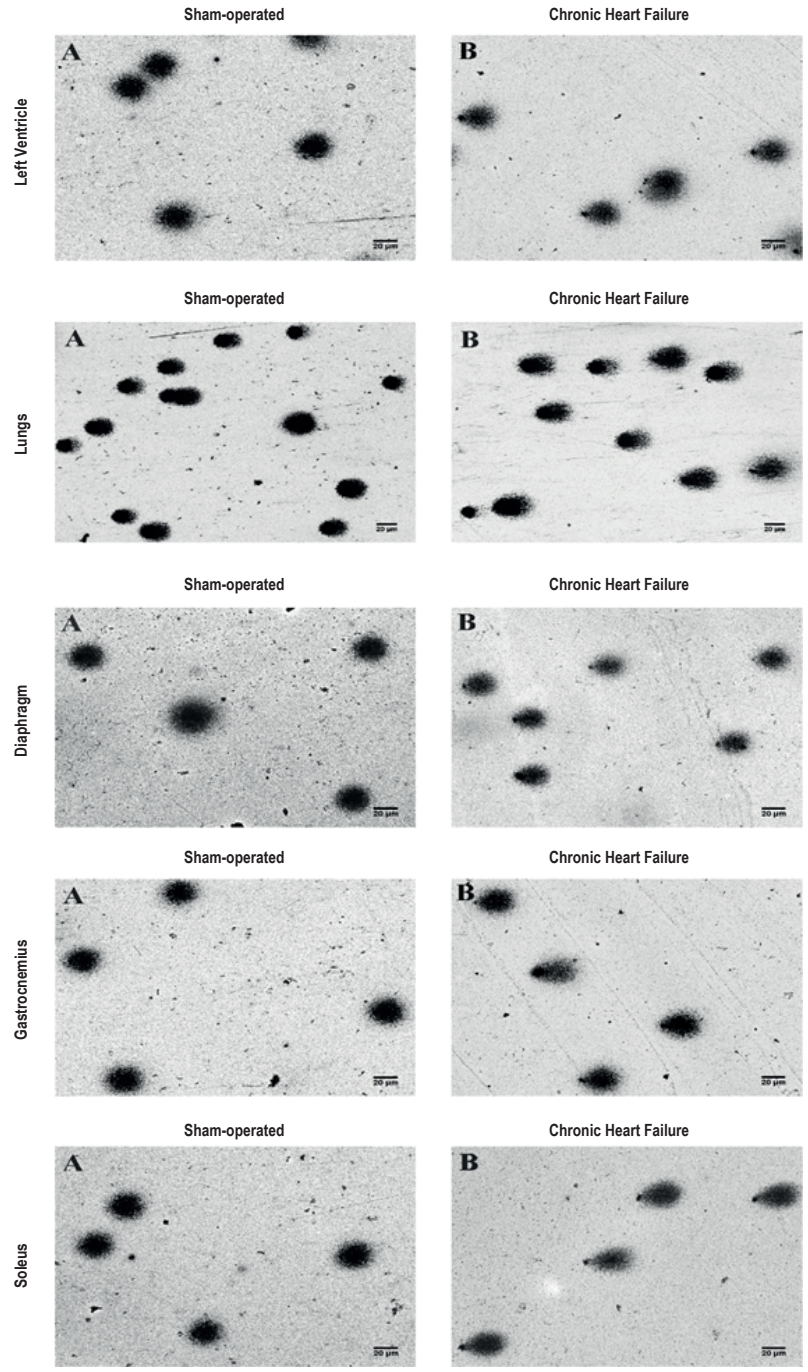

Figure 1 – *Image of cells submitted to SCGE (comet assay) of left ventricle, lungs, diaphragm, gastrocnemius and soleus of Sham-operated and rats with CHF. Panel A: Isolated cells of the respective tissue of Sham-operated rat. Panel B: Isolated cells of the respective tissue of rat with MI-induced CHF. Slides stained with silver nitrate. The image shows no formation of comets in Panel A, but in Panel B the image shows the formation of comets with distinct tails. The length of the tail represents the single strand and double strand breaks of nuclear DNA (magnification of 20x, scale bar of 20 µm).*

concentrations of 8-OHdG in CHF patients.[28] The rationale for higher concentrations of DNA oxidative products indicates that the higher extent of genotoxic damage is highly contributed to the oxidation of mitochondrial DNA.[29] Cardiac myocytes present the highest content of mitochondria, which could indicate higher formation of ROS and contribute significantly to mitochondrial dysfunction. This study did not quantify the concentration of 8-OHdG, however we considered DNA damage that is widely used in order to evaluate DNA strand breaks. The study by Jaenisch et al.,[30] also developed by our

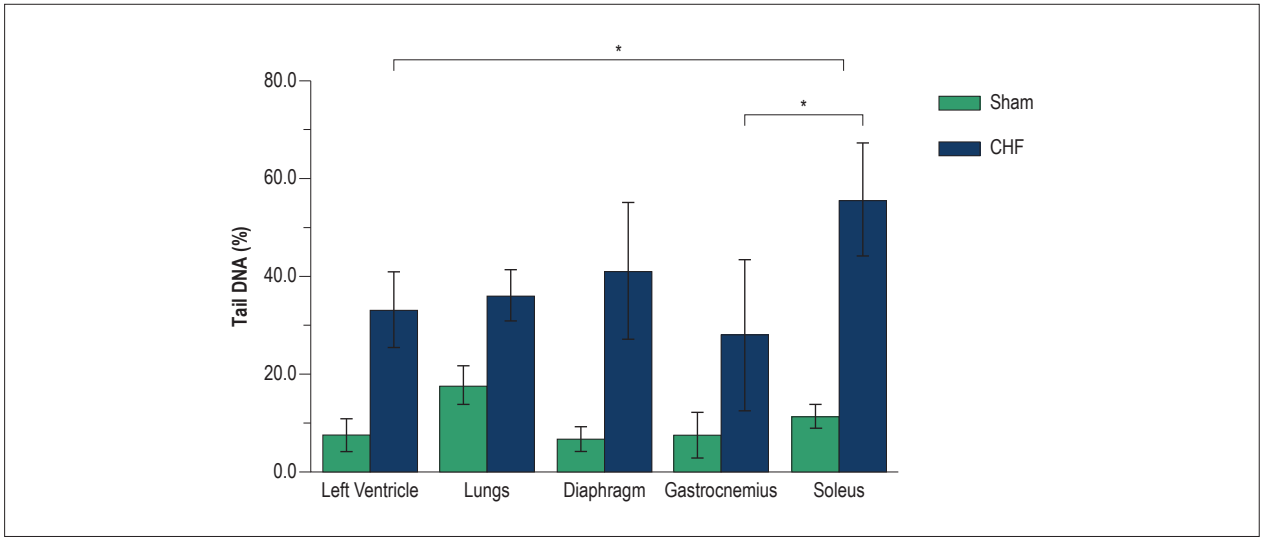

Figure 2 – *DNA damage in different tissues, according to % tail DNA, induced by CHF. Quantification of DNA damage in isolated cells of left ventricle, lungs, diaphragm, gastrocnemius and soleus muscles in Sham-operated rats and rats with CHF. Sham (n = 6), CHF (n = 6). Two-way ANOVA, with post-hoc test of Tukey. * p < 0.05 vs. Soleus.*

laboratory, used the same method of assessing DNA damage (alkaline version of the comet assay) in animals with CHF submitted to respiratory muscle training. Regarding the extent of DNA damage of Sham rats compared to rats with CHF, the percentage of DNA in the comet tail was relatively similar to the results obtained in the investigation on diaphragm cells.[30]

One interesting finding of this study was higher DNA damage in soleus cells than in left ventricle ones, which supports the fact that, after MI, the ventricle functionally and morphologically adapts and the peripheral muscle suffers histological and biochemical alterations.[31,32] The acute phase of MI is characterized by the necrosis of cardiac myocytes, which expands the area of necrosis of the left ventricle in the following hours, affecting adjacent structures.[33] In this phase of MI, the extent of DNA damage is probably higher than in any other tissue, as can be observed in pro-inflammatory cytokines and autophagic mediators.[34,35]

Since cardiomyocytes have a renewal rate of approximately 1% in young people, and about 0.45% in elderly,[36] this fact reinforce our findings regarding the difference of DNA damage among the tissues of CHF rats. The left ventricle shows high adaptability to modify its geometry, and ability to repair major oxidative products of DNA. It has been demonstrated that the main problem of CHF is not the central alterations in the heart, but it also affects, indirectly, all other organs.[37] The complexity of the CHF scenario, such as cardiac remodeling, changes in ventilatory mechanics and hemodynamics, and systemic pro-inflammatory state leads to the formation of free radicals of different ways. This critical dysfunctional status establishes an oxidative stress condition in different organs and systems.[38,39]

We hypothesized that skeletal muscle cells would have higher DNA damage in CHF.[40,41] For this reason, we chose to analyze two different skeletal muscles (soleus and gastrocnemius muscles) by their different fiber type proportions in rats with CHF. The skeletal muscle in CHF is highly affected by the hypoperfusion which augments the oxidative damage within, especially in the mitochondria.[42] Since the skeletal muscle is target of oxidative damage, it was expected to have higher damage observed in our findings. In CHF, the antioxidant defense system in skeletal muscles might be constantly decreased over time.[43] The oxidative damage observed in the soleus muscle is very likely to be explained by its morphological characteristic (e.g. higher number of capillaries per fiber, predominance of type I fibers, greater activity of aerobic metabolism).[44,45] On the other hand, the gastrocnemius muscle presents morphology of mixed characteristics with a more balanced percentage distribution in relation to the type of fibers; therefore, less dependence of aerobic metabolism. For this reason, we imagine that it presented less DNA damage than the soleus muscle.

Antioxidant machinery changes over time in the cell cycle (e.g.: myogenic proliferation and differentiation) demonstrating to have more expression of antioxidant enzymes activity in myoblasts than in myotubes, thus increasing the probability of mortality under oxidative stress.[5] This phenomenon is interesting, since the disuse of skeletal muscles due to exercise intolerance is common in patients with CHF, in addition to being related to diminished antioxidant-stimulating trigger signaling of muscle contraction.[46] Compared to the left ventricle, the soleus muscle does not have the same ability for adaptation, which may explain why the DNA damage was higher.

Limitations

This work shows few limitations, such as the absence of DNA damage evaluation in other tissues (liver, encephalic structures and other skeletal muscles). Another limitation that may enrich our findings is the measurement of mutagenesis. Evaluating the mutagenesis of the CHF, along with the SCGE,

might lead to a more robust scenario of DNA damage and its lack of repair of DNA lesions. Our design aims to evaluate the longitudinal damage that the experimental model of CHF might lead to and its differences regarding tissues; thus, the ability of DNA to repair its lesions could not be carried out.

Conclusion

Our results show DNA damage using SCGE in the CHF experimental model by MI. The left ventricle dysfunction clearly affects the cardiac tissue, lungs, diaphragm, gastrocnemius and soleus and was associated with the extent of DNA damage, affecting the soleus muscle more than the left ventricle and the gastrocnemius. The comet assay was proven to be a reliable tool for quantifying DNA damage in different tissues of animals with CHF and the soleus muscle was shown to be more affected by the heart failure than the left ventricle and the gastrocnemius.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Stefani GP, Nunes RB, Rossato DD, Hentschke VS, Di Domenico M, Dal Lago P, Rhoden CR; Statistical analysis: Stefani GP, Nunes RB, Rossato DD, Hentschke VS, Dal Lago P.

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 CEUA/UFCSPA under the protocol number 114/13. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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DNA Damage in Chronic Heart Failure: Consequences Beyond those in the Heart

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Short Editorial related to the article: Quantification of DNA Damage in Different Tissues in Rats with Heart Failure

Chronic heart failure (CHF) affects approximately 1% to 2% of the population of developed countries and its prevalence increases approximately 1% in individuals aged 55 to 64 years and up to 17.4% in individuals aged 85 years and over.[1,2] CHF is a complex disease with multiple causes and myocardial infarction (MI) is the most common cause. It is characterized by structural or functional cardiac alterations, affecting the ventilatory mechanics that impairs the oxygen uptake and supply to the systems, inducing oxidative stress.[2]

Oxidative stress, also currently called redox imbalance,[3] is known to be associated with the development of several pathologies, either as a trigger or consequence. The biological system of redox reactions may break out of its equilibrium status when the formation of oxidizing species overcomes the antioxidant defense. This scenario favors the oxidation of biomolecules (lipids, proteins, DNA) resulting in their structural and functional damage, that is, contributing to significant pathological outcomes.[4]

The research published in this issue of the *Arquivos Brasileiros de Cardiologia* aimed at evaluating DNA damage in different tissues, such as the left ventricle, lungs and skeletal muscles (diaphragm, gastrocnemius and soleus) in rats submitted to MI to induce CHF.[5] The authors' interest in assessing the influence of this pathology on other tissues is very relevant, as it shows the consequences of this condition on organs other than the heart. The indicator evaluated in this study was the DNA, a biomolecule vulnerable to several agents that can cause damage.[6] Under normal conditions, approximately 99% of DNA damage can be repaired, but approximately 1% can remain in the cell genome.[7] Unrepaired DNA damage can result in loss of genetic information, or interference with transcription and replication, therefore being deleterious to the organism.[6] Another important aspect is that DNA damage may induce mutations[8,9] that may be linked to several diseases, including cancer.[10] Thus, DNA damage detection is an important element in studies related to disease development.

The study shows that DNA damage was remarkably higher in all organs evaluated in the CHF group, probably justified by the hyperfusion at these sites, which generated a prooxidative state that is toxic to this biomolecule. Although this study analyzed global DNA damage, which may be generated for reasons other than oxidative ones, human studies have already shown the presence of O8-OHdG, a product generated by purine oxidation, in the plasma of patients with CHF, confirming that this disease causes oxidative DNA damage.

Therefore, the results of the present study confirm that there are consequences in different organs resulting from CHF and that investigations should be carried out to minimize future complications.

Keywords

DNA/genetics; Heart Failure/physiopathology; Myocardial Infarction; Tissue Distribution; Oxidative Stress; Rats Inbread.

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Long-Term Mortality in Cardioinhibitory Carotid Sinus Hypersensitivity Patient Cohort

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Abstract

Background: Cardioinhibitory carotid sinus hypersensitivity (CICSH) is defined as ventricular asystole ≥ 3 seconds in response to 5–10 seconds of carotid sinus massage (CSM). There is a common concern that a prolonged asystole episode could lead to death directly from bradycardia or as a consequence of serious trauma, brain injury or pause-dependent ventricular arrhythmias.

Objective: To describe total mortality, cardiovascular mortality and trauma-related mortality of a cohort of CICSH patients, and to compare those mortalities with those found in a non-CICSH patient cohort.

Methods: In 2006, 502 patients ≥ 50 years of age were submitted to CSM. Fifty-two patients (10,4%) were identified with CICSH. Survival of this cohort was compared with that of another cohort of 408 non-CICSH patients using Kaplan-Meier curves. Cox regression was used to examine the relation between CICSH and mortality. The level of statistical significance was set at 0.05.

Results: After a maximum follow-up of 11.6 years, 29 of the 52 CICSH patients (55.8%) were dead. Cardiovascular mortality, trauma-related mortality and the total mortality rate of this population were not statistically different from that found in 408 patients without CICSH. (Total mortality of CICSH patients 55.8% vs. 49,3% of non-CICSH patients; p: 0.38).

Conclusion: At the end of follow-up, the 52 CICSH patient cohort had total mortality, cardiovascular mortality and trauma-related mortality similar to that found in 408 patients without CICSH. (Arq Bras Cardiol. 2020; 114(2):245-253)

Keywords: Carotid Sinus,Massage/mortality; Bradycardia; Syncope; Cardiac Pacing, Artificial.

Introduction

Carotid sinus hypersensitivity (CSH) is characterized by ventricular asystole ≥3 seconds, known as cardioinhibitory carotid sinus hypersensitivity (CICSH) or systolic blood pressure fall ≥50 mmHg (vasodepressor carotid sinus hypersensitivity) in response to 5–10 seconds of carotid sinus massage (CSM).[1,2] Epidemiologic studies of patients >40 years old have shown that this population have a high prevalence of CSH (10–50%).[3,4] This prevalence is even higher among men and in patients with atherosclerosis.[3,4]

Carotid sinus hypersensitivity can be present with or without spontaneous symptoms.[1] On the other hand, diagnosis of carotid sinus syncope (CSS) requires the presence of vasodepressor or CICSH and syncope.[1,5] Carotid sinus syncope is considered one of the most frequent causes of syncope in the elderly.[6] Treatment is generally indicated for CSS patients to reduce recurrence of symptoms.[1,2] The concern that a prolonged asystole episode could lead to serious trauma, brain injury, pause-dependent ventricular arrhythmias and death is also used to justify treatment.[5,7] The main objective of present study is to describe the long-term mortality rate of a cohort of CICSH patients. Secondly, it compares total mortality, cardiovascular mortality, mortality due to ischemic heart disease and trauma-related mortality of this patient cohort with that of a cohort of patients without CICSH.

Methods

In 2006, in the first phase of the present study, 502 patients were randomly selected among 1,686 outpatients ≥50 years of age referred to electrocardiography in a public general hospital in Rio de Janeiro, Brazil.[8] These 502 patients were submitted to CSM, 52 (10,4%) were identified with CICSH (ventricular asystole ≥3) and, in 450, cardioinhibitory reflex was absent. In all cases, CSM was performed in the supine position, initially on the right side, then on the left side for 10 seconds by a single investigator. More patient selection details and more information about CSM can be found in a previous article.[8]

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In the present phase of the study, the 502 patients submitted to CSM in 2006 were divided into groups. The first group was formed by the 52 CICSH patients and, for comparison purposes, a second group of 450 patients without CICSH was studied. Survival data was assessed through active follow-up and review of Rio de Janeiro deaths database and the Rio de Janeiro medical admissions database. In the latter, we have searched for all patients who had permanent a pacemaker paid by the state government of Rio de Janeiro. In all cases, we have considered the cause of death described in Rio de Janeiro deaths database. Cardiovascular deaths were those registered under chapter IX of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10); ischemic heart disease deaths were those registered under ICD-10 codes I20 – I25, and trauma related deaths were those registered under ICD codes S00 – T14, T66 – T98, V01 – V29, V80 – V94, V98 – W19, W65 – W74, Y85 – Y89.

Ethical approval

The protocol was approved by the local ethics committee (approval statement number 2.383.341) conforming to the standards of the Brazilian National Committee of Research Ethics (resolution 466/2012).

Statistical analysis

All data were analyzed using the R Core Team (2018) software. The Shapiro-Wilk test was used to verify the normality of the data. Normally distributed continuous data are shown as mean and standard deviation and the differences between the two groups are compared using unpaired Student's t-test. Categorical data are presented as absolute and relative frequencies and are compared using χ^2 or Fisher's exact tests as appropriate. The level of statistical significance was set at 0.05.

Time to event was defined as the time between the date of CSM and death or end of the study; December 31, 2017. The time to event was analyzed using the Kaplan-Meier survival curves, which were compared using the log-rank test. Risk factors associated with mortality were analyzed using the Cox regression analysis. Two models were created, the first adjusted by sex, age and presence of atherosclerosis; the second model made additional adjustments for smoking history, history of hypertension, diabetes and dyslipidemia.

Results

Patients' characteristics

In the first phase of the study, 52 CICSH patients were identified among the 502 patients submitted to CSM.[8] Only 7 of the 52 CICSH patients had a history of syncope and 40 of them used negative chronotropic drugs. Those 52 patients were advised to avoid inadvertent stimulation of the carotid sinus and, in 12, the dosage of negative chronotropic drugs was reduced. At that time, none of the 52 patients has been submitted to permanent pacemaker implantation.

The baseline characteristics of the patients with and without CICSH are presented in table 1. Patients with CICSH were more likely to be male and had higher prevalence of structural heart disease and atherosclerosis.

Follow-up of the 52 CICSH patients

Twenty-seven of the 52 CICSH patients were actively followed up. At the end of the study, none of them had been submitted to permanent pacemaker implantation, 19 were alive and 8 had died. Data about the remaining 25 patients were retrieved at Rio de Janeiro databases of death and medical admissions. Twenty-one of those were dead and 4 were alive. None of those patients had been submitted to permanent pacemaker implantation.

Overall, 29 of the 52 patients (55.8%) identified with CICSH had died at the end of the study (maximum follow up time of 11,6 years). Figure 1

Furthermore, the mortality rate of the 7 CICSH patients with history of syncope was 57,1%. This mortality rate was similar to that found in the 45 CICSH patients that did not have this symptom (55,5%).

Follow-up of patients without CICSH

We could not find any information in 42 of the 450 patients without CICSH. One hundred and two patients were actively followed up. Data about the remaining 306 patients without CICSH were retrieved at Rio de Janeiro databases of death and medical admissions. Overall, 201 of the 408 patients without CICSH were dead (49.3%) at the end of follow-up, none had been submitted to permanent pacemaker implantation. One of the 207 patients that was alive at the end of follow-up had been submitted to permanent pacemaker implantation due do complete AV block.

Patients with and without CICSH — Endpoint comparisons

Figure 1 outlines the study design and compares the death rate of patients with and without CICSH.

Figure 2 shows the distribution of responses to right and left CSM in patients who died during follow-up and in patients who were alive at the end of the study. Median duration of RR intervals observed during CSM were similar in both groups of patients.

Table 2 compares the total mortality, cardiovascular mortality, mortality due to ischemic heart disease and trauma-related mortality of the 52 CICSH patients with the 408 patients without CICSH. Survival curves are presented in figure 3. The total mortality rate of the 52 CICSH patients was 21.1% at 5 years and 51.9% at 10 years, with median survival time of 10.0 years (95% CI: 7.4 – 12.6 years). The survival curves of patients with and without CICSH were similar without any significant statistical difference. Both Cox regression models failed to reveal any association between CICSH and mortality. In both models, age at the time of CSM, and presence of atherosclerosis were independently associated with mortality. (Table 3)

Table 1 – Baseline characteristics of the patients with and without CICSH

	42 patients lost to follow-up (without CICSH)	408 patients without CICSH	52 CICSH patients	52 CICSH x 408 without CICSH P value. OR (95% CI)
Male sex	14/42 (33.3%)	206/408 (50.5%)	39/52 (75.0%)	0.001 OR: 2.94 (1.52–5.67)
Age (mean ± SD)	65.4 ± 10.4	64.93 ± 9.74	66.31 ± 8.15	0.33
Age ≥ 65 years	20/42 (47.6%)	203/408 (49.8%)	31/52 (59.6%)	0.18
Heart rate before CSM (mean ± SD)	68.6 ± 13.6	68.7 ± 14.19	62.4 ± 15.6	0.003
Unexplained falls or syncope in the year preceding CSM	8/42 (19.0%)	56/408 (13.7%)	7/52 (13.5%)	0.95
Structural heart disease	19/42 (45.2%)	277/408 (67.9%)	46/52 (88.5%)	0.002 OR: 3.62 (1.51–8.70)
Atherosclerosis	18/42 (42.8%)	198/408 (48.5%)	37/52 (71.2%)	0.002 OR: 2.61 (1.39-4.91)
History of AMI	10/42 (23.8%)	128/408 (31.4%)	28/52 (53.8%)	0.001 OR: 2.55 (1.42-4.58)
Previous myocardial revascularization	5/42 (11.9%)	88/408 (21.6%)	20/52 (38.5%)	0.007 OR: 2.27 (1.23-4.17)
Previous CABG	2/42 (4.8%)	58/408 (14.2%)	16/52 (30.8%)	0.002 OR: 2.68 (1.40-5.14)
Previous PCI	3/42 (7.1%)	30/408 (7.4%)	4/52 (7.7%)	0.93
Atrial fibrillation	2/42 (4.8%)	20/408 (4.9%)	2/52 (3.8%)	0.73
Normal ECG	13/42 (31%)	112/408 (27.5%)	8/52 (15.4%)	0.06
Negative chronotropic drug use	28/42 (66.6%)	235/408 (57.6%)	40/52 (76.9%)	0.007 OR: 2.45 (1.25-4.18)
Hypertension	29/42 (23.8%)	311/408 (76.2%)	40/52 (76.9%)	0.91
Diabetes	10/42 (26.2%)	93/408 (22.8%)	14/52 (26.9%)	0.51
Dyslipidemia	20/42 (47.6%)	215/408 (52.7%)	35/52 (67.3%)	0.046 OR: 1.84 (1.00-3.40)
Smoking	7/42 (16.7%)	41/408 (10%)	10/52 (19.2%)	0.047 OR: 2.13 (0.99-4.56)

CICSH: cardioinhibitory carotid sinus hypersensitivity; OR: Odds ratio; CSM: carotid sinus massage; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PCI: Percutaneous coronary artery intervention.

Discussion

This study demonstrates, for the first time out of the European continent, that the mortality rate of patients with CICSH is similar to that found in a population without CICSH. Median survival of the 52 CICSH patients was 10.0 years (95% CI: 7.4 – 12.6 years). Cardiovascular mortality and trauma-related mortality, important endpoints in patients with prolonged asystole episodes, were also similar in both cohorts. These results are analogous to that described by Hampton et al.[9] Those authors did not find any association between the presence of CICSH and survival in a cohort of 1,504 English patients with CSH (median age 77 years, 59% female).[9] In that cohort, the median survival of CICSH patients was 8 years (95% CI: 7.3 – 8.7 years).[9] That survival was inferior to the one observed in the 52 CICSH patients described in the present study, but was not different to that found in English elderlies with CSH and pure vasodepressor response (median survival of 7 years; 95% CI: 6.4 – 7.4 years).[9] In the same study, Hampton et al.[9] described that the total mortality, cardiac mortality, stroke and trauma-related mortality of the CSH cohort were not different from that found in sex- and age-matched English patients without CSH.[9]

In another European study, the natural history of 262 patients with carotid sinus syncope was described by Brignolle et al.[10] Eighty-nine patients (34%) died after 46 ± 23 months of follow-up.[10] This high mortality rate was ascribed to the advanced age of the population and to the presence of important comorbidities.[10] Similar finding were published by Sutton et al.,[7] and by Claesson et al.[11] Sutton et al.[7] reported a 36% mortality rate during 5 years of follow-up.[7] Claesson et al.[11] surveyed 106 CSH patients (64 with CICSH). After a median follow-up time of 8.6 ± 2.1 years, the mortality rate of the 106 CSH patients was not significantly different from that found in 166 patients without CSH (32% x 22%; p = 0.073).[11]

Hence, until now, no one has been able to prove the presence of any independent relation between the presence of CICSH and mortality. All of these studies evaluated residents of the European Continent and, in all of them, the natural history of CICSH patients may have been altered by pacing therapy.[5,7,9,11] In the present study, we have shown that the risk of death was related to population age, to the presence of atherosclerosis and to the presence of risk factors for atherosclerosis. These findings indicate that the presence of CICSH should be interpreted as a risk marker. This hypothesis is supported by our Cox regression results, which showed a relation between the risk of mortality and age at the time of recruitment, and a relation between mortality and the presence of atherosclerosis. Furthermore, the Cox regression results failed to demonstrate any relation between the presence of CICSH and mortality.

Patients with a significant fall in blood pressure after CSM are usually managed with general measures that aim to increase their blood volume, including elastic stockings, physical counterpressure maneuvers, discontinuation/

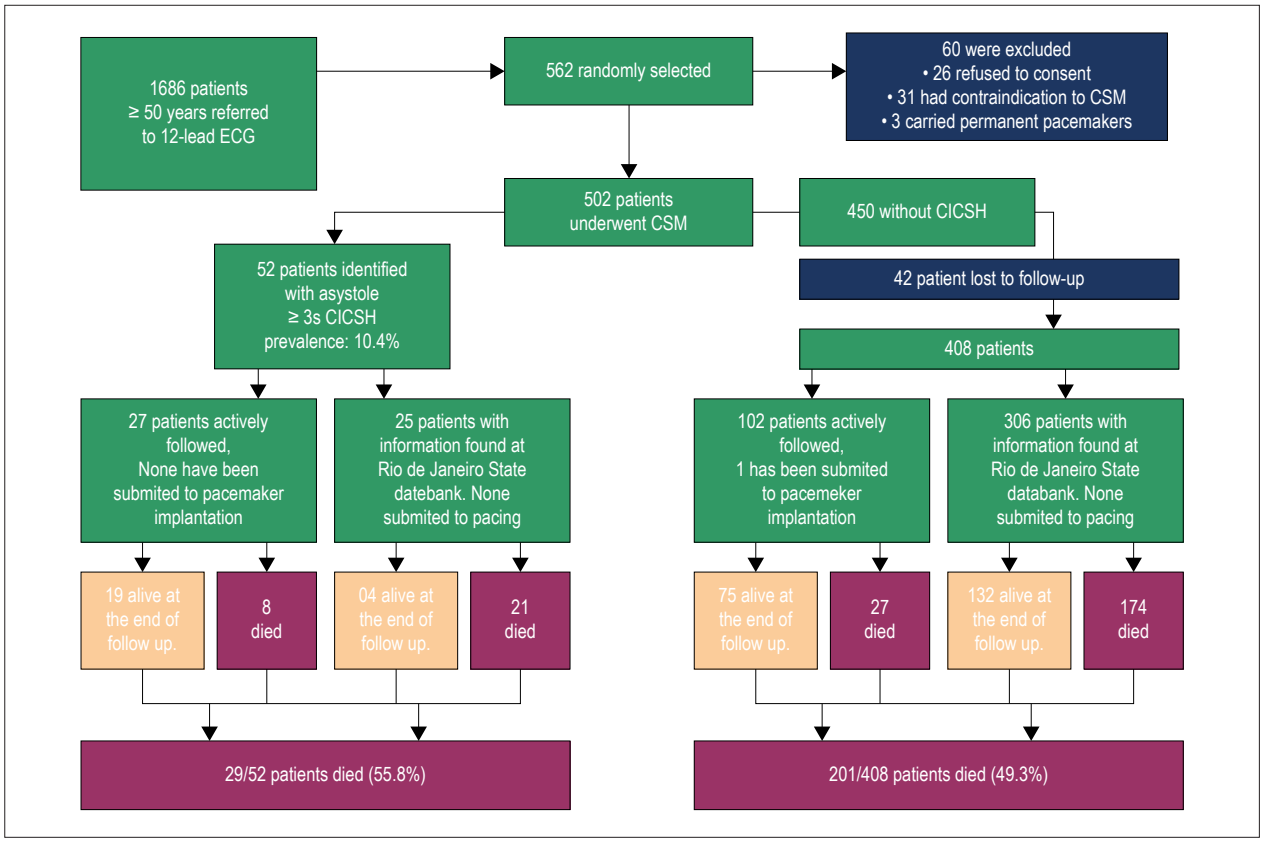

Figure 1 – *Study design and results. CSM: Carotid sinus massage; CICSH: cardioinhibitory carotid sinus hypersensitivity.*

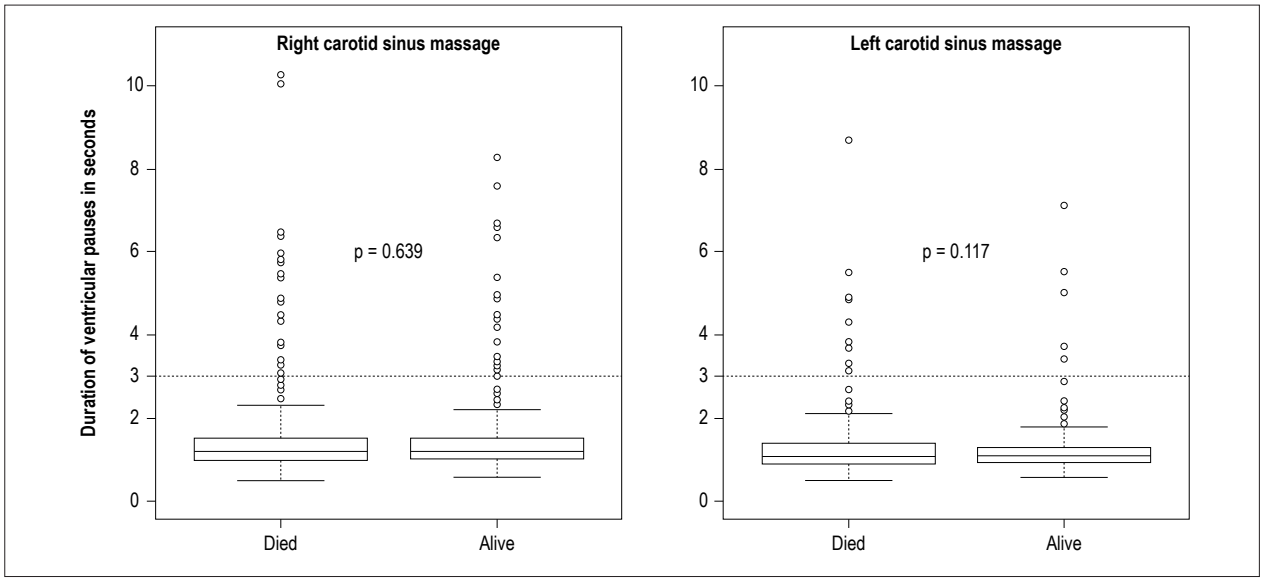

Figure 2 – *Duration of the longest RR interval observed during right and left carotid sinus massage. Boxplots on the left of each square represent patients who died during follow-up. Boxplots on the right represent patients who were alive at the end of the study.*

Table 2 – Mortality at the end of follow-up of patients with and without CICSH

	With CICSH	Without CICSH	p value
Number of dead patients at the end of follow-up	29/52 (55.8%)	201/408 (49.3%)	0.38
Number of cardiovascular deaths	11/52 (21.2%)	76/408 (18.6%)	0.66
Number of coronary artery disease related deaths	7/52 (13.5%)	32/408 (7.8%)	0.17
Number of cerebrovascular related deaths	2/52 (3.8%)	13/408 (3.2%)	0.80

CICSH: Cardioinhibitory carotid sinus hypersensitivity.

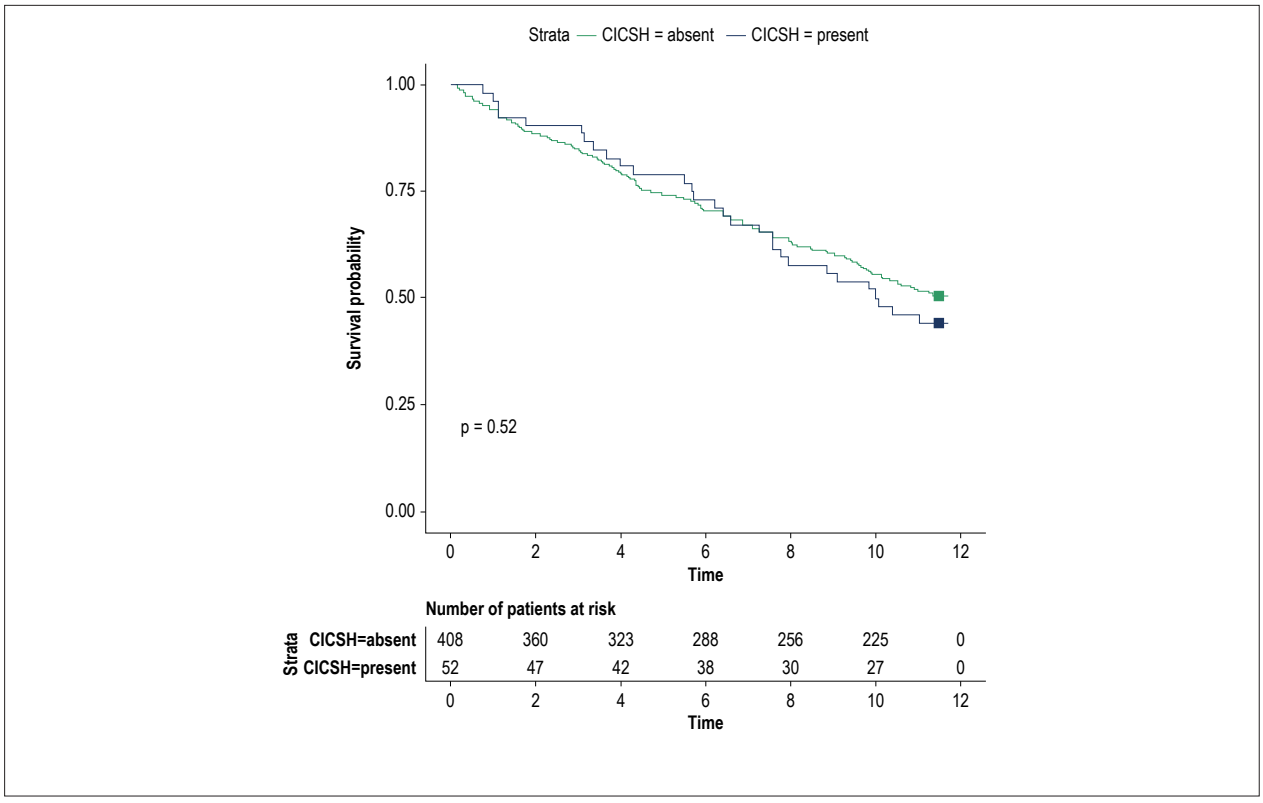

Figure 3 – *Survival curves of patients with (in blue) and without CICSH (in red) CICSH: Cardioinhibitory carotid sinus hypersensitivity.*

reduction of hypotensive therapy, fludrocortisone and alpha-agonists.[1] Patients with isolated or mixed cardioinhibitory response are usually managed with pacing when syncope is recurrent.[1,2,7] However, many studies used to justify pacing were observational, without a control group, or were small randomized open-label trials with no treatment control arm.[10-12] Those study results should be regarded with caution. The possibility of spontaneous remission of syncope, the difficulties to document the symptoms used as endpoints and the open-label design of these studies continue to raise doubts about their results. Analogous studies evaluated pacing indications in vasovagal syncope.[13-15] In an early clinical trial, with an open-label design, pacing was able to reduce syncope recurrence. However, in a later double-blind clinical trial, pacing therapy was not advantageous and failed to have any benefit in reducing syncope recurrence.[16]

Questions about the efficacy of pacing are even stronger in patients with other types of reflex syncope. Those questions are addressed in 2 recent systematic reviews.[15,16] Interestingly, in one of them an analysis of mortality is made.[16] In this analysis, which includes 3 studies of patients with CICSH and 1 study of patients with vasovagal syncope, pacing therapy did not reduce mortality.[16]

Only 2 clinical trials evaluated CICSH patients with a double-blind design.[17,18] The first was a double-blind crossover study[17] that randomized 32 elderly patients with at least 3 falls attributed to the presence of CICSH. All patients received dual-chamber pacing. The mean age of the population was 77 years. Patients were followed up for 1 year (6 months with DDD pacing turned on, and 6 months without atrial or ventricular pacing).[17] At the end of follow-up, the reduction in fall burden was similar in both groups.[17] Those results were affected by a high attrition rate. Seven of the 32 patients did not finish the study, 4 of which died during follow-up (12.5% mortality rate).[17] Three of these 4 deaths were sudden and occurred at home, 2 of which occurred in patients without pacing.[17] Autopsy of these patients revealed one death

Table 3 – Cox regression results and relation between CICSH and all-cause mortality

	Odds Ratio	95% Confidence Interval	p value
Cox model 1			
CICSH present	0.921	0.618 – 1.372	0.686
Age	1.037	1.022 – 1.051	< 0.001
Male sex	1.144	0.874 – 1.498	0.328
Atherosclerosis	1.733	1.321 – 2.276	< 0.001
Cox model 2			
CICSH present	0.946	0.633 – 1.412	0.785
Age	1.043	1.028 – 1.058	< 0.001
Male sex	1.078	0.820 – 1.418	0.588
Hypertension	1.032	0.745 – 1.431	0.847
Dyslipidemia	0.645	0.486 – 0.855	0.002
Diabetes	1.529	1.135 – 2.062	0.005
Smoking	1.617	1.090 – 2.400	0.0170
Atherosclerosis	1.884	1.408 – 2.522	< 0.001

CICSH: cardioinhibitory carotid sinus hypersensitivity.

resulting from ischemic stroke, and two from ischemic heart disease.[17] The fourth patient died after colectomy done after mesenteric infarction.[18]

The second clinical,[18] trial recruited 141 elderly patients with a history of syncope or unexplained fall attributed do the presence of CICSH. Patients were randomized to dual-chamber pacing or received an implantable loop recorder. After 2 years of follow-up, fall and syncope recurrence were similar in both groups. This trial has been criticized because the larger RR interval triggered by CSM was 3.1 seconds. Hence, the magnitude of cardioinhibitory response was considered to be small. According to pathophysiological studies, cerebral ischemic anoxia reserve time is around 7 seconds in healthy military personnel,[19] and a ventricular pause of 3 seconds is not likely to lead to loss of consciousness.[20] So, a ventricular pause of 3 seconds is not likely to produce syncope. Based on this reasoning and based on an epidemiologic study that showed that the 95th percentile for CSM response was 7.3 seconds, Krediet et al.[20] have proposed 6 seconds as a new cut off for the diagnosis of CICSH.[20] In the present study, the largest RR interval triggered by CSM was 10.3 seconds, and the 95th percentile for CSM response was 4.5 seconds. Thirteen of the 502 patients submitted to CSM had an asystole episode ≥6 seconds. (Figure 4) At the end of follow-up, the mortality rate of this small group of patients was 53.8%, which is similar to the percentage found in the 447 patients followed up without a pause ≥6 seconds (53.8% vs. 49.9%; p value: 0.77).

Study limitations

Besides reducing the heart rate and prolonging or blocking atrioventricular conduction, CSM may trigger a fall in blood pressure.[1,2] The blood pressure fall observed after CSM is a rapid and transient phenomenon. To be properly observed, this phenomenon must be documented on a beat-by-beat basis using invasive methods or digital pletismography.[1] Furthermore, this blood pressure fall is more commonly observed with the patient in the upright position on a tilt table.[1,6] In 2006, in the first phase of the present study, devices used to evaluate blood pressure non-invasively on a beat-by-beat basis and tilt tables were not available in Rio de Janeiro public hospitals, so we have evaluated blood pressure response manually with a sphygmomanometer in the supine position. This method lacks sensitivity[1,6] and, for this reason, we have decided to present only the heart rate response to CSM.

Only 7 of the 52 CICSH patients had a history of unexplained syncope, and none of them had recurrent syncope. This population had CSH, and was not affected by real CSS. It is difficult to conduct a study on the natural history of cardioinhibitory carotid sinus syncope because cardiac pacing is indicated to reduce symptoms in these patients.[1] According to many authors, this treatment could also modify the natural history of CICSH, reducing the mortality of patients with CSS.[5,7] As we have seen, pacing is also justified by the concern that a prolonged asystole episode could lead to serious trauma, brain injury, pause-dependent ventricular arrhythmias and death.[5,7] Our results suggest that this concern is excessive. However, we have to emphasize that in their most recent guidelines, the Brazilian Society of Cardiology and the European Society of Cardiology continue to recommend pacing for patients with CICSH and recurrent syncope.[1,2] It must be stressed that it is very important to document the association between symptoms and bradycardia because pauses and bradycardias without clinical significance can be easily induced by CSM in elderly individuals, especially when these patients are on negative chronotropic drugs.[1,2]

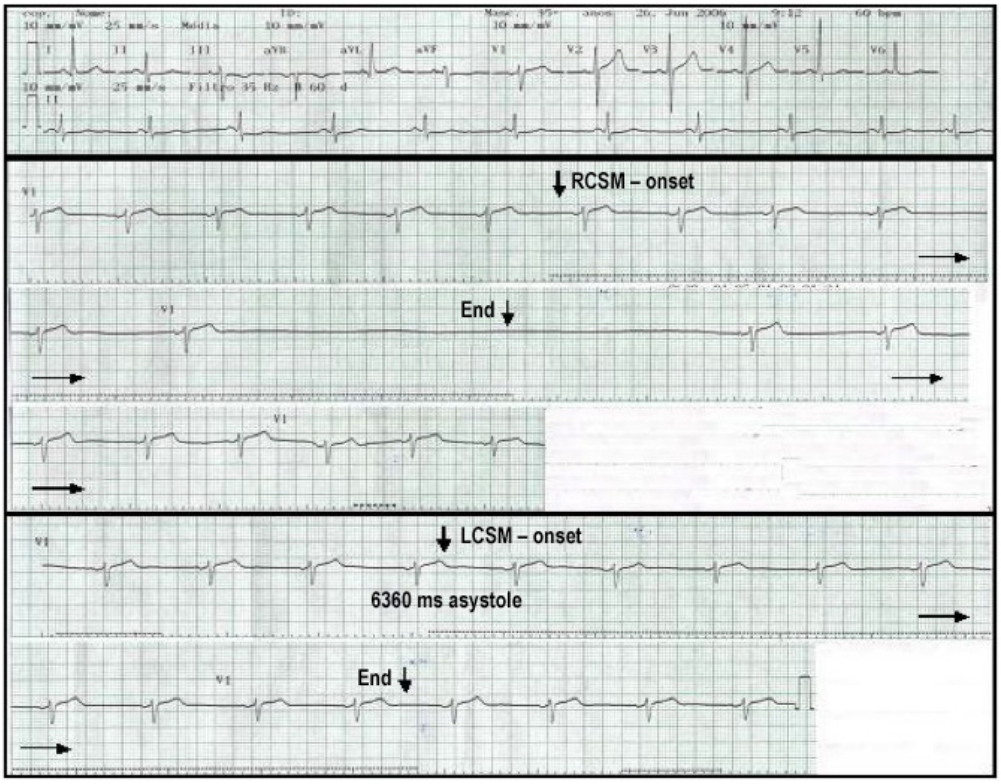

Figure 4 – *Example of a patient with CICSH. ECG of a 58 year-old male with previous percutaneous coronary intervention. He denied syncope in the past. The ECG reveals normal sinus rhythm with heart rate of 60 bpm and T-wave inversion in Lead 3 and aVF. Right carotid sinus massage triggered 6360 seconds of asystole with concomitant fall in blood pressure and pre-syncope. A few minutes later, he was submitted to left carotid sinus massage, no asystole was observed. RCSM: right carotid sinus massage.*

Conclusions

The present study showed that 55.8% of the CICSH patient cohort had died after a maximum follow-up of 11.6 years. This high mortality rate was similar to that found in a cohort of patients without CICSH. Cardiovascular mortality, ischemic heart disease and trauma-related mortalities were also similar in both patient cohorts.

Author contributions

Conception and design of the research: Lacerda GC, Lacerda RG, Pedrosa RC; Acquisition of data: Lacerda GC, Guimarães AEC; Analysis and interpretation of the data: Lacerda GC, Lorenzo AR, Tura BR, Santos MC, Guimarães AEC, Lacerda RG, Pedrosa RC; Statistical analysis: Lacerda GC, Lorenzo AR, Tura BR; Writing of the manuscript: Lacerda GC, Lorenzo AR, Santos MC, Lacerda RG, Pedrosa RC; Critical revision of the manuscript for intellectual content: Lacerda GC, Lorenzo AR, Tura BR, Santos MC.

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 Geral de Bonsucesso under the protocol number 2.383.341. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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What is the Real Clinical Significance of Carotid Sinus Hypersensitivity in Clinical Practice? A Dilemma Still Waiting for Answers

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Short Editorial related to the article: Long-Term Mortality in Cardioinhibitory Carotid Sinus Hypersensitivity Patient Cohort

Carotid sinus hypersensitivity (CSH) is defined by pause ≥ 3 seconds (sinus or atrioventricular block) and/or systolic blood pressure drop ≥ 50mmHg during carotid sinus massage (CSM).[1] The prevalence of CSH varies according to the method and population evaluated in up to 68% of elderly patients with syncope and 35% of asymptomatic individuals over 65 years of age.[2] Therefore, the cause-effect relationship between carotid sinus hypersensitivity and syncope should always be questioned, and may only be a casual finding and not necessarily the carotid sinus syndrome (CSS), one of the causes of syncope seen mainly in elderly patients.[3]

The clinical relevance of CSH obtained with CSM was questioned in a study recently published by Wu et al.[4] The authors compared the response to CSM between 99 patients with syncope to clarify and 66 asymptomatic patients and found similar rates of CSH between the two groups, with cardioinhibitory response in 24.2 and 25.8% and vasodepressor response in 8.1 and 13.6%, in symptomatic and asymptomatic patients respectively (p = 0.466).[4] Therefore, CSH may be a nonspecific response in the evaluation of syncope in these patients with dubious clinical significance, especially in the elderly population with multiple comorbidities, often with the possibility of varying etiologies.

Attempts to refine or modify the definition of positive response have been proposed to enable accuracy in the diagnosis of CSS as the cutoff value of systolic blood pressure ≤ 85 mmHg combined with symptoms suggested by Solari et al.[5] The authors concluded that one-third of the 164 patients evaluated with isolated vasodepressor form could not be identified with the current criterion (systolic blood pressure drop ≥ 50 mmHg) compared to the cutoff value of ≤ 85 mmHg systolic blood pressure. Krediet and colleagues[6] also questioned the current criteria for CSH, considering them to be very sensitive, resulting in the high prevalence observed in the elderly population.[6] They suggested changing to pause ≥ 6 seconds and/or lowering mean blood pressure to < 60 mmHg for more than 6 seconds, based on the fact that 6 seconds of asystole are required to cause loss of consciousness;[7] that in the general population the 95th percentile for response to CSM was 7.3 seconds of asystole;[6] that in clinical follow-up, patients with pauses > 6 seconds (43%) had significant recurrence of syncope compared to patients with 3-6 seconds who had only 0.7% of occurrence;[8] and that in the International Study on Syncope of Uncertain Etiology 2 (ISSUE-2) the average pause in observed syncope recurrence was 9 seconds (8-18 seconds).[9] Based on this new criterion, McDonald and colleagues analyzed mortality according to the current criterion and the criteria proposed by Krediet (described above) and Kerr (pause > 7.3 seconds and systolic blood pressure drop > 77 mmHg).[10] In a total of 272 patients, 106 of them (38.9%) had CSH according to the standard criteria, and 141 (51.8%) and 28 (10.3%) according to the Krediet's and Kerr's criteria.[10] They did not observe statistical difference in mortality in patients with and without CSH in a mean follow-up of 8.6 years by the standard criterion (32 *vs*. 22%, respectively p = 0.073), but noted differences according to Krediet's (33 *vs*. 19%, p = 0.009) and Kerr's (53 *vs*. 23%, p < 0.001) criteria. After adjusting for age and gender, only CSH defined by Kerr's criterion was associated with increased total mortality (risk rate 2.023, 95%CI 1.131-3.618, p = 0.009).

In this issue, the study by Lacerda and colleagues[11] observed the evolution of 502 patients undergoing CSM, with 52 patients presenting cardioinhibitory response or asystole ≥ 3 seconds. When compared to the 408 patients with physiological response (or without CSH), the authors did not observe differences in either cardiovascular or trauma-related mortality, with total mortality rates of 55.8 *vs*. 49.3% (p = 0.38) in patients with and without cardioinhibitory response respectively.[11] Among the 52 patients with cardioinhibitory response to CSM, only 7 patients had a history of syncope and no pacemaker implantation was required in any of them. The low prevalence of patients with syncope in the study, placed as a limitation, may have further reinforced the indifference in the evolution of patients with or without cardioinhibitory CSH. These results reinforce the hypothesis of the limitation of CSH findings to clinical applicability in most of the observed cases and are in agreement with the current literature.

Therefore, CSH remains a matter of evaluation, with controversy since its definition, based predominantly on small, old studies with technical limitations of the time, and the heterogeneity of the methods employed in the CSM. The lack of accuracy has been pointed as a factor in the low specificity of the finding, making it difficult, and sometimes confusing the clinician, for the proper diagnosis of CSS in the investigation of syncope to be performed, which requires response to CSM according to the criteria for CSH combined with reproduction of clinical symptoms during the maneuver. The findings of the article rekindle, once again in the literature, the need for reevaluation of the current parameters described in the consensus on CSH, the bases for the correct diagnosis, appropriate treatment and prognosis of CSS in syncope.

Keywords

Carotid Sinus Massage/physiopathology; Syncope; Aged; Hypotension; Mortality; Cardiac Pacing, Artificial.

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Evaluation of Myocardial Ischemia with iFR (Instantaneous Wave-Free Ratio in the Catheterization Laboratory: A Pilot Study

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Abstract

Background: The Instantaneous Wave-Free Ratio (iFR) is an invasive functional evaluation method that does not require vasoactive drugs to induce maximum hyperemia

Objective: To evaluate the contribution of the iFR to the therapeutic decision-making of coronary lesions in the absence of non-invasive diagnostic methods for ischemia, or in case of discordance between these methods and coronary angiography.

Method: We studied patients older than 18 years, of both sexes, consecutively referred for percutaneous treatment between May 2014 and March 2018. Coronary stenotic lesions were classified by visual estimation of the stenosis diameter into moderate (41-70% stenosis) or severe (71%-90%). An iFR ≤ 0.89 was considered positive for ischemia. Logistic regression was performed using the elastic net, with placement of stents as outcome variable, and age, sex, arterial hypertension, diabetes, dyslipidemia, smoking, family history, obesity and acute myocardial infarction (AMI) as independent variables. Classification trees, ROC curves, and Box Plot graphs were constructed using the R software. A p-value < 0.05 was considered statistically significant.

Results: Fifty-two patients with 96 stenotic lesions (56 moderate, 40 severe) were evaluated. The iFR cut-off point of 0.87 showed a sensitivity of 0.57 and 1-specificity of 0.88, demonstrating high accuracy in reclassifying the lesions. Diabetes mellitus, dyslipidemia, and presence of moderate lesions with an iFR < 0.87 were predictors of stent implantation. Stents were used in 32% of lesions in patients with stable coronary artery disease and AMI with or without ST elevation (non-culprit lesions).

Conclusion: The iFR has an additional value to the therapeutic decision making in moderate and severe coronary stenotic lesions, by contributing to the reclassification of lesions and decreasing the need for stenting. (Arq Bras Cardiol. 2020; 114(2):256-264)

Keywords: Myocardial Ischemia, Fractional Flow Reserve Myocardial; Stents; Coronary Artery Disease; Risk factors; Percutaneous Coronary Intervention.

Introduction

In functional evaluation of coronary stenosis, the use of fractional flow reserve (FFR) to measure pressure instead of flow has been recommended by the American College of Cardiology-American Heart Association, the European Society of Cardiology, and the Brazilian Society of Hemodynamics and Interventional Cardiology guidelines[1-6] in case of absence or inconclusive results from non-invasive methods to assess ischemia. FFR is an easy-to-perform technique and its efficacy has been demonstrated by several clinical trials, especially those on stable coronary artery disease patients. However, the FFR method is not widely used in clinical practice. One reason for that is that FFR is measured during maximal hyperemia, which is achieved by administration of vasodilator drugs (e.g. adenosine).[7]

The instantaneous wave-free ratio (iFR) is a recent, invasive method for functional diagnosis of coronary stenosis, introduced to solve some FFR-related issues, such as the need for intravenous drugs and new vascular access, with higher risk of complications.[8-10] The comparison between these methods showed a strong correlation of iFR < 086 with positive FFR (≤ 0.80) for ischemia, and of iFR > 0.93 with negative FFR (FFR > 0.80) for ischemia, indicating the high accuracy of the method. Values of iFR located in the range of 0.86–0.93 (called the "grey-zone") showed a weak correlation, and results were confirmed by FFR. This analysis using both iFR and FFR is known as a hybrid approach.[11,12] The iFR was subsequently validated in randomized, controlled clinical trials which showed that the method was non-inferior to FFR, with cut-off points of 0.89 and 0.80 for iFR and FFR, respectively.[6] The iFR was also shown to be faster to perform and have less adverse events compared with FFR.[10-12]

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However, whether these results from randomized studies, suggesting that iFR can be used as surrogate for FFR in percutaneous interventions in CAD, can be transposed to clinical practice is still uncertain. Besides, factors like the costs of equipment, inadequate reimbursement, the interventional cardiologist preference, signs and symptoms reported by patients, and the costs and risks associated with adenosine treatment may limit the use of both methods. The use of iFR in a routine manner in patients with multi-vessel diseases and in non-culprit lesions in acute myocardial infarction (AMI) patients still need to be investigated.[13]

The present study aimed to evaluate the additional contribution of iFR to the therapeutic decision-making. The iFR was used in coronary disease patients in which the correlation between obstructive atherosclerotic disease and myocardial ischemia had not been clearly established by other conventional diagnostic methods.

Methods

The study was approved by the ethics committee of Marcilio Dias Naval Hospital (approval number CAAE: 58741716.0.000.5256).

We studied patients older than 18 years, of both sexes, consecutively referred for percutaneous treatment between May 2014 and March 2018. All patients were referred for invasive investigation of myocardial ischemia and decision-making process by the Heart Team, composed by interventional cardiologists, clinical cardiologists and cardiovascular surgeons.

All patients with moderate (41-70% stenosis) or severe (71%-90%) stenosis according to coronary angiography were included. In all these patients there were doubts about the degree of obstruction, determined by coronary angiography, and its correlation with the presence of ischemia determined by non-invasive methods including ergometric test, myocardial scintigraphy and stress echocardiography.

The study population was composed of a wide variety of patients – patients with suspected or confirmed diagnosis of stable CAD but inconclusive diagnosis of myocardial ischemia using non-invasive methods; non-ST-elevation myocardial infarction patients in which the culprit artery had been treated, and invasive functional analysis had been performed in another coronary vessel with moderate-to-severe lesion by angiography; ST-elevation myocardial infarction patients in which invasive functional analysis of moderate-to-severe non-culprit lesion had been performed at least 5 days after the acute event.

The iFR was performed using the Volcano S5 Imaging System (San Diego, California, USA). The 0,014" Primewire Prestige® Pressure Guide Wire was used in 2014, and the 0,014" Verrata Pressure Guide Wire, substitute for the previous version, used in 2015. A guiding catheter was used to advance the guide wire through the lesion.[14-16]

All procedures were performed according to good practice guidelines for iFR measurements, as follows – the 0.014'' guidewire was stabilized before handling by infusion of 0.9% saline until completion of the circuitry where the catheter was packed, and connection of the catheter to the console; during this process, the device was kept in stable position until it was recognized by the console software. After the guide wire was introduced into the catheter, it was externalized through the proximal coronary segment, and the guide pressure equalized using a transducer. The transducer guide was then positioned about 3 cm below the lesion.[15] Also, guide pressure equalization was confirmed at the end of each measure to ensure its stability.[16] To confirm the stability of the results, three consecutive measures were performed for each lesion; in case of diverging values, the lowest value was considered for analysis. Intracoronary nitroglycerin (200 μg, bolus) was administered before the measures were performed.[16]

The iFR was considered positive for myocardial ischemia 0.89 or less.[12]

Statistical analysis

Categorical variables were described as numbers and percentages. Age (continuous variable) was described as mean and standard deviation, and as minimum, median and maximum values. Normality of the variable age was confirmed by the Shapiro-Wilk test ($p = 0.3663$). Distribution of the variable iFR was not tested for normality, and described as median and interquartile range.

A logistic regression was initially performed using the elastic net,[17] which is a variable selection method that identifies strongly correlated predictors. This method is particularly useful when the number of predictors (P) is much bigger than the number of observations (n). In this model, the requirement of a stent was the outcome variable, and the independent variables were age, sex, comorbidities (such as systemic arterial hypertension, diabetes mellitus, dyslipidemias, smoking, family history, obesity and previous AMI). Two logistic regression models were built using the variables selected by the elastic net. In addition, we used a non-parametric classification tree,[18] which is useful to detect possible interactions between predictors and provide easily interpreted visual information. The end nodes show the bar graph for the variable 'stenting'. Additionally, the ROC curve was used to evaluate sensitivity and 1-speciticity of the iFR cut-off, established by the classification tree. Box plots[19] were constructed to depict the distribution of the iFR values for moderate and severe stenoses, considering the use of stents. Statistical calculations were performed using the R package.[20] The partykit package of the R software was used for construction of the classification tree.[21,22] A p-value < 0.05 was considered statistically significant.

Results

Characteristics of the patients

The iFR was used for assessment of 96 stenotic lesions of 52 patients, with a mean of 1.85 lesions/patient. Median iFR was 0.93 (0.855–0.97); 56 of them were classified as moderate stenosis (58.3%) and 40 of them as severe (41.7%) stenosis. Figure 1 shows the study flowchart. Thirty percent of the lesions were treated with stent placement, and in 6.2% of them, despite the presence of ischemia confirmed by functional analysis, the first therapeutic choice was other than stent placement – revascularization surgery due to the

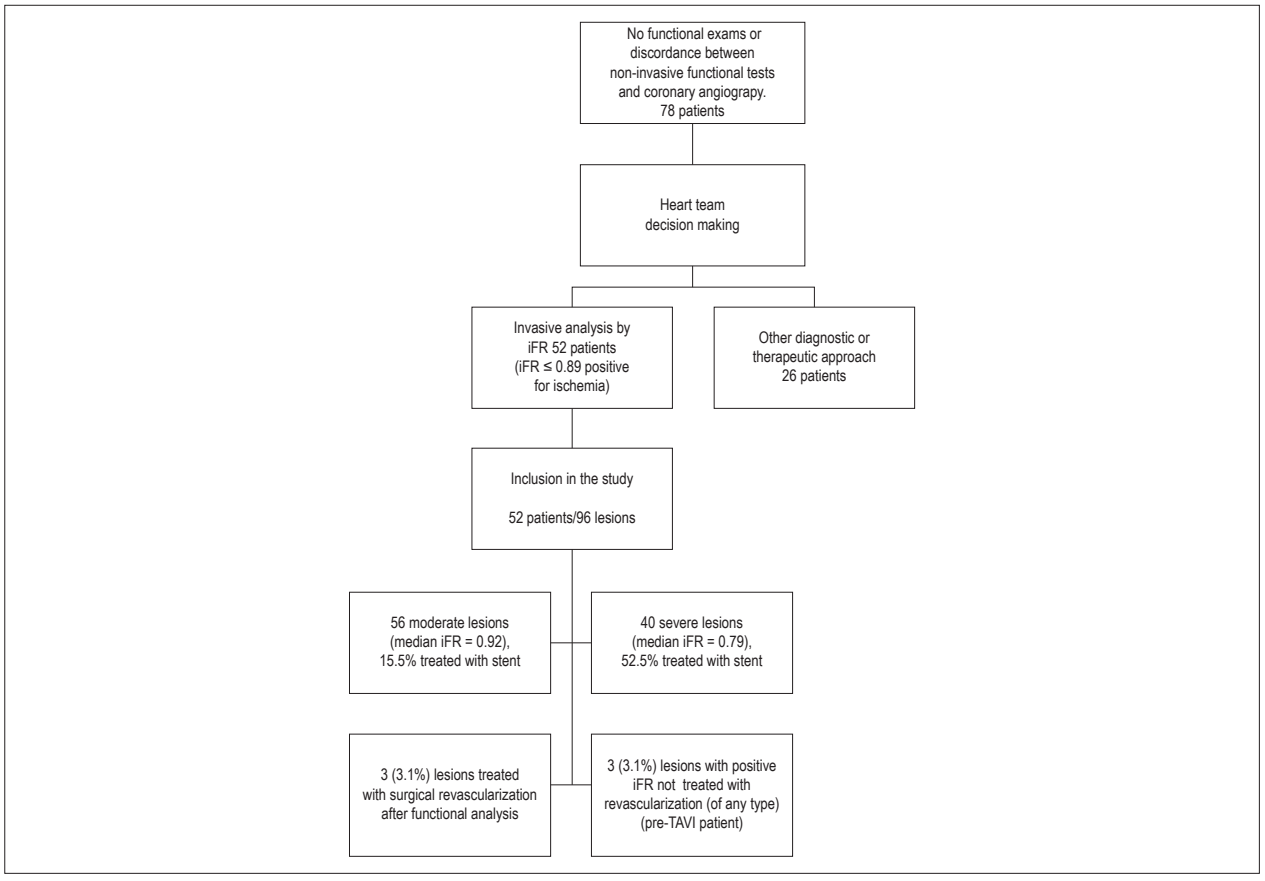

Figure 1 – *Flow chart of the study showing the heart team decision making for the stenotic lesions evaluated. iFR: instantaneous wave-free ratio; TAVI: transcatheter aortic valve implantation.*

coronary anatomy (3.1%) and transcatheter aortic valve implantation (TAVI) (3.1%) – these therapeutic decisions were made by the Heart Team.

Regarding the localization of the stenotic lesions, 52 lesions were located in the anterior descending artery (54.1%), 11 in the circumflex artery (11.4%), 9 in the right coronary artery (9.3%), 10 in the diagonal branch (10.4%), 9 in the marginal branch (9.3%), 1 in the left posterior descending coronary artery (1.1%), 1 in the right posterior descendent artery (1.1%), 1 in the intermediate artery (1.1%), 1 in the posterior ventricular branch (1.1%), and 1 in the left main (1.1%). Characteristics of the patients are described in Table 1. There was a predominance of men and a high frequency of coronary risk factors, especially diabetes mellitus and smoking. The frequency of clinical manifestations was not different between chronic CAD and acute CAD patients. Most patients showed significant lesion in only one vessel, and approximately two thirds of them were not treated with stent placement.

Statistical modelling and graphic analysis

Two logistic regression models were constructed to evaluate the need for stent placement. Model 1 was implemented using the variables selected by the elastic net - diabetes mellitus, dyslipidemia, presence of moderate stenosis and positive iFR. Model 2 was composed by the variables that showed statistical significance in the previous model - presence of moderate stenosis and positive iFR. Both dyslipidemia and diabetes mellitus lost statistical significance in the second model (Table 2).

Classification trees were developed to evaluate interactions between the predictors identified by logistic regression and facilitate their interpretation. (Figures 2 and 3). An iFR ≤ 0.87 was statistically associated with the occurrence of stent implementation, in nearly 37.5% of moderate stenotic lesions.

Figure 4 shows the box plot of the distribution of iFR values for moderate and severe lesions treated with stent placement. Among these, median iFR was 0.92 (0.82-0.94) for moderate lesions and 0.79 (0.61–1.00) for severe lesions, *i.e.*, there was a higher variability in iFR values in severe lesions.

The ROC curve evaluated sensitivity and 1-specificity of the iFR cut-off determined using the classification tree. Figure 5 depicts the ROC curve for the iFR, with an area under the curve of 0.7933 (95%CI, 0.6918-0.8949). A sensitivity of 0.57 and a 1-specificitity of 0.88 were obtained for an iFR cut-off of 0.87.

Discussion

Previous studies have validated the iFR method in comparison with the FFR. the iFR was shown to be non-inferior to the FFR for

Table 1 – Characteristics of the patients

Variables	n (%)
Number of patients	52 (100%)
Age	
Mean ± SD	66.85 ± 11.27
Median (minimum, maximum)	66.5 (41, 86)
Sex	
Female	14 (26.9%)
Male	38 (73.1%)
Arterial hypertension	45 (86.5%)
Diabetes mellitus	22 (42.3%)
Dyslipidemia	36 (69.2%)
Smoking	17 (32.7%)
Family history of coronary artery disease	11 (21.2%)
Obesity	3 (5.8%)
Previous infarction	7 (13.5%)
Clinical manifestation	
Stable angina	19 (36.5%)
Myocardial acute infarction	21 (40.4%)
Others	12 (23.1%)
Moderate stenoses	
Without stenosis	16 (30.8%)
With stenosis	
1 lesion	18 (34.6%)
2 lesions	16 (30.8%)
3 lesions	2 (3.8%)
Severe stenoses	
Without stenosi	25 (48.1%)
With stenosis	
1 lesion	16 (30.8%)
2 lesions	9 (17.3%)
3 lesions	2 (3.8%)
Stents	
Without stent	30 (57.7%)
With stent	
1 stent	15 (28.8%)
2 stents	6 (11.5%)
3 stents	1 (1.9%)

SD: standard deviation.

composite outcomes in the DEFINE FLAIR study and for all-cause mortality, non-fatal AMI, and unplanned revascularization in the iFR-SWEDEHEART study after one-year follow-up. It is worth pointing out that in the iFR-SWEDEHEART trial, 17.5% of the patients treated had acute coronary syndrome.[7,23] There are no randomized studies comparing iFR-guided revascularization *versus* medical therapy. Also, there is no strong evidence for the use of this new technique in AMI-related lesions or extrapolation of the outcomes to follow-up periods longer than one year. However, in a recent European guideline, a Class I recommendation with a level of evidence A has been issued to the iFR for intermediate lesions with no documentation of previous ischemia.[3]

The analysis of coronary physiology as a prerequisite for the prognostic assessment of moderate stenosis will be probably be incorporated to clinical practice, especially considering the iFR as an alternative to the FFR. As compared with the FFR, iFR is easier and faster to be performed, and prevent the side effects caused by intravenous infusion of vasodilators, especially CAD with acute clinical manifestations.[13]

In this context, this study corroborates previous findings of the literature,[9,24] showing that, in situations where there were disagreements between anatomic and functional methods, moderate stenotic lesions in coronary angiography were reclassified, preventing stent implantation in 58% of the cases.

It is of note that the use of iFR helped in the therapeutic decision-making process, for stent placement, in moderate stenotic lesions in patients with stable CAD, and in non-culprit lesions of STEMI and non-STEMI patients. The combined analysis of the DEFINE-FLAIR and the iFR- SWEDEHEART studies,[13] involving 440 patients with acute coronary syndrome, demonstrated a relative advantage of the iFR over FFR in these patients, but more robust studies are needed to confirm this. In the iFR-SWEEDHEART study, 38% of the patients had acute coronary syndrome, 17% of them with AMI without ST elevation, and 21% with unstable angina. The DEFINE-FLAIR trial, however, also included patients with AMI with ST elevation, 3.9% in the iFR group and 3.4% in the FFR group, in which the non-culprit vessel was analyzed at least 48 hours after the acute event.

Quantification of myocardial ischemia in the presence of serial lesions is challenging,[25] as it is frequently seen in the descending coronary artery (DA), where the FFR has not been validated. In our study, 8 patients (15%) showed two or three serial lesions in the DA, with a total of 17 lesions analyzed by iFR. The ischemic component of the lesions was assessed, which was successfully treated with the placement of 5 stents, with no need to approach all the lesions. These data are corroborated by the iFR-GRADIENT Registry with 128 patients, in which the use of the iFR showed high accuracy in reclassifying the lesions in 31% of the cases.[26]

In the present study, the iFR cut-off of 0.87 showed high accuracy, with 0.57 sensitivity and 1-specificity of 0.88. The inclusion of severe lesions in our analysis may explain the lower sensitivity, as compared with literature data.

Discordance between FFR and iFR has been reported to occur in 20% of the cases and may be explained by differences in the hyperemic coronary flow velocity,[27] which, in the presence of FFR (+) and iFR (-), is similar to that reported in non-stenotic vessels (by angiography). It is possible that such divergence is associated with pathophysiological mechanisms of the measures. Significant pressure differences caused by stenosis between resting and hyperemia indicate

Table 2 – Logistic regression models

	Variable	Estimative	Standard error	Odds ration (95%CI)	p
Model 1	(Intercept)	7.8161	3.0611		0.0107
	Diabetes mellitus	0.4511	0.6360	1.570 (0.451; 5.461)	0.4782
	Dyslipidemia	0.9722	0.7391	2.644 (0.621; 11.256)	0.1884
	Moderate stenosis	-1.5000	0.5819	0.223 (0.071; 0.698)	0.0099
	iFR	-9.7182	3.4198	0.000 (0.000; 0.049)	0.0045
Model 2	(Intercept)	9.7209	2.8715		0.0007
	Moderate stenosis	-1.2414	0.5389	0.289 (0.100; 0.831)	0.0212
	iFR	-10.9861	3.2441	0.000 (0.000; 0.010)	0.0007

CI: confidence interval.

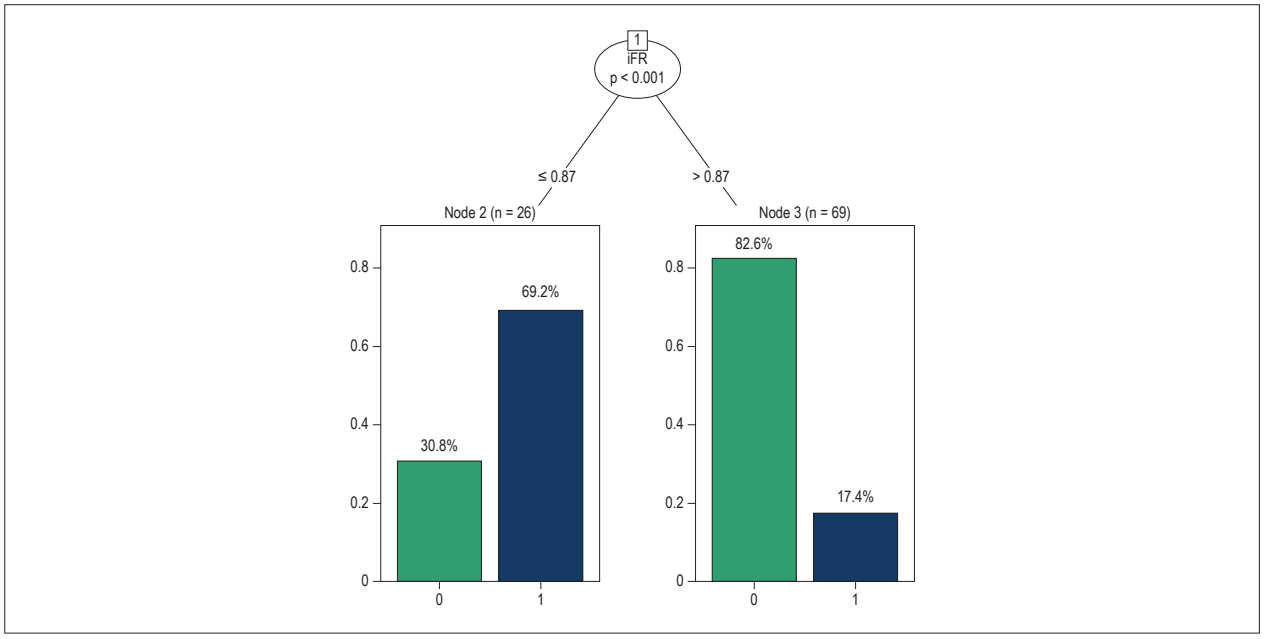

Figure 2 – *Classification tree for the logistic regression model 1; stent placement was observed in 69.2% of patients with iFR (instantaneous wave-free ratio) ≤ 0.87; and in 17.4% of patients with iFR > 0.87.*

a considerable increase in flow, similarly to a coronary flow reserve (which is a directly measured parameter) greater than 2.0. In this context, the presence of an iFR > 0.90 and an FFR < 0.80 has been associated with a coronary flow reserve not limited by flow.[28]

In the present study, an iFR > 0.70 was found in the moderate lesions, and a higher variability was observed in severe lesions (0.61-1.00), mostly treated with stent placement. Such variability may be due flow changes associated with collateral supplied by microcirculation, more commonly seen in chronic lesions and in vessels that the irrigated area is not significant. In addition, there were 23 lesions in diagonal, marginal, posterior descending and posterior ventricular branches, corroborating previous hypothesis. Recently, the iFR/FRR-guided assessment has been suggested in complete revascularization in coronary three-vessel disease, venous grafts, and grafts in the circumflex system.[29]

The logistic regression models and the classification tress enabled the identification of the variables more frequently related with the coronary flow reserve. Diabetes mellitus, dyslipidemia, the presence of moderate stenosis and an iFR lower than 0.87 were predictors of stent implantation in moderate and severe lesions of CAD patients, in which results obtained from non-invasive tests and those of coronary angiography were discordant. However, when the model was constructed with significant variables only, only iFR < 0.87 and the presence of moderate stenosis remained in the model, indicating the importance of a functional analysis in this group of patients.

The main limitation of this study is the lack of both short-term and long-term follow-ups, which would allow us to evaluate whether there was an improvement in the clinical outcomes of the patients. Although a mere visual estimation of the lesion is a known limitation because of interobserver variation, it in fact reflects real-world clinical practice. The primary objective of the

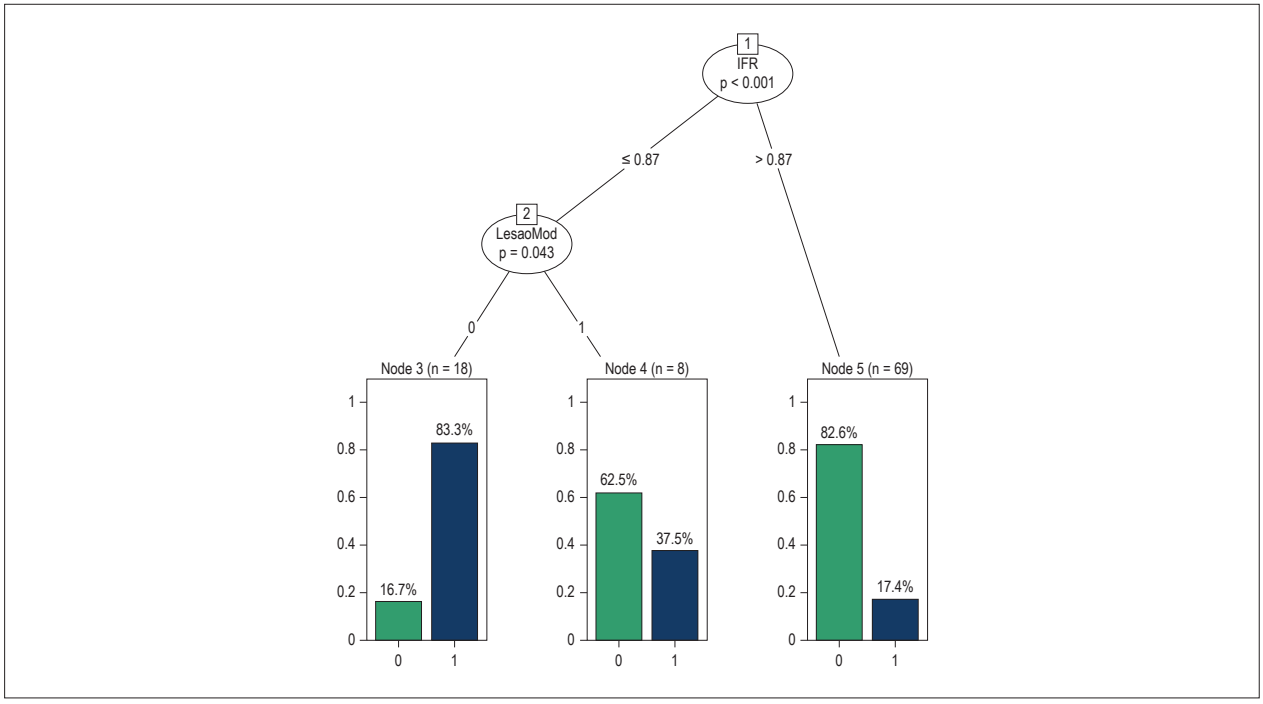

Figure 3 – *Classification tree for the logistic regression model 2; stent implantation was observed in 7.5% of patients with moderate stenosis and iFR (instantaneous wave-free ratio) ≤ 0.87.*

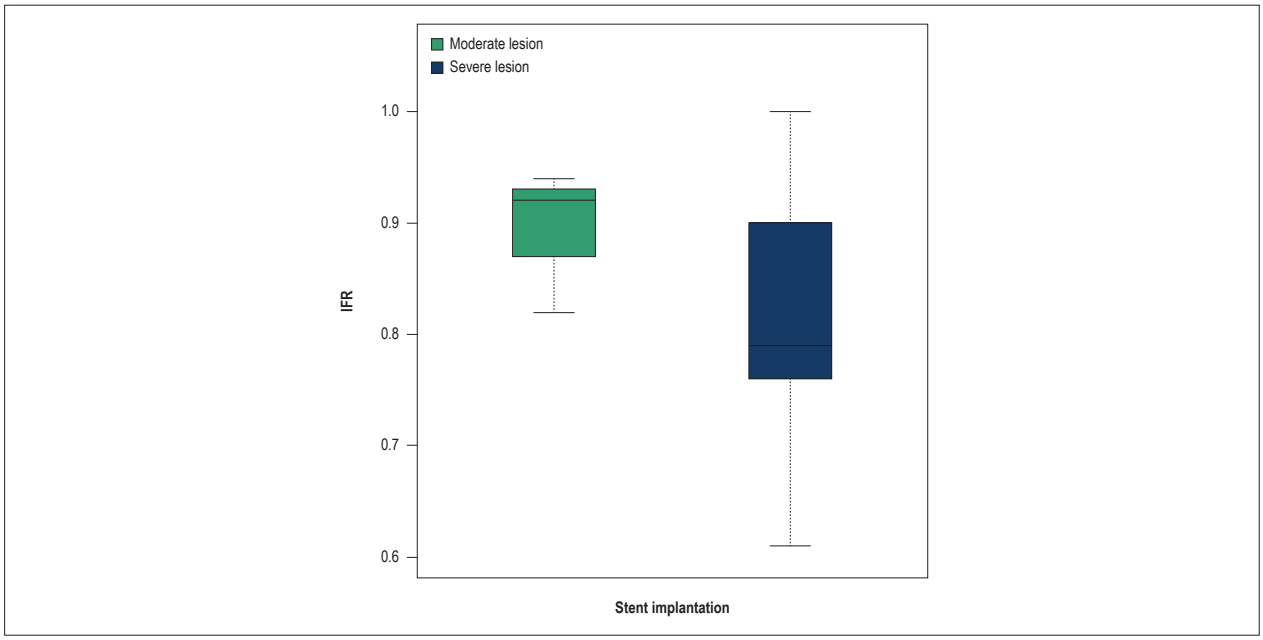

Figure 4 – *Box Plot of the iFR (instantaneous wave-free ratio) values for moderate and severe lesions considering the presence of stents. Median iFR was 0.92 (0.82-0.94) in moderate lesions and 0.79 (0.61-1.00) in severe lesions.*

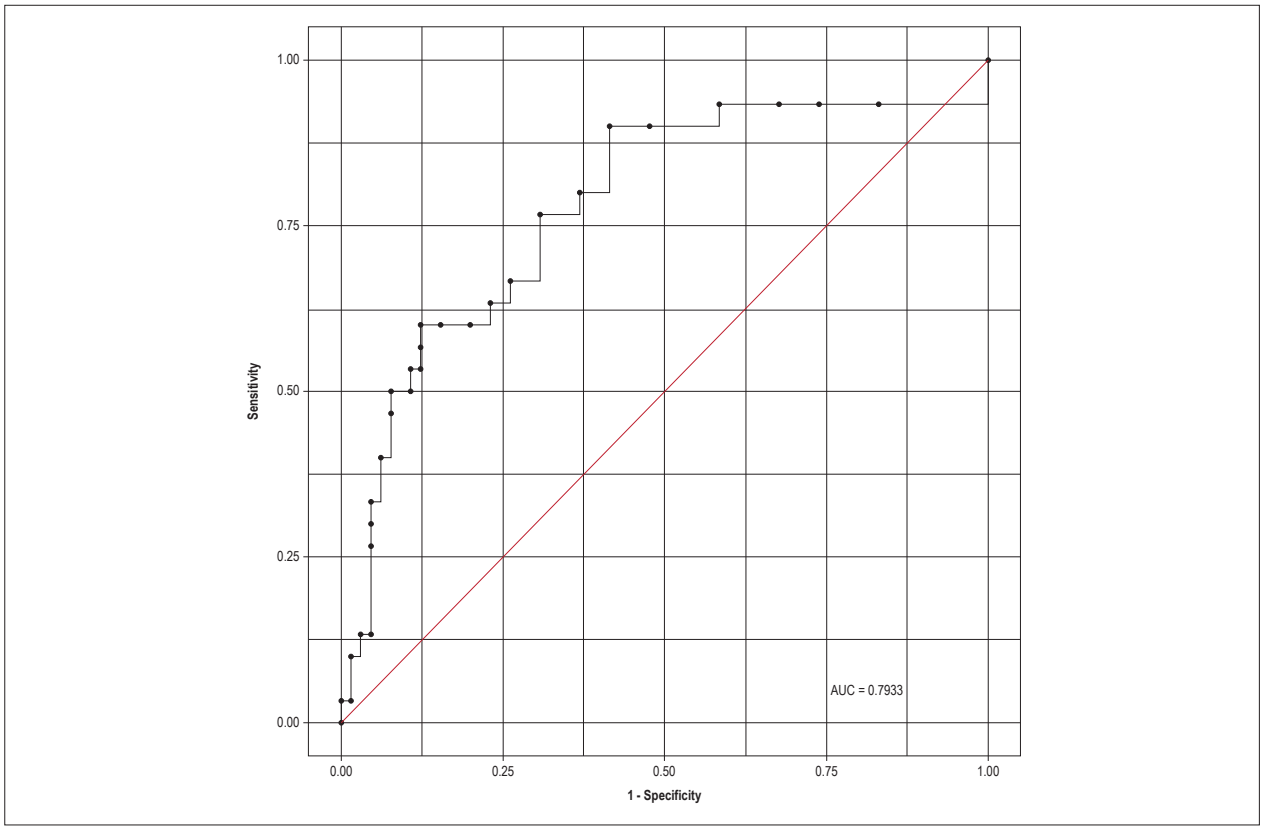

Figure 5 – *ROC curve for the iFR (instantaneous wave-free ratio); a sensitivity of 0.57 and 1-specificity of 0.88 was observed for the iFR cut-off point of 0.87, obtained from the classification tree. AUC: area under the curve.*

study was achieved – we showed the additional contribution of the iFR to the therapeutic decision making in moderate and severe coronary disease, when the correlation between obstructive coronary artery disease and myocardial ischemia is not clearly defined by conventional diagnostic methods.

Author contributions

Conception and design of the research: Ferreira MCM, Oliveira GMM; Acquisition of data: Vieira HCA, Ferreira MCM, Nunes LC, Cardoso CJF; Analysis and interpretation of the data: Vieira HCA, Ferreira MCM, Nascimento EM, Oliveira GMM; Statistical analysis: Nascimento EM, Oliveira GMM; Writing of the manuscript: Vieira HCA, Ferreira MCM, Oliveira GMM; Critical revision of the manuscript for intellectual content: Ferreira MCM, Nascimento EM, Oliveira GMM.

Potential Conflict of Interest

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Study Association

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

Ethics approval and consent to participate

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

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Invasive Physiological Assessment: From Binary to Continuous

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Short Editorial related to the article: Evaluation of Myocardial Ischemia with iFR (Instantaneous Wave-Free Ratio in the Catheterization Laboratory: A Pilot Study

Described by Pijls et al., in 1993, and based on extensive validation and robust clinical data, fractional flow reserve (FFR) was incorporated into the guidelines of myocardial revascularization to guide the need for revascularization of angiographically intermediate stenosis in patients with stable coronary artery disease (CAD).[1-3] The broadest arguments for this decision were: (1) by depicting a complex tridimensional structure as a planar silhouette coronary angiography suffers from well-known limitations, it presents large variability in estimating coronary stenosis severity, and it has low ability in predicting the functional significance of epicardial coronary stenoses, and (2) revascularization in stable coronary artery disease based solely on the severity of luminal narrowing, as determined by coronary angiography, does not improve clinical outcomes as compared to optimized medical treatment[8] or versus revascularization of only physiologically significant lesions.[9-11]

The central premise of invasive assessment of coronary physiology is to identify myocardial ischemia with superior spatial resolution (per vessel) compared to non-invasive methods (per territory), aiding in the identification of lesions (and, therefore, patients) that are more likely to benefit from revascularization. However, despite the clinical benefits and guideline recommendations, the FFR uptake in clinical practice remains low (< 10%) in most catheterization laboratories around the globe. Costs, time added to procedures, patient discomfort to hyperemic stimulus or contraindications to adenosine use, as well as difficulties in interpretation of physiological traces in certain anatomic situations (e.g., serial/diffuse stenosis), are some of the reasons for FFR underutilization.

Recently, the introduction of instantaneous wave-free ratio (iFR) led to renewed interest in the use of invasive physiology. The iFR is measured at rest – without the need to achieve maximal hyperemia –, which simplifies the use of coronary physiology in several anatomic scenarios, with shorter procedure time and fewer adverse symptoms for the patient. Seven years after its initial description by Sen et al.,[12] two large randomized studies documented the non-inferiority of iFR compared with FFR on the occurrence of adverse clinical outcomes when they were used to guide revascularization of coronary stenoses.[13,14] These results were achieved despite a classification mismatch between FFR and iFR in approximately 20% of the cases.[15]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Vieira *et al*[16] describe their initial experience with the use of iFR to guide coronary revascularization decision-making in 96 lesions from 52 patients, accumulated for over four years. Out of these, 56 stenoses (58.3%) were graded as intermediate (between 41% and 70%), and 40 (41.7%) were classified as severe (between 71% and 90%), as determined by visual assessment of coronary angiography. In agreement with extensive previous validation, the authors used a cut-off value of iFR of ≤ 0.89[15] to classify stenoses as hemodynamically significant and decide upon the need for revascularization. Percutaneous coronary intervention (PCI) with stent implantation was the primary outcome used, which was performed in 32% of all studied lesions. However, the median and the interquartile range of iFR observed in intermediate (0.92 [0.82 to 0.94]) and severe (0.79 [0.61 to 1.00]) lesions draw our attention to the fact that a non-negligible proportion of lesions were treated with stent despite the absence of physiological significance as per the iFR evaluations – particularly those of intermediate severity (Figure 4, Vieira et al.[16]). These findings corroborate the idea that physiological information is just one (important) piece of the decision-making puzzle, which should take into account other equally important factors, such as clinical presentation, presence, type and frequency of anginal symptoms, target lesion location, left ventricular function and perspective of long-term prognosis.

Although relieving significant stenosis through mechanical intervention improves anginal symptoms more effectively than optimal medical treatment,[17,18] this practice does not result in major significant reductions of hard clinical events such as death and myocardial infarction.[8] It is noteworthy that about half the patients with a positive FFR have a favorable long-term prognosis when maintained on optimal medical therapy alone.[19,20] Thus, there is a significant opportunity for medical optimization of some stable patients regardless of the physiological significance of the lesion under investigation, particularly in asymptomatic or oligosymptomatic individuals with lesions that produce minimal physiological impact. These arguments leave room for disagreements with the outcome adopted by Vieira et al,[16] which was the performance of PCI or not. On the contrary, a much more complex and thorough assessment (including the physiological evaluation) should support the revascularization decision than simply the "positive" or "negative" value of a diagnostic index.

Keywords

Myocardial Ischemia; Fractional Flow Reserve; Myocardial Coronary Artery Disease; Coronary Stenosis; Risk Factors; Percutaneous Coronary Intervention.

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Short Editorial

Although the clinical decision for revascularizing coronary stenoses is binary, which ends up justifying the search for cut-off points that determine the choice of one strategy over another, we advocate that invasive coronary physiology should be assessed in a more comprehensive, continuous and interpretative manner. In this sense, similarly to what was demonstrated in the classical study by Hachamovitch et al.,[21] robust evidence indicates a linear association between FFR and the risk of adverse cardiac outcomes. Adverse outcome rates increased proportionally with reduced FFR values, revealing a risk continuum, far beyond a fixed cut-off point.[22,23] In addition, lesions with lower FFR values are the ones which receive the greatest absolute benefits from PCI.[23] On the other hand, for lesions with FFR values around the cut-off point, the benefits of revascularization are lower and at times uncertain.

Although ischemia determined at the vessel level – in other words, "positive" or "negative", as the sum of all lesions throughout the artery length – has been the traditional basis for FFR utilization, a series of technological advances have allowed for a more global and systematic approach to assessing the presence of myocardial ischemia. Through manual pullback of the pressure sensor, the non-hyperemic iFR index allows for the assessment of the functional impact of each lesion along the target vessel segment. Moreover, overlaying these results onto the angiographic images provides a valuable functional-anatomical co-registration. This technique yields a more accurate characterization on the distribution of the physiological effects of coronary heart disease, enabling the diagnosis of focal and diffuse disease (which frequently coexist in the same vessel), in addition to quantifying the contribution of each for the iFR value at the artery level. Furthermore, it is possible to simulate several PCI strategies and estimate the physiological results of the possible intervention. Hence, the result is an evolution from the binary negative/positive to a more comprehensive assessment of the physiological impact of CAD, and the potential benefits of PCI, in case this is the chosen therapeutic strategy. This concept proved to be particularly important in the recent DEFINE-PCI[24] pilot study. In a population of 500 patients undergoing PCI with stent implantation, whose procedures were considered successful by angiographic criteria, iFR pullback showed that 24% of the patients treated remained with physiologically significant stenoses. It is worth mentioning the finding that in more than 80% of the cases, the abnormal iFR matched focal stenoses, which are easily treatable, reaffirming the limitations of angiography in identifying coronary flow-limiting lesions. In cases with serial lesions or diffuse disease, the hyperemic flow through one stenosis is affected by the presence of another stenosis in the same artery, making interpretation of FFR values challenging in this frequent anatomic subset. On the other hand, resting flow is stable across almost the entire range of epicardial coronary stenosis severity. Thus, changes in resting pressure are more predictable, and the contribution of each stenosis along the vessel can be more easily estimated, representing a practical advantage of iFR over FFR.[25,26]

Therefore, we believe that the introduction of new indexes (e.g. angiography-derived FFR, coronary computed tomography-derived FFR, resting indexes, among others) and new possibilities of understanding the functional effects of coronary stenosis have promoted growing interest in invasive and non-invasive assessment of cardiac physiology in the "post-FFR era". We keep waiting the development of new physiological tools that enable the measurement of myocardial ischemia in an easier and more accurate way (instead of using surrogate outcomes), as well as tools to simplify the study of the coronary microcirculation status. These advances will contribute to a more individualized approach to coronary revascularization decision-making, better understanding of focal and diffuse disease, and treatment of post-MI patients whose microcirculation has been impaired. Until then, we advance our application of physiological assessment, from binary to continuous.

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Association between Periodontitis, Genetic Polymorphisms and Presence of Coronary Artery Disease in Southern Brazil

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Abstract

Background: **Periodontitis and coronary artery disease (CAD) share an inflammatory etiology; there is a recent concern regarding the investigation of an association between these two conditions. Current theories indicate that cytokines and proteins have an important role in this process. C-reactive protein and interleukin-6 are inflammatory derivatives produced in the presence of periodontitis and in the pathophysiology of coronary disease. The polymorphisms of CRP + 1444 C > T and IL6-174 G > C are recognized in the literature as being related to CAD.**

Objective: **This study investigates the association between periodontitis and coronary artery disease, through the presence of PCR and IL-6 polymorphisms.**

Methods: **We selected 80 patients who underwent diagnostic catheterization in the HU of UFSM. The presence of periodontitis was determined by the Community Periodontal Index, whereas the CAD was established by the medical report. DNA was collected from a saliva sample and the presence of polymorphism was determined by PCR and restriction enzymes. A significance level of 5% was adopted.**

Results: **The mean age of all participants (p = 0.035, OR 2.65; 95%CI: (1.02-6.87) male gender (p = 0.012, OR 3.37; 95% CI: (1.28- (p = 0.013, OR 3.66; 95% CI: (1.27-10.5)), PCR polymorphism + 1444C > T (p = 0.001, OR 6.37; 95% CI:, (2.25-17.9)) and IL6 -174 G > C polymorphism (p = 0.025, OR 2.87, 95% CI: (1.09-7.55)) were statistically associated with the presence of CAD. Age > 60 years and presence of the PCR +1444 C > T polymorphism remained independently associated with CAD after adjustment by logistic regression.**

Conclusions: **The presence of the PCR + 1444 C > T polymorphism in this study was independently associated with the presence of coronary artery disease. (Arq Bras Cardiol. 2020; 114(2):268-272)**

Keywords: **Periodontitis; Polymorphism, Genetic; Coronary Artery Disease; C-reactive Protein; Epidemiology.**

Introduction

Periodontitis is a chronic inflammatory disease, induced by biofilm consisting of gram-negative bacteria, leading to the destruction of the tissues supporting the tooth,[1-3] with high prevalence worldwide.[4] The presence of periodontitis triggers the immune system, locally and at distant sites, high concentrations of cytokines and proinflammatory proteins, as well as bacteremia and endotoxemia caused by the bacteria that populate the disease site.[5]

Coronary artery disease (CAD) is a chronic, complex, multifactorial, continuous inflammatory condition that consists in the accumulation of atheromatous plaques in the intima layer of the coronary arteries,[6-9] being responsible for acute coronary syndromes, the main cause of death in the Western hemisphere.[6,7]

Inflammation plays a very important role in both periodontitis and CAD. In order to associate these two conditions, two biologically plausible theories were developed, focusing on the direct and indirect action of the oral bacteria present in periodontitis with the inflammatory and pro-atherogenic mediators.[1,2,4,10-14]

Based on the inflammatory and immunological theories, several studies have been conducted aiming to establish this association through the genetic factor, the presence of polymorphisms in the genes that express the production of these factors and are associated to periodontitis, such as C-Reactive Protein (CRP) and interleukin-6 (IL-6).[15-19]

The simple nucleotide polymorphism (SNP) of the IL-6 promoter gene may affect the production and expression of this cytokine; consequently, this change in serum levels may result in a relevant biological response.[18] The association between the SNP variant -174 G > C (rs1800795) and the increased risk of inflammatory diseases such as CAD has been previously demonstrated.[17,20]

Studies point to the SNP rs1136804, also represented as 3 'UTR +1444 C > T, as the polymorphism with greater associations with CAD.[15,17]

The high prevalence of periodontitis, as well as the high risk of mortality from CAD and a scarcity of studies in this area led to the study of the association between periodontitis and coronary artery disease, by assessing the presence of PCR and IL-6 polymorphisms.

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Methods

The sample consisted of 80 patients (mean age 60.5 ± 10.5) who underwent diagnostic cardiac catheterization in the hemodynamic laboratory of the University Hospital of *Universidade Federal de Santa Maria* (HUSM) from September 1, 2010 to March 30, 2011 and who agreed to participate in the study by signing the informed consent form.

Were excluded for the sample Patients who were smokers, diabetics, those with autoimmune diseases and those with fewer than two teeth present in one of the sextants, as well as those who did not agree to participate in the study.

The study was approved by the Ethics and Research Committee of the São Leopoldo Mandic Dental Research Center on 11/26/2014, CAAE: 35879614.7.0000.5374.

Periodontal examination was performed by the researcher, using the Community Periodontal Index (CPI) and Periodontal Insertion Loss Index (PIP), as recommended by the World Health Organization.[21] The use of this index was justified by the partial immobilization of the patient in bed and the short time in which it was available to the examiner. Patients with a CPI score of 3 or 4 and a PIP score above 1 were considered as having periodontitis.

DNA was extracted from a saliva sample obtained through a mouthwash with 3% glucose solution for 1 minute, and then this material was deposited in capped, sterile test tubes and frozen at -20°C.[22]

The diagnosis of CAD was performed through cardiac catheterization, via femoral or radial access, performed by the physicians of the hemodynamic laboratory of the Santa Maria University Hospital. Patients with a positive medical report for the presence of coronary stenosis were considered as having CAD.

Genotyping

DNA was extracted from saliva samples had using a genomic DNA extraction kit (Norgen Biotek Corp, Canada), and gene amplification was performed by the polymerase chain reaction using the following primer pairs for the +1444 PCR: forward 5 '- AGCTCGTTAACTATGCTGGGGCA-3' and reverse 5 - CTTCTCAGCTCTTGCCTTATGAGT-3 ', with an annealing temperature of 60 °C and for IL-6 -174: forward 5'-AACCTAATTCTACCCCCCTTGG-3 and reverse 5'-TCAGAGGCAGCCGAAGAGTT-3', with an annealing temperature of 59°C.17

The amplification was carried out using one cycle at 95°C for 3 min, 29 cycles at 95°C for 1 minute, with annealing temperature varying as cited, for 1 minute, 72°C for 1 minute and a of 72°C cycle for 10 minutes, performed in an automatic cycler.

Polymerase chain reaction results were then digested by SduI (Thermo Fischer Scientific, Massachusetts, USA) for +1444 PCR and HaeIII (Thermo Fischer Scientific, Massachusetts, USA) for IL-6 -174, using the specified amounts. The resulting fragments were identified by silver-stained 8% polyacrylamide gel electrophoresis. Genetic analyses were performed in July 2017 at the São Leopoldo Mandic molecular biology laboratory, Campinas, SP.

Statistical analysis

The variables were categorized as follows: CAD as present or absent, periodontitis as present or absent, age ≥ 60 years or ≤ 59 years, gender as male or female, ethnicity as white or non-white, overweight and obesity when BMI was ≥ 25 and ≤ 24 and polymorphisms by the presence or absence of the risk allele. The outcome was the presence or absence of CAD.

A significance level of 5% ($p < 0.05$) was used. The sample was divided into two groups, according to the presence of CAD; case group with 52 patients (mean age of 62.8 ± 11.2) and control group with 28 patients (mean age of 56.2 ± 8.8).

The distribution of the genotypes of the two SNPs was tested for the Hardy-Weinberg equilibrium by chi-square test (x2), the collected variables were crossed with the chi-square with odds ratio (OR) and 95% confidence interval (95%CI)

The variables that showed statistical significance were submitted to adjustment through a binary logistic regression with CAD as outcome and 95% CI.

All data collected were treated using the SPSS© version 25 software (IBM© Corp., New York, NY).

Results

Table 1 shows the association between the studied variables and the presence of coronary artery disease, and it was observed that the age categorized as the cut-off of the mean of all participants, 60 years ($p = 0.035$), male gender ($p = 0.012$) and patients with periodontitis ($p = 0.013$) were statistically related to the presence of CAD. Patients with the + 1444 C > T polymorphism, with the presence of risk allele T ($p = 0.001$), as well as those with the IL6 -174 G > C polymorphism, with risk allele C ($p = 0.025$), were associated with the presence of CAD.

A binary logistic regression analysis was carried out, in which all the significant independent variables were included in the bivariate analyses in a direct way, with the objective of verifying which of them would be predictors of the dependent variable, i.e., the presence of CAD.

The result of this adjustment (Table 2) showed that the presence of CAD was still associated with age > 60 years ($p = 0.029$) and the presence of the PCR polymorphism +1444 C > T ($p = 0.014$).

Discussion

Periodontitis is a chronic, multifactorial inflammatory disease, resulting from a series of dysbiosis processes, activating the production of proteins and proinflammatory cytokines and signaling processes, thus, according to recent epidemiological, interventional and functional studies, establishing a causal association with the development of coronary artery disease.[10-12,16]

The dichotomized age over 60 years and the male gender were also statistically associated with a higher probability of presenting CAD. It is noteworthy that age and male gender are already known risk factors for coronary artery disease and periodontitis,[23] so much so that many studies adjust for these factors only when analyzing atherosclerosis. However,

Table 1 – Variables analyzed by chi-square with CAD as outcome

Analyzed variables		CAD n = 80		OR	CI (95%)		p
		Present (%)	Absent (%)		Min.	Max.	
Age	≥ 60 years	31 (59.6)	10 (35.7)	2.65	1.02	6.87	0.04
	≤ 59 years	21 (40.4)	18 (64.3)				
Gender	Male	32 (61.5)	9 (32.1)	3.37	1.28	8.9	0.01
	Female	20 (38.5)	19 (67.9)				
Overweight and obesity	BMI ≥ 25	30(57.7)	22 (78.6)	2.68	0.93	7.73	0.35
	BMI ≤ 24	22 (42.3)	6 (21.4)				
Ethnicity	White	45 (86.5)	22 (78.6)	1.75	0.52	5.84	0.06
	Non-White	7 (13.5)	6 (21.4)				
Periodontitis	Present	26 (50%)	6 (21.4)	3.66	1.27	10.5	0.01
	Absent	26 (50%)	22 (78.6)				
CRP +1444 C>T RS 1130864	T Allele	43 (82.7)	12 (42.9)	6.37	2.25	17.9	0.001
	Non T allele	9 (17.3)	16 (57.1)				
IL6-174 G>C RS 1800795	C Allele	30 (57.7)	9 (32.1)	2.87	1.09	7.55	0.029
	Non C allele	22 (42.3)	19 (67.9)				

CAD: coronary artery disease; OR: Odds Ratio, CI: confidence interval, significant when the range does not contain the unit. significant p-value < 0.05. Source: The author.

Table 2 – Variables adjusted by logistic regression

Variables	Chi-square				Logistic regression			
	p	OR	CI (95%)		p	OR	CI (95%)	
			Min.	Max.			Min.	Max.
Age ≥ 60 years	0.04	2.65	1.02	6.87	0.02	3.6	1.14	11.3
Male gender	0.01	3.37	1.28	8.91	0.37	1.71	0.51	5.67
Periodontitis present	0.01	3.66	1.27	10.5	0.16	2.47	0.68	8.9
CRP +1444 polymorphism	0.001	6.37	2.25	17.9	0.014	4.31	1.34	13.8
IL6 -174 polymorphism	0.029	2.87	1.09	7.55	0.06	2.94	0.94	9.19

Significant p-value < 0.05; OR: Odds Ratio; CI: confidence interval, significant when the range does not contain the unit. Source: The author.

regarding the association between periodontitis and CAD, with the influence of other independent covariates, it was decided to keep them, in view of the contribution of adjustments in logistic regression models.

The presence of periodontitis in the bivariate analysis was significantly associated with CAD (p = 0.013; OR = 3.66 CI (95%) 1.27-10.5). This association has been studied for decades. A cross-sectional study with 60,174 participants that analyzed the association between periodontitis and CAD found a statistically significant association between the two conditions with an odds ratio of 1.59 and CI (95%) between 1.31 and 1.81, after adjustment for confusion factors.[23]

In the present study we verified the association between periodontal inflammation and polymorphisms (IL6 and CRP) aiming to verify its possible association with CAD. We observed a strong association (p = 0.001) between the presence of the PCR + 1444 C > T polymorphism, risk allele T and the case group with OR = 6.37; (95%) 2.25 - 17.9, which contradicts authors who analyzed five studies, totaling 18,637 participants, where the PCR + 1444 C > T polymorphism was adjusted for confounding factors and compared regarding the presence of CAD, but found no association between this polymorphism and coronary disease.[24] It is possible to infer that this association may arise from CRP serum levels maintained by chronic periodontitis over several years.

The presence of this association is corroborated by studies comparing the size of atherosclerotic plaques in relation to the PCR polymorphism at this SNP (+1444 C > T) in 196 patients with CAD from a database of studies evaluating the use of nitrates (ENCORE) in Switzerland, concluding that the carriers of this polymorphism were independently prone to larger plaque volumes.[15]

These results lead us to believe that somehow the presence of this polymorphism, probably through CRP serum levels, acts directly in the atherosclerotic process, as indicated by recent studies.[25,26]

The IL6 -174 G > C polymorphism was statistically associated with the presence of CAD (p = 0.025, OR = 2.87 CI (95%)

1.09-7.55). These findings are in agreement with authors who investigated the association of this polymorphism with the risk of CAD in 484 Chinese individuals, and found that the IL6 -174 G > C polymorphism was positively associated with the risk of CAD (p = 0.001 OR = 2.18 CI 95%) 1.26 - 3.77), in agreement to our findings, but with a higher statistical significance.[18]

In a recent study, 280 patients were analyzed in an attempt to correlate five polymorphisms, among them IL6 -174 G > C, with CAD in a population from northern India. In this analysis, the authors did not find any statistical significance regarding this polymorphism and CAD.[20] Similarly, Brazilian authors analyzed 200 patients with acute coronary syndrome and their association with the presence of the IL6 -174 G > C polymorphism in Pernambuco, Brazil, and found no significant association between the presence of the risk alleles and acute coronary syndrome.[27]

The variables that were significant were included in a bivariate logistic regression model with the purpose of adjusting the independence of these associations, verifying which of them would predict CAD. The most uniform model was the one that remained independently associated with CAD, age > 60 years and the presence of the +1444 C > T PCR polymorphism (table 2).

Considering the limitation of the type of study (case-control) where the information about the exposure or factor is obtained after the occurrence of the disease and there is no way to differentiate the chronology between the exposure and the disease onset, to determine a direct causal association between periodontitis and CAD becomes more difficult. The fact that this association is present may indicate preventive and curative treatments for the control of periodontitis, aiming to reduce the group of factors that contribute to the formation and development of CAD, besides the known risk factors.

Conclusions

Based on the analyzed data, it can be concluded that the age over 60 years and the presence of the PCR + 1444 C > T polymorphism were independent predictors associated with coronary artery disease.

The presence of periodontitis and male gender did not remain associated with CAD after adjusting by logistic regression.

Author contributions

Conception and design of the research and Obtaining financing: Rocha LO, Brito Junior RB; Acquisition of data: Rocha LO, Rocha E, Brito Junior RB; Analysis and interpretation of the data: Rocha LO, Rocha E, Succi GM, Brito Junior RB; Statistical analysis: Rocha LO, Rocha E; Writing of the manuscript: Rocha LO, Rocha E, Succi GM, Brito Junior RB; Critical revision of the manuscript for intellectual content: Rocha LO, Succi GM, Brito Junior RB.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of Doctoral submitted by Luiz Otávio Rocha, from *Centro de Graduação São Leopoldo Mandic*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Centro de Graduação São Leopoldo Mandic* under the protocol number CAAE: 35879614.7.0000.5374. 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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Atherosclerosis, Inflammation, and Genetics – And you Thought it Was Just LDL-cholesterol

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Short Editorial related to the article: Association between Periodontitis, Genetic Polymorphisms and Presence of Coronary Artery Disease in Southern Brazil

As the twentieth century unfolded, based on numerous epidemiological observations and intervention trials, cardiovascular risk factors were identified and targeted with the aim of decreasing cardiovascular disease burden worldwide. Along the centuries, changes in human eating patterns, a progressive decrease in physical activity, and a higher prevalence of obesity, all of which are contributing factors to the alarming rates of diabetes, hypertension, and hypercholesterolemia we see in our daily practice, have led us to assume that atherosclerosis-related disorders (myocardial infarction, ischemic cardiomyopathy, stroke, and peripheral artery disease) are an inevitable consequence of the evolutionary process we have to face in present times. However, due to advances in noninvasive imaging of the vascular system, atherosclerotic lesions in the aorta and coronary and carotid arteries happen to be found in mummies from ancient Egypt,[1] whose estimated mean age at the time of death was only 45 years.

If the so-called "classical risk factors" were less prevalent in ancient times, different, non-traditional factors must have played a significant role in the development and progression of atherosclerosis.[2] Microbial and parasitic inflammatory burdens that were likely present in ancient cultures inherently lacking modern hygiene and antimicrobials could have evoked a chronic inflammatory status. Given that patients with today's chronic systemic inflammatory diseases, including human immunodeficiency virus infection, systemic lupus erythematosus, and rheumatoid arthritis experience early-onset atherosclerosis and coronary events, is it possible that the chronic inflammatory load secondary to infection resulted in atherosclerosis in ancient times? Moreover, atherosclerosis is a complex, multifactorial biological process, and, as such, it is also subject to gene-environment interplay; therefore, although the contribution of today's classical risk factors to the development of atherosclerosis is inquestionable, their role in the appearance of atherosclerotic lesions in the vascular tree involves not only inflammation and activation of the immune system but also genetic factors that facilitate or oppose the formation of lipid accumulation in the arterial wall.

Progress in cell and molecular biology has allowed us to refine our understanding of the mechanisms involved in the onset of atherosclerosis. LDL-cholesterol particles play a significant role in the genesis of atherosclerotic plaque in the presence of endothelial dysfunction, an omnipresent feature in individuals with cardiovascular risk factors.[3] Proliferation and migration of smooth muscle cells in response to the release of growth factors and the accumulation of mononuclear phagocytes rich in plasma-derived lipids (foam cells) contribute to the development of atheroma.[4] Further studies revealed that the immune system played a role in atherosclerosis through not only innate (macrophages) but also adaptive (T cell and other lymphocytes) pathways.[5] Cells directly involved in atherosclerosis establish a complex network of cross-talking by the release of cytokines, notably interleukin-1.[6]

Once recognized as an inflammatory disease, a highly sensitive assay for the measurement of C-reactive protein (hsCRP) proved to be a marker for patients at high risk for cardiovascular events due to atherosclerosis and a useful tool in selecting patients for aggressive lipid control for risk reduction. In the JUPITER trial, statin therapy in patients with hsCRP values above the median for the population (> 2 mg/L) but with LDL-cholesterol level < 130 mg/dL had a 44% reduction in first-ever cardiovascular events.[7] More recently, the CANTOS trial allocated the anti-interleukin-1 antibody (canakinumab) to patients with stable post-acute coronary syndromes who had hsCRP values > 2 mg/L on statin therapy.[8] Individuals who achieved a reduction of hsCRP to < 2 mg/L in response to anti-inflammatory therapy had a > 30% reduction in cardiovascular and all-cause mortality.[9]

It is now widely accepted that genetic factors also contribute significantly to the risk of coronary artery disease (CAD), and the heritability of CAD has been estimated to be between 40% and 60%.[10] Using genome-wide association studies (GWAS), common single nucleotide polymorphisms (SNP) present in ≥ 5% of the population across the human genome can be identified, and the allele frequency of each SNP can be compared in cases and controls. The first association of CAD revealed by the GWAS approach was a block containing multiple SNP at 9p21.3 locus.[11] Since then, new SNP have been found to correlate significantly with the presence and extension of atherosclerotic CAD; these SNP are related to different aspects that govern the biology of atherosclerosis including, but not limited to, cell-to-cell interactions, immune response, cholesterol absorption, and lipoprotein(a) levels.[12] The CRP gene +1444C > T variant in the 3' untranslated region (UTR) influences both basal and stimulated CRP levels.[13]

Keywords

Atherosclerosis/physiopathology; Inflammation; Coronary Artery Disease/history; Mortality and Morbidity; Polymorphism, Genetic; Risk Factors.

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Short Editorial

Investigators from different research facilities have produced a complex, most likely still incomplete picture of the intricate relationship between inflammation-infection, genetics, and atherosclerotic diseases like CAD. In this issue of the *Brazilian Archives of Cardiology*, Rocha et al.,[14] sought to investigate the link between periodontal disease (as a model of chronic inflammatory condition) and two specific polymorphisms in genes knowingly related to inflammation (C-reactive protein and interleukin-6), with the presence of CAD in 80 patients from the South Region of Brazil referred for invasive coronary angiography. They found in the multivariate model that male gender and the CRP gene +1444C > T variant were significantly associated with the presence of CAD.

The authors should be congratulated for their contribution to the field, because replicating the finding of a significant association between a specific SNP and clinical outcomes in different populations strengthens the finding's relevance to the occurrence of the measured outcome. Nevertheless, the study would benefit from providing the levels of hsCRP in the population study (as a measurement of chronic inflammatory status) and further detailing the extension of the obstructive pattern, rather than only a dichotomous classification of CAD present/absent based on the medical report. Additionally, I would be very cautious in dismissing the possible association between the IL-6 gene variant and the presence of CAD because of the small number of patients included in the study, which yielded a marginal statistical significance in the multivariate model (p-value = 0.06), given that this association has been validated in previous studies mentioned by the authors.

Despite its limitations, the work by Rocha et al.[14] draws clinical cardiologists' attention to the fact that genetics has gone beyond the laboratory and is currently making its way into clinical practice, at least as a tool to help us better understand how different our patients are, even if they are exposed to the same risk factors with which we are all too familiar. We will have to learn how to apply genetic risk scores that may improve our ability to predict the risk of CAD[14] beyond what is estimated based on traditional risk factors alone. Gregor Mendel would be delighted to see how far we have come from his early experiments with pea plants more than 150 years ago, but the road to fully understanding the role of genetic factors in complex diseases such as atherosclerosis or hypertension is a long, albeit fascinating one.

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Evaluation of Electrocardiographic Ventricular Depolarization and Repolarization Variables in Type 1 Diabetes Mellitus

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Abstract

Background: **The risk of cardiovascular events and sudden death increases with type 1 diabetes mellitus (T1DM).**

Objective: **To evaluate electrocardiographic markers of arrhythmias in T1DM patients.**

Methods: **Electrocardiographic parameters reflecting ventricular depolarization and repolarization, namely, QT, QTc, QTd, QTdc, Tp-e, JT, and JTc intervals and Tp-e/QT and Tp-e/QTc ratios, of 46 patients diagnosed with T1DM were retrospectively analyzed and compared with 46 healthy age-, sex-, and body mass-matched controls. Correlations between T1DM duration, hemoglobin A1c (HbA1c), and ventricular repolarization variables were analyzed. P values lower than 0.05 were considered statistically significant.**

Results: **Diabetes duration was 16.6 ± 7.1 years, and HbA1c was 10.81% ± 3.27% in the T1DM group. In comparison with the control group, heart rate, QTc, QTd, QTdc, Tp-e and JTc intervals, Tp-e/QT ratio ($p < 0.001$), and Tp-e/QTc ratio ($p = 0.007$) were significantly higher in T1DM patients. T1DM duration and HbA1c levels were significantly correlated with QTc, QTd, QTdc, Tp-e, and JTc intervals and Tp-e/QT and Tp-e/QTc ratios.**

Conclusions: **In T1DM patients, potential electrocardiographic repolarization predictors were significantly increased in correlation with disease duration and HbA1c levels. These findings may contribute to the understanding of sudden cardiac death in patients with T1DM. (Arq Bras Cardiol. 2020; 114(2):275-280)**

Keywords: **Diabetes Complications; Risk Factors; Prevention and Control; Arrhythmias, Cardiac; Electrocardiography/methods.**

Introduction

Diabetes is a major health problem that is associated with various comorbidities such as hypertension, cardiovascular diseases, metabolic syndrome, and cardiopulmonary diseases. Over long periods of time, it is also a major underlying risk factor for coronary heart disease, heart failure, peripheral artery disease, atrial fibrillation, chronic renal failure, and stroke. It is also associated with an increased mortality risk.[1-4]

The interval between the beginning of the QRS complex and the end of the T wave in the surface electrocardiogram (ECG) reflects ventricular depolarization and repolarization. Cardiac electrical changes during ventricular repolarization may lead to lethal arrhythmias.[5] Sudden death risk is also increased in type 1 diabetes mellitus (T1DM) subjects.[6] Accordingly, prolonged repolarization has been speculated to play a role in sudden death among T1DM patients.[6]

In this study, we aimed to evaluate potential ventricular arrhythmia predictors of surface ECG, namely, QT and corrected QT (QTc) intervals, QT dispersion (QTd), corrected QTd (QTdc), Tp-e, JT and JTc intervals, and Tp-e/QT and Tp-e/QTc ratios, in patients with T1DM.

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Methods

Study population

ECG records of 46 patients with T1DM, who were followed in the endocrinology and metabolism diseases outpatient clinic of our hospital between January 2017 and May 2018, were retrospectively analyzed and compared with the ECG results of 46 age-, sex-, and body mass-matched controls. T1DM was defined according to the American Diabetes Association criteria.[7]

Patients over the age of 45 were not included due to increased probability of unknown atherosclerosis and comorbidities that may affect ECG. Subjects who had history of coronary artery disease, peripheral artery disease, heart failure, structural heart disease, chronic lung disease, liver or renal failure, thyroid disorders, malignancies, electrolyte imbalances, or any other systemic disease and subjects who were using any drug (e.g. betablockers, calcium channel blockers, antidepressant drugs, etc.) other than insulin were excluded. Subjects who had history of ventricular arrhythmias or atrial fibrillation and subjects who had low QRS voltage, increased QRS duration, left-axis deviation, hypertrophic findings, nonspecific flattening of the T waves, left atrial abnormalities, or ST segment depression on ECG were also excluded due to the probable effects of these ECG changes on the measured ECG parameters.

Electrocardiography

Twelve-lead ECGs were obtained following a 10-minute rest period, with 10 mm/mV amplitude and 25 mm/s rate with standard lead positions in a supine position, using a commercially available machine (Nihon Kohen Cardiofax ECG-1950 VET). Depending on heart rate, there were four to six beats per lead. ECGs were manually measured, using a magnifying glass (TorQ 150 mm Digital Caliper LCD) by two blinded cardiologists who had no information about the patients. QT intervals were taken from the onset of the QRS complex to the end of the T wave, which was defined as its return to the TP baseline. If U waves were present, the QT interval was measured at the nadir of the curve between the T and U waves. The R-R interval was measured and used to compute the heart rate and to correct QT interval (QTc) with Bazett's Formula.[8] QT dispersion (QTd) was determined as the difference between the maximum and minimum QT interval in different leads. The Tp-e interval was defined from the peak of T wave to the end of T wave. Measurements of Tp-e interval were performed from precordial leads. Rate QTc and corrected QT dispersion (QTdc) were calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). JT intervals were measured from the end of the QRS complex (J point) to the end of the T wave (JTend interval). JTc was calculated using Bazett's formula ($JTc = JT/\sqrt{RR}$). Tp-e/QT and Tp-e/QTc ratios were also calculated. No patient had fewer than nine measurable leads. Intraobserver and interobserver variations for measurements were less than 5%, and the means of the values defined by the cardiologists were used for analysis.

Statistical analysis

Analyses were carried out using SPSS 20.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA). Quantitative variables are expressed as mean ± standard deviation (SD), and qualitative variables are expressed as numbers and percentages. The Kolmogorov-Smirnov Test was used to determine if the data were normally distributed. ECG parameters were normally distributed, and disease duration and hemoglobin A1c (HbA1c) levels were not normally distributed. Differences between independent groups were assessed by Student t-test for quantitative variables that were normally distributed and chi-square test for qualitative variables. Spearman correlation analysis was used to examine possible associations between T1DM duration, HbA1c, and ventricular repolarization parameters. P values lower than 0.05 were considered statistically significant.

Results

Mean diabetes duration was 16.6 ± 7.1 years, and mean HbA1c was 10.81% ± 3.27% in the T1DM group. Mean age, systolic blood pressure (BP), diastolic BP, body mass index (BMI), and frequencies of sex, smoking, and hyperlipidemia were not significantly different between study patients and control group (Table 1).

In comparison with the control group, heart rate, QTc, QTd, QTdc, Tp-e and JTc intervals, and Tp-e/QT and Tp-e/QTc ratios were significantly higher in T1DM patients (Table 2).

T1DM duration and HbA1c levels were significantly correlated with QTc, QTd, QTdc, Tp-e and JTc intervals, and Tp-e/QT and Tp-e/QTc ratios (Table 3).

There were no significant correlations between gender, age, BMI, blood pressure, and the measured ECG parameters.

Discussion

In this study we have found that, in correlation with disease duration and HbA1c levels, QTc, QTd, QTdc, Tp-e, and JTc intervals and Tp-e/QT and Tp-e/QTc ratios on surface ECG, which may be associated with ventricular arrhythmias and sudden death, were significantly increased in T1DM patients. As far as we know, there is no study in the literature that investigates Tp-e and JT intervals or Tp-e/QT and Tp-e/QTc ratios in T1DM patients.

T1DM patients are at major risk for ventricular arrhythmias and sudden cardiac death.[9] Presence of reentry circuits, triggered activity, and increased autonomy are among possible mechanism for ventricular arrhythmias. The pathophysiological mechanisms behind arrhythmias have not been fully established in diabetic patients. Structural abnormalities caused by prolonged hyperglycemia and increased fibrosis in the myocardium have been speculated.[10,11] Myocardial fibrosis, cell loss in the living myocardial tissue and myocardial conduction pathways can create a favorable environment for the formation of micro-reentry circuits. Ventricular arrhythmias may also be triggered by the contribution of impaired electrical balance of the heart and increased sympathetic activity.[12,13]

QT, QTc, and QTd have been shown to predict ventricular arrhythmic events and sudden death in various clinical situations.[14,15] QT interval is an independent predictor of all-cause and cardiovascular mortality in individuals with type 2 diabetes.[16] QT interval represents the time from beginning of ventricular

Table 1 – General characteristics of the study groups

Baseline characteristics	T1DM (n = 46)	Control group (n = 46)	p value
Age (years)	33.8 ± 8.8	33.8 ± 6.2	1.000
Male/female	28/18	28/18	1.000
Systolic BP (mmHg)	124.4 ± 8.7	121.4 ± 6.7	0.069
Diastolic BP (mmHg)	81.0 ± 4.1	78.4 ± 3.3	0.581
Smoking	7 (15.2%)	9 (19.6%)	0.587
Hyperlipidemia	3 (6.5%)	3 (6.5%)	1.000
BMI	24.2 ± 4.7	24.1 ± 4.8	0.955

BMI: body mass index; BP: blood pressure; T1DM: type 1 diabetes mellitus.

Table 2 – Electrocardiographic findings of the study population

	T1DM (n = 46)	Control group (n = 46)	p value
Heart rate (bpm)	84.0 ± 16.9	68.3 ± 11.3	< 0.001
QT ms	352.6 ± 27.4	362.4 ± 22.9	0.068
QTc ms	412.9 ± 36.0	384.2 ± 24.6	< 0.001
QTd ms	29.7 ± 13.8	15.2 ± 6.0	< 0.001
QTdc ms	34.5 ± 15.0	16.1 ± 6.6	< 0.001
Tp-e ms	90.3 ± 8.1	74.8 ± 9.9	< 0.001
JT ms	275.1 ± 23.7	278.8 ± 24.7	0.456
JTc ms	321.6 ± 26.0	295.5 ± 24.7	< 0.001
Tp-e/QT	0.26 ± 0.03	0.21 ± 0.03	< 0.001
Tp-e/QTc	0.22 ± 0.03	0.20 ± 0.03	0.007

Bpm: beats per minute; JT: interval from the end of the QRS complex (J point) to the end of the T wave; JTc: corrected JT interval; ms: millisecond; QT: interval from the beginning of the QRS complex to the end of the T wave; QTc: corrected QT interval; QTd: QT dispersion, the difference between the maximum and minimum QT intervals; QTdc: corrected QT dispersion; Tp-e: T-peak to T-end interval.

Table 3 – Correlations of T1DM disease duration and HbA1c levels with electrocardiographic parameters

	T1DM duration (years)	HbA1c (%)
QTc ms	r = 0.417, p < 0.001	r = 0.414, p < 0.001
QTd ms	r = 0.600, p < 0.001	r = 0.353, p < 0.001
QTdc ms	r = 0.669, p < 0.001	r = 0.608, p < 0.001
Tp-e ms	r = 0.606, p < 0.001	r = 0.602, p < 0.001
JTc	r = 0.443, p < 0.001	r = 0.525, p < 0.001
Tp-e/QT	r = 0.615, p < 0.001	r = 0.608, p < 0.001
Tp-e/QTc	r = 0.357, p < 0.001	r = 0.352, p = 0.001

depolarization to completion of repolarization. Because QT is typically affected by heart rate, the heart rate-corrected QT interval (QTc) has been proposed as a more appropriate measure of QT.[17] In many cardiovascular and non-cardiovascular diseases, QTc was shown to be increased.[18] QTc prolongation has been suggested as an independent marker of ventricular arrhythmias, sudden death, and increased mortality in patients with T1DM as well.[17,19-22] T1DM patients have been shown to present a positive association of QTc prolongation with age, diabetes duration, and poor metabolic control.[23] Accordingly, we have also found a positive correlation between QTc and T1DM duration and HbA1c levels.

QTd, which is defined as the difference between the maximum and minimum QT interval on surface 12-lead ECG,[24] represents ventricular repolarization heterogeneity and is reported as a predictor of ventricular arrhythmias.[24,25] Increased QTd has also been associated with sudden cardiac death.[26,27] Tokatli et al. reported that QTd was prolonged in patients with type 2 diabetes mellitus in comparison with controls.[28] In this paper, we found that QTd was significantly increased in T1DM patients as well, in correlation with disease duration and glycemic control measured by HbA1c. Uysal et al. have found that QTc and QTdc were prolonged in children and adolescents with T1DM.[29] This prolongation, however, was not associated with disease duration and glycemic control, which may be explained by the relatively young age and short disease duration.

QT interval is composed of depolarization and repolarization components, and it is also affected by QRS period.[30] However, JT interval is the component of the QT interval that reflects ventricular repolarization alone.[31] It has been suggested that JT interval may be a more specific repolarization marker than the QT interval.[32] JT interval may also be affected by heart rate. Therefore, JTc may be more appropriate. Accordingly, Alizade et al.[33] reported that prolonged JTc was associated with ventricular arrhythmias.

Tp-e interval is also a relatively new ECG parameter showing ventricular repolarization. It has been associated with ventricular arrhythmias and sudden death, even in patients with normal QTc.[34,35] Tp-e/QT ratio has also recently been used as a new electrocardiographic marker for ventricular repolarization,[36] and it has been reported to be associated with malignant ventricular arrhythmias.[37]

Most studies assessing ventricular depolarization or repolarization abnormalities in T1DM have used QTc duration and QTdc. However, Tp-e, JT, JTc intervals, and Tp-e/QT and Tp-e/QTc ratios have not been studied. We have found that, in addition to QTc and QTdc, Tp-e and JTc intervals and Tp-e/QT and Tp-e/QTc ratios are increased in T1DM subjects, in association with disease duration and HbA1c levels.

Limitations

Manual calculation of measurements instead of computer-assisted calculations may be a limitation. Automated measurement systems have been developed for QT measurement, but some problems currently exist with these systems.[38] Manual identification of T-end is also problematic, cardiologist-dependent, and poorly reproducible. Therefore, automated methods may be preferrable.[39] Long-term ambulatory ECG monitorization methods might be valuable for documenting the association between the surface ECG parameters studied and arrhythmias. The number of patients in our study was relatively small. A larger patient population would provide more precise results. Association between ECG parameters may be evaluated along with other potential mechanisms for sudden death, such as autonomic dysfunction and fibrosis detected by magnetic resonance imaging. Lack of clinical follow up of the patients regarding arrhythmias and sudden death is another important limitation.

Conclusions

Previous studies have shown that QTc and QTdc prolongation is important in terms of malignant ventricular arrhythmias in patients with T1DM.[40] However, Tp-e and JTc intervals and Tp-e/QT and Tp-e/QTc ratios had not previously been measured in patients with T1DM. This study shows that these relatively new repolarization indices and potential electrocardiographic predictors of ventricular arrhythmias are significantly increased in T1DM. Further studies are needed to confirm our results. We hope that clinical significance of this finding for the prediction of malignant arrhythmias will be evaluated in future long-term follow-up and large-scale prospective studies.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Inanır M, Gunes Y, Sincer I, Erdal E; Acquisition of data: Inanır M, Gunes Y; Obtaining financing: Inanır M, Gunes Y, Erdal E; Critical revision of the manuscript for intellectual content: Inanır M, Gunes Y.

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 Abant Izzet Baysal University Hospital under the protocol number 2018-216. 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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Clinical Significance of Statistical Diferences

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Short Editorial related to the article: Evaluation of Electrocardiographic Ventricular Depolarization and Repolarization Variables in Type 1 Diabetes Mellitus

Diabetes is a serious chronic condition that occurs when your body cannot produce any or enough insulin or cannot effectively use the insulin it produces, resulting in high blood glucose levels. The so-called type 1 diabetes is caused by a set of genetic, environmental and autoimmune factors affecting insulin-producing pancreatic beta cells.[1]

Elevated blood glucose levels even below the diagnostic threshold of diabetes are associated with complications with the greatest impact on morbidity and mortality among people with diabetes.[2] Systematic reviews involving 102 prospective studies in diabetic patients indicate that the relative risk of cardiovascular disease (CVD) is between 1.6 and 2.6, greater in younger people and slightly higher in women.[3]

Data published in the recent International Diabetes Federation (IDF Atlas) Atlas confirm that diabetes is one of the largest public health emergencies of the 21st century. By 2019 it is estimated that 468 million people have diabetes and projected to 578 million in 2030, and the alarming number of 700 million in 2045. The estimates are impressive: 135 million cases over 65 years of age; more than one million children and adolescents have type 1 diabetes; four million diabetes-related deaths in 2019 among 20- to 79-year-olds. All these numbers with a significant variation between the various regions of the world.[4]

The search for risk markers with the potential to predict diabetes-related adverse outcomes is constant. The high mortality risk of individuals with diabetes cannot be fully explained only by CVD or cardiovascular risk factors.[5]

The article by Inanir et al.[6] in this issue retrospectively analyses electrocardiograms of patients with type 1 diabetes without comorbidities and without any medication except insulin, followed at the endocrinology outpatient clinic of Bolu City University Hospital, Turkey. Patients were compared to a control group of non-diabetic patients matched for age, sex, and body mass index, both groups younger than 45 years. The tracings were analyzed by two cardiologists blinded to the patients' conditions, focusing on the period of ventricular depolarization / repolarization with the various intervals and corrections for heart rate and the relationship with each other. The intervals QT, QTc, QTd, QTdc, Tp-e, JT, and Tp-e/QT, and Tp-e/QTc ratios were calculated. The correlation of these variables with disease duration and HgA1c value was also analyzed. There were statistically significant differences between the two groups with QTc of 412.9 ± 36 ms versus 384.2 ± 24.6 ms in diabetics compared with controls, respectively ($p < 0.001$), with a correlation with disease duration and HgA1c levels.

Several reports in the literature support that an increased QT interval represents a trigger for ventricular arrhythmias and even sudden death, with predictive value for all-cause mortality in diabetic and non-diabetic patients. However, QTc in a healthy population included in the Framinghan Heart Study was not predictive of cardiovascular death or sudden cardiac death. In another study, in healthy elderly, QTc > 450 ms in men and > 470 ms in women was an independent predictive risk factor for sudden cardiac death.[7,8]

The Polish Norwegian study (PONS), with a sample of 11,068 participants aged 45 to 64 years, distributed according to metabolic status, showed that the QTc interval progressively increased from those with normal blood glucose to those with impaired glucose tolerance, and was even higher in those with diabetes. The authors concluded that the results suggest that abnormal glucose metabolism affects ventricular repolarization regardless of other concomitant cardiovascular risk factors for diabetes.[9]

A literature review from 1990 assessing the association between prolonged QTc and risk of cardiovascular mortality and sudden death included seven prospective studies with 36,031 individuals, where 2,677 (8.7%) had QTc ≥ 440 ms. In this qualitative review, there was no definitive association between QTc interval and cardiovascular mortality or morbidity, except, without much consistency, in those with prior cardiovascular disease. The lack of coherence of the findings between the various subgroups underscores the likelihood that chance, bias, and/or confounding factors are plausible explanations for such disagreements. In addition, the small sample size in each study reduces power, and contributes to the inaccuracy of measurements given the technical challenges and follow-up time, among other uncontrolled factors. There are also variations among protocols used to obtain and analyze measurements in electrocardiographic tracings. When only one recording is used, the individual variability of the QTc interval over 24 hours is highlighted but drawing conclusions from one-time measurements about clinical events that usually occur years later ignores several other common factors in this population. The observation that patients with QTc

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Diabetes Mellitus/complications, Risk Factors; Prevention and Control; Arrhythmias,Cardiac; Electrocardiography/methods; Data Interpretation Statistical.

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interval ≥ 440 ms have a higher risk of total or cardiovascular mortality than those with lower values may reflect the role of QTc as a marker of still subclinical cardiovascular disease. In this analysis, none of the seven studies was designed to test the hypothesis that QTc interval is associated with total or cardiovascular mortality. Thus, uncontrolled confounders arising from uncollected or unknown variables may have influenced the results in either direction.[10]

QT dispersion (QTd) is defined as the difference between the longest and shortest QT intervals in any of the measured leads. The use of low number of leads was certainly the main cause of the lack of reproducibility repeatedly demonstrated in several studies that analyzed this parameter, making it difficult to determine its clinical significance especially in patients without known heart disease.[11]

Making use of technologies that allow for a larger number of derivations and recordings, with extended time, allowing the analysis of several records at different times is a trend in studies that explore the depolarization / repolarization periods. A study using the body surface mapping system, QT interval was measured in 80 unipolar chest leads, showing QTc 415.2+/-4.1 ms in DM 1 and 401.4+/-6.6 ms in controls (NS).[12] The method allows the analysis of the electrocardiogram, the vetocardiogram and the mapping of depolarization / repolarization in more detail.[13] The advantage of this procedure is its improved spatial sampling, allowing abnormalities that may be difficult to detect and measure using the 12-lead approach be better defined with the additional electrodes.

In the 1990s, at our Cardiology Service of the Hospital Federal dos Servidores do Estado, we had the opportunity to use the body surface mapping system in a sample of our population and the results were presented in a scientific conference held in Karlovy Vary, Czech Republic, where the method is quite used at Charles University, Prague. From this center there is an important review published in 2015 analyzing electrocardiographic changes in diabetes, revealing tachycardia, QRS and QT shortening, increased QT dispersion, reduced depolarization wave amplitude, reduced ventricular myocardial activation time, and T wave flattening confirmed by the lowest maximum and minimum value in the isopotential repolarization body surface maps. Most of these changes are even more pronounced in patients with cardiac autonomic neuropathy. Comparison with electrocardiographic changes in other diseases suggests that those present in patients with diabetes are not specific and are caused by an increase in sympathetic nervous system tone, which was indirectly confirmed by findings of heart rate variability in these patients.[14]

As we can see, obtaining measures of the depolarization/repolarization period has a long history and constant challenges. Some of the disparities in interpretation of findings arise from inconsistencies in the measurements obtained. The numerous factors involved in the inaccuracy of QT measurements and their repercussions as predictors in the clinical context make it difficult to assess the significance of minor QT changes even when they are statistically significant.

In summary, based on these observations, we cannot affirm that changes in depolarization / repolarization estimated by electrocardiography can be used as predictors of mortality and cardiovascular outcomes in the general population and apparently healthy diabetics. Further research is needed, which should include new technologies for serial measurements of these intervals and their measurement by a central electrocardiography laboratory. Such studies should be specifically designed to test the hypothesis that these depolarization / repolarization changes are associated with cardiovascular mortality.

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Longitudinal Shortening of the Left Ventricle by Cine-CMR for Assessment of Diastolic Function in Patients with Aortic Valve Disease

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Abstract

Background: **Diastolic dysfunction, commonly evaluated by echocardiography, is an important early finding in many cardiomyopathies. Cardiac magnetic resonance (CMR) often requires specialized sequences that extends the test time. Recently, feature-tracking imaging has been made available, but still requires expensive software and lacks clinical validation.**

Objective: **To assess diastolic function in patients with aortic valve disease (AVD) and compare it with normal controls by evaluating left ventricular (LV) longitudinal displacement by CMR.**

Methods: **We compared 26 AVD patients with 19 normal controls. Diastolic function was evaluated as LV longitudinal displacement in 4-chamber view cine-CMR images using steady state free precession (SSFP) sequence during the entire cardiac cycle with temporal resolution < 50 ms. The resulting plot of atrioventricular junction (AVJ) position versus time generated variables of AVJ motion. Significance level of $p < 0.05$ was used.**

Results: **Maximum longitudinal displacement (0.12 vs. 0.17 cm), maximum velocity during early diastole (MVED, 0.6 vs. 1.4s^{-1}), slope of the best-fit line of displacement in diastasis (VDS, 0.22 vs. 0.03s^{-1}), and VDS/MVED ratio (0.35 vs. 0.02) were significantly reduced in AVD patients compared with controls, respectively. Aortic regurgitation showed significantly worse longitudinal LV shortening compared with aortic stenosis. Higher LV mass indicated worse diastolic dysfunction.**

Conclusions: **A simple linear measurement detected significant differences on LV diastolic function between AVD patients and controls. LV mass was the only independent predictor of diastolic dysfunction in these patients. This method can help in the evaluation of diastolic dysfunction, improving cardiomyopathy detection by CMR, without prolonging exam time or depending on expensive software. (Arq Bras Cardiol. 2020; 114(2):284-292)**

Keywords: **Cardiovascular Diseases/mortality; Cardiomyopathy, Hypertrophic/complications; Diagnostic Imaging; Echocardiography; Magnetic Resonance Spectroscopy; Heart Failure; Aortic Valve Insufficiency.**

Introduction

Diastolic dysfunction is an early marker of cardiac disease and precedes systolic dysfunction. It can occur in the presence or absence of symptoms and with normal or abnormal systolic function.[1,2] There is a high morbidity and mortality associated with this condition due to the potential transition to diastolic heart failure, but it may be underdiagnosed because of the diagnostic criteria. Diastolic dysfunction has an increasing incidence with age and is associated with diabetes mellitus, atrial fibrillation, coronary artery disease, pulmonary hypertension,[3-6] and congenital heart diseases. Left ventricular (LV) hypertrophy has been associated with impaired diastolic function, which is commonly described in systemic hypertension, aortic valve diseases and hypertrophic cardiomyopathy.[7-9]

Echocardiography is the most used technique for diastolic dysfunction evaluation in daily clinical routine. Cardiovascular magnetic resonance (CMR) has been widely used for the evaluation of LV morphology and systolic function due to its excellent image quality and lack of geometric assumptions.[9] However, CMR is less used for evaluating diastolic function despite the development of several relevant techniques,[10] including the use of volumetric filling curves,[11] phase-contrast imaging,[12] myocardial tissue tagging,[13] and strain-encoded imaging.[14] The reasons for the limited utilization of these techniques in clinical practice are the time-consuming processes for additional image acquisition and post-processing. For instance, obtaining LV volume curves over the entire cardiac cycle, with the mandatory tracking of endocardial and epicardial contours for all cardiac phases in a cine-CMR series takes a long time and requires a specialized software with automated contour detection. Additionally, other specialized techniques of diastolic dysfunction evaluation

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require additional sequences of images, such as phase-contrast images, which mean longer CMR exam time. In two recent publications by Saba et al.[9] and Dusch et al.,[7] CMR longitudinal LV shortening has been shown to be useful for diastolic dysfunction assessment.

In the current study, we hypothesized that patients with severe aortic valve stenosis or regurgitation and preserved ejection fraction have diastolic LV dysfunction defined by motion of the atrioventricular junction (AVJ) at CMR.

Methods

Study population

We retrospectively identified 26 patients with severe aortic valve disease (AVD) and normal ejection fraction, who underwent CMR and were scheduled for aortic valve replacement surgery, and 19 normal control subjects. Eleven of AVD patients (42.3%) had predominantly aortic insufficiency, and 15 of them (57.7%) had predominantly aortic stenosis. This sample size was based on the number of patients with confirmed diagnosis, available for analysis.

The patients were clinically followed up at valve disease outpatient clinic of our institution. The exclusion criteria were: age under 18 and over 85 years old, diabetes mellitus, systemic arterial hypertension, dyslipidemia or concomitant significant coronary artery disease. All patients over 40 years old had a coronary angiography, and those with significant coronary artery disease (luminal stenosis >50%) were excluded. Patients with concomitant mitral valve disease were also excluded, as well as the ones with previous cardiac surgery and contraindications for CMR such as pacemaker use, metal clips or other ferromagnetic structures and claustrophobia.

Healthy volunteers with no significant past medical history had been recruited to establish baseline AVJ motion values. In addition, 19 healthy volunteers (10 men), aged between 24 and 58 years old, without hypertension, diabetes mellitus, coronary artery disease or other significant past medical history, and all with normal CMR examinations were used for comparison with the 26 AVD patients.

The CMR tests were performed with a 1.5 Tesla clinical scanner (Signa CV/i, GE Medical Systems, Waukesha, Wisconsin/USA) and dedicated cardiac surface phased-array coil. After localization of the heart, eight to 12 contiguous short-axis slices (8.0 mm slice thickness and 2mm gap between the slices), encompassing the entire LV and 4 long-axis slices were selected. The analysis was performed in a four-chamber view. Cine images were acquired with a steady-state free precession pulse sequence (SSFP) with temporal resolution of less than 50 ms and standard parameters: TR 3.9 ms, TE 1.8 ms, flip angle 45°, receiver bandwidth ± 125 kHz, field of view (FOV) of 34 x 34 cm, 256x160 matrix, voxel size 1.3 x 2.1 x 8.0mm.

Image and data analyses

The longitudinal motion of the AVJ was tracked through the cardiac cycle over 20 cardiac phases, on four-chamber view SSFP cine CMR images. The baseline position of the AVJ was defined at end diastole and its longitudinal displacement was measured relative to a reference line drawn between the LV apex (epicardial border, hypointense line corresponding to interface of myocardium and epicardial fat) and the inferior limit (hypointense line) of the coronary sinus running through the AV groove, immediately lateral to AVJ. These specific landmarks showed clear visualization on the cine-MR SSFP images and allowed for a robust tracking throughout the cardiac phases, with minimal blurring or loss of image definition. We did not use the midpoint of the mitral annulus[9] as we aimed to find the septal and lateral AVJ precisely; we also simplified the measure when we traced a unique line with well-defined landmarks. A simple straight line was traced between basal and apical landmarks using the Webpax software tool (Heart Imaging Technologies, LLC. Durham, NC, USA) (Figure 1). This line is a regular caliper available in all softwares capable of visualization of DICOM images.

LV longitudinal lengths were divided by the longitudinal length at end diastole (maximum length) to provide a percent reduction of longitudinal length, corrected for individual heart sizes. Based on the plots of AVJ position versus time in the cardiac cycle (Figure 2), four motion variables were calculated: maximum longitudinal displacement (MD) of the AVJ, maximum velocity during early diastole (MVED), slope of the best-fit line of AVJ velocity in diastasis (VDS), and the ratio of VDS/MVED. The MVED values for each patient were calculated according to the time-versus-displacement graph, a linear regression (straight line) was adjusted for early diastole (slope). The same method was used for VDS considering now the diastasis time. All measurements were performed by two independent blinded radiologists. Cine-CMR images were used for the assessment of LV volume, mass, and function.

Statistical analysis

Continuous variables of the AVJ motion are presented as means and standard deviation. Normality distribution was assessed by Shapiro-Wilk test. Data obtained in AVD patients were compared to normal control subjects using the unpaired Student t-test. The categorical variables are presented in percentage.

Bland-Altman plots were used to compare LV displacement parameters between patients and controls obtained by two independent blinded observers.

The SAS System and SPSS statistical software packages were used for data analysis with a significance level of $p < 0.05$.

Results

Patients' age ranged between 26 and 72 years old, with 19 men and seven women. The mean age of AVD patients and healthy volunteers in the study was 46.8 ± 13.7 and 43.1± 11.8 years, respectively. All patients were symptomatic, complaining of exertional dyspnea, angina, and syncope (Table 1). Indexes of LV volume and mass are shown in Table 2. All patients had normal or mild reduction of ejection fraction reduction (mean LV ejection fraction of 53.1 ± 9.9%). As expected, patients with predominant aortic regurgitation showed an eccentric hypertrophy pattern with end-diastolic volume and end-systolic volume significantly increased when compared with patients with predominant aortic stenosis, who presented a concentric hypertrophy pattern.

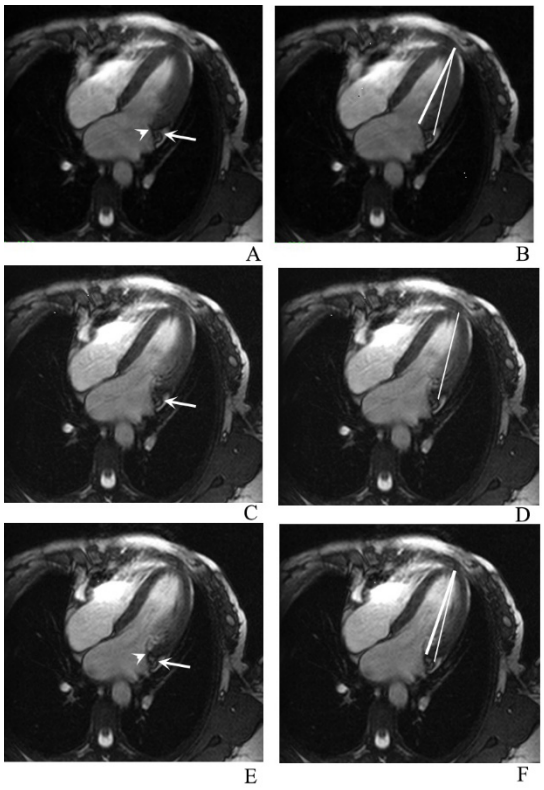

Figure 1 – *Longitudinal displacement of the atrioventricular junction (AVJ). The same four- chamber slice is shown in three different cardiac phases during AVJ rapid movement: A and B, C and D, E and F. On the left column the arrowhead represents the reference used by Saba et al.[9] and the thin arrow shows the anatomical reference used in the present study. Note that when the cardiac motion is faster (small arrow in C and D), we could not precisely identify the site of the mitral valve insertion; however, the adjacent coronary sinus wall is still well defined. On the right column, we showed the lines used for the LV longitudinal measurements on this study (thinner line) and by Saba et al.[9] (thicker line)*

AVJ motion analysis

Means and standard deviations were calculated for each of the AVJ motion variables (MD, MVED, VDS, VDS/MVED) of AVD patients and normal control subjects. AVJ data were compared between patients and controls. We found statistically significant differences in MD and the three CMR correlates of diastolic LV function (MVED, VDS, VDS/MVED) in patients with AVD compared to normal controls, as noted in Table 3 and Figure 3. Patients with AVD showed significantly lower normalized MD at the AVJ compared to healthy volunteers. AVJ of patients with AVD recoiled at significantly slower normalized maximum velocities (s^{-1}) in early diastole compared with healthy volunteers. Conversely, during diastasis, AVJ motion occurred at significantly faster normalized velocities in patients with AVD. We found a 17-fold higher VDS/MVED ratio in AVD compared with healthy volunteers (Figures 3 and 4, Table 3).

The Bland-Altman analysis (Figure 5) for MD revealed a bias of -2.81 and 95% CI (confidence interval) of (-3.66 to -1.95) for normal controls ($p < 0.001$) and a bias of -2.97, 95% CI of (-4.11 to -1.83) for AVD patients with $p < 0.001$.

Comparison of diastolic function based on AVJ parameters between patients with predominant stenosis and predominant regurgitation did show significant differences in all diastolic function at CMR (Table 4). Impairment of diastolic function was higher in patients with aortic regurgitation compared to stenosis.

Diastolic function, LV structure and clinical parameters

Results of univariate and multiple linear regression analysis including LV mass, volumes and function as well as patient characteristics such as age, gender, heart rate and blood pressure are shown in Table 5.

In a univariate analysis, MD and MVED correlated significantly with LV volume, left ventricular ejection fraction (LVEF) and LV mass. MVED also correlated to systolic blood pressure (SBP). VDS/MVED correlated with LV mass, LVEF and heart rate (HR). VDS showed correlation only with LV mass and HR (Table 5). In a multivariate linear regression model, MD and MVED were predicted only by LV mass. All other parameters of LV structure, volume and function were not predictive of MD and MVED in this multivariate approach. Gender and LV mass independently predicted VDS, while VDS/VMED ratio was predicted by LV mass and LVEF.

In summary, these results indicate that LV mass maintains a significant correlation across the four measured diastolic parameters in the univariate and forward stepwise multiple linear regression. Additionally, gender maintained a significant correlation with VDS and LVEF with VDS/MVED ratio. The remaining variables were not independently correlated with diastolic function parameters derived from linear measurements. Thus, body size (body mass index), HR and blood pressure did not influence significantly linear diastolic parameters measured by CMR.

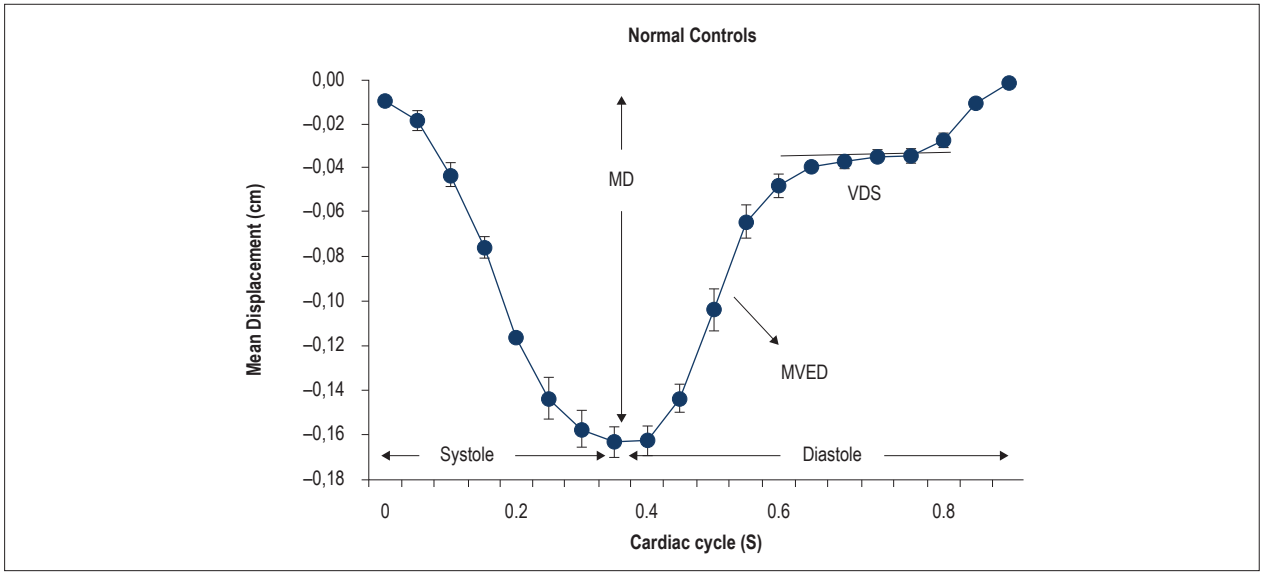

Figure 2 – *Atrioventricular junction (AVJ) displacement-versus-time plot of the normal controls. AVJ position at multiple time points during the cardiac cycle. Error bars represent one standard deviation above and below the mean. MD: maximum displacement; MVED: maximum velocity early diastole; VDS: velocity in diastasis.*

Table 1 – Characteristics of patients with aortic valve disease and controls

	Aortic regurgitation	Aortic stenosis	Controls	p
n (%)	11(42.3)	15 (57.7)	19	
Age, years	46.0 ± 15.7	48.7 ± 11.3	38.1 ± 10.5	0.610/0.039*
Men, n (%)	10(90.9)	9(60.0)	10(52.6)	0.079/0.101*
Weight (kg)	76.6 ± 10.6	71.2 ± 11.9	67.9 ± 15.3	0.336/0.356*
BMI (kg/m²)	27.9 ± 3.5	26.3 ± 3.8	23.5 ± 3.6	0.382/0.021*
Etiology				
Rheumatic	9(81.8)	3(20.0)	-	
Bicuspid	2(18.2)	8(53.3)	-	
Degenerative/Calcification	0 (0.0)	4(26.7)	-	0.007
NYHA Functional class				
I	1(9.1)	0(0.0)	19(100.0)	
II	7(63.6)	8(53.3)	0(0.0)	
III	3(27.3)	7(46.7)	0(0.0)	0.526
Heart rate, bpm	65.0 ± 11.9	81.5 ± 20.7	70.1 ± 10.6	0.027/0.019*
SBP	126.7 ± 15.1	121.5 ± 15.2	111.6 ± 8.98	0.505/0.018*
DBP	80 ± 8.9	71.8 ± 12.8	71.3 ± 6.6	0.183 / 0.143*
Angina	0(0.0)	1(6.7)	-	0.465
Syncope	0(0.0)	1(6.7)	-	0.465
Hypertension	6(54.6)	6(40.0)	-	0.100
Diabetes	0(0.0)	1(13.3)	-	0.342
Hypercholesterolemia	0(0.0)	0(0.0)	-	-
Smoking	0(0.0)	5(33.3)	-	0.100
Family History of CAD	4(36.4)	3(20.0)	-	0.190

*BMI: body mass index; NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; CAD: coronary artery disease; * = comparison the three groups including controls; remaining p values for comparison between aortic regurgitation and stenosis only.*

Table 2 – Cardiac magnetic resonance parameters of patients with aortic valve disease and controls

	Aortic regurgitation	Aortic stenosis	Controls	p
n (%)	11(42.3)	15 (57.7)	19	
LVEDV, ml	299.6 ± 68.5	179.99 ± 42.1	129 ± 24.7	< 0.001
LVESV, ml	148.9 ± 60.4	82.0 ± 28.7	45.5 ± 9.4	< 0.001
LVEF, %	51.7 ± 11.4	55.1 ± 9.1	64.7 ± 5.3	< 0.001
LV mass, g	264.2 ± 42.4	272.8 ± 45.5	118.1 ± 40.5	< 0.001
Eccentric Hypertrophy, n (%)	10(90.9)	1(6.7)	-	
Concentric Hypertrophy, n (%)	1(9.1)	14(93.3)	-	< 0.001

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; LV: left ventricular. Definition criteria of concentric hypertrophy is LV mass to LVEDV ratio > 1.16 g/ml.

Table 3 – Comparison of atrioventricular motion variables between patients with aortic valve disease (AVD) and healthy volunteers

	Control	AVD	p
MD (cm)	–0.169 ± 0.034	–0.115 ± 0.035	< 0.0001
MVED (s^{-1})	1.439 ± 0.388	0.65 ± 0.413	< 0.0001
VDS (s^{-1})	0.029 ± 0.069	0.224 ± 0.232	< 0.0001
VDS/MVED	0.021 ± 0.051	0.352 ± 0.292	< 0.0001

MD: maximum displacement; MVED: maximum velocity early diastole; VDS: velocity in diastasis.

Discussion

Novel correlates of diastolic LV function measured by CMR originally investigated in this study were markedly abnormal in patients with AVD. Measured at the AVJ, patients with AVD had significantly lower maximum displacement, slower velocity during early diastolic filling, and higher velocity during diastasis compared to normal control subjects.

Saba et al.[9] reported diastolic LV function alterations evaluated through the AVJ motion by CMR in patients with hypertrophic cardiomyopathy compared to normal control patients. Results from our control group were very similar to those reported by these authors, although with slightly greater values mainly because we used a more lateral anatomical landmark. Also, we used only one measurement instead of two of AVJ displacement, hence adopting one well-defined reference point of the AVJ lateral wall, in a more simplified method.

LV hypertrophy and diastolic function

LV hypertrophy is a recognized risk factor for cardiac morbidity and mortality[15] and is associated with systolic and/or diastolic function disturbances.[16-18] In patients with AVD, diastolic and systolic function disturbances have important implications for morbidity and mortality, before and after aortic valve replacement.[16-21] In the study by Lamb et al.,[22] the ejection fraction was largely unaffected in the group of patients with severe AVD, suggesting that a deterioration of the ejection fraction should be considered as a sign of severe and advanced disease,[22] which was corroborated by other authors.[20,22] After aortic valve replacement, LV diastolic function improves, as indicated by parameters of transmitral flow.[22] In our results, we not only detect diastolic dysfunction in AVD patients compared to normal controls, but also demonstrated a worse diastolic dysfunction in patients with aortic regurgitation. LV mass was significantly and independently correlated with all linear measurements of diastolic function evaluated by CMR.

Diastolic dysfunction evaluation

Phase contrast magnetic resonance imaging allows measurement of flow velocity as well as flow volumes across the mitral valve orifice, providing a new means of diastolic function assessment that may be even more sensitive than Doppler echocardiography. Although it is a well-established tool to assess systolic dysfunction, it is rarely used clinically to assess LV diastolic function, which may require additional dedicated sequences and extensive post-processing.[7] In this sense, in a recently published study by Dusch et al.,[7] similar to our study, the authors used a horizontal-long axis SSFP sequence, which they called midwall longitudinal fractional shortening. They verified the percentage of shortening of the distance from the anterior leaflet mitral valve basis to apical endocardium in diastole in relation to systole, comparing these measures to the echocardiogram of 80 patients with varied cardiomyopathies and different degrees of diastolic function.[23,24] Using a simpler method than the one used in the present study, Dusch at al.[7] were able to detect that the midwall longitudinal fractional shortening of grade II/III was significantly lower than that of grade 0/I.

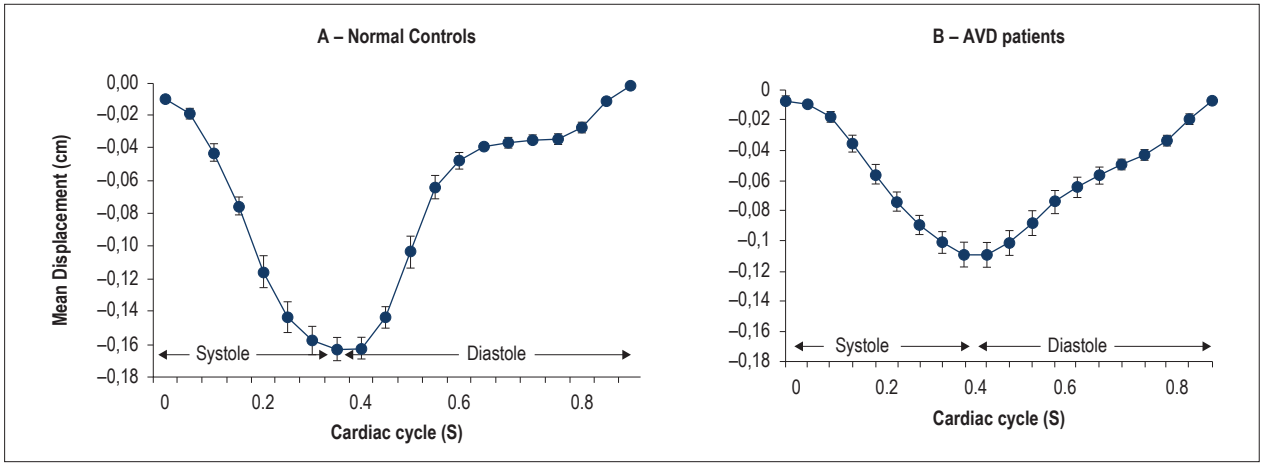

Figure 3 – *Displacement-versus-time plot in normal controls (A) and aortic valve disease patients (B). Error bars represent one standard deviation above and below the mean. AVD: aortic valve disease.*

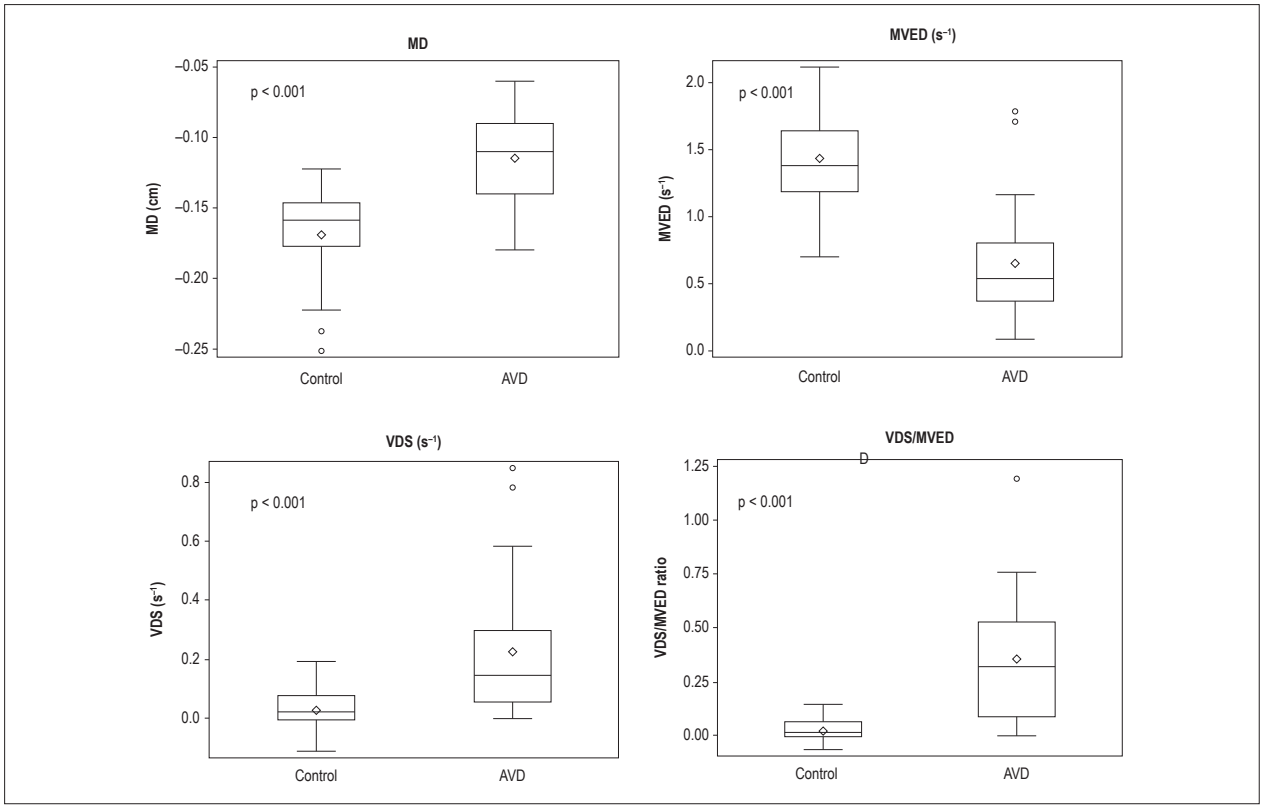

Figure 4 – *Box plots of the variables of atrioventricular junction motion in patients with aortic valve disease and healthy volunteers. In both groups, the box plots display the sample minimum (lower whisker), lower quartile (lower box subdivision), median (horizontal band), upper quartile (upper box subdivision), and sample maximum (upper whisker) for each of the AVJ motion variables – maximum displacement (MD); maximum velocity early diastole (MVED); velocity diastasis (VDS) and VDS/MVED. Circles indicate outliers (p < 0.0001 for all)*

Our study shows many advantages of using this new and accurate method for evaluation of LV diastolic function. It does not require the development of an acquisition sequence or post-processing software, and LV diastolic function can be easily evaluated by existing equipment. LV diastolic function can be retrospectively evaluated if prior cine image datasets were stored.

Nonetheless, our study has several limitations. One of the most significant ones in terms of practicality is the need to perform manually 20 linear measurements in each phase of one cardiac cycle. However, the use of more automated software would help in a faster measurement. Another significant limitation was that AVJ motion and echocardiography variables were not directly correlated. It is possible that LV longitudinal

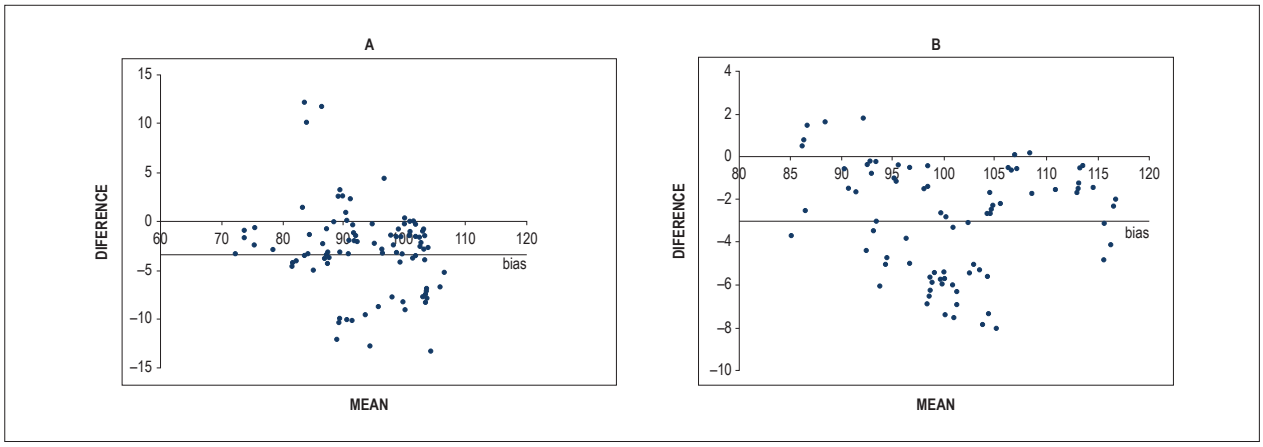

Figure 5 – *Interobserver comparison of maximum displacement measures in normal controls (A) and patients with aortic valve disease (AVD) (B).*

Table 4 – Atrioventriculr junction motion variables of patients with predominant aortic stenosis and aortic regurgitation

	Stenosis	Regurgitation	p
MD (cm)	–0.130 ± 0.036	–0.093 ± 0.018	0.0026
MVED(s^{-1})	0,790 ± 0.479	0.470 ± 0.200	0.0312
VDS(s^{-1})	0.317± 0.262	0.097 ± 0.093	0.0075
VDS/MVED	0.440 ± 0.295	0.231 ± 0.252	0.0703

AVJ: atrioventricular junction; MD: maximum displacement; MVED: maximum velocity early diastole; VDS: velocity diastasis.

Table 5 – Univariate and multiple linear regression analysis (p-values) for the prediction of the diastolic function parameters derived from linear measurements

	MD		MVED		VDS		VDS/MVED	
	Univariate	Multiple Linear Regression	Univariate	Multiple Linear Regression	Univariate	Multiple Linear Regression	Univariate	Multiple Linear Regression
Age	0.087		0.059		0.912		0.130	
Gender	0.070		0.272		0.819	0.04	0.705	
LV mass	< 0.001	< 0.001	< 0.001	0.001	0.001	< 0.001	0.002	0.003
LVEDV	< 0.001		< 0.001		0.366		0.154	
LVESV	< 0.001		< 0.001		0.605		0.083	
LVEF	0.002		< 0.001		0.610		0.004	0.006
HR	0.886		0.645		< 0.001	0.081	0.025	
SBP	0.140		0.028		0.399		0.051	
DBP	0.190		0.616		0.846		0.232	

MD: maximum displacement; MVED: maximum velocity early diastole; VDS: velocity diastasis; LV: left ventricle; LVEDV: end-diastolic volume; LVESV: end-systolic volume; LVEF: left ventricular ejection fraction; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

displacement and the velocity of this displacement might suffer influence from LV geometric morphology. However, the LV dimensions measured as LV end-diastolic volume and diameter did not have significant effect on diastolic parameters. Additionally, LV longitudinal displacements are, by definition, normalized by the LV longitudinal dimension, and the other dimensions are incorporated to volume measurements. Despite the practical advantages of using this new method for LV diastolic function evaluation, it would be important, in future studies, to evaluate its accuracy compared to other existing methods in general evaluation of cardiac diseases that cause LV diastolic dysfunction, verifying the sensitivity and specificity in classifying different diastolic dysfunction degrees. Another limitation of the present study was the relatively small number of AVD patients.

Finally, we have demonstrated that diastolic function evaluation can be performed by the SSFP cine sequences routinely acquired by conventional CMR tests, with no

need for additional specific sequences or specific software. The incorporation of this technique to clinical routine would improve the CMR ability to analyze diastolic function, even retrospectively using previously acquired CMR images.

Conclusion

In conclusion, LV longitudinal shortening is a quick and reliable technique for assessment of diastolic dysfunction in AVD patients that can be performed in routine CMR studies without the use of specific or sophisticated software.

The AJV curve showed significant differences in all diastolic parameters analyzed between AVD patients and normal controls. Further studies should confirm that this method is valuable for other cardiac diseases.

Author contributions

Conception and design of the research: Ribeiro SM, Azevedo Filho CF, Sampaio R, Tarasoutchi F, Grinberg M, Kalil-Filho R, Rochitte CE; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Ribeiro SM, Azevedo Filho CF, Rochitte CE; Critical revision of the manuscript for intellectual content: Azevedo Filho CF, Sampaio R, Tarasoutchi F, Grinberg M, Kalil-Filho R.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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New Paradigms in the Evaluation of Diastolic Function by Cardiac Magnetic Resonance Imaging in Aortic Valvopathy

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Short Editorial related to the article: Longitudinal Shortening of the Left Ventricle by Cine-CMR for Assessment of Diastolic Function in Patients with Aortic Valve Disease

The noninvasive analysis of left ventricular diastolic function is a challenge in clinical practice. Estimation of the time constant of isovolumetric relaxation - or Tau constant - is the best and most established parameter for ventricular diastolic function analysis. However, this measure is obtained through an invasive assessment and it is very difficult to acquire.[1] In clinical practice, echocardiography is considered a key tool, among all the complementary exams that can be used to evaluate diastolic function, validated in relation to the pressure-volume curves by catheterization, restricting the invasive evaluation to be used in exceptional cases.[2] Thus, echocardiography remains the first-line noninvasive method, providing data on early diastolic dysfunction through indices that reflect relaxation, compliance, and also indirect measurements of ventricular filling pressures.

The latest recommendations for diastolic dysfunction assessment by echocardiography basically include analysis of the left ventricle without structural changes and preserved ejection fraction, as well as a flowchart for cases of left ventricular ejection fraction reduction/structural change.[5] However, the classification of the degree of diastolic dysfunction and its application in the therapeutic management of valvular heart disease remains controversial.[3,4] Moreover, aortic stenosis may be associated with mitral annulus calcification, which may lead to a reduction of the mitral orifice area, with an increase in early transmitral diastolic velocity (E), while the Doppler lateral mitral annulus velocity (e') may be reduced due to limitation of the posterior cusp excursion, which may lead to an artificial increase in the E/e' ratio. In aortic regurgitation, however, the aortic reflux jet may interfere with the mitral flow, which, when significant, can lead to a restrictive ventricular filling pattern; however, the accuracy of E/e' ratio is questionable.[5]

The present study proposes the analysis of diastolic function by analyzing left ventricular (LV) longitudinal movement, quantified by cardiac magnetic resonance imaging (cMRI).[6] The study population consists of three groups according to hemodynamic stress: aortic stenosis (significant afterload increase), aortic regurgitation (consistent preload increase), both valvopathies compared with a healthy group. Both valvopathies comprised a comparative group with the controls. This study demonstrated that the LV longitudinal movement analysis was reduced in patients with aortic valve disease when compared to the control group, and that among patients with valvular disease, patients with aortic regurgitation had lower values than those with stenosis.

The cMRI is an attractive imaging modality capable of providing morphological, functional, perfusion and tissue characterization data in a single examination, with irrefutable spatial resolution. In the evaluation of diastolic function, recent techniques have shown encouraging results, especially those based on the myocardial strain assessment through feature tracking. However, the need for improvements in image postprocessing and acquisition times, together with the limited availability and relatively high cost of the employed software, limit a broader use of these relatively new technologies in clinical practice.[7] It is in this context that the elegant study by Ribeiro et al.[6] is located and has its greatest strength: in the cost-benefit of four variables obtained simply and quickly in the four-chamber view for indirect evaluation of diastolic dysfunction, without the need for additional specific sequences or the use of specific software. However, before proposing the incorporation of this technique into clinical routine, some important methodological considerations are necessary. We know that the ventricular longitudinal shortening measured by cMRI is classically related to ventricular systolic function and, more recently, also to diastolic dysfunction measured by echocardiography, even in patients with preserved ejection fraction.[8-10]

However, the authors did not directly correlate the ventricular longitudinal movement variables with Doppler echocardiographic variables, data with broad and widespread importance in the noninvasive investigation of diastolic dysfunction, or with invasive variables to validate these measurements.[10] Although the authors assumed this fact as an important limitation of the study, this absence makes it impossible to estimate the accuracy, sensitivity, specificity and predictive values of this methodology. Furthermore, the lack of interobserver agreement assessment and internal and external validation, associated with the fact that the case group consisted of a very heterogeneous population (stenosis and valve regurgitation), require that these results be interpreted with extreme caution and cannot be extrapolated to other samples or distinct cardiomyopathies before being clinically validated. Other relevant data is consensually accepted that patients with severe aortic valve disease, either stenosis or regurgitation, already showing morphological alteration and ventricular compliance, are symptomatic. Patients with

Keywords

Echocardiography; Aortic Stenosis; Diastolic Function; Cardiac Magnetic Resonance; Aortic Valvopathy.

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advanced aortic valvopathy have higher ventricular mass and reduced ejection fraction, when compared with the healthy group. In this context, measures of systolic and diastolic function can be expected to differ from those of the healthy control group.

As a suggestion for future studies, the inclusion of other variables, easily obtained in the basic cMRI sequences, such as left atrial volume (a chronic marker of diastolic dysfunction and cardiovascular risk) or the presence of late LV enhancement (indicator of fibrosis as a potential substrate for myocardial impairment) would certainly add important data to the debate on the role of cMRI in LV diastolic dysfunction. Moreover, it would be interesting to perform its validation with methods that are clinically used as invasive measures of the Tau constant, or through echocardiography parameters, which are validated measures for the analysis of diastolic function in different heart diseases.

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Passive Cigarette Smoking Impact on Blood Pressure Response to Epinephrine and Felypressin in 1K1C Hypertensive Rats Treated or not with Atenolol

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Abstract

Background: **Cigarette smoking is usually associated with hypertension and may modify vasoconstrictor response.**

Objective: **The present study aimed to analyze and compare the interaction of passive cigarette smoking and hypertension on epinephrine and felypressin blood pressure effects after intravascular injection.**

Method: **45-day male Wistar rats had the main left renal artery partially constricted and the right kidney removed (1K1C model). Rats were placed in the chamber for exposition to passive cigarette smoking (10 cigarettes) during 10 min (6 days a week). Hypertensive rats received atenolol (90 mg/kg/day) by gavage for two weeks. Hypotensive and hypertensive response, response duration and heart rate were recorded from direct blood pressure values. The significance level was 5%.**

Results: **Passive cigarette smoking increased maximal hypertensive response to epinephrine in normotensive and 1K1C-atenolol treated rats and to felypressin only in 1K1C-atenolol treated rats; it also reduced epinephrine hypotensive response. Epinephrine increased heart rate in normotensive and hypertensive passive smokers or non-smoker rats. Comparing the two vasoconstrictors, epinephrine showed greater hypertensive response in normotensive smokers, 1K1C-atenolol treated smokers and non-smokers. However, in normotensive-nonsmoker rats, felypressin showed a greater and longer hypertensive effect.**

Conclusions: **Our results suggest that passive cigarette smoking may reduce epinephrine vasodilation and increase hypertensive response when compared to felypressin. Therefore, felypressin may be safe for hypertensive patients to avoid tachycardia and atenolol interaction, but for normotensive and non-smoker patients, epinephrine may be safer than felypressin. (Arq Bras Cardiol. 2020; 114(2):295-303)**

Keywords: **Tobacco Use Disorder; Hypertension; Rats; Felypressin; Atenolol; Epinephrine; Tobacco Smoke Pollution; Nicotine/adverse effects.**

Introduction

Vasoconstrictor drugs are essential for dental and medical procedures performed under local anesthesia, since the local anesthetic must stay in contact with sensitive nerves. One single local anesthetic cartridge administered via intravascular route can be fatal.[1] Therefore, vasoconstrictors are also used to avoid its absorption and adverse effects: seizures, arrhythmia and cardiac arrest. There are studies indicating vasoconstrictor absorption and systemic effects. Epinephrine can be detected in plasma after infiltration and can increase heart rate in normal subjects.[2] There are no clinical data comparing epinephrine and felypressin efficacy or safety, but there is evidence that isolated local anesthetics results in shorter and low quality pain control.[3]

Vasoconstrictor drugs have systemic effects that can be critical in patients with cardiovascular diseases: coronary vasoconstriction, tachycardia, increases in cardiac contraction force, etc. Such effects are related to the most common causes of death in the modern world: heart attack, stroke and thrombosis; and patients usually have multifactorial diseases. Cigarette smoking and hypertension are included in the National Cholesterol Education Program algorithm to predict cardiovascular disease risk, addressing both as modifiable causes of atherosclerosis in prevention efforts.[4] The WHO estimates that the global prevalence of adults smoking any tobacco product is 36% in adult men and 8% in adult women.[5]

The number of cigarettes show a positive correlation with higher blood pressure values but not with heart rate.[6] Nicotine also affects the autonomous nervous system, having a different effect than cigarette smoking products.[7] Catecholamine release and atherosclerotic lipoproteins

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are increased in the blood levels of smoker patients.[8] The vasoactive drugs present, therefore, alter the vascular response of smokers, since the nitric oxide (NO) pathway, adrenergic and cholinergic systems are affected. Although epinephrine is considered the safest vasoconstrictor drug in patients with cardiovascular disease by The American Dental Association,[9] patients receiving betablocker treatment who smoke cigarettes must be treated differently.

Felypressin may be a safe alternative vasoconstrictor in such populationce since it is a non-adrenergic vasoconstrictor. There is no reported interaction between cigaretes smoking and vasopressin. A previous study showed reduced hypertensive effect of felypressin in rats treated with atenolol.[10] In order to increase the knowledge about the safety of epinephrine and felypressin, this study attempted to test them isolated in intravascular administration to simulate the maximal error in local anesthesia, providing information for the formulation of safer local anesthetic solutions. Therefore, the aim of this study was to evaluate and compare the effects of direct intravenous injection of epinephrine and felypressin on blood pressure of smoker or non-smoker normotensive, hypertensive and atenolol-treated hypertensive rats.

Methods

For the present study, all norms for animal research were reviewed and approved by the institutional review board before the experiments (protocol #010/2010). Male Wistar rats weighing 140 to 320 g provided by *Faculdade de Odontologia de Bauru* facilities were used in all groups of this study. The experimental hypertension method, indirect and direct BP measurements, were performed as previously described[10]. All rats received a normal diet, free water and food access and were submitted to 12 hour light/dark cycle. Rats weighing 110 to 150 g were anesthetized with an injection of ketamine (50 mg/kg weight, im, Dopalen® - Sespo Industry and Trade Ltda., Animal Health Vetbrands Division – Jacareí, São Paulo, Brazil) plus xylazine (10 mg/kg weight, im, Anasedan® - Sespo). The left renal artery was isolated, and a 0.25 mm gap silver clip was installed around it, and the right kidney was completely removed. 40,000 IU of small-animal antibiotic (Fontoura Wyeth S.A. – São Bernardo do Campo, São Paulo, Brazil) was injected. It is worth mentioning that surgery for clips implantation in the renal arteries was performed in 10 animals per group, that is, 120 rats. However, each groups consisted of 6 animals, since part of the rats did not have systolic blood pressure above 150 mmHg. Therefore, 72 was the total number of animals used in the study and there were no criteria for the definition of this sample, being defined by convenience.

Passive Smoking Method

Passive smoking was performed based on previous emphysema induction studies[11]. One day after hypertension induction, the rats were intoxicated one time a day (10 cigarettes per exposure period), 6 days a week. The exposure protocol consisted of confining 10 rats in the inhalation chamber during 10 min of compressed air ventilation (10 L/min).

Indirect and Direct Blood Pressure Measurements

1K1C rats were heated in individual cages containing an electrical resistance and tail pneumatic cuffs were installed and connected to a digital system for indirect blood pressure record (Physiological Pressure Transducer, ADInstruments Pty. Ltd. – Dunedin, Otago, New Zealand). Rats that presented systolic blood pressure equal to or higher than 150 mmHg in the indirect measurement 15 days after clip surgery were accepted in the hypertensive group or treated with atenolol (90 mg/kg/day; Cristália Pharmaceutical and Chemical Products – Itapira, São Paulo, Brazil) administered by gavage in 1mL for 2 weeks.

All groups had blood pressure measured directly for 28-35 days after clip surgery, or the equivalent time in the control group: after ketamine/xylazine anesthesia, a saline-filled polyethylene catheter PE-50 (Clay Adams – Franklin Lakes, New Jersey, USA) with an occluded external extremity was implanted in the left carotid artery and in the right jugular vein. The arterial catheter was connected to a pressure transducer coupled to an invasive blood pressure recording system, using appropriate software (Physiological Pressure Transducer; PowerLab 4/30; Chart Pro – ADInstruments Pty. Ltd). The experiments of intravenous injection of vasoconstrictor drugs were performed with anesthetized rats right after catheter implantation. A scheme of the experiments design are detailed in Figure 1.

Dose-Response Curves to Epinephrine and Felypressin

Exogenous epinephrine (Adren® - HipolaborFarmacêuticaLtda – Belo Horizonte, Minas Gerais, Brazil) diluted in saline solution was injected at the doses of 80, 160, 320, 640 and 1,280 ng in bolus through tin venous catheter to obtain dose-response curves. Felypressin alone (Dentsply Pharmaceutical, Catanduva, São Paulo, Brazil) was used at doses of 0.125, 0.25, 0.5, 1, 2 and 3mIU. Intravenous injections in random order were performed after a 3-min interval for each response to stabilize blood pressure. Animals were euthanized with intravenous injection of excessive doses of the anesthetic drug thiopental (Thiopentax®, Cristália – Chemical and Pharmaceutical Products). The following parameters were analyzed using PAM values (PAM = 1/3 Systolic Pressure + 2/3 Diastolic Pressure): minimal hypotensive response, maximal hypertensive response and response duration. Duration was determined using global pressure alterations, since epinephrine has a complex blood pressure response where there is a hypertensive peak followed by hypotensive response and normalization; previous studies have clarified this pattern[10]. Heart rate was recorded 30 s after the injection during one min to avoid bias caused by longer duration or great blood pressure changes since the program used pulsatile pressure to determine these parameter. In order to compare epinephrine and felypressin, doses that corresponded to 1, 2, 4 and 8 local anesthetic cartridges which would have been administered to the rats, were used. The following formula was used: D = 18,000 (for epinephrine*) or 54 mIU (for felypressin*) x 4,286 x 10^{-3} (a weight correction from humans (70 kg) to rats (300 g).

** total content in a local anesthetic cartridge*

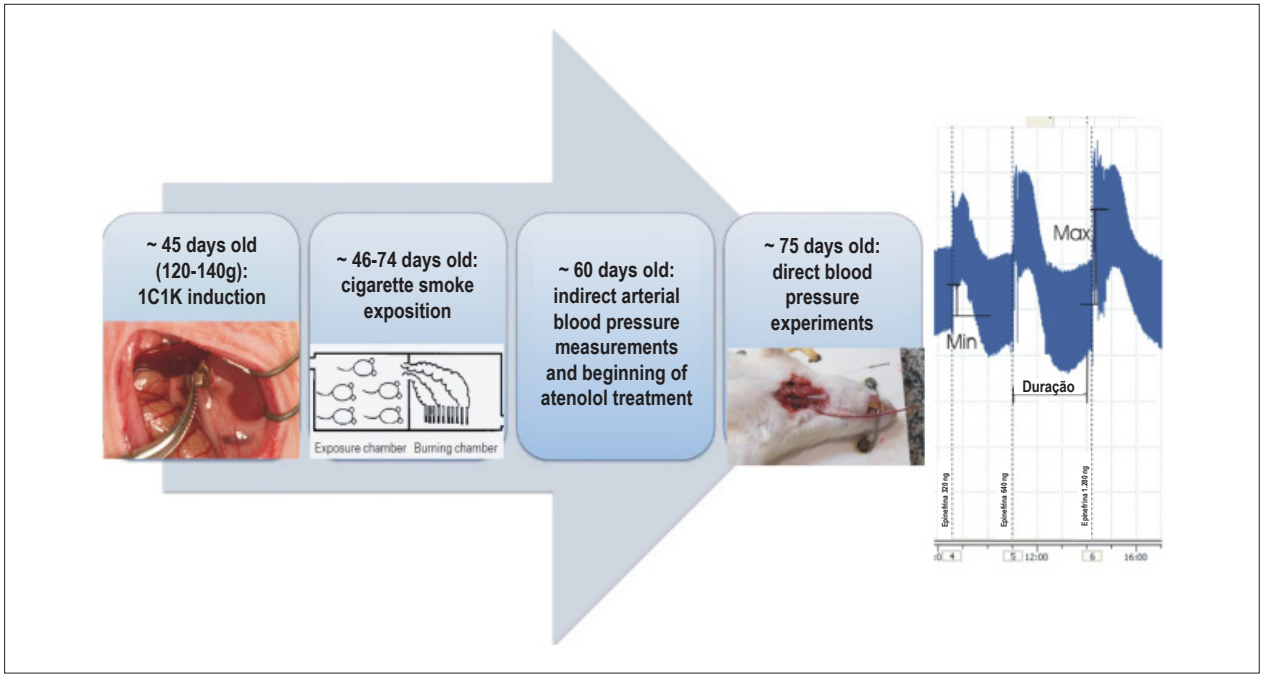

Figure 1 – *Schematic study protocol: at 45 days of life, the rats were submitted to clip implantation (1K1C hypertension induction); on the next day, the smoker groups were exposed to cigarette smoke; at 60 days of life, blood pressure was measured by indirect means and atenolol treatment was started; approximately at 75 days of life, direct blood pressure experiments were performed. An example of pulsatile recording after epinephrine administration details how parameters were calculated.*

Statistics

For all groups, n = 6. The results were expressed as Mean ± Standard Deviation (SD) for data with normal distribution according to Kolmogorov-Smirnov test. In cases where normal distribution did not occur in one group or more, data were presented as Median ± interquartile interval.

When more than one response was obtained from the same animal, repeatd -measures one-way analysis of variance was used (Repeaed- measures One-Way ANOVA). To compare complete curves from two or more groups, repeaed- measures Two-Way analysis of variance was used (Repeaed- measures Two-Way ANOVA). When there was a significant difference between the doses in each curve or in independent groups and normal distribution, comparison was performed by Holm-Sidak's or Tukeyhodtest. For non-parametric results, Mann-Whitney and Kruskal-Wallis tests were used. The level of significance in this study was set at 5% ($p < 0.05$). All tests were performed using STATISTICA Software (StatSoft South America).

Results

Basal blood pressure values during the first five minutes are summarized in Table 1 and used as the initial reference. Atenolol significantly reduced blood pressure in hypertensive animals, whose values were still significantly higher than in control animals.

Maximal Hypertensive Response

Maximal hypertensive response curves for epinephrine and felypressin, smokers vs. non-smokers, are shown in Figure 2. Smoking significantly increased epinephrine maximal hypertensive responses in normotensive and atenolol-treated rats. Smoke significantly increased felypressin maximal hypertensive response only in the atenolol-treated group.

Minimal Hypotensive Response

Figure 3 shows epinephrine minimal hypotensive response curves. Smoke significantly reduced the hypotensive response in normotensive rats ($p < 0.05$). There was a significant reduction in vasodilator response in 1K1C atenolol-treated group after epinephrine administration. Felypressin, as expected, did now result in significant hypotensive response in the three studied groups (Figure 3B).

Heart Rate

Epinephried caused a significant increase in heart rate in normotensive and 1K1C hypertensive rats when compared with basal values for each group, but smoking did not alter such effect (Figure 4A). 1K1C atenolol-treated rats showed no changes in this parameter, probably due to the antagonistic effect of atenolol on β_1-receptors. Felypressin showed a significant reduction in heart rate for non-smoker, normotensive rats when compared with basal values (Figure 4B). Smoke significantly increased heart rate only at 1 and 2 mIU doses of felypressin, when compared with non-smoker normotensive control rats.

Response Duration

Response duration is described in Table 2. Felypressin showed a significantly longer duration of blood pressure responses than epinephrine in all studied groups.

Table 1 – Basal values

		Weight (g)	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart rate (BPM)
Non-smoker	Normotensive	285.00 ± 25.09	112.7 (101.7-118.8)	140.5 (123.2-144.0)	99.6 (93.1-103.4)	210.5 (194.1-225.1)
	1K1C Hypertensive	297.83 ± 30.20	163.1 (155.3-177.7)[a]	201.1 (188.3-231.9)[a]	135.2 (127.9-148.6)[a]	205.9 (196.2-248.9)
	1K1C Atenolol-Treated	215.00 ± 34.29[a]	148.9 (136.1-163.4)[a,b]	184.9 (175.3-201.2)[a,b]	132.5 (119.3-142.8)[a,b]	185.7 (176.5-207.7)
Smoker	Normotensive	302.50 ± 19.04	104.1 (93.6-112.4)	134.8 (119.2-145.2)	86.2 (81.6-95.8)	225.1 (206.2-249.4)
	1K1C Hypertensive	250.58 ± 16.21[c]	156.6 (152.7-160.3)[a]	194.35 (188.8-203.3)[a]	129.7 (126.5-145.3)[a]	219.7 (207.6-231.1)
	1K1C Atenolol-Treated	254.42 ± 21.86[c]	126.2 (117.7-138.1)[a,b]	153.5 (148.6-167.5)[a,b]	106.1 (102.8-111.1)[a,b]	212.6 (200.0-218.7)

Values of weight; basal values for mean, systolic, diastolic arterial pressure and heart rate obtained during the first five minutes for smoker and non-smoker normotensive, 1K1C hypertensive and 1K1C atenolol-treated groups (n = 12). Weight – Mean ± Standard Deviation. Arterial Pressure and Heart Rate - Median (25th Percentile-75th Percentile). [a] p < 0.05 compared with normotensive group. [b] p < 0.05 compared with hypertensive group. [c] p < 0.05 compared with non-smoker respective group.

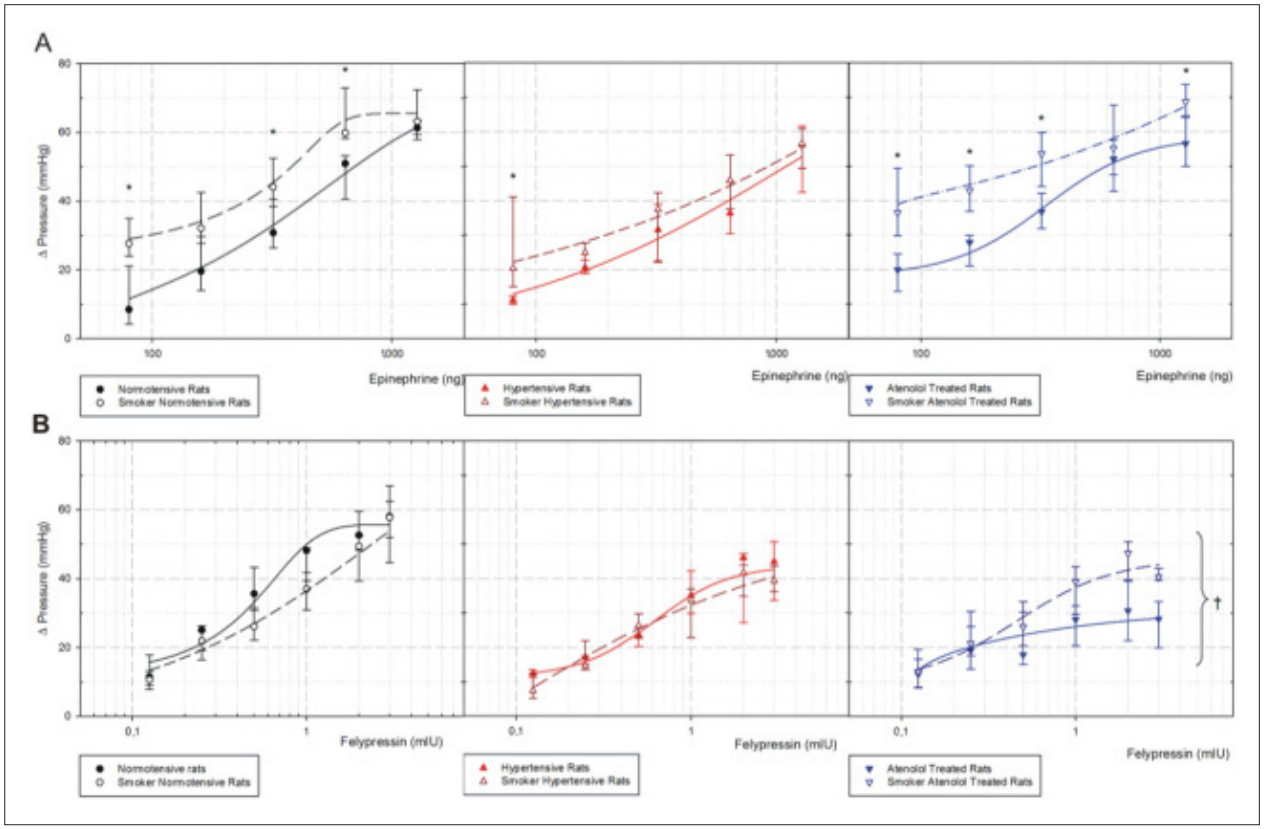

Figure 2 – *Maximal hypertensive response curves after intravenous injection in bolus of epinephrine (A) or felypressin (B) in control non-smoker normotensive and smoker normotensive rats, non-smoker 1K1C hypertensive and smoker 1K1C hypertensive, non-smoker 1K1C atenolol-treated and smoker 1K1C atenolol-treated rats. n = 6 for all groups. Median (25th Percentile-75th Percentile). *p < 0.05 vs non-smokers groups.*

Comparison between Epinephrine and Felypressin

When comparing felypressin to epinephrine responses in each group, felypressin showed a reduced hypertensive effect on smoker normotensive, smoker 1K1C-atenolol treated and non-smoker 1KC -atenolol-treated rats (Figure 5). In smoker and non-smoker hypertensive rats, there was no significant difference between both vasoconstrictors. In non-smoker normotensive rats, felypressin resulted in a greater hypertensive effect when compared with epinephrine.

Discussion

We associated smoke with hypertension and atenolol treatment in an attempt to reproduce a multifactorial disease. In order to provide safety information about isolated use of vasoconstrictors via intravascular route, which cannot be tested in humans, our study aimed to test if epinephrine is contraindicated in the smoker and hypertensive population and to provide a safe alternative through the analyses of systemic effects. Epinephrine was used as the vasoconstrictor

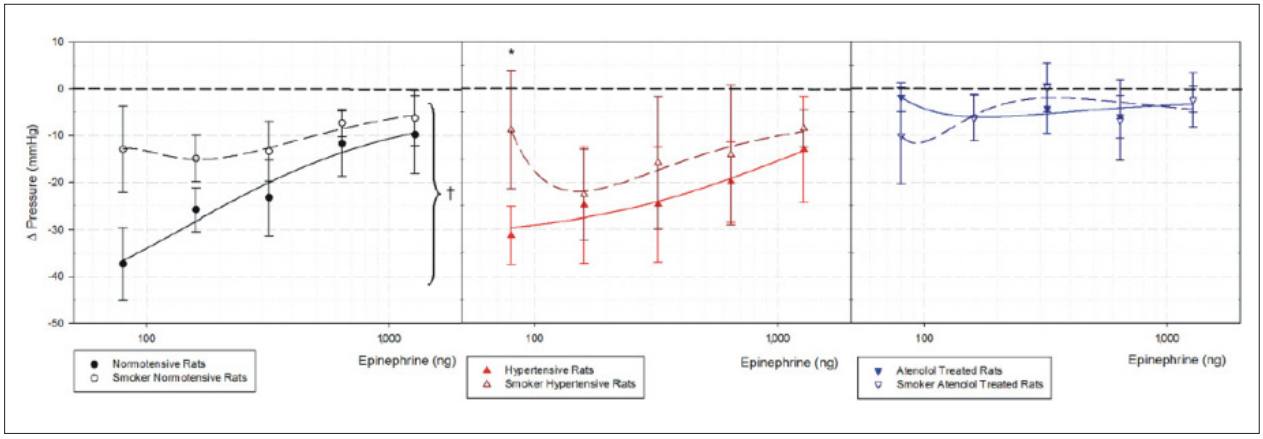

Figure 3 – *Minimal hypotensive response curves after intravenous injection in bolus of epinephrine in control non-smoker normotensive and smoker normotensive rats, non-smoker 1K1C hypertensive and smoker 1K1C hypertensive, non-smoker 1K1C atenolol-treated and smoker 1K1C atenolol treated rats. n = 6. Mean ± Standard Deviation. *p < 0.05 vs non-smokers groups.*

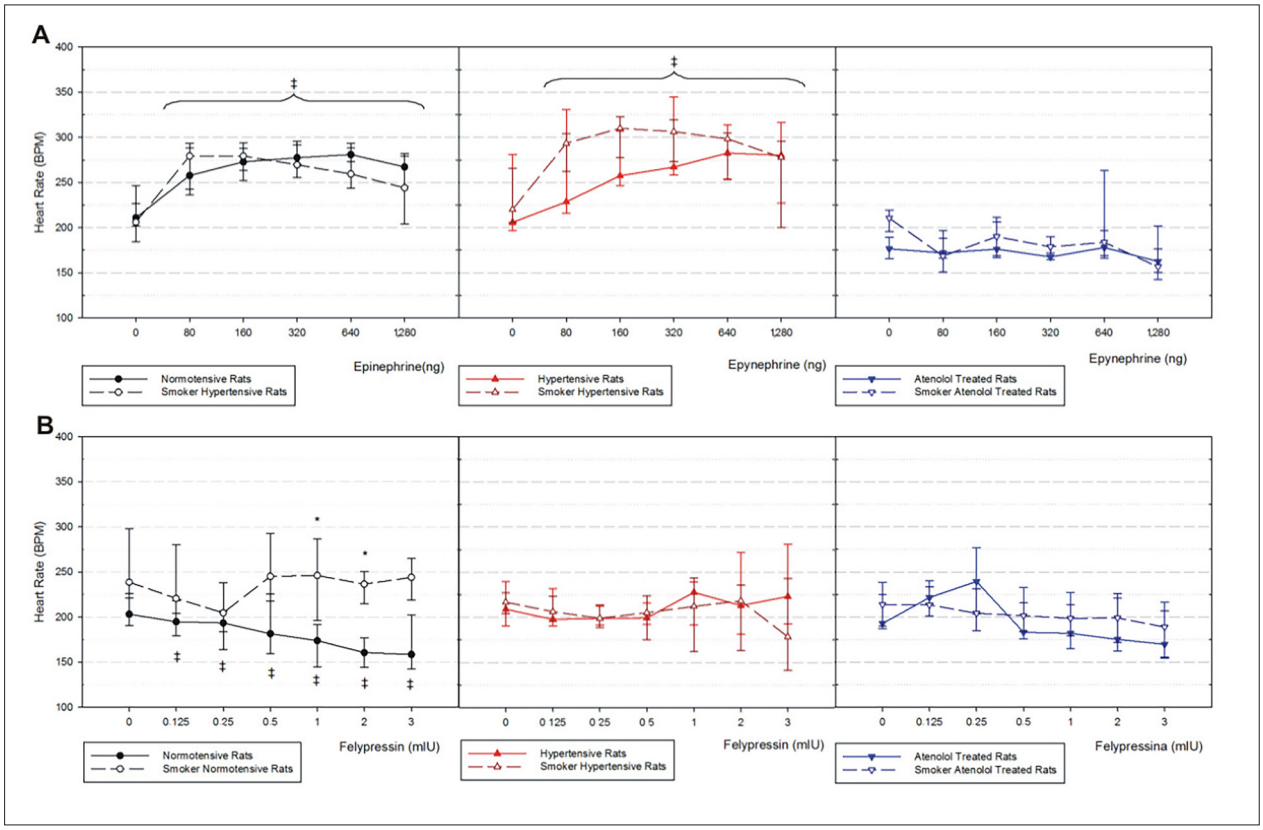

Figure 4 – *Heart rate before and after intravenous injection* in bolus *of epinephrine (A) and felypressin (B) in control non-smoker normotensive and smoker normotensive rats, non-smoker 1K1C hypertensive and smoker 1K1C hypertensive, non-smoker 1K1C atenolol-treated and smoker 1K1C atenolol-treated rats. n = 6 for all groups. Median (25th Percentile-75th Percentile). *p < 0.05 vs non-smokers groups. ‡ p < 0.05 compared to basal values.*

of choice for hypertensive patients according to the American Heart Association (AHA,[9], compared to felypressin, less often studied and not associated with the sympathetic autonomous nervous system[12].

Our data show that epinephrine maintained the same blood pressure responses, either in hypertensive smoker or hypertensive nonsmoker rats without atenolol treatment (Figures 2A and 3), but significantly increased heart rate (Figure 4A). However, in atenolol-treated non-smoker rats, the blood pressure response was higher compared with smokers. Considering all data about epinephrine safety in combination with local anesthetic use in the hypertensive

Table 2 – Response Duration

Number of cartridges	Normotensive				Hypertensive				Atenolol-treated rats			
	Nonsmoker		Smoker		Nonsmoker		Smoker		Nonsmoker		Smoker	
	Epinephrine	Felypressin	Epinephrine	Felypressin	Epinephrine	Felypressin	Epinephrine	Felypressin	Epinephrine	Felypressin	Epinephrine	Felypressin
1	453.5 (412-517)	905.2 (748,6-945)*	276.5 (214-298)	908 (880-948)*	297 (278-333)	911.5 (880-949)*	325.5 (277-492)	818.5 (610-876)*	291.5 (260-352)	811 (754-914)*	426 (382-470)	692.5 (552-738)*
2	427 (399-471)	1,042 (928.2-1118.9)*	268.5 (256-302)	888.5 (796-947)*	421 (376-436)	979.5 (934-1012)*	344 (329-497)	875.5 (771-972)*	398 (345-444)	545 (496-708)*	498 (413-616)	960 (920-976)*
4	445 (378-466)	1,117 (1,050-1,184.4)*	287 (294-323)	1,004.5 (876-1,086)*	422.5 (351-464)	1,021 (920-1,080)*	475 (357-513)	954.5 (882-1,042)*	415.5 (380-453)	712 (552-858)*	421 (405-464)	938 (783-1,111)*
8	455 (423-506)	1,077.1 (983-1,193)*	353 (332-365)	1,066.5 (1,000-1,170)*	455 (425-538)	1,032.5 (1,011-1,229)*	472.5 (400-507)	1,087 (998-1,154)*	454 (393-489)	946 (800-1,103)*	511.5 (479-586)	1,063.5 (987-1,240)*

*Response duration (in seconds) after intravascular administration of epinephrine or felypressin (dose contained in the corresponding number of local anesthetic cartridges) in smoker and non-smoker normotensive, 1K1C hypertensive and 1K1C atenolol-treated groups (n = 6 for all groups). Median (25th Percentile-75th Percentile). * p < 0.05 compared with epinephrine.*

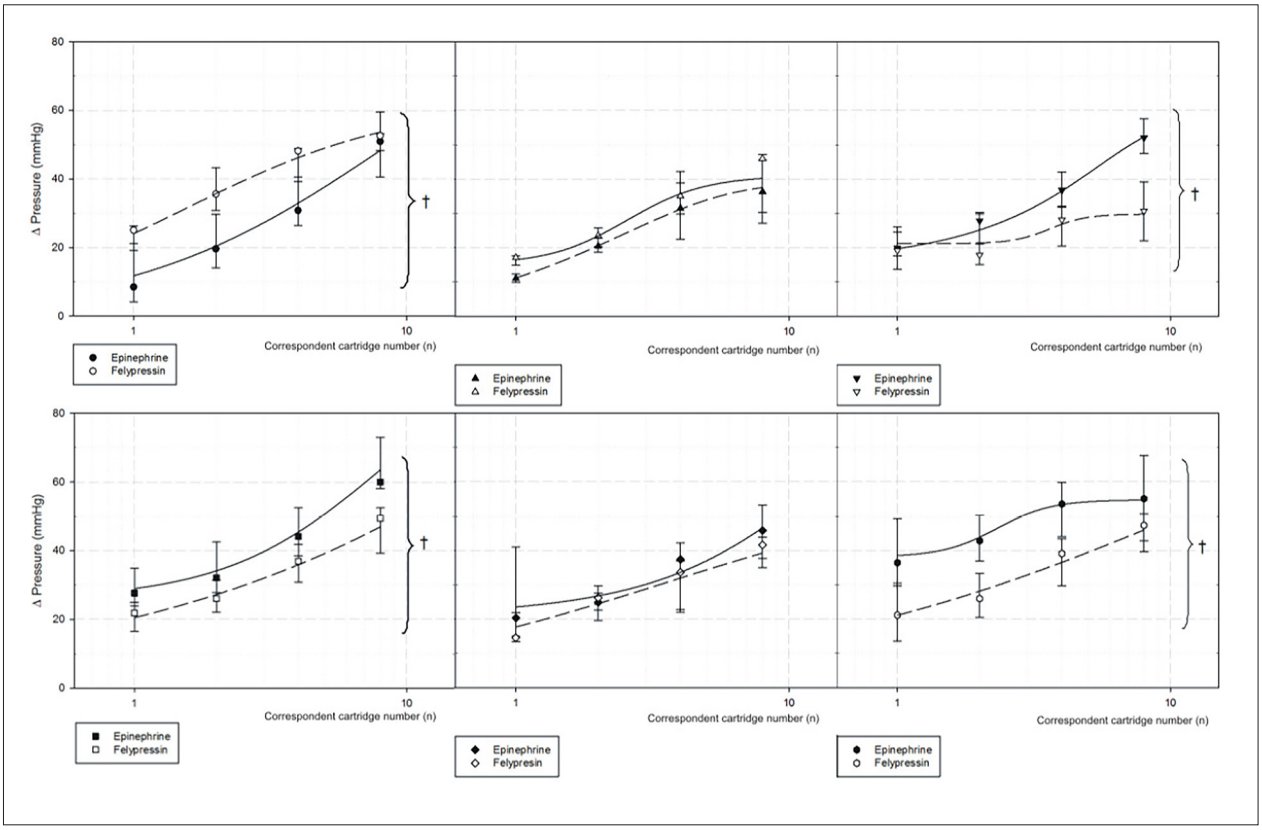

Figure 5 – *Comparison of maximal hypertensive response curves after intravenous injection* in bolus *of epinephrine and felypressin in control non-smoker normotensive, smoker normotensive rats, non-smoker 1K1C hypertensive, smoker 1K1C hypertensive, non-smoker 1K1C atenolol-treated and smoker 1K1C atenolol-treated rats. n = 6 for all groups. Median (25th Percentile-75th Percentile). *p < 0.05 in the comparison between drugs.*

population[13], our results suggest that the hypertensive response to epinephrine in hypertensive smoker and non-smoker rats without atenolol treatment, remains unchanged. On the other hand, the hypertensive, smoker and atenolol-treated rats showed significantly higher blood pressure measurements when compared with non-treated animals.

It is still not clear if cigaretes smoking increases blood pressure values, as some studies indicted that it can potentiate family history and increase systolic, diastolic and mean arterial pressure value.[6]. In our study, the smokers groups did not show increased basal blood pressure values when compared with non-smokers (Table 1). Smoke exposure was carried out for 4 weeks, as expected, and this time was sufficient to alter vasoconstrictor response. Rats were submitted to an epinephrine or felypressin intravascular injection under ketamine/xylazine anesthesia; it was shown in a previous study

by our group that such mixture reduced basal heart rate but did not alter blood pressure responses[10].

Smoke and nicotine can act diversely; nicotine seems to reduce blood pressure when administered acutely, while cigaretes smoking products are associated with increased blood pressure value.[7]. Tobacco smoke sidestream reduces acetylcholine endothelium-dependent relaxation when compared to non-smokers.[14] Our data show that epinephrine-induced hypertensive responses were increased in normotensive and atenolol-treated hypertensive smoker rats when compared to the non-smokers groups (Figure 2) and when compared to felypressin (Figure 5). Blood pressure is defined by cardiac output multiplied by vascular peripheral resistance. Felypressin injected by the intravenous route shows only a vasoconstrictor effect, increasing vascular resistance and leading to an increase in blood pressure values. Epinephrine, on the other hand shows vasoconstrictor and vasodilator, cardiac inotropic and chronotropic effects, leading to complex blood pressure responses after an intravenous injection. Vasodilation reduces hypertensive responses when global blood pressure is measured in and normotensive non-smoker rats showed the highest values of hypotensive response for the lowest doses of epinephrine (Figure 3), reducing hypertensive response when compared with felypressin (Figure 5). Felypressin presents less cardiac effects, but significantly reduced heart rate on normotensive non-smoker rats; such results are consistent with previous studies, where this vasoconstrictor response was associated with prilocaine,[15] which was associated with coronary artery constriction and baroreflex.

There is a complex cardiovascular response to nicotine because of ganglionar nicotine receptors which influence autonomous sympathetic and parasympathetic nervous systems. This response includes increase in catecholamine release and altered lipids metabolism which explains increase in cardiovascular disease development on in smokes.[8]. According to the Third Report of National Cholesterol Education Program (NCEP), smoking cigarettes has a direct impact on atherosclerosis formation and increases cardiovascular disases risk.[4] The association of hypertension and cigarettes smoking represents a delicate case for vasoconstrictor use. Felypressin response duration was significantly higher than epinephrine's in all groups, which was expected since vasopressin half-life is approximately 17-35min,[16] while epinephrine has a short half-life due to metabolism and synaptic reuptake.

Cigarette smoking increases blood vessel stiffness by different pathways, including oxidative stress increase of endothelin-1 production and formation of smooth muscle cell.[17]. Nicotine-free cigarette smoke extract administered by subcutaneous injection induced endothelial dysfunction, increased blood pressure values and reduced acetylcholine-induced vasodilatation.[18] Although the chemical component responsible for epithelial dysfunction is not clear, cigarettes smoke extract reduces vascular relaxation by increasing oxidative stress and reducing NO bioavailability.[19] Smokers also showed altered lipoprotein metabolism, increased levels of oxidized low density lipoprotein (LDL) which may contribute to vasoconstriction.

Chronic smoking impairs NO synthesis and enhances production of reactive oxygen species, while nicotine administration leads to hypertension due to increased sympathetic nervous system.[2,21] Our study showed a significantly reduced minimal hypotensive response on the smoker normotensive group (Figure 3). This reduced vasodilation caused by epinephrine may be related to the increase on the smooth muscle layer promoted by smoke. The heart rate effect was similar in both smoker and non-smoker groups.

Conclusion

Epinephrine and felypressin dosage corresponded to the content of 0.5 to 16 local anesthetic cartridges administered *in bolus* via intravascular route in hypertensive rats but there were no deaths. Our results support vasoconstrictor safety in associated vascular problems, mostly especially felypressin seems to be promising vasoconstrictor to smoker patients since there is no interaction with the sympathetic nervous system.

Author contributions

Conception and design of the research: Fleury CA, Almeida EPM, Amaral SL, Santos CF, Faria FAC; Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Fleury CA, Moretto E, Dionisio TJ, Calvo AM, Oliveira GM, Amaral SL, Santos CF, Faria FAC; Statistical analysis: Fleury CA, Dionisio TJ, Calvo AM, Oliveira GM, Santos CF, Faria FAC; Writing of the manuscript: Fleury CA, Dionisio TJ, Calvo AM, Oliveira GM, Amaral SL, Santos CF, Faria FAC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Elizandra P. M. Almeida, from *Faculdade de Odontologia de Bauru - Universidade de São Paulo*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade de Odontologia de Bauru - Universidade de São Paulo* under the protocol number 10/2010. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Short Editorial – Effect of Passive Smoking on Blood Pressure Response to Epinephrine and Felypressin in 1K1C Hypertensive Rats Treated or not with Atenolol

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Short Editorial related to the article: Passive Cigarette Smoking Impact on Blood Pressure Response to Epinephrine and Felypressin in 1K1C Hypertensive Rats Treated or not with Atenolol

I begin this text highlighting the importance of multidisciplinarity in the development of knowledge.

In 1842, Johann Christian Doppler, an Austrian physicist, defined that the frequency of the star's light changed with its motion, as it moved closer or away. One and a half century later, such "useless curiosity" started to be applied for the diagnosis of congenital heart diseases. And for a long time, we do know when the train is coming or going.

Needless to highlight the similarities among the areas of biological sciences, with emphasis on animal experiments. Affinities with Cardiology are described in this publication.[1]

Felypressin is an analogue of vasopressin (also called antidiuretic hormone or ADH), a hormone produced in the neurohypophysis. In Dentistry, felypressin is of special interest because it acts as a vasoconstrictor that prolongs the anesthetic effect.

In an artificially induced hypertensive model (and using a protocol illustrated in Figure 1 of the commented text), the effect of atenolol and felypressin on blood pressure was assessed in artificially hypertensive rats submitted to anesthesia, exposed to cigarette smoke. The results indicated that smoking can reduce epinephrine-induced vasodilation and increase the hypertensive response compared with felypressin.

These data add to the literature on the cardiac effects of vasoconstrictors. A recent review,[2] however, concluded that more studies are needed to increase the strength of the evidence.

It is interesting to note the elevated blood pressure of the anesthetized rats. Systemic arterial hypertension is not a common response to ketamine and xylazine,[3] suggesting that the dose of anesthetic was not sufficient to prevent the increase in sympathetic activity in the operated rats.

A recent study with awake humans, published in Arquivos Brasileiros de Cardiologia,[4] concluded that "felypressin increased the diastolic blood pressure of hypertensive patients with controlled blood pressure. Patients with high trait anxiety presented increases in systolic blood pressure upon some procedures". It is worth pointing out that the arterial catheter was placed after occlusion of the left carotid artery, which may have activated baroreceptors located in the carotid sinus, resulting in arterial hypertension. Maybe femoral artery catheterization would have been better.

Also, the time of cigarette smoke exposure was short (10 minutes/day), different from other studies in which the animals are exposed for longer periods.[5]

The publication of this study in the Arquivos Brasileiros de Cardiologia is timely; many heart disease patients want to know about the risks involved in their dental treatment, and physicians should be prepared for it.

Keywords

Rats; Tobacco Use Disorder; Tobacco/adverse effects; Anesthesia, Dental; Epinephrine; Felipressin; Hypertension; Atenolol.

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Cardiac Alterations in Patients with Familial Lipodystrophy

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Abstract

Familial lipodystrophy is a rare genetic condition in which individuals have, besides metabolic changes and body fat deposits, a type of cardiomyopathy that has not been well studied. Many of the patients develop cardiovascular changes, the most commonly reported in the literature being the expression of a type of hypertrophic cardiomyopathy. This article, presented as a bibliographic review, reviews the clinical and cardiovascular imaging aspects in this scenario of cardiomyopathy in a rare metabolic disease, based on the latest scientific evidence published in the area. Despite the frequent association of congenital lipodystrophy and ventricular hypertrophy described in the literature, the pathophysiological mechanisms of this cardiomyopathy have not yet been definitively elucidated, and new information on cardiac morphological aspects is emerging in the aegis of recent and advanced imaging methods, such as cardiac magnetic resonance.

Introduction

Lipodystrophy is a rare disease characterized by the loss of adipose tissue, which may be generalized or partial.[1] Its etiology may be congenital or acquired and there is a deficiency in the leptin hormone production, making the carriers of this pathology hyperphagic. Due to the absence of energy storage sites, an ectopic deposition of triglycerides occurs in the skeletal muscle and liver.[2]

The reduced ability to store triglycerides and their ectopic deposition are determinant for the predisposition and severity of complications, such as insulin resistance, diabetes mellitus, hypertriglyceridemia, hepatic steatosis[3] and, recently discovered, cardiomyopathy. Presentations such as left ventricular hypertrophy or even dilated cardiomyopathy have been described in patients with lipodystrophy.

Genetic lipodystrophies can be divided and subdivided into various types, each one with its specific mutation, which determine the most diverse clinical presentations and possible associations with the development of heart disease. Despite that, this condition is extremely rare, with a higher prevalence in populations with high levels of consanguinity.

This paper aimed to describe familial lipodystrophy and its association with the development of cardiomyopathies, in the light of the latest scientific evidence.

Keywords

Lipodystrophy, Familial Partial/genetics; Cardiomyopathy, Hypertrophic, Magnetic Resonance Imaging/trends; Metabolic Diseases/complications.

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Classification of congenital lipodystrophies

Congenital Generalized Lipodystrophy (CGL)

One of the most frequent types of genetic lipodystrophy is the generalized congenital type, characterized by an autosomal recessive disorder, occurring most often in cases of parental consanguinity. This form is present in all geographical regions and, because of the consanguinity cause, it probably has the highest prevalence reported in some regions of Brazil, such as the Northeast.[4] Individuals with this alteration have an almost total lack of adipose tissue, leading to prominent skeletal musculature regarding its phenotypic aspect. During childhood, many individuals develop hepatosplenomegaly and umbilical prominence; and during adolescence, complications such as diabetes arise.

This syndrome can manifest in many different forms, being related to one of four existing subtypes and, consequently, to the affected chromosome. Among these subtypes, the Berardinelli-Seip syndrome (BSCL) is well-known, described through the scientific collaboration of the great Brazilian researcher W. Berardinelli. Today it is known that this syndrome is identified by a mutation in chromosome 11q13, which encodes the protein seipin, present in the endoplasmic reticulum, being responsible for the formation of lipid droplets and their fusion within adipocytes. Its absence causes a lack of both metabolically active adipose tissue and mechanical adipose tissue since birth, which may lead to mild mental retardation and cardiomyopathies, making it the most severe of the subtypes.

Mandibuloacral dysplasia (MAD) - associated with lipodystrophy

This is a type of genetic lipodystrophy, in which the individuals have skeletal abnormalities, such as mandibular and clavicular hypoplasia, associated with skin atrophy, delayed teething, cranial suture closure and joint stiffness. As a common feature of lipodystrophies, MAD leads to metabolic complications such as diabetes, insulin resistance, hypertriglyceridemia, and low HDL-cholesterol levels.

Familial partial lipodystrophy (FPL)

Familial partial lipodystrophy is, mostly, an autosomal dominant disorder characterized by loss of upper and lower-limb fat as well as trunk[5] fat. These patients have

normal fat distribution during childhood and begin to have progressive and variable loss of subcutaneous fat during puberty, typically from the extremities, and in varying degrees from the abdomen and chest.

Many patients, especially females, show fat accumulation in the face, neck and perineal and intra-abdominal regions. (Figure 1) Excess fat accumulation in the dorsocervical (buffalo hump), supraclavicular and submental regions gives these patients a "cushingoid" appearance. In women, there may be masculinization, menstrual irregularity and high prevalence of polycystic ovary syndrome.[5]

Five genes may be involved in the pathophysiology of this type of lipodystrophy, all leading to subcutaneous fat loss in the extremities. The most prevalent form of familial lipodystrophy is autosomal dominant type 2, the first familial partial lipodystrophy more formally described: FPLD2 (Familial Partial Lipodystrophy Type 2), also referred to as variant or Dunnigan Syndrome. This syndrome has a prevalence of 1 in 15 million people, affecting both genders equally. The patients develop several metabolic complications such as dyslipidemia, hypertriglyceridemia and diabetes. In addition, they may manifest varying degrees of myopathy, cardiomyopathy, and other conduction system abnormalities, thus proving to be a multisystem dystrophy.[6]

FPLD2 is characterized by a mutation in the long arm of chromosome 1 (1q21-22) specifically involving lamins A and C or the LMNA gene. Commonly, the mutation that causes FPLD2 affects exon 8 (replacement of arginine by a neutral amino acid at position 482 - R482W), but other mutations in exon 8 and 11 (codon 644 - R644C) have already been described.[6,7] It has been shown that the LMNA R482W mutation is more associated with muscle and cardiac abnormalities, such as muscular atrophy and dystrophy, cardiac hypertrophy and advanced atherosclerosis.[8] But the phenotypic differences associated with each specific mutation determinant of FPLD are yet to be elucidated.

Numerous mutations spread throughout the LMNA protein give rise to diseases commonly called laminopathies that affect muscle, heart, fat, cartilage and bone tissues or lead to early aging syndromes.[9]

A-type lamins include lamins A (LMNA) and C (LMNC) that arise from alternative splicing of RNA from the LMNA gene. These proteins are expressed in most cells, and they are located in the nuclear envelope and nucleoplasm and play a relevant role in directing the transcription of heterochromatin located on the periphery of the nucleus.[9] It is believed that the alteration of these proteins weakens the integrity and structure of the nuclear envelope, which would profoundly deteriorate the structure of the adipocyte nucleus, ultimately leading to premature cell death. In addition, it is known that A-type lamin is capable of interacting with transcription factors such as SREBP1 (Sterol Regulatory Element Binding Protein 1), which is involved in the differentiation of adipocytes.[6,7,9] Furthermore, it has been observed that type A and C-lamins bind to telomeric sequences, having a role in regulating telomere length.

The main point common to all types of lipodystrophy is the total or almost total absence of adipose tissue, thus compromising the affected individual's storage of triglycerides and their metabolic activity. Before that, most patients clinically manifest muscular appearance, prominent superficial veins,

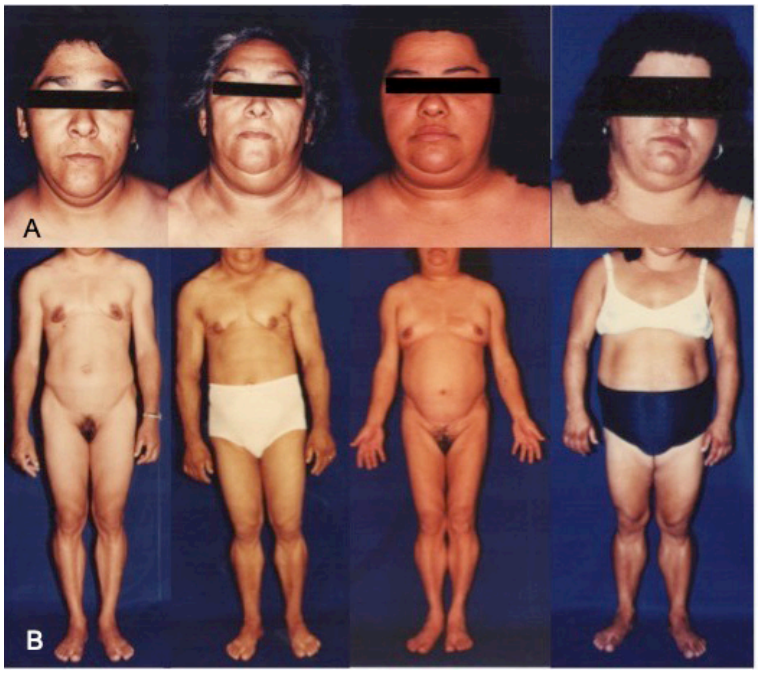

Figure 1 – *Characteristics of patients with familial partial lipodystrophy. Panel A shows fat accumulation on the face and neck and panel B, fat accumulation in the perineal and intra-abdominal regions.*

extremity enlargement, acanthosis nigricans, umbilical prominence or hernia, hyperphagia and accelerated growth, menstrual period irregularity , precocious puberty and menarche, among other signs and symptoms that may include cardiac autonomic changes.[10]

One of the key points possibly related to the occurrence of cardiomyopathies in patients with lipodystrophy and also associated with all the described types is the accumulation of fat in ectopic tissues, such as the liver and skeletal muscle. Also, the lower capacity to oxidize and store fat promotes dyslipidemia, insulin resistance, development of diabetes mellitus and its complications, which may involve the cardiovascular system.[10]

Cardiac impairment in patients with congenital lipodystrophy

The World Health Organization, together with the International Society and Federation of Cardiology, has defined cardiomyopathy as a myocardial disease associated or not with cardiac dysfunction and can be classified according to morphological and physiological changes, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic left ventricular cardiomyopathy, metabolic cardiomyopathy, among others.[11]

Special attention should be paid, in this context, to metabolic cardiomyopathy, which develops before various pathological conditions associated with systemic metabolic disorders, being characterized by structural and functional changes without concomitant coronary artery disease or hypertension.[12] The condition, known as diabetic cardiomyopathy, is an under classification of metabolic cardiomyopathy and is defined by the presence of myocardial involvement in patients with diabetes, after excluding other causes such as ischemic myocardial disease. In diabetic cardiomyopathy, there may be left ventricular remodeling and dilation, associated with diastolic and, in some cases, systolic dysfunction.[13]

The glucose metabolism impairment present in diabetes is associated with the higher consumption of fatty acids as an energy source, which is justified by the lack of insulin or resistance to it.[13] The almost exclusive use of this compound leads to excess lipids, which may be accumulated in the heart muscle or diverted to non-oxidative pathways, disrupting normal cell function and causing organ dysfunction and apoptosis, a fact called lipotoxicity.[14] In addition, permanently hyperglycemia can cause damage to the myocardium through proteins modified by advanced glycation end products, as well as oxygen free radicals, leading to their accumulation and myocardial fibrosis, which can result in dysfunction, initially only diastolic.[13]

Several cardiac alterations have been described in the literature in patients with lipodystrophy, whether solely morphological alterations or alterations associated with cardiac dysfunction, but the pathophysiological basis involved has not been completely elucidated.[10] Early atherosclerosis, especially in patients with familial partial lipodystrophy, may have a prevalence rate of over 60% and manifests before age 45. With such aggressiveness, the pathophysiological mechanisms involved seem not only to be dependent on metabolic changes, but perhaps on a direct effect of gene mutation on endothelial function.[15]

In a collection of case series of lipodystrophy prior to the year 2000, several cases with hypertrophic cardiac changes have been described, with or without systolic obstruction to ventricular ejection, many with cardiomegaly and associated systemic arterial hypertension (Table 1).[16]

After the 2000s, publications on isolated or grouped cases showing an association between lipodystrophy and ventricular hypertrophy[17] can also been found in the literature, even in very young or still infant patients,[18-20] and, in some cases, the progression of ventricular hypertrophy has been documented.[21] In some of these cases identified at early ages, the evolution of cardiomyopathy to global systolic dysfunction in childhood or youth has been documented.[19,21,22]

Hubert Pan et al.[23] considered that LMNA mutations are generically expressed with muscular dystrophy, lipodystrophies, bone dysplasias, and cardiovascular disease, and, before that, they reported the case of a family with Chinese ancestors with three generations of heart disease, in which 100% of the relatives older than 40 years had the clinical manifestations. The cardiovascular disease shown by the carriers of this mutation consisted of arrhythmias, atrioventricular blocks and dilated cardiomyopathies. Part of these individuals died because of cardiovascular disease.[23]

In 2010, Rêgo et al.[24] reported a group of 22 patients with CGL2, of which 86.4% had a family history of the disease. Most patients had the common metabolic signs associated with the pathology, such as diabetes mellitus, insulin resistance, acanthosis nigricans, hepatosplenomegaly, elevated fasting blood glucose and triglyceride levels and low HDL-cholesterol levels, which contributed to many patients being diagnosed with metabolic syndrome. On cardiovascular examination, part of the patients had arterial hypertension, 50% of the patients had left ventricular concentric hypertrophy and 4.5% had left ventricular eccentric hypertrophy, but all cases had normal patterns in both left ventricular systolic and diastolic function, when evaluated by conventional echocardiography.[24]

Lupsa et al.[1] studied 44 patients with lipodystrophy, of whom 31 had CGL. The individuals were submitted to genotypic and phenotypic diagnoses, as well as cardiac morphological and geometric analysis. Of the 31 individuals with CGL, 18 had some degree of ventricular hypertrophy, although none of them had LV systolic dysfunction.[1] (Table 2)

The pathological analysis of the heart was performed in part of this series; in one of the individuals submitted to heart transplantation because of refractory heart failure, and in two others who died from respiratory failure secondary to pneumonia. Two of the patients had CGL1. In one of them, biventricular dilation and myocyte hypertrophy was evidenced, with the presence of vacuolated subendocardial myocytes, as well as subendocardial and epicardial fibrosis with fat and infiltrated with dispersed lymphocytes. The other individual with CGL1 showed mild left ventricular hypertrophy, especially posterolateral. Finally, in the last individual, who had CGL2, left ventricular hypertrophy and an irregular perivascular and interstitial fibrosis were observed.[1]

Nelson et al.[2] studied 5 patients with congenital generalized lipodystrophy (2 of them with CGL1 and 3 with CGL2) and 5 control subjects with similar characteristics of age and

Table 1 – Case reports of patients with congenital generalized lipodystrophy

Authors/year	Findings
Seip (1959)	3 patients; one with a systolic murmur. 2 had increased blood pressure and cardiomegaly.
Seip (1963)	5 patients, all with cardiomegaly.
Choremis (1965)	1 patient: cardiomegaly and arterial hypertension
Gold et al. (1967)	2 patients (siblings) with moderate cardiomegaly.
Brunzell et al. (1968)	Presence of cystic angiomatosis in patients with CGL.
Montenovesi et al. (1971)	1 patient with cardiomegaly.
Bjorntad et al. (1985)	7 patients, 6 of them with CGL. They had systolic murmur, 3 with left ventricular hypertrophy and 2 with biventricular overload.
Rheuban et al. (1986)	4 patients, all with systolic ejection murmur and non-obstructive hypertrophic cardiomyopathy.
Klair et al. (1993)	1 patient with progressive hypertrophic cardiomyopathy.
Chandalia et al. (1995)	1 patient with 20% obstruction of coronary arteries and presence of atheromatous plaques.
Westvik et al. (1996)	8 patients, 7 of them with CGL. Presence of cardiomegaly and one death secondary to congestive heart failure.
Bjornstad et al. (1996)	8 patients, 7 of them with CGL. Presence of cardiac hypertrophy.
Viegas et al. (2000)	1 patient with hypertension and severe symmetric hypertrophy.

CGL: Congenital Generalized Lipodystrophy. Adapted from Rego AR, et al.[16] Source: [Adapted from Rego AR, MAG; Faria, CA; Baracho, MFP; Egito, EST; Mesquita, ET; Brandão Neto, J. Alterações cardiovasculares e metabólicas da lipodistrofia generalizada congênita (síndrome de seip-berardinelli)]

Table 2 – Genotypic and phenotypic analysis of patients with CGL

Genetic alteration	Geometrical alteration of the left ventricle	Electrocardiographic and/or functional analysis
CGL1 (AGPAT2 mutation)	9 patients with normal LV mass. 3 patients with mild hypertrophy. 4 patients with moderate hypertrophy. 3 patients with severe hypertrophy.	17 ECGs were assessed, 9 of them with abnormalities.
CGL2 (seipin mutation)	2 patients with normal LV mass. 2 patients with mild hypertrophy. 2 patients with moderate hypertrophy. 4 patients with severe hypertrophy.	7 ECGs were assessed, 5 of them with abnormalities.
LMNA (R133L) mutation	Normal left ventricular mass.	Ejection fraction of 35% and low exercise tolerance.
Unknown mutation	Normal left ventricular mass with concentric remodeling.	

ECG: Electrocardiogram; LV: left ventricle. Adapted from Lupsa BC, et al.[1] Source: [Adapted from Lupsa BC, Sachdev V, Lungu AO, Rosing DR, Gorden P. Cardiomyopathy in congenital and acquired generalized lipodystrophy: A clinical assessment.]

body mass. Parameters such as total cholesterol levels and blood pressure were similar in both groups. Individuals with lipodystrophy, however, had low HDL cholesterol levels, high fasting blood glucose levels, three-fold higher circulating triglyceride content, and detection of pericardial adipose tissue by cardiovascular imaging methods (Figure 2). A morphological and functional analysis of the heart of these patients by cardiac magnetic resonance imaging showed an increase in left ventricular mass with a concentric pattern. However, there was no difference between the final systolic and diastolic volume values or left ventricular ejection fraction when compared to a control group.[2] Thus, in the first clinical study that controlled variables such as blood pressure levels and age between subjects with lipodystrophy and controls, there was still a LV geometric difference between the groups, although both showed no functional alterations.

Sims-Williams et al.[25] reported the case of a 62-year-old patient with dilated cardiomyopathy and symptomatic heart failure whose twin brother had died from heart failure, as well as their father. The grandfather, on the other hand, had suffered an embolic stroke and also had ventricular hypertrophy. The entire family had an LMNA gene mutation. The echocardiographic evaluation of this individual revealed marked dilation and deterioration of the left ventricular systolic function, with an LV ejection fraction of 18%, associated with a thickness increase in the left ventricular posterior wall. There was also reduction in the right ventricular function and bi-atrial dilation. Based on these facts, the authors hypothesized that most of the cardiomyopathies found in this group of patients also have a familial etiology, and part of them, caused directly by LMNA mutations.[25]

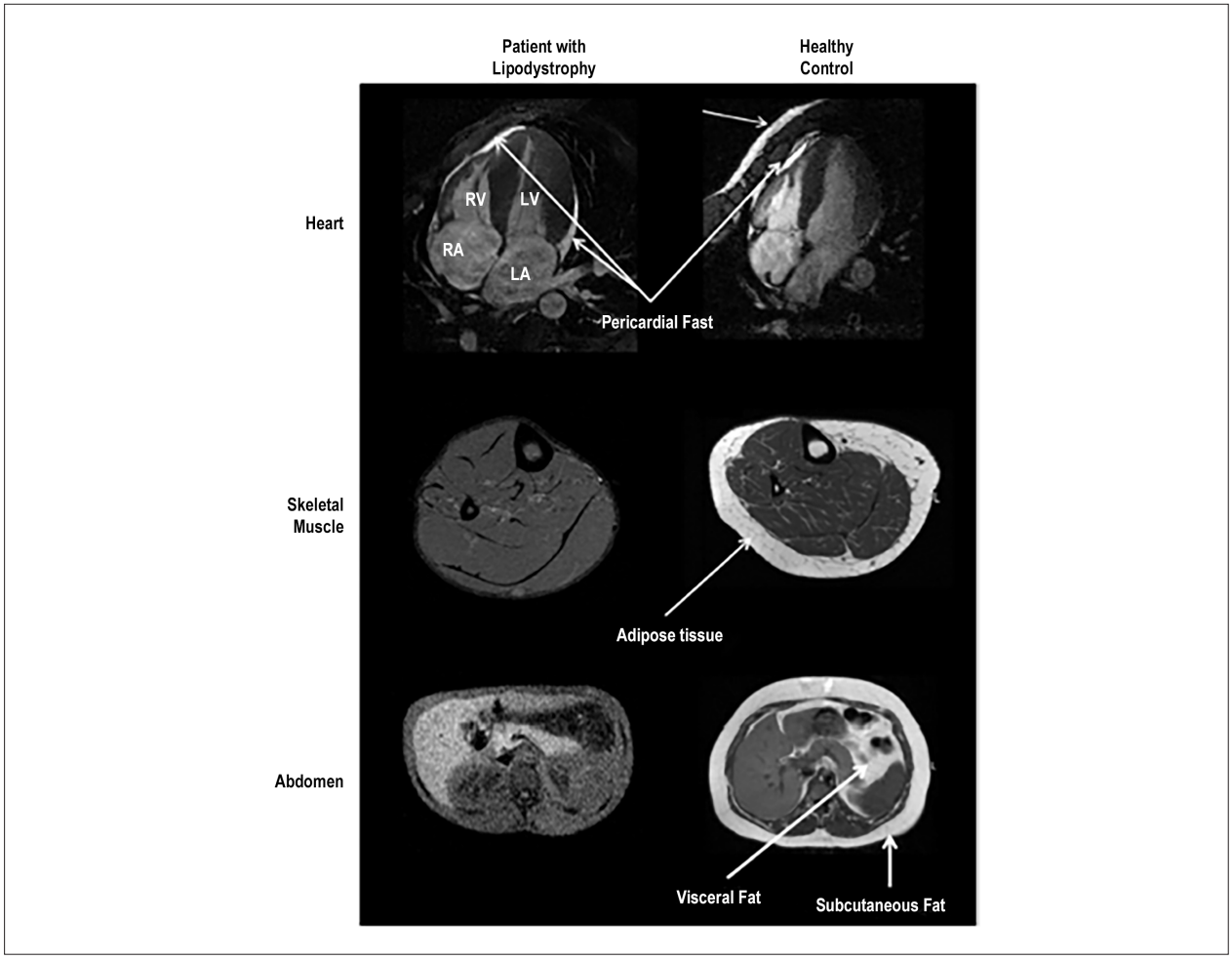

Figure 2 – *High resolution magnetic resonance images. (Upper) Four-chamber cardiac magnetic resonance images showing pericardial fat in the patient and in the control. (Middle) The control has fat in the chest wall, while the patient does not, demonstrating a general lack of adipose tissue in the patient. (Lower) The liver appears bright because of hepatic steatosis in the patient with lipodystrophy. The general lack of subcutaneous and visceral adipose tissue in the patient with lipodystrophy can be observed. [Adapted from Nelson et. al. Cardiac Steatosis and Left Ventricular Hypertrophy in Patients With Generalized Lipodystrophy as Determined by Magnetic Resonance Spectroscopy and Imaging].*[2]

Scatteia et al.[26] described the case of a 30-year-old man with generalized lipodystrophy, diagnosed from birth and with ejection systolic murmur from childhood. Echocardiographic examinations showed asymmetric hypertrophic cardiomyopathy, predominantly in the interventricular septum, mitral regurgitation, but without obstruction of the left ventricular outflow. At the age of 30, the cardiac geometric changes became more evident and ventricular hypertrophy progressed, with an ejection fraction of 71%. With the support of magnetic resonance imaging, it was possible to exclude the presence of myocardial edema, as well as fatty infiltration. This examination revealed a focal area of gadolinium late enhancement, suggesting local myocardial fibrosis (Figure 3). The presence of signs of fibrosis scattered in hypertrophic muscle usually suggests that hypertrophy is primary and not secondary to hemodynamic situations, such as systemic arterial hypertension.[26]

Therefore, as most data in the literature involving lipodystrophy and cardiac geometric and functional changes are based on case reports and case series, the mechanisms involved in this association have yet to be elucidated. The hypothesis of myocardial lipotoxicity is supported by the finding of high triglyceride levels in the hypertrophied cardiomyocytes of some patients, besides the presence of myocardial fat. A probable pathophysiological explanation for lipotoxicity would be a repetitive mechano-sensitive stimulation of elements present in adipogenesis, similarly to patients with preserved residual adipose tissue. In addition, it is also believed that insulin resistance, present in practically all of these individuals, causes an imbalance in the use of substrates by the myocardium, leading to a higher absorption of fatty acids, which may lead to the observed alterations.[2]

Published in 2017, the study by Joubert et. al.,[27] in an experimental animal model (rodent) of lipodystrophy,

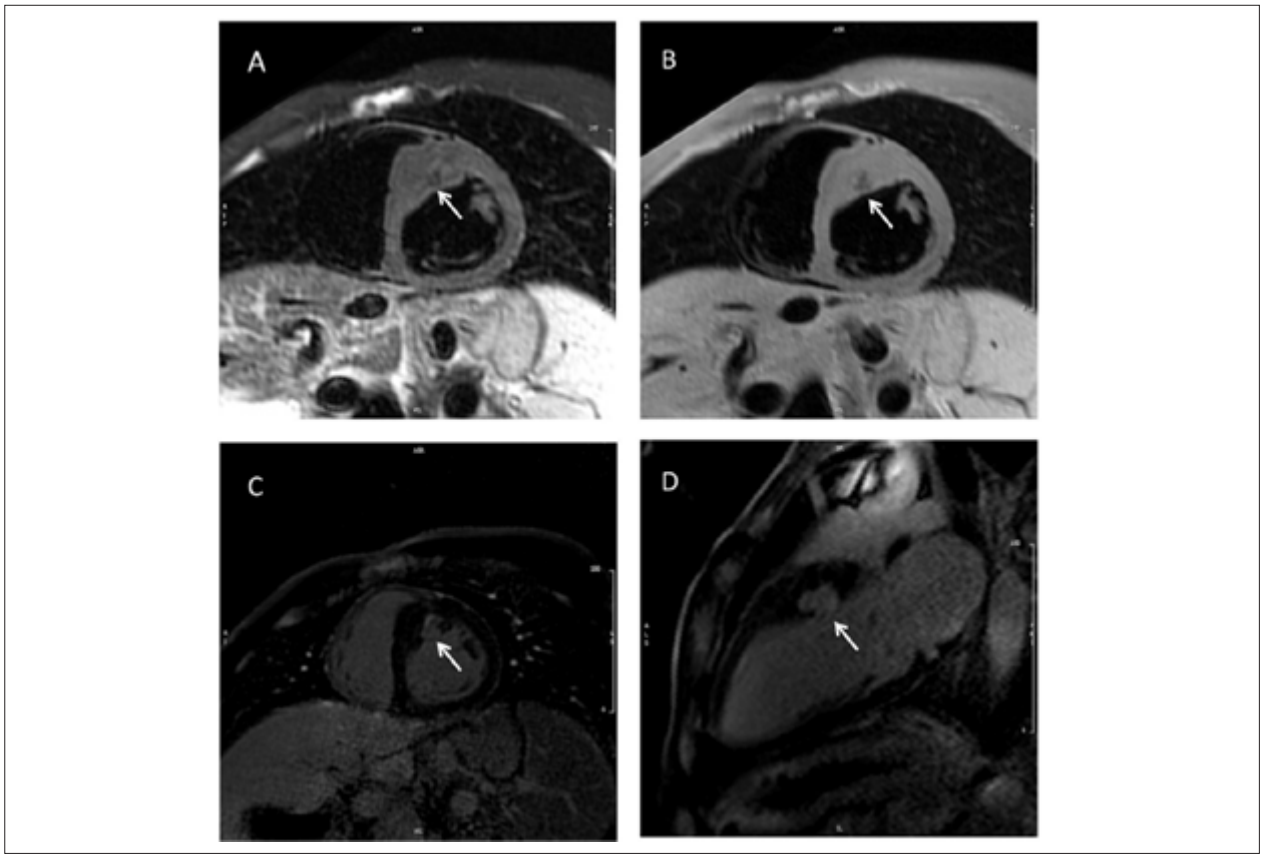

Figure 3 – *A and B are pre-contrast images. C and D are late post-enhancement images. (A) and (B), both showing a hypodense area (arrow) in the anterior hypertrophic region/anteroseptal region excluding, respectively, the presence of fatty infiltration or edema. (C) and (D) showing late gadolinium enhancement area (arrow) involving the anterior/anteroseptal hypertrophic region and compatible with myocardial fibrosis / necrosis [Adapted from Scatteia et al. Asymmetric hypertrophic cardiomyopathy in generalized lipodystrophy].*[26]

was designed to elucidate the pathophysiological basis of myocardial aggression in this disease. Genetically modified mice with no gene for seipin, when compared to controls, showed left ventricular hypertrophy associated with both diastolic and systolic ventricular dysfunction. However, in contrast to what was suggested in other studies, they did not have cardiac triglyceride deposits, contradicting the hypothesis of myocardial lipotoxicity. However, myocardial changes induced in this model correlated with altered glucose metabolism. Based on the findings of this study, it cannot be confirmed that cardiac lipotoxicity is the pathophysiological mechanism involved with hypertrophy and ventricular dysfunction in this disease. But it is quite plausible that the metabolic alteration of glycemic control is indirectly related to transcription factors responsible for the regulation of pro-hypertrophic gene activation.[27]

Conclusion

Familial lipodystrophy is a rare condition where individuals show, besides metabolic and skeletal muscle changes, adipose tissue alterations, a type of cardiomyopathy. Cardiac changes commonly described in the literature, in case series, show a hypertrophic cardiomyopathy phenotype. The evolution to left ventricular systolic dysfunction can happen in a percentage of cases. There is not enough information to conclude on the frequency of cardiac functional impairment, such as the diastolic dysfunction type, or even incipient systolic changes.

Still, despite the frequent association of congenital lipodystrophy and ventricular hypertrophy, the pathophysiological mechanisms remain unknown. Hypotheses that the altered glucose metabolism caused by the disease is responsible for activation of pro-hypertrophy genes could explain such association.

Author contributions

Conception and design of the research: Romano MMD; Acquisition of data: Chacon PAI, Ramalho FNZ; Analysis and interpretation of the data: Romano MMD, Chacon PAI; Writing of the manuscript: Romano MMD, Chacon PAI, Ramalho FNZ; Critical revision of the manuscript for intellectual content: Romano MMD, Foss MC, Schmidt A.

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

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Treatment of Aortic Stenosis in Elderly Individuals in Brazil: How Long Can We Wait?

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The growing life expectancy of the population is increasing the occurrence of diseases affecting the elderly age group, notably the non-rheumatic degenerative valvular diseases and, in particular, aortic stenosis, whose prevalence in elderly individuals older than 75 years has been estimated at 3 to 5%. This is the most common valvular heart disease among elderly individuals, and its severe form is associated with high morbidity and mortality. The life expectancy of patients with aortic stenosis presenting with heart failure and rhythm disturbances is estimated to be less than 2 years. The standard treatment for this disease is cardiac surgery with replacement of the aortic valve by a prosthesis. However, due to high surgical risk, especially in very elderly patients with associated comorbidities, cardiac surgery is contraindicated in about 30% of the cases or is performed with high morbidity and mortality rates according to preoperative scores. For these critically ill patients, a new, less invasive technique consisting of transcatheter aortic valve implantation (TAVI) of a bioprosthesis has been considered the therapeutic option of choice, initially tested in patients at very high surgical risk, but currently with evidence of noninferiority compared to open surgery in lower-risk individuals.[1,2] The first TAVI procedure in the world was performed in France in 2002 by Professor Alain Cribier, and the method was pioneered in Brazil in 2008. Since then, a considerable number of patients has been treated. However, despite robust evidence of safety and efficacy, this therapy has still not been incorporated into the supplemental or public health care systems (*Sistema Único de Saúde* [SUS]) in the country.

Despite the fact that TAVI has already been evaluated and accepted in the health care systems of several countries with evidence of cost-effectiveness even in individuals at intermediate operative risk,[3] the Ministry of Health, based on a position stand from the National Commission for Incorporation of Technologies in the SUS (Conitec), established in 2013, in response to a request by the Brazilian Society for Hemodynamics and of Interventional Cardiology (SBHCI) acting as the petitioner, considered that there was no convenience in incorporating this therapy in Brazil. Conitec, at the time, based on the opinion of a reviewer and disregarding the opinion of prestigious national universities presented in a public consultation on the subject, recommended against the incorporation of the procedure, justifying this decision on three points: a) TAVI would not be a safe and effective procedure due to an allegedly high incidence of stroke within the first 30 days after the procedure, b) the budgetary impact of incorporating TAVI into the SUS would approach 1 billion reais per year, and c) methodological inaccuracies could have affected the economic model presented by the petitioner and the PARTNER B study, which served as the main background for the incorporation of this procedure by all health technology assessment agencies in the world that have requested the incorporation of this technology.

Currently, robust data published since the issuance of this report, from at least six major randomized clinical trials and international registries,[1,2,4] suggest no doubt about the appropriateness of the technique in selected patients, resulting in a recent expansion of risk groups in which TAVI would have similar results compared to open surgery, including a reduction in important outcomes like length of hospital stay and neurological events. However, there is no way to obscure the fact that the budgetary impact of the procedure can be high, especially given the demographic changes that the country has been going through in recent decades. Estimates of costs with the technique by the Ministry of Health, as discussed below, seem at first glance inaccurate and based on data that may not reflect the national reality. Estimates of the frequency of use of the procedure calculated by technicians of the Ministry of Health overestimate the access to TAVI in Brazil, projecting a budgetary impact that exceeds a billion dollars.

Data from the 2017 Global Burden of Disease (GBD) study analyzing non-rheumatic heart valve diseases show that even though the age-standardized prevalence of these grouped diseases has remained relatively stable in Brazil from 1990 to 2017, there was a significant increase in Non-rheumatic calcific aortic valve disease, from 53.5 (95% uncertainty interval [95%UI]: 48.1 – 59.9) per 100,000 inhabitants in 1990 to 64.4 (95%UI: 57.2 – 72.5) per 100,000 inhabitants in 2017 for both men (18.5%) and women (24.2%).[5] The increase in the absolute prevalence rate of this valvular disease was even more significant, surpassing 114% (95%UI: 105.5 – 124.3%) over 27 years, and suggesting a progressive and still growing impact from aortic valve diseases on the country's health care systems (Figure 1).[5,6]

Keywords

Life Expectancy; Aging; Aged; Stenosis Valve Aortic/surgery; Heart Valve Prosthesis; Heart Valve Prosthesis Implantation; Transcatheter Aortic Valve Replacement/trends.

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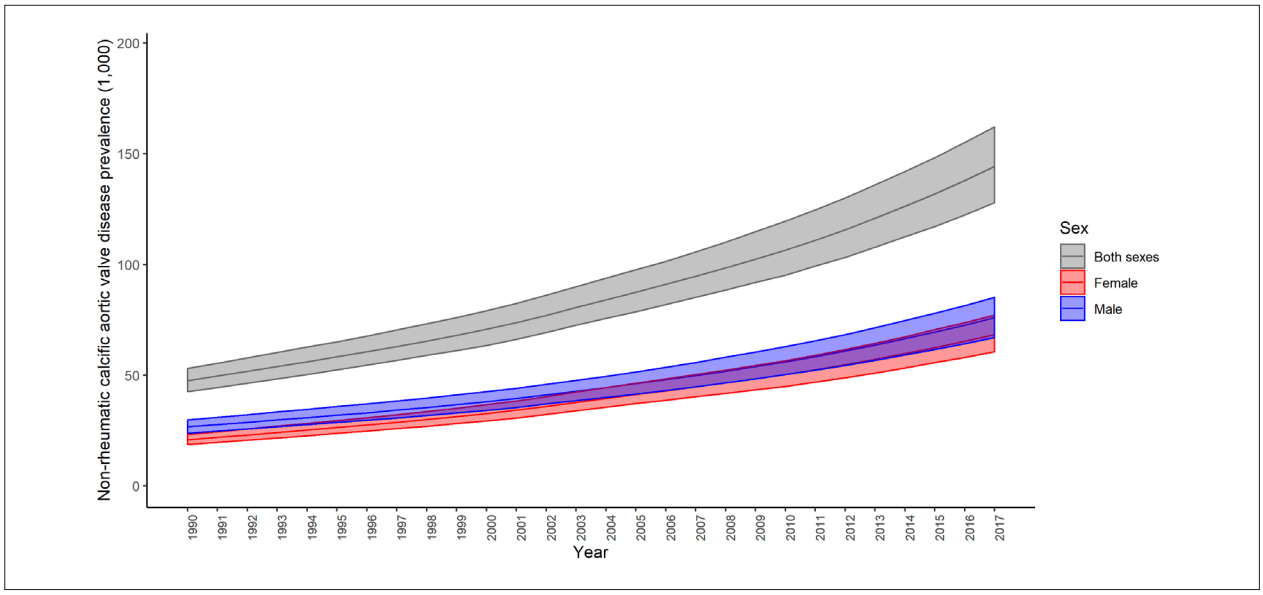

Figure 1 – *Absolute prevalence of Non-rheumatic calcific aortic valve disease in Brazil from 1990 to 2017 (Global Burden of Disease 2017).*[7]

Regarding the causes of death in Brazil, non-rheumatic valvular diseases rose from the 10th position in 1990 to the 9th position in 2017. Although the age-standardized mortality associated with these valvular diseases has remained relatively stable, a considerable increase was observed for degenerative aortic valvular disease. The mortality rate at all ages due to non-rheumatic valvular diseases increased significantly by 87.5% (95%II: 63.5 – 96.9%) (Figure 2), with a large contribution from the population over the age of 70 years, especially in relation to Non-rheumatic calcific aortic valve disease, which showed a 108% increase in this age group in the evaluated period.[7] These trends have also resulted in increased proportional mortality associated with Non-rheumatic calcific aortic valve disease in both sexes (Figure 3), suggesting a striking contribution from the changes in the age profile of the population in recent decades to the global burden of valvular disease in Brazil, with a notable impact by the aging of the population.[6]

Additionally, GBD 2017 data suggest that socioeconomic development is also a determinant of some types of valvular diseases, notably Non-rheumatic calcific aortic valve disease: percentage changes in age-standardized mortality rates from 1990 to 2017 correlated significantly with the sociodemographic development index (SDI) of the Brazilian states in these years (1990: $r^2 = 0.17$, $p = 0.005$; 2017: $r^2 = 0.23$, $p = 0.003$) (Figure 4), and a similar pattern was observed for morbidity, with significant correlations between disability-adjusted life years (DALY) and the SDI in the period.[6] These trends are in line with those observed for cardiovascular disease in general in Brazil and in other Portuguese-speaking countries.[8] However, it should be noted that primary epidemiological data on degenerative aortic valvular disease in Brazil are still scarce, and most estimates derive from statistical modeling.

Despite the progressive increase in the prevalence and disease burden associated with degenerative valvular diseases in the country, the number of annual hospitalizations by the SUS for treatment of valvular heart disease remained stable between 2008 and 2018, with a modest increase in costs of around 40%, not adjusted for the inflation in the period[9] (Table 1). At the beginning of the period evaluated in this time series (2008), the first TAVI implantation was performed in Brazil, and current data from the RIBAC national registry, organized by the SBHCI, compute over 800 procedures, with rates of success and complications exceeding those in the literature.[10,11] The approximate cost per transfemoral implantation is estimated at R$ 82,826.38, with the prosthesis corresponding to about 80% of this amount.[12]

Conitec defended that the budgetary impact estimate was not the main determinant for its unfavorable opinion, but gave evidence contrary to this assertion when insisted on maintaining the estimate at levels completely dissonant from the reality of health care in Brazil, especially concerning the SUS. The new budgetary impact estimate was calculated after public consultation but was presented without emphasis in the final report (restricted to two lines on page 25), hindering its visibility, while the prior estimate modified by Conitec after the public consultation continued to be largely detailed on a table over several pages (for example, pages 17, 18, and 19), leading the reader to an inaccurate conclusion that this would still be the estimate that the commission considered to be correct.

The new estimate reduced the budgetary impact by more than 300 million reais per year. The Conitec considered that the budgetary impact would still be high, but did not indicate with clarity which levels were considered acceptable. Also unclear were the reasons why Conitec abandoned its first budgetary impact estimate without adopting the new estimate presented by the petitioner, which was based on the reality of health care in Brazil through its expert panel, indicating a far more feasible impact in view of the Ministry of Health budget and the provision of medical procedures to

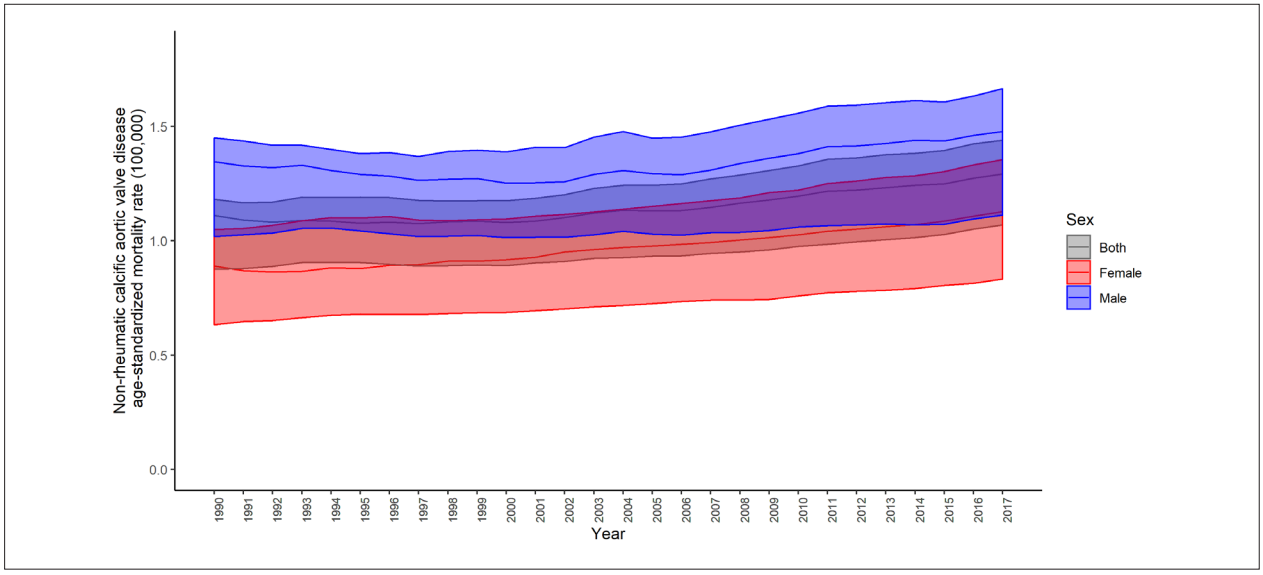

Figure 2 – *Mortality rate at all ages due to Non-rheumatic calcific aortic valve disease in Brazil from 1990 to 2017 (Global Burden of Disease 2017).*[7]

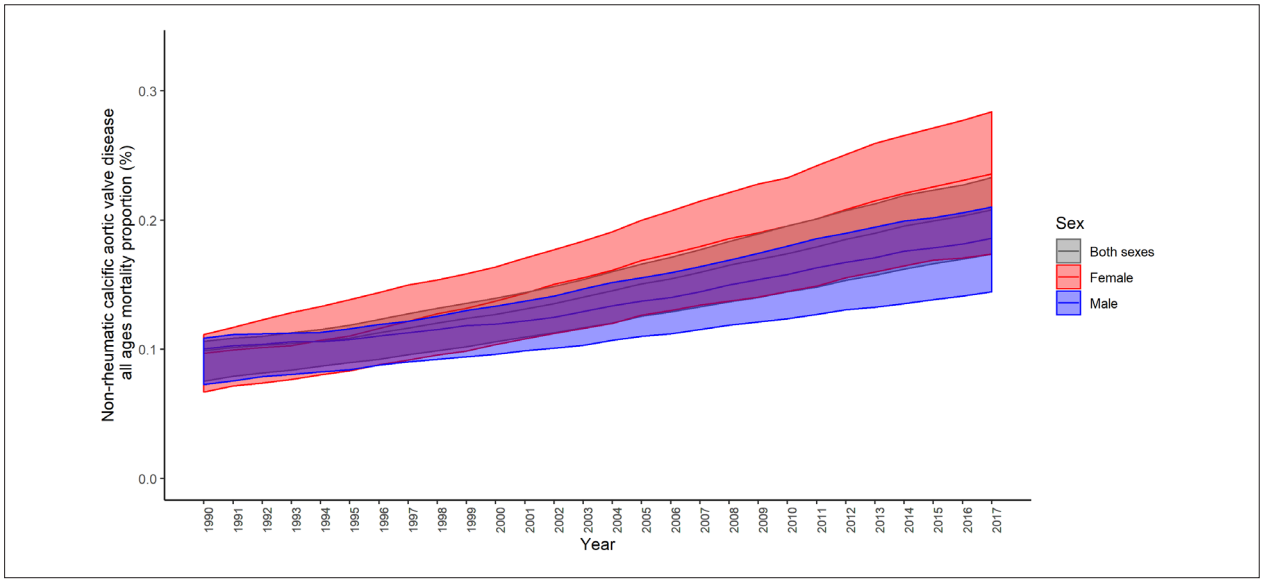

Figure 3 – *Proportional mortality from non-rheumatic calcific aortic valve disease in Brazil from 1990 to 2017 (Global Burden of Disease 2017).*[7]

the Brazilian population by SUS. Instead, estimated data from other countries were primarily considered for the analysis.

Without a clear connection with the remainder of the opinion, page 25 of the final Conitec report presents the budgetary impact estimate, which is subject to several criticisms in addition to those presented. First, it should be emphasized the mentioning of the study by Wood[13] showing the estimated increasing use of TAVI in Europe, with an annual rate of 40.9 million inhabitants, which would be proportional to 8,025 procedures/year in Brazil.

Conitec constantly criticizes the use of international instead of national data. Interestingly, in this case, to calculate the budgetary impact, Conitec used an European estimate, which would be particularly questionable in this context, since 1) TAVI has been registered and practiced for much longer in Europe than in Brazil; 2) the epidemiological characteristics of the European population are different from those of the Brazilian population in terms of being older and with a longer time elapsed since the epidemiological transition, which increases the number of patients aged over 75 years, and consequently the prevalence and the number of procedures. It is important to mention that the European population is estimated at 700 million inhabitants, that is, much larger than the Brazilian population; 3) the European health care systems, particularly in Germany, have a different stance from that of the Brazilian government regarding the emergence of technological innovations and is much more receptive to new

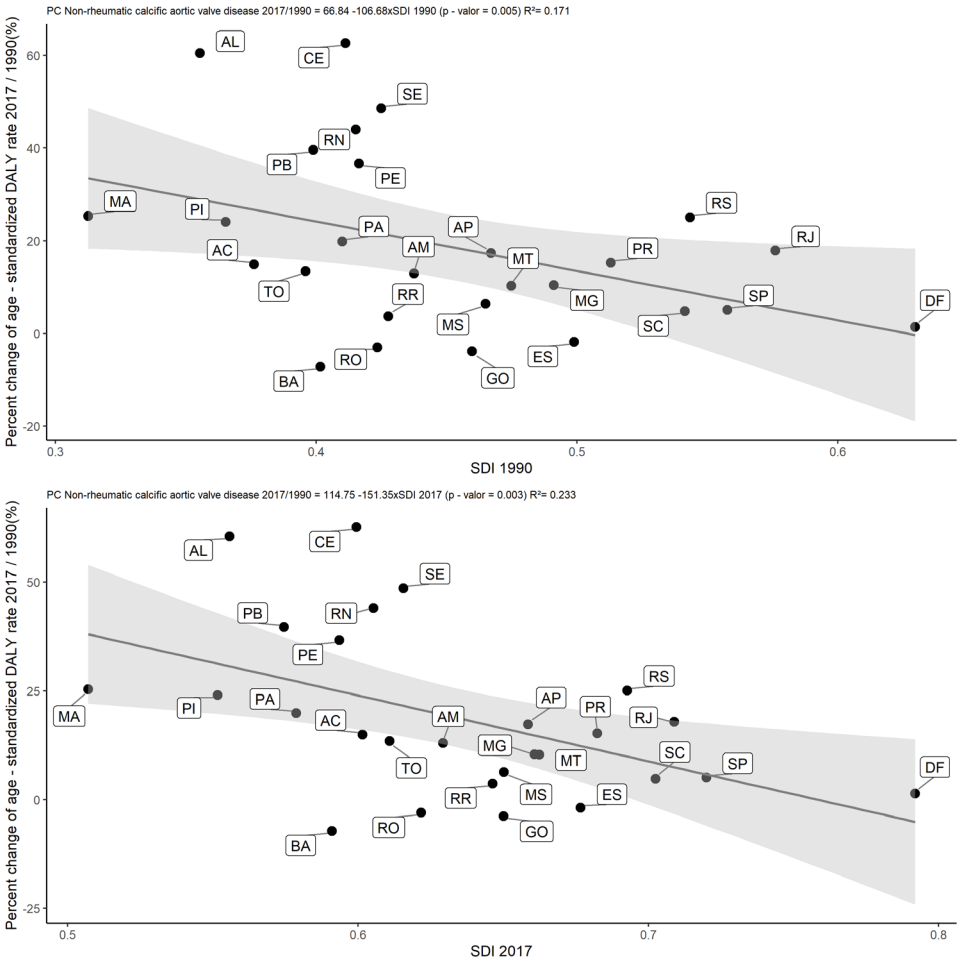

Figure 4 – *Correlation between the percentage change in mortality rates from non-rheumatic calcific aortic valve disease and the sociodemographic development index (SDI) by Brazilian state in 1990 (A) and 2017 (B).*

health care technologies; 4) the Brazilian health care system, particularly specialized and medium/high complexity care, as is the case with TAVI, is not evenly distributed throughout the country, and besides, Brazilian hospital structure, diagnostic infrastructure, and clinical staff is not as widely available or efficient as those in European countries, and thus, the rate of diagnosis and procedures performed in the country would not be nearly compatible with European ones; 5) the number of 8,518 procedures/year is very close to the 9,000 procedures/year performed in the United States upon the request for incorporation (with the United States having a much larger population than Brazil), and, as mentioned in the public consultation, is a number incompatible with the epidemiological and health care access characteristics of the Brazilian population.

Still regarding the estimate of the number of procedures per year, it is noteworthy that, through a comparative analysis with similar procedures offered by the SUS, it is easily seen that such estimate is at least unrealistic. Table 1 shows, based on official data from the Department of Informatics of the Unified Health System (DATASUS), the number of surgical cardiac valvular procedures performed in Brazil between 2008 and 2018. It is noteworthy that the data provided by DATASUS do not allow the identification of the age of the patients, the valve treated, or the etiology and type of valvular disease. Data related to prosthetic valve implantation include both mitral and aortic implantations.

In this DATASUS estimate, the total number of surgeries for prosthetic valve implantation does not exceed 8,518 per year. In 11 years, 88,280 surgeries for prosthetic valve implantation were performed in Brazil considering all age groups and implantations of any heart valve. Additionally, the total number of valvular surgeries, including those associated with myocardial revascularization, multiple valvular replacement, and prosthetic valve implantation, reached a maximum of 11,315 procedures in the year of 2012. Because it is intended for a subgroup of older patients (> 75 years) with aortic stenosis, TAVI would certainly not have been performed with a frequency similar to that of all valvular surgeries performed in the SUS. Also, a large meta-analysis has suggested that

Table 1 – Number of hospitalizations related to the treatment of valve disease in Brazil from 2008 to 2018. Source: DATASUS.[9]

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	TOTAL
VALVE DISEASE*	1,606	1,753	1,647	1,878	1,938	1,938	1,849	1,940	2,068	2,023	2,090	20,730
VULVAR SURGERY	8,045	8,344	7,745	8,297	8,518	8,176	8,130	7,937	7,756	7,758	7,574	88,280
MITRAL VALVULOPLASTY	477	551	478	473	403	431	408	341	206	236	200	4,204
OTHER VALVULOPLASTY	451	477	445	486	456	527	515	513	399	427	391	5,087

** Hospitalizations due to other surgical procedures related to valve diseases*

among patients with aortic stenosis – even in developed countries – around 20% have a severe form of the disease. Of these, only about 60% would be eligible for TAVI, with 20% of inoperable or intermediate or high-risk patients. Of these, only about 60% would be eligible for TAVI, with 20% of inoperable or intermediate or high-risk patients - the better established indications for the procedure.[14]

Despite the absence of primary estimate data for TAVI indication in Brazil, we can apply demographic and epidemiological data for further detailing. Considering the latest GBD 2017 modeling in relation to the prevalence of calcific aortic valvular disease, we would have 64.4/100,000 inhabitants.[5] Data from an IBGE census estimated an approximately 12.9 million elderly individuals aged ≥ 70 years in Brazil in 2019, which would result in roughly 8,400 patients with clinically significant disease in a very conservative estimate. If, alternatively, the estimated prevalence in the literature of about 3 to 5% in individuals ≥ 75 years is applied to IBGE data[15] (a population of 7.7 million), and extrapolating the results from the largest available meta-analysis of aortic stenosis,[14] we would have about 9,300 to 12,000 patients presumably eligible for TAVI in Brazil in 2019. Considering the estimates of the National Supplementary Health Agency that 24.3% of the Brazilian population had access to private health care plans in 2019, and also the aforementioned issues related to difficulties in access and infrastructure limitations in the annual history of valvular surgeries in the SUS,[9] the projections of financial impact presented by Conitec are undoubtedly overestimated against objective data.

Of note, the Ministry of Health's technical position remains unchanged, at least in relation to the frequency of use and the budgetary impact of TAVI in Brazil. In the discussion of Project Act 5.460/2016 determining the mandatory coverage of TAVI in the SUS, which has already been approved by the Chamber of Deputies, the Ministry of Health – in response to the Finance and Taxation Commission on June 26, 2018, after 11 years from the request to Conitec – maintained its position regarding the projections discussed here.[16]

Finally, in addition to budgetary issues, it is of fundamental importance the development of technological infrastructure and professional training in the Brazilian public health system for the implementation of complex treatments in most diverse areas, in a process of industrial development of health care, contemporary to the inexorable process of medical innovation. Regarding the example of structural cardiovascular interventions, other modalities – such as percutaneous repair of mitral regurgitation and percutaneous treatment of congenital valvular heart disease – have already been described in the literature, and should soon be brought also to the discussion table of public policy managers and lawmakers. In this sense, emphasis should be placed on recent efforts by the national cardiological societies, with the seal of the Brazilian Medical Association, for the development of courses for training and professional certification.

In conclusion, the process of incorporating new technologies into the SUS – notably TAVI – must be currently discussed in depth and in a multidisciplinary and professional fashion, based on objective data and technical discretion, with due emphasis on epidemiological, technical, infrastructural, and budgetary issues.

The persistence of the overly restrictive position in the incorporation of technologies into the health care system in Brazil (in TAVI's case, the delay in the incorporation exceeds a decade), in addition to resulting in the inconvenient phenomenon of requiring a judicial process, impels to other routes to obtain treatment access, which are much slower and more complex, such as the legislative path, thwarting the just expectations placed by the civil society in the Public Power, especially considering that universal, full, equal, and free access to the health care system has been established in Brazil in article 196 of the Federal Constitution.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Lopes MACQ, Nascimento BR, Oliveira GMM

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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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Abdominal Pain: an Uncommon Presentation of Myocardial Rupture

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An 84-years-old woman with hypertension and dyslipidemia was admitted in the emergency room with acute abdominal pain; patient complained of chest pain three weeks before hospital admission. On physical examination, she was hypotensive, tachycardic (with arrhythmic pulse), tachypneic and with diffuse abdominal pain. Electrocardiogram showed atrial fibrillation with rapid ventricular response, complete left bundle branch block and inferior Q waves. Abdominal computed tomography (CT) revealed a thrombus in the superior mesenteric artery (Figure 1, white asterisk). The patient showed a clinical course with congestive heart failure and low cardiac output. Transthoracic echocardiogram (Videos 1-2) showed mild left ventricular dilatation with a mild dysfunction and a pseudoaneurysm of the basal half of the posterior and inferior walls with left-to-right shunt, confirmed by color Doppler imaging (Figure 2 A-D). Cardiac CT (Video 3) revealed contained myocardial rupture, located at the basal segments of the inferior and posterior septal walls, extending to the free wall of the right ventricle, forming a pseudo-cavity, which communicates with the true cavity of the right ventricle (Figure 3). Despite vasopressor and inotropic support and proposal for cardiac surgery, the patient had an unfavorable course.

Keywords

Abdominal Pain; Myocardial Infarction/complications; Echocardiography, Doppler/methods; Thrombosis/surgery; Hypertension; Dyslipidemias; Tomography, X-Ray Computed/methods.

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Myocardial rupture demands a prompt diagnosis.[1] Occurrence of late myocardial infarction should raise suspicion and clinical signs may be atypical.[2]

This case illustrates an interesting entity – pseudoaneurysm, with left-to-right shunt and contained myocardial rupture, which extended to the right ventricle, leading to a dismal prognosis.

Contribuição dos autores

Conception and design of the research: Seabra D; Acquisition of data, analysis and interpretation of the data and writing of the manuscript: Seabra D, Neto A, Oliveira I; Critical revision of the manuscript for intellectual content: Seabra D, Santos RP, Azevedo J, Pinto P.

Potential Conflict of Interest

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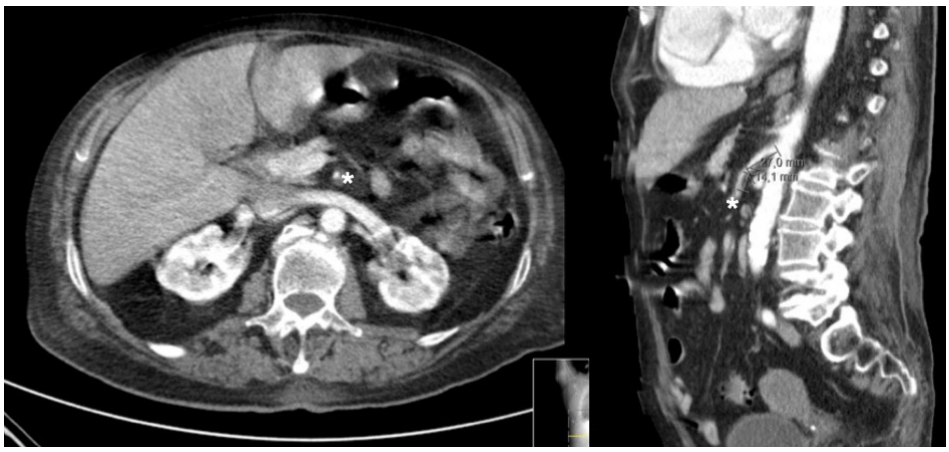
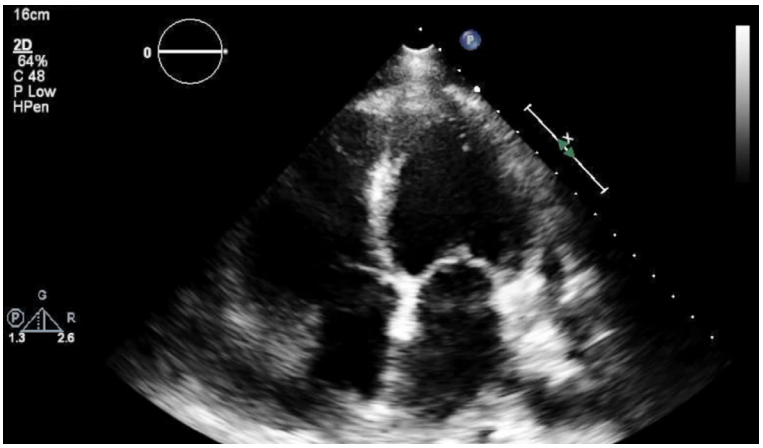
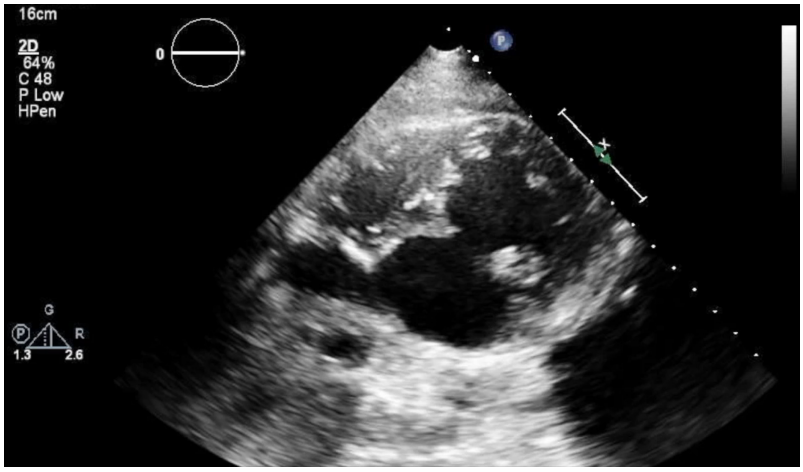


Figure 1 – *Abdominal computed tomography showing a thrombus in the superior mesenteric artery (white asterisk).*



Video 1 – *Transthoracic echocardiogram - apical windows. Link: http://publicacoes.cardiol.br/portal/abc/portugues/2020/v11402/dor-abdominal-uma-apresentacao-incomum-de-ruptura-miocardica.asp*



Video 2 – *Transthoracic echocardiogram - modified subcostal window. Link: http://publicacoes.cardiol.br/portal/abc/portugues/2020/v11402/dor-abdominal-uma-apresentacao-incomum-de-ruptura-miocardica.asp*

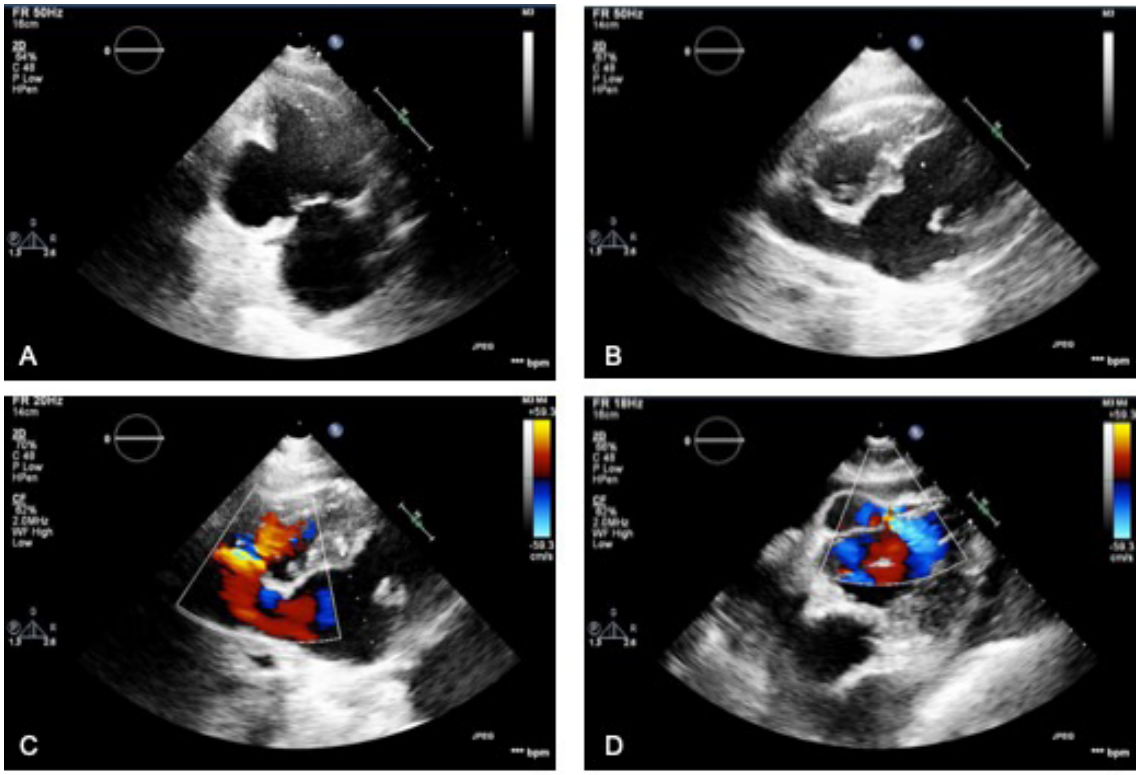
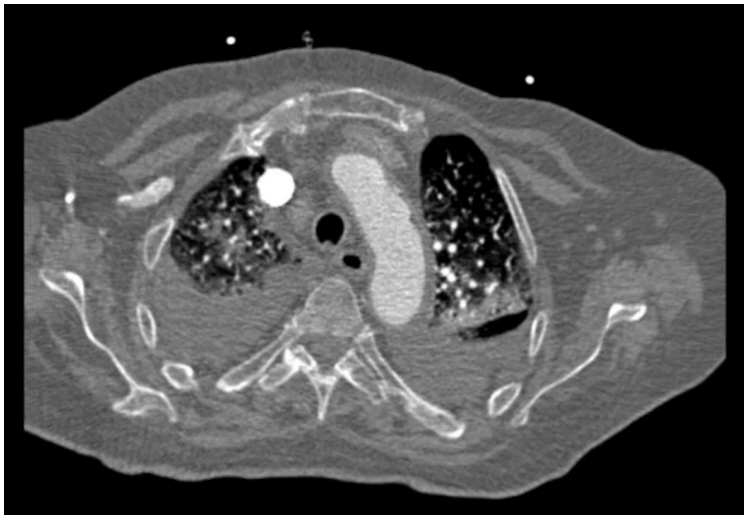


Figure 2 – *Pseudoaneurysm of left ventricular inferior wall on transthoracic echocardiography (TTE), apical two-chamber view (A). Left-right shunt in the basal segment of interventricular septum (B, C and D).*



Video 3 – *Thoracic CT scan .Link: http://publicacoes.cardiol.br/portal/abc/portugues/2020/v11402/dor-abdominal-uma-apresentacao-incomum-de-ruptura-miocardica.asp*

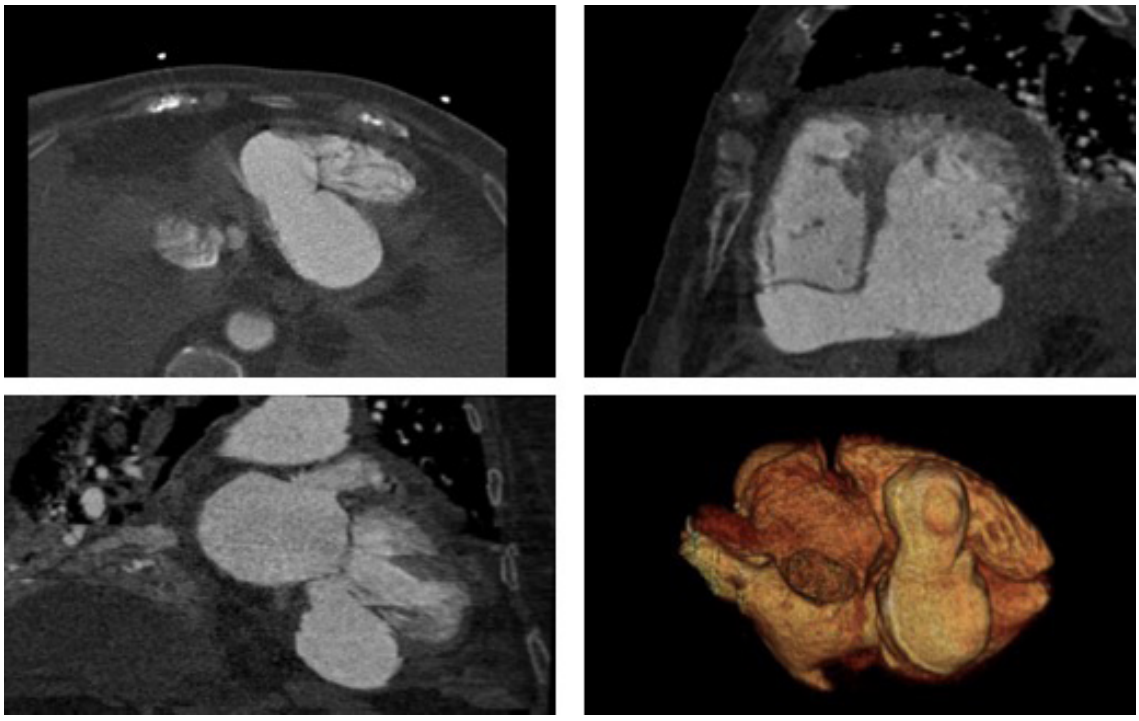


Figure 3 – *Cardiac computerized tomography showing contained myocardial rupture forming a pseudocavity that communicates with the true cavity of the right ventricle*

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How to Approach Elevated NT-pro BNP Level on Admission to Prevent Left Ventricular Aneurysm Following Acute ST-Segment Elevation Myocardial Infarction

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I have read with great interest the article written by Celebi and colleagues,[1] demonstrating that elevated plasma N-terminal pro-B-type natriuretic peptide (NT-pro BNP) level on admission is a significant predictive biomarker of development of left ventricular aneurysm following acute ST-segment elevation myocardial infarction (STEMI) in the current era.

Keywords

Heart Failure/physiopathology; Natriuretic Peptide, B-Type; ST Elevation Myocardial Infarction; Coronary Aneurysm/complications; Stroke Volume; Indicators of Morbidity and Mortality.

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Their findings are straightforward and would lead us the next concerns. The first concern is reversibility of NT-pro BNP and its impact on post-STEMI outcomes. Is the reduction of NT-pro BNP following STEMI associated with a lower rate of left ventricular aneurysm formation?

Another concern is the methodology to improve NT-pro BNP. The uses of several medications including P2Y12 inhibitors were associated with the avoidance of left ventricular aneurysm. However, given the retrospective nature of their study, they cannot exclude the confusion between the use of medications and the severity of STEMI. Prospective studies are warranted to investigate the implication of aggressive interventions using mechanical cardiac unloading (for example, Impella) or medical cardiac unloading (for example, aggressive dose-titration of beta-blocker) on the prevention of left aneurysm formation post-STEMI.

Reference

1. Celebi S, Celebi OO, Cetin S, Cetin HO, Tek M, Gokaslan S, et al. The usefulness of admission Plasma NT-pro BNP Level to Predict Left Ventricular Aneurysm Formation after Acute ST-Segment Elevation Myocardial Infarction. Arq Bras Cardiol. 2019;113(6):1129-37.

Reply

Dear Editor,

We would like to thank the authors for their interest in our study.

The authors raised important future aspects about the findings of our study.[1] Regarding our study results, there is a relationship between N-terminal pro-B-type natriuretic peptide (NT-pro BNP) level and LV (left ventricular) aneurysm formation. However, further studies are needed to address the details of this relationship.

Our study did not include serial measurement of NT-pro BNP.[1] Therefore, we do not have any relevant answer for the reversibility of NT-pro BNP. However, this may be an interesting approach during myocardial infarction regarding LV aneurysm formation.

Medical or mechanical interventions on the prevention of LV aneurysm are another debate. In the IABP Shock trial, the authors did not determine a significant difference between the groups treated with IABP and without IABP concerning NT-pro BNP levels.[2] In contrast, they determined a significant improvement of B-type natriuretic peptide (BNP) levels using IABP. We agree that further prospective trials are needed to determine the association between the methods of reducing NT-pro BNP or BNP and LV aneurysm formation.

Savas Celebi
Ozlem Ozcan Celebi
Berkten Berkalp

Letter to the Editor

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1. Celebi S, Celebi OO, Cetin S, Cetin HO, Tek M, Gokaslan S, et al. Usefulness of admission plasma NT –pro-BNP Level to Predict Left Ventricular Aneurysm Formation after Acute ST-Segment Elevation Myocardial Infarction. Arq Bras Cardiol. 2019;113(6):1129-37.
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Update of the Brazilian Guideline on Nuclear Cardiology – 2020

Development: The Area of Nuclear Cardiology of the Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC) and of the Department of Cardiovascular Imaging (DIC) of the Brazilian Society of Cardiology (SBC) and the Brazilian Nuclear Medicine Society (SBMN)

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Note: This guideline is for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Update

Declaration of potential conflict of interest of authors/collaborators of Update of the Brazilian Guidelines on Nuclear Cardiology – 2020
If the last three years the author/developer of the Update:

Names Members of the Update	Participated in clinical studies and/or experimental trials supported by pharmaceutical or equipment related to the guideline in question	Has spoken at events or activities sponsored by industry related to the guideline in question	It was (is) advisory board member or director of a pharmaceutical or equipment	Committees participated in completion of research sponsored by industry	Personal or institutional aid received from industry	Produced scientific papers in journals sponsored by industry	It shares the industry
Barbara Juarez Amorim	No	No	No	No	No	No	No
Claudio Tinoco Mesquita	NIH	Bayer	No	No	Pfizer	No	No
Gabriel Blacher Grossman	No	No	No	No	No	No	No
João Vicente Vitola	No	No	No	No	No	No	No
José Claudio Meneghetti	No	No	No	No	No	No	No
José Roberto Nolasco de Araújo	No	No	No	No	No	No	No
Lara Cristiane Terra Ferreira Carreira	No	No	No	No	No	No	No
Luiz Eduardo Mastrocola	No	No	No	No	No	No	No
Rafael Willain Lopes	No	No	No	No	No	No	No
Ronaldo de Souza Leao Lima	No	No	No	No	No	No	No
Simone Cristina Soares Brandão	No	No	No	No	No	No	No
William Azem Chalela	No	No	No	No	No	No	No

List of Abbreviations and Acronyms

HED - ^{11}C - meta-hydroxyephedrine labeled with Carbon-11
PIB-^{11}C - PET - pittsburgh B compound labeled with carbon-11 by PET imaging
MIBG-^{123}I - metaiodobenzylguanidine labeled with iodine 123
$^{13}NH^{3}$ - ammonia labeled with Nitrogen-13
H_2O-^{15}O - water labeled with Oxygen-15
FDG-^{18}F - fluorodeoxyglucose labeled with Fluorine-18
FDG-^{18}F - PET/TC - fluorodeoxyglucose labeled with fluorine-18 by hybrid imaging (positron emission tomography coupled with computerized tomography)
Sodium fluoride-^{18}F - fluorine-18 labeled Sodium Fluoride for PET Amyloid Imaging
^{201}Hg - mercury-201
^{201}Tl - thallium-201
^{82}Rb - rubidium-82
^{82}Sr - strontium-82
^{99m}Tc - technetium-99m
MIBI-^{99m}Tc - technetium-99m-labeled SESTAMIBI or MIBI
Pyrophosphate-^{99m}Tc - technetium-99m-labeled pyrophosphate
ACEI - angiotensin converting enzyme inhibitors
ACS - acute coronary syndrome
Aden - adenosine
ADMIRE-HF - AdreView Myocardial Imaging for Risk Evaluation in HF
AF - atrial fibrillation
AHA - American Heart Association
AL - light chain immunoglobulin
ALARA - as low as reasonably achievable
AMI - acute myocardial infarction
angio-CT - angiotomography of coronary arteries
ARB - angiotensin receptor blockers
ATP III - Adult Treatment Panel, from the Program for Detection, Evaluation, and Treatment of High Cholesterol in Adults
AUC - area under the curve
AVB - atrioventricular blockage
BMI - body mass index
BNP - B-natriuretic peptide
CA - cardiac amyloidosis
CABG - coronary artery bypass graft
CC - coronary calcium
CAD - coronary artery disease
CCA - coronary cineangiography
CFR - coronary flow reserve
CHF - congestive heart failure
CIED - cardiac implantable electronic devices
CMR - cardiac magnetic resonance
CONFIRM - Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry
COURAGE - Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation Trial
CPU - chest pain unit
CRP - C reactive protein
CRT - cardiac resynchronization therapy
CS - calcium score
CTX - cardiotoxicity
CV - cardiovascular
Cx - circumflex coronary artery
CZT - cadmium zinc telluride semiconductors
DDD - artificial pacemaker stimulation mode
DG1 - diagonal 1 coronary artery
Dipy. - dipyridamole
DM - diabetes mellitus
Dobut. - dobutamine
DS - duke score
ECG - 12-lead electrocardiogram
ECHO - echocardiogram
EDV - end diastolic volume
ERASE Chest Pain -The Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain Trial
ESV - end systolic volume
ET - exercise testing
FAME - Fractional Flow Reserve versus Angiography for Guidance of PCI in Patients with Multivessel Coronary Artery Disease
FBP - filtered back-projection
FDA - food and drug administration
FDG-6-P - fluorodeoxyglucose - 6 - phosphate
FFA - free fatty acids
FFR - fractional flow reserve
FRS - Framingham risk score
Gated-SPECT - myocardial perfusion imaging by single photon emission computed tomography technique synchronized with electrocardiogram
HBP - high blood pressure
HF - heart failure
HFpEF - heart failure with preserved ejection fraction
HFrEF - heart failure with reduced ejection fraction
HMR - heart to mediastinum ratio
HR - heart rate
IAEA - International Atomic Energy Agency
ICD - implantable cardioverter defibrillator
ICNC - International Conference of Nuclear Cardiology
IE - infectious endocarditis
IFR - instantaneous flow reserve/instantaneous wave-free ratio
INCAPS - IAEA Nuclear Cardiology Protocols Cross-Sectional Study
ISCHEMIA - International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
IV - intravenously/intravenous
keV - kilo-electron volts
LAD - left anterior descending coronary artery
LAFB - left anterior fascicular block
LBBB - left bundle branch block

LV - left ventricle
LVAD / VAD - left ventricular assist device / ventricular assist devices
LVEF - left ventricular ejection fraction
MBF - myocardial blood flow
MBFR - myocardial blood flow reserve
MBq - megabequerel
mCi - milicurie
MET - metabolic equivalent.
MFR - myocardial flow reserve
MIBI / SESTAMIBI - 2-methoxy-isobutyl-isonitrile
MPS - myocardial perfusion scintigraphy
MR - magnetic resonance
MRS - myocardial revascularization surgery
mSv - millisieverts
MVO_2 - myocardial oxygen consumption
NaI - sodium iodine
NE - norepinephrine
NPV - negative predictive value
NSTEMI - non-ST segment elevation myocardial infarction
NSVT - nonsustained ventricular tachycardia
NYHA HF - New York Heart Association Heart Failure Class
OMT - optimized medical therapy
OR - odds ratio
OSEM - ordered subset expectation maximization
PAREPET - prediction of arrhythmic events with positron emission tomography
PARR-2 - PET and Recovery after Revascularization study
PCI - percutaneous coronary intervention
PET - positron emission tomography
PET/CT - positron emission tomography coupled with computed tomography (hybrid imaging)
PET/MR - positron emission tomography coupled with magnetic resonance (hybrid imaging)
PM - pacemaker
PREMIER - Performance of Rest Myocardial Perfusion Imaging in the Management of Acute Chest Pain in the Emergency Room in Developing Nations
PROCAM - PROSpective CArdiovascular Munster Study
PROMISE - Prospective Multicenter Imaging Study for Evaluation of Chest Pain
RCA - right coronary artery
Regad. - regadenoson
RESCUE - Randomized Evaluation of patients with Stable angina Comparing diagnostic Examinations
ROC - receiver operating characteristics
ROI - regions of interest
ROMICAT II - rule out myocardial infarction by cardiac computed tomography
RV - right ventricle/ventricular
SBC - Brazilian Society of Cardiology
SBMN - Brazilian Society of Nuclear Medicine
SBP - systolic blood pressure
SCORE - Systematic Coronary Risk Evaluation Study
SDS - summed difference score
Shining / Shine Through - residual activity effect
SPECT - myocardial perfusion imaging by single photon emission computed tomography
SRS - summed rest/redistribution score
SSS - summed stress score
STEMI - ST segment elevation myocardial infarction
STICH - Surgical Treatment for Ischemic Heart Failure study
SUS - Brazil's public Single Health System (acronym in Portuguese)
SUV - standard uptake value
TIA - transient ischemic attack
TID - transient ischemic dilatation
TOF - time of flight
TTR - transthyretin
TTR CA - transthyretin cardiac amyloidosis
UA - unstable angina
USA - United States of America
VAD - ventricular assist devices
VF - ventricular fibrillation
VT - ventricular tachycardia
WR - myocardial washout rate

Content

Update

1. Introduction

Nuclear cardiology is a non-anatomical, physiological imaging method. The use of radioactive or radiopharmaceutical substances makes it possible to study several physiopathological mechanisms of cardiovascular disease *in vivo*. Via this imaging technique, it is also possible to visualize and accompany an instituted therapy's physiological effects on cardiac function, on the cellular and biochemical level. Of all the applications of nuclear medicine in cardiology, scintigraphy or myocardial perfusion imaging with technetium-99m-labeled radiopharmaceuticals synchronized with electrocardiogram (Gated-SPECT), is the most common exam in clinical practice. For this reason, this technique will be the most discussed in these Guidelines.

Recent years have, however, seen a growing concern among the scientific community regarding rational and optimized use of ionizing radiation in medicine. Cardiovascular imaging, moreover, encompasses all functional and anatomical imaging techniques and should, in this context, be used rationally and cost-effectively. Other applications of nuclear medicine in cardiology have also emerged and gained prominence during the past decades, especially positron emission tomography (PET) for the study of coronary flow reserve, cardiac sympathetic activity, and inflammatory/infectious processes, and cardiac amyloidosis (CA). All of these aspects have been taken into consideration and will be covered in detail in the chapters developed herein.

Guidelines recommendations are highly valuable tools for medical activity of the highest quality. The objective is to support and aid doctors in making decisions regarding their patients, by elaborating orientations which may be useful as part of the decision-making process. No Guidelines, however, should be replaced by the abilities, experience, and clinical judgments of specialized professionals who are have the final say in their decisions concerning each individual patient.

In general, whenever possible and applicable, classifications of recommendation have been adopted for indicating cardiac scintigraphy, supported by levels of evidence, in accordance with the recommendations established by classical cardiology guidelines (Table 1).

Based on current evidence, this document, which does not function as a substitute, practically and objectively adds important data to and updates the Brazilian Cardiology Society's (SBC) **First Guidelines** and **Update** on **Nuclear Cardiology**, both of which were published by the Brazilian Archives of Cardiology (Arquivos Brasileiros de Cardiologia), in 2002 and 2005, respectively.

As in the previously mentioned documents, those who participated in the elaboration of these Guidelines are considered specialists in their respective areas and were, for this reason, chosen to develop the chapters thereon. The committed involvement of all colleagues representing the SBC and the Brazilian Society of Nuclear Medicine (SBMN) have made the elaboration of these **new update of Brazilian Guidelines on Nuclear Cardiology** possible. It is our hope that they will be of great use, especially to Cardiologists and Nuclear Medicine and Clinical Physicians in Brazil. The Organizing Committee appreciates the collaboration of all those involved.

2. Addendum to the ISCHEMIA Study*

At the time of publication of this guideline, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) had not been published yet, although the main findings were presented on November 16, 2019 at the American Heart Association (AHA) annual congress in Philadelphia, USA, available on the study's website. Considering its importance for medical decision-making and the potential implications for nuclear cardiology, a few relevant concerns should be highlighted on the findings available so far:

1. The main objective of the ISCHEMIA study was to assess whether patients (P) with at least moderate ischemia on a functional examination would benefit from myocardial revascularization (coronary artery bypass grafting or percutaneous coronary intervention) added to optimal medical therapy). Were randomized 5,179 patients with stable CAD and myocardial ischemia documented by one of many different methods (myocardial perfusion scintigraphy, stress echocardiography, cardiac magnetic resonance imaging, exercise testing not associated with cardiac imaging). These noninvasive methods were used to define the etiology of chest pain and for cardiovascular

Table 1 – Classes of recommendation and levels of evidence

Classes of recommendation
Class 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
Class II – Conditions for which there are conflicting evidence and/or divergent opinions regarding the procedure's safety and usefulness/effectiveness
Class IIA – Weight or evidence/opinion in favor of the procedure. The majority of studies/experts approve.
Class IIB – Safety and usefulness/effectiveness less well established, with no prevailing opinions in favor
Class III – Conditions for which there is evidence and/or consensus that the procedure is not useful/effective and could, in some cases, be harmful
Levels 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

risk stratification, a management approach established in clinical practice that is not invalidated by the findings of the study. Prior knowledge indicates that patients with lower ischemic burden have a better prognosis than individuals with larger and more intense ischemia;

2. The ISCHEMIA trial demonstrated no benefit of myocardial revascularization (Invasive Group - IG) versus optimal medical therapy (OMT) to reduce the major outcomes of "death" and "acute myocardial infarction." Despite the methodological differences, these results were somewhat similar to those of the COURAGE study. It is noteworthy that the mortality curves began to separate after two years of medical follow-up, apparently benefiting the IG and potential long-term implications, which justified the increased clinical follow-up of P, underway at the moment. Note that the IG had an improved quality of life assessment, reduced frequency of angina and lower use of specific medication compared to the OMT group;
3. The ISCHEMIA trial is one of the most relevant studies on stable CAD, with important messages for clinical practice. The validity of the results is emphasized for the population sample evaluated in the study and for the definitions of ischemia and its severity levels employed. However, for exclusion situations, such as P with left main disease, recent acute coronary syndrome, angioplasty in the previous 12 months, ejection fraction < 35% and progressive or unstable symptoms, prior knowledge remains unchanged. Both CAD and ischemic heart disease represent a broad spectrum of patients, with inherent heterogeneity and important prognostic implications (extensive evidence base in the literature and described in detail in the current guideline). Were excluded from the trial an impressive number of P that had at least moderate angina and ischemia in the absence of coronary obstructions, showing the diversity of the disease and the value of functional assessment;
4. The main question is whether the ISCHEMIA study has properly evaluated a significant number of P with moderate/severe ischemia, aiming to determine whether myocardial revascularization adds prognostic benefit to these patients, as documented by scintigraphy, which was not the exclusive method of documentation. There was the inclusion (randomization) of cases with nonexistent or mild ischemia (12% of the total randomized), which is surprising for a study that was initially intended to include only patients with moderate to severe ischemia. There was also a change in the criteria for inclusion of P with severe ischemia in the study, with a significant number based on the results of exercise testing, without imaging, a decision made after the study was in progress. From this change, the percentage of these P that would effectively have severe myocardial ischemia on scintigraphy is questioned;
5. Therefore, the Editorial Board of this guideline believes that the definitive analysis of the results will only be possible after the formal publication of the trial results.

Editorial Board of the New Update of The Brazilian Guideline on Nuclear Cardiology, February 2020

3. The Application of Nuclear Medicine Techniques to Justify Financial Resources Available for Attending Cardiology Patients in Brazil

3.1. Introduction

Cardiovascular diseases are the main cause of death in Brazil, and they are responsible for 30% of deaths worldwide every year.[1] They are responsible for approximately 8% of total healthcare costs in Brazil, a figure which has been increasingly annually, in parallel with population aging.[1] Teich and Araújo estimated that in 2011, approximately 200,000 events associated with acute coronary syndromes occurred in Brazil, entailing a massive impact of 3.88 billion Brazilian reals, considering only hospital and indirect costs, associated with loss of productivity.[2] Considering these findings, it has been demonstrated that (preventive) measures play a crucial role in reducing morbidity and mortality, and they should be a priority in national healthcare policy design, as they have profound additional impacts on reducing costs and maintaining productivity. Another significant point, however, which has contributed to reducing the outcome of "cardiovascular death" and to justifying expenses, involves the use of tools which make accurate diagnosis of a determined condition possible (?) and which aid and guide the conduct of physicians, based on these results. Myocardial perfusion scintigraphy (MPS) plays a significant role in justifying financial resources for attending patients with established or potential cardiovascular disease.

3.2. Cost-Effectiveness in Comparison with Cardiac Catheterization

One of the main fundaments of MPS is its good ability to identify low-risk patients, who do not require invasive intervention, in spite of established coronary disease, such as anatomical lesions on coronary angiography.[3] Observational studies in the 1990's have demonstrated that MPS was able to identify high- and low-risk groups, resulting in reduced costs for patients with coronary artery disease (CAD) and avoiding procedures that are not associated with improved patient health outcomes. A major prospective study carried out in the United States of America (USA) recruited 11,372 patients with stable angina, who were referred to either MPS or cardiac catheterization. Patients were adjusted by clinical risk, and the costs of direct cardiac catheterization (aggressive strategy) were compared to initial scintigraphy followed by selective catheterization in high-risk patients (conservative strategy). Although both strategies had similar adverse outcomes, such as cardiac death and non-fatal myocardial infarction, revascularization rates were higher (between 13% and 50%) in patients who underwent catheterization directly.[4] This reflex of revascularizing anatomical lesions which do not determine ischemia led to unnecessary associated medical costs of around 5,000 dollars per patient in this study.[4] Currently, the use of medical resources for conditions that do not have consequences for patients or that could be managed conservatively is known as "overtreatment."[5] The study of

*To access the Addendum bibliography, go to: https://sbc-portal.s3.sa-east-1.amazonaws.com/diretrizes/Publicacoes/2020/Bibliografia-adendo/Bibliografia_ADENDO_INGLES_24-01-2020.pdf

the impact of MPS on reducing costs has shown that its main function is to prevent patients who have low or moderate risks on single photon emission computed tomography (SPECT) from being treated with unnecessary catheterizations and revascularizations. Similarly to this North American study, Underwood et al.[6] have demonstrated that strategies which incorporate myocardial scintigraphy to evaluate patients with stable coronary diseases are both cheaper than and as effective as strategies involving invasive anatomical assessment.[6] Cerci et al.[7] evaluated the impact of diagnostic exams on patients with CAD in different scenarios within Brazil's public Single Health System (SUS, acronym in Portuguese). The study's most relevant finding is that, although non-invasive functional tests are the most frequently solicited exams for evaluating patients with suspected or known CAD, the majority of healthcare costs for these patients are related to procedures/invasive treatment. In other words, in the Brazilian context, the costs of diagnostic exams continue to be significantly lower than those of invasive and therapeutic procedures. In this manner, it seems logical to affirm that, if scintigraphy exams are made available to patients attended by the SUS, there will be a similar impact on the reduction of healthcare costs, which has been the case in the USA and some countries in Europe. Another relevant piece of data from this study refers to the fact that the majority of patients who were revascularized had not undergone tests to document ischemic burden; only anatomical diagnostic techniques had been applied.[7]

3.3. Cost-Effectiveness of Myocardial Perfusion Scintigraphy in Relation to Coronary Angiotomography

Angiotomography (angio-CT) of coronary arteries offers very accurate, non-invasive anatomical assessment, and it has proved to be an excellent technique for ruling out obstructive coronary disease in low- to intermediate-risk patients. Angio-CT, however, has presented results similar to those of cardiac catheterization in relation to triggering a higher number of myocardial revascularizations, which do not necessarily (means) reduced cardiovascular outcomes. In a recent meta-analysis comparing angio-CT to functional methods, no differences were observed regarding the outcomes of death or cardiac hospitalization, but there was a 29% reduction in the number of non-fatal infarctions. On the other hand, the use of this method was associated with 33% and 86% higher rates of invasive coronary angiography and myocardial revascularization, respectively. It is not known whether the reduction in non-fatal infarctions may be attributed to the higher number of revascularizations, which is (unlikely) considering in light of other studies on stable CAD, or to the higher use of statins and aspirin associated with the recognition of anatomical coronary lesions.[8] With the objective of elucidating the role of angio-CT on cost-effectiveness of approaches to stable CAD in comparison with myocardial scintigraphy, the Randomized Evaluation of Patients With Stable Angina Comparing Diagnostic Examinations (RESCUE) study, which is being developed, is expected to compare these strategies in a prospective, randomized manner.[9]

The authors of a recent meta-analysis published by the American Heart Association (AHA)/Circulation, have reinforced 2 important aspects of cost-effectiveness:[10]

- The importance of performing appropriate exams as a way of (ensuring) their cost-effectiveness, especially techniques like MPS.
- The results of appropriate exams should effectively lead to appropriate decision making in clinical conduct and patient management.

4. Indications for Myocardial Perfusion Scintigraphy

Over the past years, different medical societies have published criteria for defining scenarios in which myocardial scintigraphy may be adequately utilized. In addition to traditional classification of recommendation and levels of evidence, more recent criteria on appropriate MPS exam referral have been suggested, dividing indications into appropriate, possibly appropriate, and rarely appropriate, resulting from the application of scores constructed based on clinical scenarios and specific methodologies.[11] In this classification, indications with scores from 1 to 3 are considering rarely appropriate; 4 to 6, possibly appropriate; and 7 to 9, appropriate. Published documents are based on evidence from American and European Guidelines, as well as the recently published Brazilian Guidelines on stable coronary disease.[12-15]

Regardless of classification type, there is consensus that symptomatic patients with intermediate risks of ischemic heart disease are the ones who most benefit from MPS in terms of diagnostic and prognostic evaluation. The exam should preferably be performed in association with physical exercise in patients with sufficient physical and clinical conditions (estimated ability for activities of daily living with metabolic expenditure greater than 5 METs), in order to measure their functional capacity, hemodynamic responses (heart rate and blood pressure behavior), stress-induced arrhythmias, and other responses. It is recommended that patients with complete left bundle branch block, regardless of functional ability, undergo MPS under pharmacological stress (dipyridamole or adenosine). In the same manner, regardless of pretest probability of ischemic heart disease, patients with low functional ability or uninterpretable electrocardiogram (ECG) are indicated to undergo MPS. On the other hand, patients with low probability of ischemic heart disease, higher functional ability, and interpretable ECG are not indicated for MPS (Table 2).

In patients with heart failure (HF) and left ventricular systolic dysfunction or recent-onset atrial fibrillation (AF), ventricular tachycardia (VT) or syncope, the indication for MPS is appropriate or possibly appropriate, unless the patient in question is low risk or has low pretest probability. Asymptomatic patients with no history of ischemic heart disease and without abnormal exercise testing (ET) generally do not benefit from undergoing MPS. In specific situations, in patients with high calcium scores (greater than or equal to 400), diabetes, chronic renal insufficiency, or a prevalent family history of ischemic heart disease, performing MPS may aggregate value to the medical decision-making process, with satisfactory cost-effectiveness. Asymptomatic patients with abnormal stress ECG who are re-stratified

Table 2 – Indication criteria for myocardial perfusion scintigraphy in symptomatic patients

Assessment of patients with non-acute chest pain or ischemic equivalent	Score
Low pretest probability of CAD, with interpretable resting ECG and ability to exercise	3
Low pretest probability of CAD, with uninterpretable resting ECG or inability to exercise	7
Intermediate pretest probability of CAD, with interpretable resting ECG and ability to exercise	7
Intermediate pretest probability of CAD, with uninterpretable resting ECG or inability to exercise	9
High pretest probability of CAD, regardless of interpretable resting ECG and ability to exercise	8

ACS: acute coronary syndrome; CAD: coronary artery disease; ECG: 12-lead electrocardiogram.

with the use of prognostic scores, such as the Duke score, may also benefit from complementary investigation via MPS, especially if their risk scores are intermediate or high (Table 3). Diverse examples of clinical situations cited in Table 3 may also be found in the *section on integration of diagnostic modalities*.

When patients have established ischemic heart disease and are asymptomatic, early myocardial perfusion studies with radiopharmaceuticals should be avoided following percutaneous coronary intervention and/or myocardial revascularization surgery procedures. In the event of percutaneous coronary intervention and myocardial revascularization surgery, the application of MPS has been observed to have a favorable cost-benefit ratio for follow up after more than 2 and 5 years, respectively, even in asymptomatic patients. Symptomatic patients with specific clinical conditions (or equivalent manifestations) may benefit from the exam before this period (Table 4).

For patients with previous exams who manifest new symptoms or who require assessment of the repercussion of diagnosed intermediate lesions and characterization of arteries with obstructive lesions "responsible" for a larger myocardial area at risk, as well as patients with multivascular diseases, the indication for MPS is classified as appropriate or possibly appropriate. In patients with established coronary disease and worsening symptoms, MPS may aid in quantifying ischemic burden (extent and intensity of defects) and in determining medical management. In clinically stable patients with previous exams performed more than 2 years prior, MPS may be appropriate (Table 5).

In patients who present acute chest pain, with clinical suspicion of acute coronary syndrome (ACS), normal or uninterpretable ECG (old left bundle branch block or pacemaker) and normal biomarkers, resting myocardial scintigraphy may exclude acute cardiovascular events with a high degree of safety (high negative predictive value [NPV]), allowing patients to be discharged from the emergency room. If the exam is normal, investigation may continue with outpatient tests involving physical or pharmacological stress, whether associated or non-associated with non-invasive imaging, and even anatomical assessment via coronary angio-CT, in specific conditions. For patients with ACS who are clinically stable, with neither recurring chest pain nor HF, and who have not undergone any invasive exam, MPS is useful for detecting presence and extent of myocardial ischemia (Table 6).

Indications for MPS to assess pre-operative risk of non-cardiac surgeries and vascular surgeries have also been recently revised.[16] Patients who will undergo low-risk surgeries do not need to undergo MPS. If the surgery is not low-risk, functional capacity is the factor that determines

Table 3 – Indication criteria for myocardial perfusion scintigraphy in asymptomatic patients and/or patients with prior exams

Asymptomatic patients – detection of CAD/risk stratification	Score
Low risk (ATP III criteria)	1
Intermediate risk (ATP III criteria) – interpretable ECG	3
Intermediate risk (ATP III criteria) – uninterpretable ECG	5
High risk (ATP III criteria)	7
High risk and calcium score (Agatston) between 100 and 400	7
Calcium score (Agatston) > 400	7
Low-risk Duke score (> +5)	2
Intermediate-risk Duke score (between −11 and + 5)	7
High-risk Duke score (< −11)	8

Agatston: score that defines the presence and quantity of calcium in coronary arteries, characterizing atherosclerosis; ATP III: Adult Treatment Panel, from the program for detection, evaluation, and treatment of high cholesterol in adults; CAD: coronary artery disease.

Table 4 – Indication criteria for myocardial perfusion scintigraphy in patients who have undergone revascularization procedures (CABG or PCI)

Previous percutaneous revascularization or surgical procedures	Score
Symptomatic	8
Asymptomatic, CABG less than 5 years prior	5
Asymptomatic, CABG 5 or more years prior	7
Asymptomatic, percutaneous revascularization less than 2 years prior	3
Asymptomatic, percutaneous revascularization 2 or more years prior	6

CABG: myocardial revascularization surgery; PCI percutaneous coronary intervention.

Table 5 – Indication criteria for myocardial perfusion scintigraphy for risk stratification and prognostic assessment of patients with proven stable coronary artery disease and/or prior exams

Asymptomatic patients or patients with stable symptoms – previously "normal" stress imaging exams	Score
Intermediate/high risk (ATP III) – stress imaging exam ≥ 2 years prior	6
Asymptomatic patients or patients with stable symptoms – CCA or abnormal imaging exams, without prior CABG	
CAD on CCA or "abnormal" stress imaging exam (exam performed > 2 years prior)	5
CAD on CCA or "abnormal" stress imaging exam (exam performed < 2 years prior)	3
Previously "unclear," "contradictory," or "borderline" non-invasive assessment – obstructive CAD as initial concern	8
New, recent, or progressive symptoms	
Abnormal CCA or abnormal stress imaging exam	9
Normal CCA or normal stress imaging exam	6
Coronary cineangiography (invasive or non-invasive)	
Coronary stenosis or anatomical abnormality whose significance is unclear	9

ACS: acute coronary syndrome; ATP III: Adult Treatment Panel, from the program for detection, evaluation, and treatment of high cholesterol in adults; CAD: coronary artery disease; CCA: coronary cineangiography; CABG: myocardial revascularization surgery.

Table 6 – Indication criteria for myocardial perfusion scintigraphy in patients with acute chest pain or post-acute coronary syndrome

Assessment of patients with acute chest pain	Score
Resting image only	
Possible ACS – ECG without ischemic alterations or LBBB or pacemaker; low-risk TIMI score; borderline, minimally elevated, or negative troponin	8
Possible ACS – ECG without ischemic alterations or LBBB or pacemaker; high-risk TIMI score; borderline, minimally elevated, or negative troponin	7 / 8
Possible ACS – ECG without ischemic alterations or LBBB or pacemaker; negative initial troponin. Recent (up to 2 hours) or evolving chest pain	7
Assessment of post-ACS patients (infarction with or without elevated ST segment)	
Stable, post-AMI patients, with ST segment elevation, for assessment of ischemia; cardiac catheterization not performed	8
Stable, post-AMI patients, without ST segment elevation, for assessment of ischemia; cardiac catheterization not performed	9

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAD: coronary artery disease; ECG: 12-lead electrocardiogram; LBBB: left bundle branch block.

whether MPS will be necessary. In patients with functional capacity estimated at greater than or equal to 4 METs, without cardiac symptoms, regardless of clinical or surgical risk, non-invasive assessment of myocardial ischemia is generally not recommended. However, for patients with low functional capacity and elevated clinical/surgical risks, there is an indication to perform MPS under pharmacological stress. The following are considered clinical risks: history of ischemic heart disease, congestive heart failure (CHF), cerebrovascular disease, diabetes mellitus (DM), and renal insufficiency (creatinine > 2.0 mg/dl). In the absence of these risk factors, regardless of functional capacity, surgery may be performed without complementary functional exams (Table 7).

In patients with accentuated left ventricular dysfunction who are eligible for myocardial revascularization, assessment of myocardial viability may aid selection of patients who will benefit from this treatment (Table 8).

MPS is, therefore, an appropriate indication in diverse clinical manifestations of ischemic heart disease, from acute manifestations in the emergency room to diagnostic investigation of stable patients, aiding in therapeutic decision making through various tools which make it possible to define disease severity, as well as in pre-operative assessment in specific situations and in defining the benefits of revascularization for patients with significant myocardial

Table 7 – Indication criteria for myocardial perfusion scintigraphy for pre-operative assessment of non-cardiac surgeries

Pre-operative assessment of non-cardiac surgeries	Score
Low-risk surgery	1
Intermediate-risk surgery or vascular surgery Functional capacity greater than or equal to 4 METs	1
Intermediate-risk surgery or vascular surgery Functional capacity unknown or less than 4 METs No clinical risk factors	1
Intermediate-risk surgery Functional capacity unknown or less than 4 METs One or more clinical risk factors	7
Vascular surgery Functional capacity unknown or less than 4 METs One or more clinical risk factors	8

MET: metabolic equivalent.

Table 8 – Indication criteria for myocardial perfusion scintigraphy for assessment of myocardial viability

Assessment of myocardial viability	Score
Accentuated left ventricular dysfunction	9
Eligible for myocardial revascularization	9

viability. It is worth noting that, for diagnostic investigation, patients with intermediate probability of ischemic heart disease are those who most benefit from MPS and that it is rarely appropriate in patients with low probability.

5. Myocardial Perfusion Scintigraphy Methods – types of Cardiovascular Stress

5.1. Radiopharmaceuticals Used to Perform Myocardial Perfusion Scintigraphy

In Brazil, the main radiopharmaceuticals available for obtaining images of the myocardium are thallium-201 (^{201}Tl) and those labeled with technetium-99m (^{99m}Tc), which mainly include 2-methoxy-isobutyl-isonitrile, known as Sestamibi (or MIBI), and tetrofosmin. Given that these are the most widely used, the specific methods used for acquiring images with them will be presented.

Thallium-201 or ^{201}Tl [17] is a monovalent cation with biological properties analogous to those of potassium. It is both intracellular and absent in scar tissue, and it is thus designated for differentiating ischemic myocardium from fibrosis. It has a physical half-life of 73 hours, and it decays by electron capture to mercury-201 (^{201}Hg), and the photons emitted for imaging are primarily x-rays (of ^{201}Hg itself) between 68 and 80 kilo-electron volts (keV), in addition to lower quantities of gamma radiation in the energy range of 135 keV and 166 KeV. Upon intravenous injection, initial myocardial uptake is proportional to regional blood flow, depending on the integrity of the cellular membrane. It penetrates the cellular membrane via active transport, involving energy expenditure (Na^+/K^+ATPase system), with a high first-pass extraction fraction in the myocardium (the proportion of ^{201}Tl which is extracted from blood and absorbed by myocytes), of around 70% to 85%.

Maximum concentration of thallium-201 in the myocardium occurs approximately 5 minutes after injection, which is generally administered during peak exercise or clinical and/or electrocardiographic alterations triggered during an ET or a pharmacological test. It presents rapid disappearance or clearance from the intravascular compartment. Following initial distribution of the radioisotope throughout the myocardium, related to blood flow, the phenomenon of redistribution begins 10 to 15 minutes after injection. This is dependent on clearance or washout of thallium-201 from the myocardium, which no longer depends on blood flow but rather on the concentration gradient between myocytes and blood levels. Redistribution of thallium-201 is quicker in normal myocardium than in ischemic myocardium, resulting in different activities in these tissues (differential "washout").

Due to the characteristics described and the ability to evaluate the integrity of the cellular membrane, thallium-201 has the additional property of studying myocardial viability, predominantly related to hibernating myocardium (Figure 1).[18-20] This represents the condition of resting left ventricular dysfunction, resulting from chronic hypoperfusion in myocardial regions where, although the myocytes have remained viable (alive), they have chronically depressed contractile function. Hibernation may also be seen as a "flow-contraction" agreement process, where metabolism remains dependent on residual myocardial flow in a manner sufficient for minimum substrate supply and inhibitory substance removal. Therefore, the condition of hibernation, notwithstanding reduced resting coronary flow, is not necessarily associated with the presence of chronic ischemia, given that oxygen supply and consumption ratio may be preserved.[21,22]

Technetium-99m-labeled SESTAMIBI or MIBI (MIBI-^{99m}Tc):[23,24] The most frequently used marker for myocardial perfusion studies, is 2-methoxy-isobutyl-isonitrile, a stable, lipophilic, cationic compound belonging to the isonitrile family, which has the property of crossing cellular (sarcolemmal) membranes and binding to myocyte mitochondria through the mechanism of passive diffusion, depending on the electrochemical transmembrane gradient. It therefore involves no energy expenditure. It has a lower first-pass extraction fraction in the myocardium than thallium-201, of approximately 60%.[25]

It does not expressively present the phenomenon of redistribution, largely remaining retained within mitochondria. This property makes it necessary to deliver 2 separate injections of the radiopharmaceutical, 1 during the resting and 1 during the stress phase. This may be done either on the same day or on different days. As MIBI is not radioactive, it must be labeled with technetium-99m (^{99m}Tc), which has a physical half-life of 6 hours and emits gamma photons in the energy range of 140 keV (photopeak). Similarly to thallium-201, initial myocardial uptake is proportional to regional blood flow, depending on the integrity of the cellular membrane. In this manner, a linear relationship is observed between the intravenous dose per gram of myocardium and blood flow per minute (Figure 2), starting at minimal flow ranges of approximately 2.0 to 2.5 milliliters per gram. minute^{-1}, values normally found in maximum exercise testings. When very high coronary flow are reached, generally over 3.0 mililiters per gram.minute $^{-1}$, the linear relationship between this variable and myocardial uptake is lost, with decreased blood extraction of the radiopharmaceutical, in a phenomenon known as "roll off".[26-28] Nonetheless, owing to higher energy emission (higher photopeak), measured in keV, it presents higher quality images, in comparison with thallium-201. Finally, the elimination of MIBI-^{99m}Tc takes place through the hepatobiliary system, whereas elimination of thallium-201 is mainly achieved through the renal system. Regarding other isonitriles approved by the FDA for assessment of obstructive CAD, only tetrofosmin, whose properties are similar to those of MIBI-^{99m}Tc, has been made available for clinical use.

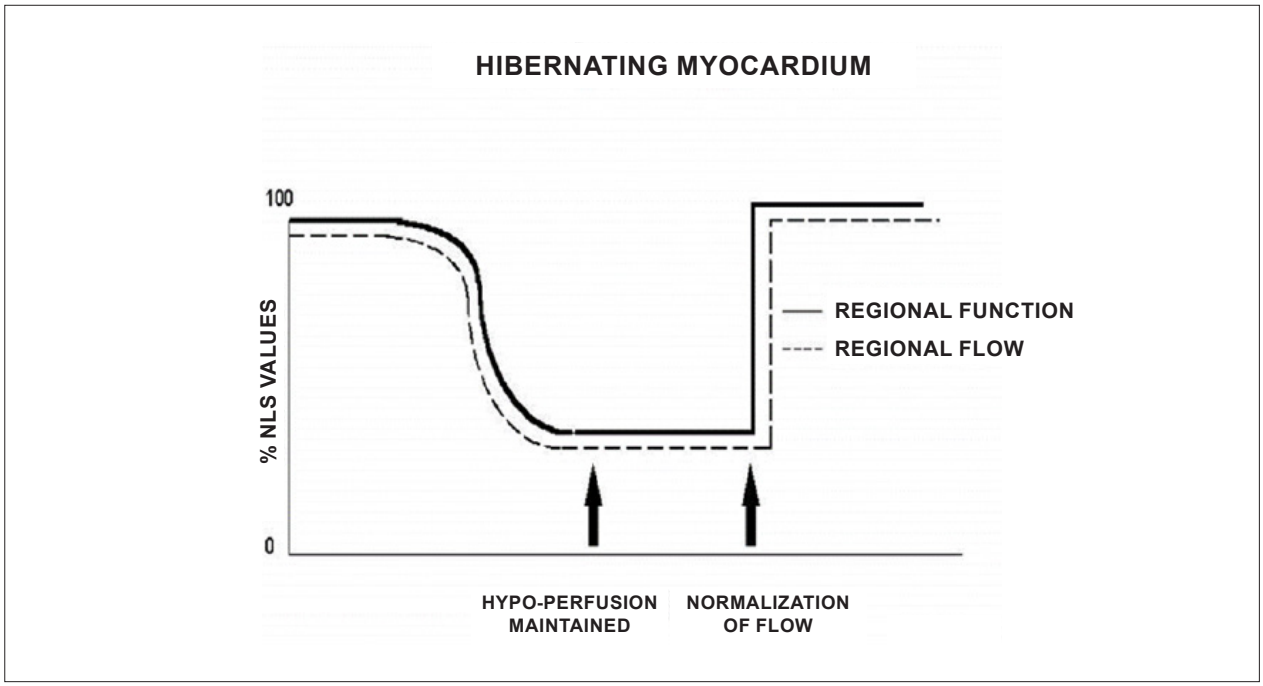

Figure 1 – *Hibernation represented as persistent decrease of blood flow and contractile function. Recovery of function is immediate following restoration of coronary flow. %: percent values; NLS: normals. Source: Adapted from Dilszian.[277]*

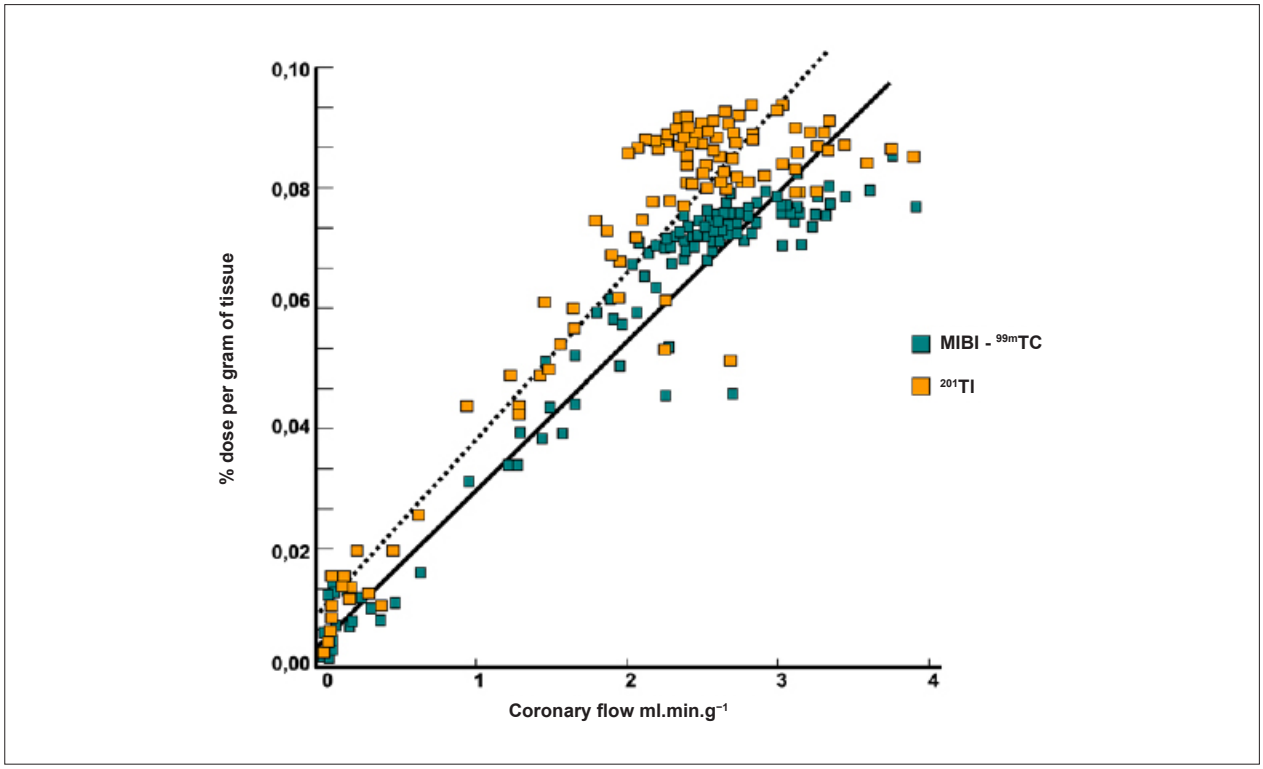

Figure 2 – *Linear association between intravenous dose per gram of myocardium and blood flow per minute, using the radiopharmaceuticals ^{201}TI and MIBI-^{99m}Tc. Once coronary flow exceeds 2.5 ml.min.g^{-1}, a loss of linear relationship is observed (phenomenon of "roll off"). Source: Adapted from Berman DS.[116]*

5.2. Myocardial Perfusion Scintigraphy with Tomography Imaging (SPECT)

Technological evolution of computerized systems has made it possible to divide the myocardium of the left ventricle (LV) into tomographic slices measuring only a few millimeters. In conventional gamma cameras (with iodide sodium crystals) the size of a pixel (the smallest component of a digital image) is 6.4 mm, and in CZT (cadmium zinc telluride semiconductors) technology it is 4 mm, representing related cross sections and, consequently, the method's spatial resolution.[29-31] The resulting images facilitate the separation of nearby regions, improving contrast resolution and allowing for better detection of differences in concentrations of radioactivity in the myocardium. The SPECT technique also allows for detection of ischemic regions, even those that are small in size, i.e., approximately 2% of LV mass, in tissue with relatively normal tracer concentration.

Protocols: The preferred means of obtaining perfusion images of the myocardium and LV function with tracers labeled with technetium-99m (^{99m}Tc) is known as the "1-day protocol" (Figure 3A), made up of 2 stages, (resting-stress or stress-resting). During the first step, the injected dose of MIBI-^{99m}Tc, measured in millicuries (mCi) or megabecquerels (mBq), is three times lower than the dose administered during the second phase, thus avoiding the residual activity effect or "shining through" phenomenon. Another option is the "2-day protocol" (Figure 3B), where in each phase is performed on a separate day. In this case, similar doses and acquisition parameters are used. It is important to emphasize that, in situations where stress images are taken before resting ones, even if the perfusion images are normal, it is nevertheless important to obtain resting images, except in specific cases, given that analysis of LV function in both situations may provide relevant information, including the possibility of detecting patients with homogenous tracer distribution due to balanced severe coronary diseases. Furthermore, the detection of transient LV dilatation may also be useful in this case, and this requires that both phases be performed. However, in asymptomatic patients who have intermediate/low risks and no clinical evidence of CAD, who have undergone the stress phase as the initial MPS stage and whose perfusion images are normal, it is possible to dispense with the resting phase, in what is known as the "stress only protocol." In this situation, recent studies have provided evidence that the test's prognostic value is maintained and that diagnostic ability is similar to the costs of high sensitivity. Furthermore, the patient receives a lower dose of radioactive activity, and total exam time is reduced.[32,33]

5.3. Myocardial Perfusion Scintigraphy with Tomographic Images Synchronized with Electrocardiogram (Gated-SPECT)[34-41]

Cardiac images should be acquired synchronized with patient ECG, allowing for additional analysis of ventricular

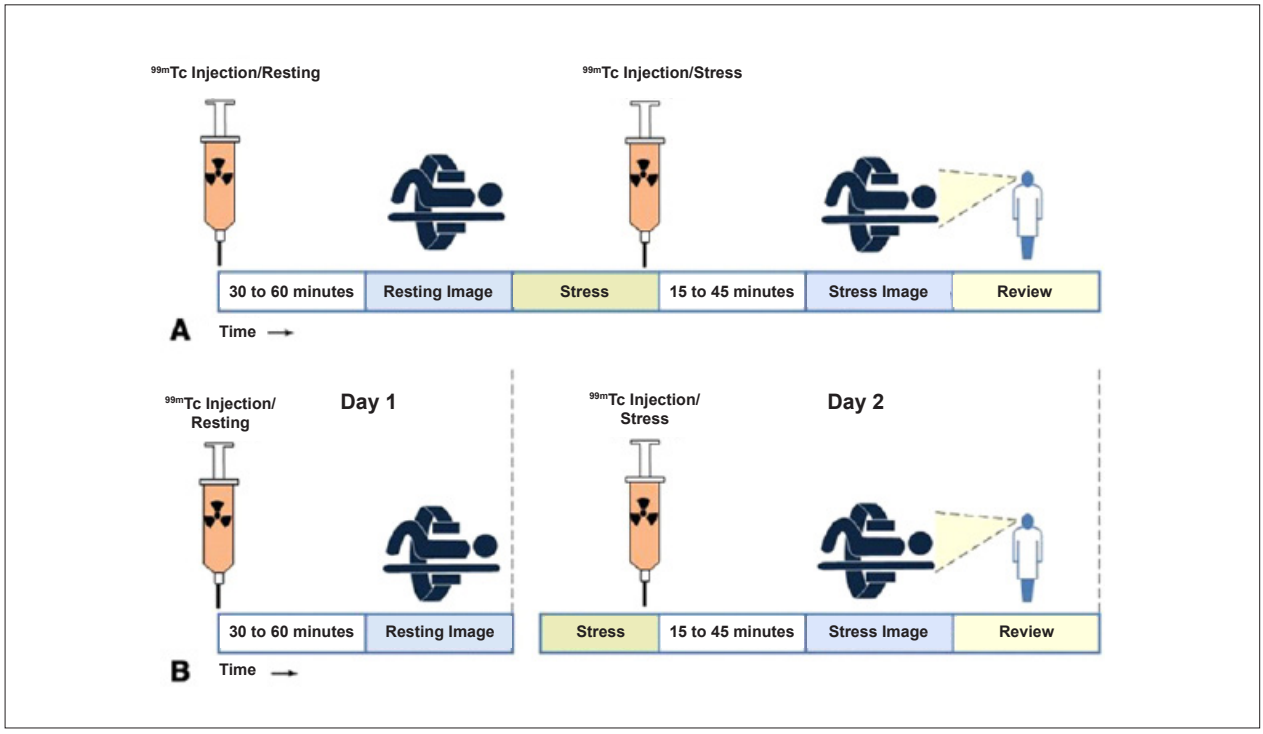

Figure 3 – *Perfusion image acquisition and myocardial function with the radiopharmaceuticals sestamibi (MIBI) or tetrofosmin labeled with technetium-99m or ^{99m}Tc: "one-day" protocol (A) and "two-day" protocol (B). The legends "^{99m}Tc Injection/Resting" and "^{99m}Tc Injection/Stress" represent administration of the radiopharmaceutical MIBI-^{99m}Tc during both stages, with dosage measured in millicuries (mCi), established in accordance with equipment and acquisition model used, as well as patient weight. In Protocol A, the stress dose is 3 times higher than the resting dose; in Protocol B, the resting and stress doses are similar, considering an interval of 24 hours between image acquisition.*

function, simultaneous with myocardial perfusion evaluation. This information adds data to the medical decision-making process within known incremental prognostic values, and it improves test accuracy, especially regarding specificity values. Considering this aspect, in situations where there are doubts between persistent perfusion defects and/or artifacts (due to breast or diaphragmatic attenuation), analysis of ventricular wall motility and thickness may contribute to differentiating these two causes. When apparent reduced relative uptake of a radiopharmaceutical is due to an artifact, the motility and systolic thickness of this wall are normal.

The estimated results of left ventricular ejection fraction (LVEF) that are conventionally considered normal vary according to technique and methodology employed. With the Gated-SPECT technique, this value is ≥ 50% for both sexes; there are few references with differentiated values for men and women, in addition to different established limits of normality. Due to specific aspects related to methodologies used to calculate LVEF, values found in individuals who are shorter and individuals with smaller ventricular cavities and/or hypertrophic ventricles, especially in women, may be overestimated, at times exceeding values of 75% to 80%.

Calculations of LVEF and ventricular volumes obtained by Gated-SPECT may be utilized for prognostic stratification. LVEF < 45% and end systolic volume (ESV) > 70 ml are associated with increased risks of cardiac death.[42,43] This analysis may be carried out either while resting or under stress; it should preferably be done during both steps, however, considering the possibility of detecting transient LV dysfunctions induced by physical exercise or pharmacological stress.

Cardiac arrhythmias pose difficulties to the acquisition of ECG-synchronized images and may significantly influence the results obtained for ejection fraction and produce artifacts in myocardial perfusion images. There is a technically defined time window for RR interval variation, generally around 20%, after which point heartbeats are rejected. This situation means that if there is an arrhythmia which produces variations between RR intervals above these established limits, such as persistent AF, the corresponding data from that specific cardiac cycle will be rejected, and there will consequently be lower counting statistics. In these cases, images should be acquired without ECG synchronization in order to avoid the occurrence of artifacts.

5.4. Cardiovascular Stress

The basic principle of using cardiovascular stress associated with myocardial perfusion images consists of creating heterogeneity in blood flow between vascular territories irrigated by normal coronary arteries with significant obstructive stenoses.[44,45] The use of myocardial perfusion agents makes it possible to visualize this heterogeneity in regional blood flow. In practice, of all existing cardiovascular stressors, only ET and pharmacological tests have been used.

Both stress modalities, physical exercise and pharmacological vasodilation, have similar sensitivity and specificity for the detection of CAD via analysis of perfusion images.[46-48]

Physical stress: ET is the associated method of choice for diagnostic and prognostic values, which have already been established in conformity with clinical, hemodynamic, and electrocardiographic variables obtained during exercise, which add incremental data to myocardial perfusion study. Stress tests have a higher chance of revealing abnormalities in patients with more severe and extensive obstructive arterial disease. Chest pain and/or decreased systolic blood pressure (SBP) during low levels of exercise are highly important findings that are associated with adverse prognoses and multivessel coronary disease. Other markers of unfavorable prognosis include high-magnitude ST segment depression, with a horizontal or downsloping aspect, which may appear early during low workloads or be characterized by late recovery after stress has ceased, present in multiple leads, among others (Table 9).

Some studies have incorporated stress test variables into diagnostic and prognostic scores.[49] The most widely used in our context is the Duke prognostic score. Using Cox's regression analysis, Mark DB et al. proposed[50] and validated[51] this score for use with the exercise treadmill test and the Bruce protocol. It is calculated by the following formula:

DS = T (min) - (5 x ST) - (4 x AI)

or

Duke Score = exercise time (in minutes) - (5 × ST deviation in millimeters) – (4 × angina *index)*

The angina index has a value of 0 (zero) if there are no symptoms during exercise, 1 (one) if non-limiting chest pain

Table 9 – Exercise testing parameters associated with unfavorable prognosis and multivessel coronary disease.

- ECG:
  - ST-segment depression ≥ 2 mm, with descending morphology and early appearance (metabolic load < 5 - 6 METs), involving multiple leads, usually lasting for ≥ 5 minutes of recovery
  - Exercise-induced ST-segment elevations
  - Reproducible, symptomatic, or sustained ventricular tachycardia (> 30 s)
- Metabolic load < 5 – 6 METs*
- Chronotropic incompetence
- Systolic blood pressure: inability to reach values ≥ 120 mmHg, or sustained decrease ≥ 10 mmHg, or fall below resting values during progressive exercise
- Symptoms: angina pectoris when performing a lower workload , generally during the beginning of exercise, when conventional protocols are applied

*ECG: electrocardiogram; MET: metabolic equivalent. (*1 MET = oxygen consumption in supine resting conditions, equivalent to 3.5 mL.kg^{-1}.min^{-1})*

occurs, and 2 (two) if the pain is impeditive (growing intensity) as exercise proceeds. In accordance with the results of the regression equation, patients are classified as follows:

- **High-risk group**: patients with scores ≤ -11, with an annual cardiovascular mortality rate ≥ 5%.
- **Low-risk group**: patients with scores ≥ 5, with an annual cardiovascular mortality rate < 1%. In clinical practice, when patients are considered high-risk, this reinforces *a priori* the indication for invasive study with the aim of managing and directing medical treatment, be it interventional or not, while always taking the possibility of improving morbimortality and quality of life into account. In patients with intermediates results, i.e., scores between > -11 and < +5, in order to reclassify risk, complementary exams associated with imaging, such as the following, may be required:
  - Myocardial perfusion scintigraphy (MPS) with ET or vasodilators.
  - Vasodilator stress cardiac magnetic resonance (technique associated with inability to exercise).
  - Doppler echocardiogram under stress or specific conditions.
  - Computerized angiotomography of coronary arteries.

Finally, in patients considered low-risk, medical management is related to prevention measures. On the other hand, based on a growing base of evidence, these methods,[52] especially MPS, have become of paramount importance for quantifying ischemic area, even in patients who are considered high-risk, with the aim of assisting and directing the medical approach to be adopted,[53-58] notwithstanding the unavailability of information from randomized clinical trials such as the "Ischemia Study," which will be able to assist in better management of patients with extensive areas of the myocardium at risk.[59]

Furthermore, emphasis given to exercise as the primary stress-producing agent of choice within the cardiovascular system has become clear, given that it is the most physiological method for triggering myocardial ischemia, based on sympathetic stimulation and the increase in the main determinants of myocardial oxygen consumption (MVO_2), such as HR, blood pressure, and myocardial contractility. Likewise, exercise leads to coronary vasodilation through biochemical mechanisms, resulting in increased blood flow to the myocardium and greater oxygen supply, thus meeting the necessary demands imposed during the application of extreme effort. This ability to increase coronary blood flow, which reaches three to four times baseline values during peak exercise, in the absence of significant obstructive coronary lesions, conceptually represents the phenomenon known as "coronary reserve," considered the main characteristic of MPS with radiopharmaceuticals. Moreover, with respect to the limitations and contraindications of this methodology,[60] joint analysis of both stress test and cardiac imaging exams will play a fundamental role in the medical decision-making process, albeit in view of previous clinical information or pretest probability of obstructive CAD.

With relation to the main methodological aspects, the following stand out:

- Prior venous access in an arm, in a "Y" shape (separate routes), for radiopharmaceutical injection during peak exercise and subsequent flush with saline solution, respectively.
- Safety criteria for administering and interrupting stress should be in accordance with established guidelines, reinforcing the need for a maximum test.[61]
- Following intravenous administration of the radiopharmaceutical, stimulate continuation of stress for 1 more minute.
- When using MIBI-^{99m}Tc (absolute preference in Brazil), image acquisition follows conventional protocols (30 to 60 minutes after stopping stress). Variations in initial acquisition time depend on patient type (obesity, prior abdominal surgery, prominent extracardiac activity in the resting images phase.
- When using thallium-201, considering the phenomenon of redistribution, images should be taken 10 to 15 minutes after stopping stress.

Pharmacological tests: Represent excellent alternatives for evaluating patients with physical limitations or clinical impediments to undergoing efficacious exercise testing . The most frequent conditions are found in Table 10. They represent around 20% to 30% of all cases of scintigraphy referral and approximately 50% of elderly patients.[62] The drugs used in these circumstances are dipyridamole, adenosine or regadenoson, and dobutamine. These drugs induce maximum vasodilation and increase coronary flow, allowing for assessment of coronary reserve, with diagnostic and prognostic power similar to that of exercise,[63,64] which has recently been extended to elderly patients and women.[65,66]

In cases of left His bundle branch block or artificial pacemaker with ventricular stimulation, the first option is a pharmacological test with dipyridamole or adenosine, with the aim of avoiding what are known as false-positive results (alterations in relative radiopharmaceutical uptake, in the absence of obstructive lesions). These are caused by atypical movement of the interventricular septum, which occurs in these situations and is accentuated when myocardial scintigraphy is performed with ET. Reduced radiopharmaceutical uptake is often observed in these patients and is most frequently related to the septal region, which may be exacerbated by the stress test, as increased HR increases paradoxical septal motion and, consequently, reduces perfusion in this wall.[67,68]

Primary vasodilators: Dipyridamole, adenosine, and regadenoson (not available for routine clinical practice in Brazil) provoke a significant increase in coronary flow in normal arteries and a small or nonexistent increase in arteries with functionally significant stenosis, thus resulting in relative heterogeneity of flow between LV walls. During maximum vasodilatation, when the radioisotope is injected, the difference in relative radiopharmaceutical uptake in LV walls will also be observed, making it possible to diagnose coronary disease:

- **Dipyridamole:** the total dose of dipyridamole is 0.56 $mg.kg^{-1}$ up to a maximum dose of 60 mg or 6 vials (a 2-ml vial = 10 mg), administered intravenously (IV), preferably with a 4-minute infusion pump, diluted in 50 ml of saline

Table 10 – Main indications for use of pharmacological stress in patients with contraindications or limitations to undergoing exercise stress[24,46]

• Motor sequelae from cerebral vascular insufficiency and degenerative or inflammatory musculoskeletal pathologies
• Compensated congestive heart failure
• Chronic pulmonary obstructive disease with important functional restriction, but without recent hyperresponsiveness
• Low functional capacity
• Other non-cardiac conditions that result in an inability to exercise efficiently
• Severe arterial hypertension
• Complex ventricular arrhythmias triggered by effort
• Pre-operative cardiological assessment for major abdominal vascular surgery
• Presence of left bundle branch intraventricular conduction disorders
• Risk stratification for recent evolution of myocardial infarction
• Use of drugs that interfere with oxygen consumption elevation
• Presence of artificial electric stimulation

solution (SS). It may, alternatively, be injected manually (with a 20-ml syringe), using the same dilution. Alternatively, a more elevated dose of 0.84 mg.kg^{-1} may be used in select cases. The radiopharmaceutical is administered IV during hyperemia or maximum vasodilation, 2 to 4 minutes after the end of dipyridamole infusion (Figure 4). Dipyridamole inhibits the action of the enzyme adenosine deaminase, wich degrades endogenous adenosine, in addition to blocking reuptake of adenosine into the cellular membrane, with a consequent increase in extracellular concentration and resulting coronary vasodilation. Its biological half-life is approximately 45 minutes.

- **Adenosine:** The usual dose is 140 μg.kg^{-1}.min^{-1}, and it must mandatorily be administered via a 6-minute continuous infusion pump, diluted in 50 ml of SS, with the injection of the radiopharmaceutical administered during the third minute via a different intravenous access (Figure 5). It is, also, possible to inject the solution for 4 minutes, in which case the radiopharmaceutical is administered during the second minute.[69] Because xanthines block the vasodilation effect, patients should be instructed to suspend them for 24 hours before a scheduled exam with dipyridamole or 12 hours before a scheduled exam with adenosine, in addition to any other drug or product, food, or drink that contains methylxanthines or theophyllines, including coffee, tea, soft drinks, chocolate, energy drinks, compound analgesics containing caffeine, especially for treatment of muscular pain or migraines, et al. Reference lists are available for consultation.[70] Adenosine induces coronary vasodilation via specific activation of A_{2A} receptors in the cellular membrane, resulting in increased coronary flow up to 4- or 5-fold resting values.

Accuracy for detecting CAD with the use of MPS is comparable between both drugs. It is worth reiterating that, in exams using dipyridamole and adenosine, modifications in the ST segment occur relatively infrequently, even in patients with obstructive CAD (lower sensibility). In some instances, only the relative difference in flow observed in patients with different degrees of luminal obstruction and coronary reserve will determine perfusion defects, and ischemia will not necessarily be present. For this condition, collateral circulation is necessary, which causes coronary steal, with consequent alterations in contractility. Nevertheless, the sensitivity of scintigraphy images associated with the use of pharmacological agents or stress tests is similar. Adverse effects or "paraeffects" of using these drugs[23,71] occur in approximately 50% of patients with dipyridamole and in up to 80% of patients with adenosine. Common side effects include headache, dizziness, flushed face, feeling hot, chest pain, ST alterations and others (Tables 11 and 12).[72] These manifestations generally do not last long, and in most cases they may be reversed by administering intravenous aminophylline at 1 to 2 mg.kg^{-1} or 72 mg (3 ml) to 240 mg (10 ml or 1 vial) 2 minutes after injecting the radiotracer, when MPS is associated with dipyridamole. When adenosine is used, there is no need to inject an antagonist, given its ultrashort half-life, from 2 – 10 seconds, the recommendation being simply to interrupt the infusion. When it is not medically possible to perform either the physical stress or the pharmacological dilation modality with dipyridamole or adenosine, intravenous administration of dobutamine solution may be the best option for assessing coronary reserve flow, with regards to increased MVO_2. Contraindications to dipyridamole and adenosine use are listed in Table 13.

It is, finally, important to stress that, with both dipyridamole and adenosine, no significant increases are observed in MVO_2, which, in clinical practice, is translated as the product of heart rate (HR) × systolic blood pressure (SBP), or the double product. During pharmacological stimulation, SBP values generally drop by around 10% while HR increases by approximately the same proportion, with no consequent increase in MVO_2.

Drugs that promote elevated myocardial oxygen consumption: These drugs represent an alternative for patients who cannot undergo ET or pharmacological stress with *dipyridamole* or *adenosine*. Examples include patients

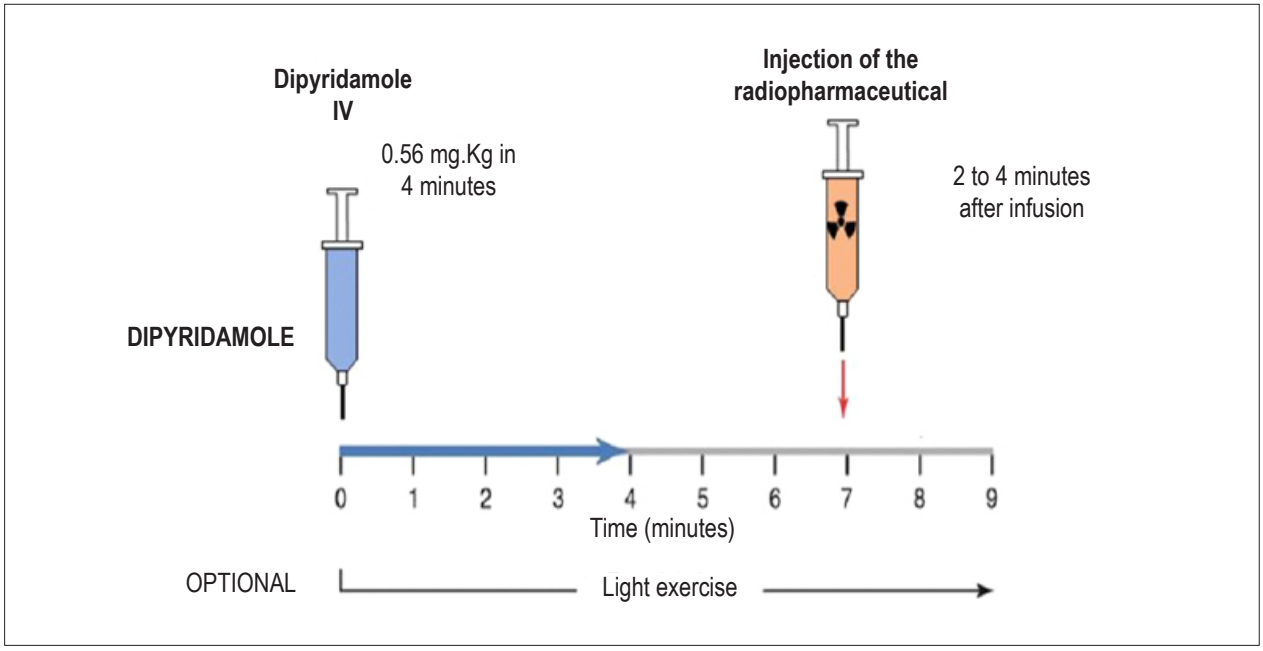

Figure 4 – *Myocardial perfusion scintigraphy associated with injection of dipyridamole. The moment of maximum vasodilation or coronary hyperemia occurs between 2 and 4 minutes after completing intravenous dipyridamole administration (blue arrow, 4 minutes), at which point the radiopharmaceutical (99mTc-tetrofosmin or MIBI-^{99m}Tc, orange arrow) is injected. Clinical observation should be continuous throughout the exam, registering blood pressure, heart rate, and electrocardiogram every 2 minutes or in accordance with medical decision, with a typical total exam time of 9 to 10 minutes.*[24,46]

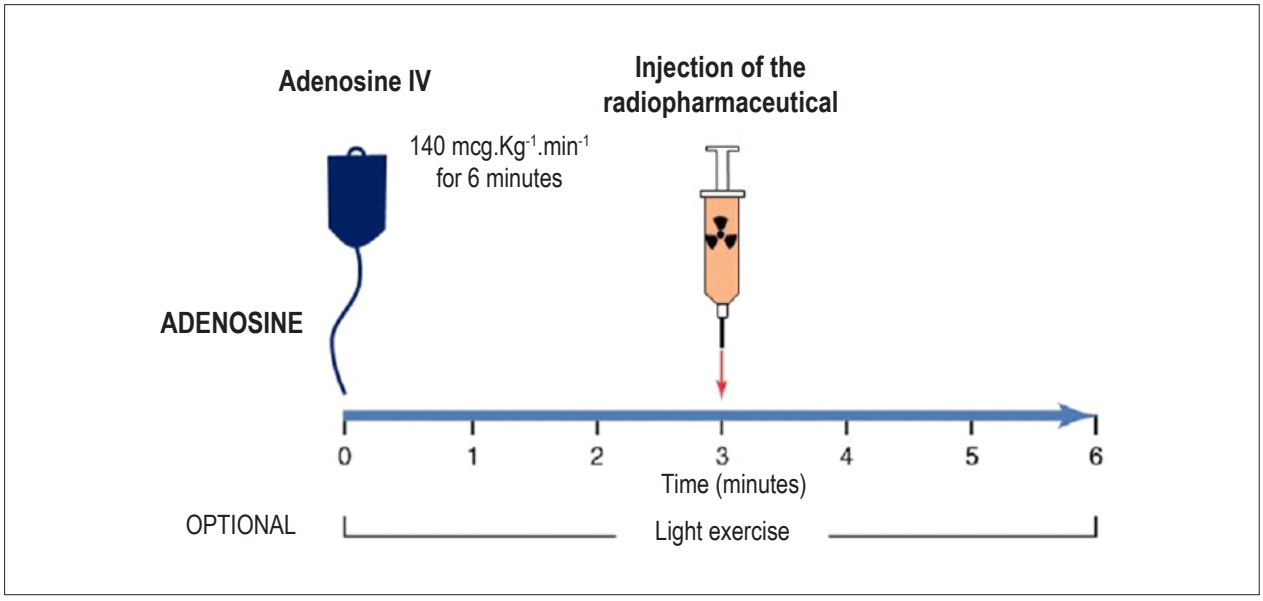

Figure 5 – *Myocardial perfusion scintigraphy associated with injection of adenosine. The need for continuous intravenous administration is due to the drug's ultra-short plasma half-life (2 to 10 seconds), with the aim of maintaining coronary hyperemia, which reaches its peak close to the third minute. At this moment, the radiopharmaceutical (MIBI-^{99m}Tc) is injected. After completing the solution at 6 minutes, frequent monitoring of blood pressure, heart rate, and electrocardiographic registers is maintained for a variable time of 4 to 6 minutes*

who have contraindications or limitations for stress test, as well as pulmonary obstructive disease with recent crises of bronchial hyperreactivity, arterial hypotension (SBP < 90 mmHg), and significant obstructive carotid artery lesions on both sides. This is also an alternative modality in patients indicated for dipyridamole or adenosine who have ingested substances derived from caffeine or methylxanthines (competitive antagonists) over the past 24 and 12 hours,

respectively. The most commonly used is *dobutamine*, which acts on beta-1 (β-1) adrenergic receptors, with chronotropic and inotropic stimulation, depending on the infused dose, in addition to direct effects on beta-2 (β-2) receptors, with peripheral vasodilation response. This results in an increase in cardiac output, HR, and SBP, leading to an increase in MVO_2 and, consequently, in coronary vasodilation. **Protocol:** The protocol begins with venous administration of the solution (250 mg of dobutamine diluted in 250 ml of saline solution - 1 mg per 1 ml) via infusion pump at a dose of 10 ug.kg^{-1}.min^{-1} for 3 minutes (first step), followed by 20 μg.kg^{-1}.min^{-1} for 3 minutes (second step), adding 10 μg.kg^{-1}.min^{-1} every 3 minutes (third and fourth steps) until the maximum dose of 40 μg.kg^{-1}.min^{-1} has been reached (Figure 6).[73,74] In patients who have not reached submaximal HR and who do not have evidence of ischemia, it is possible to associate intravenous atropine (0.25 to 2 mg) and perform isometric stress with hand grip maneuvers (e.g., compressing a tennis ball). A Brazilian study has demonstrated that early use of atropine (following the first phase of dobutamine infusion) is safe and that it reduces infusion time and complaints during stress, without affecting diagnostic precision.[75] Furthermore, the presence of perfusion defects induced by pharmacological vasodilatation and motility abnormalities triggered by stress aggregate incremental prognostic value to the test, which has recently been validated with the use of ultrarapid cameras (CZT technology).[76] Contraindications to dobutamine use may be found in Table 14. Patients on betablockers should stop taking these medications for 48 to 72 hours before the test. Special attention should be given to patients with bronchospasm undergoing MPS with dobutamine, whose plasma half-life is around 2 to 3 minutes, considering that its antagonist is metoprolol at an intravenous dose of 5 mg and that it is contraindicated in the presence of pulmonary obstructive disease. The most frequent adverse events or paraeffects associated with administration of dobutamine solution are listed in Table 15. To reverse them, in addition to metoprolol, other intravenous short-acting betablockers, such as esmolol (0.5 mg.kg), which is available, should be injected after the first minute of radiotracer injection.

Combined stress: The association of dynamic stress with low workloads (e.g., until the *second stage of the Bruce protocol* or *until feeling light fatigue*, equivalent to the number 13 on the subjective Borg stress scale) and vasodilators has been shown to reduce subdiaphragmatic (hepatic) activity and improve the ratio of radiation activity emitted between the target organ and the viscera (background), with consequent improvements in image quality.[77] It has similarly shown a decrease in the occurrence of adverse effects resulting from the infusion of dipyridamole or adenosine, as well as the incidence of atrioventricular blockage. This protocol is ideal for patients who are able to

Table 11 – Adverse effects or "paraeffects" related to intravenous administration of dipyridamole for performance of myocardial perfusion scintigraphy[24,46]

Adverse effects or paraeffects	%
Chest pain	20
Headache	12
Dizziness	12
Alterations in ST	8
Ventricular extrasystoles	5
Nausea	5
Arterial hypotension	5
Facial flushing	3
Atrioventricular blockage	2
Fatal or non-fatal myocardial infarction	Extremely rare
Any minor event	50

Table 12 – Adverse effects or "paraeffects" related to intravenous adenosine administration via infusion pump for performance of myocardial perfusion scintigraphy[24,46]

Adverse effects or paraeffects	%
Facial flushing	35 to 40
Chest pain	25 to 30
Shortness of breath	20
Dizziness	7
Nausea	5
Symptoms of hypotension	5
Atrioventricular blockage	8
Alterations in ST	5 – 7
Atrial fibrillation	Case reports
Convulsions	Case reports
Hemorrhagic/ischemic stroke	Case reports
Any minor event	80

Table 13 – Contraindications to use of adenosine and dipyridamole[24,46]

Absolute
• Bronchospastic disease during activity, recent hyperreactivity (< 3 months), status asthmaticus
• Second- or third-degree atrioventricular blockage, in the absence of a pacemaker
• Arterial hypotension (systolic blood pressure less than 90 mmHg)
• Recent transient ischemic attack or cerebrovascular accident (< 2 months)
• Recent use (less than 24 hours) of dipyridamole in patients who are to receive adenosine
Relative
• History of reactive pulmonary disease, with no recent crises (> 3 months)
• Sinus node disease
• Severe sinus bradycardia
• Severe bilateral carotid disease

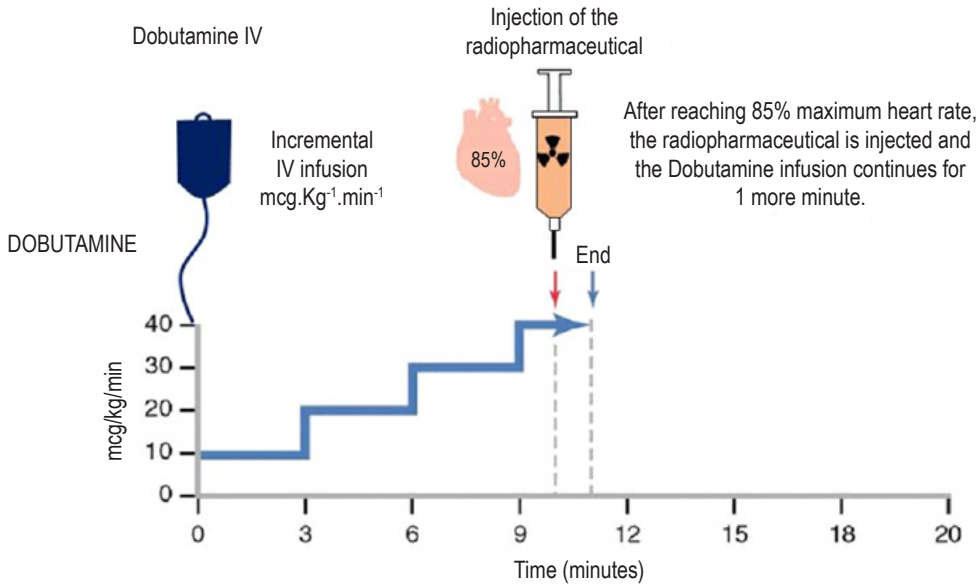

Figure 6 – *Myocardial perfusion scintigraphy associated with intravenous administration of dobutamine solution (250 mg or 1 vial diluted in 250 ml of saline solution). It may begin with an alternative initial dose of 5 mcg.kg-1.min-1, for 3 minutes, with sequentially increasing doses every 3 minutes, up to 40 mcg.kg-1.min-1 or until 85% of maximum heart rate has been reached (explained in the figure and the text), at which point the radiopharmaceutical (MIBI-99mTc or 99mTc-tetrofosmin) is injected. In the event of inadequate increase in heart rate and in the absence of contraindications (glaucoma, prostatic hypertrophy), atropine is additionally recommended, either early on or starting at the third step.*

Table 14 – Contraindications to dobutamine use[24,46]

Absolute
• Cardiac arrhythmias including atrial fibrillation and ventricular tachycardia (sustained or non-sustained)
• Severe aortic stenosis and hypertrophic obstructive cardiomyopathy
• Systolic arterial hypotension (< 90 mmHg), uncontrolled systolic arterial hypertension (systolic > 200 mmHg), severe or stage III hypertension
• Unstable angina or recent myocardial infarction
• Aneurysms or aortic dissection
• Symptomatic vascular cerebral insufficiency
• Presence of implanted cardiac defibrillator
• Alterations in metabolism of potassium
Relative
• Abdominal aortic aneurysm (> 5 cm in diameter)
• Presence of thrombi in left ventricle
• Left ventricular ejection fraction < 25% (due to increased risk of ventricular arrhythmias)

Table 15 – Adverse effects related to dobutamine infusion for myocardial perfusion scintigraphy[24,46]

Adverse effects	%
ST alterations	33
Precordial pain	31
Palpitation	29
Headache	14
Facial flushing	14
Dyspnea	14
Significant arrhythmias (supraventricular and ventricular)	8 to 10

exercise but who are using medications that limit increases in HR (betablockers, antiarrhythmic drugs, et al.).

New drugs: There are 3 types of adenosine receptors (Table 16). The use of specific selective antagonists to A_2 receptors has shown evidence of adequate coronary hyperemia and lower intensity of systemic effects, especially chest pain and atrioventricular blockage. A double-blind, randomized (regadenoson or adenosine), multicenter study[78] involving 784 patients has shown that diagnostic information is similar and that there were no serious adverse effects; regadenoson, however, was tolerated better than adenosine. Second-degree atrioventricular blockage occurred in 3 patients with adenosine and in no patients with regadenoson. Regadenoson's short biological half-life minimizes and limits the duration of adverse effects, diminishing monitoring time. It is administered via bolus, and it is not necessary to adjust dose to body weight (Figure 7). Its use is promising in patients with chronic obstructive pulmonary disease. The incidence of serious complications[79] with the performance of cardiovascular stress is related in Table 17.

5.5. Image Generation and Perfusion Defects in Myocardial Scintigraphy with Radioisotopes

Resting coronary flow is 1 ml.g.min^{-1}, increased 3- to 5-fold during maximal vasodilation or hyperemia, under physical or pharmacological stress (Figure 8).[28] In the presence of obstructive coronary lesions, resting coronary flow decreases when luminal narrowing is greater than 80%, due to exhaustion of the coronary reserve. When physical or pharmacological stress are applied, early exhaustion of the coronary reserve is observed, and it then exhibits a drop, generally beginning with lesions with luminal narrowing of 50%.[80] This information has currently been validated based on invasive measures of coronary flow reserve (CFR), fractional flow reserve (FFR), and instantaneous flow reserve (IFR), considered "standard" for characterizing myocardial ischemia; some have also been reproduced by non-invasive PET methods.[81-86] Tests with pharmacological stimulation using dipyridamole or adenosine associated with MPS are considered frequently to result in coronary flows in the range of 4 ml per gram of myocardium per minute,[87-89] generating homogenous relative uptake patterns of the radioisotopes in the myocardium, and scintigraphy images are considered normal when the coronary arteries are free of atherosclerotic processes. There are, however, specific situations in which patients with balanced multivessel disease (lesions in 3 arteries with similar coronary reserve) in which perfusion images appear with apparently homogeneous radiopharmaceutical distribution.[90]

From the conceptual point of view, it is necessary to comprehend that the generation of scintigraphy images is based on relative radiopharmaceutical uptake, which is injected intravenously during physical exercise or pharmacological test, predominantly in the LV myocardium. Comparison of radiopharmaceutical uptake between ventricular walls is expressed in images based on a scale of colors, created by specific computer programs, which, in addition to allowing for subjective analysis of perfusion, make semi-quantitative and quantitative evaluation of affected myocardial area possible.

Table 16 – Types of existing receptors in the cellular membrane and responses to stimuli

Type	Resulting effects
A1	Atrioventricular blockage
A2a	Coronary artery vasodilation
A2b	Peripheral vasodilation, bronchospasm
A3	Bronchospasm

5.6. Possible Scintigraphy Imaging Results, Using Qualitative, Semi-quantitative, and Quantitative Analyses

Visual or qualitative analysis: By simply inspecting images resulting from perfusion tomography and ventricular function exams (Gated-SPECT technique), it is possible to assess blood flow and regional contractility of the LV myocardium indirectly. Tomography images are reconstructed as multiple slices along the anatomical axis of the LV, defined as corresponding regions and respective relations with coronary territory. The slices are taken on

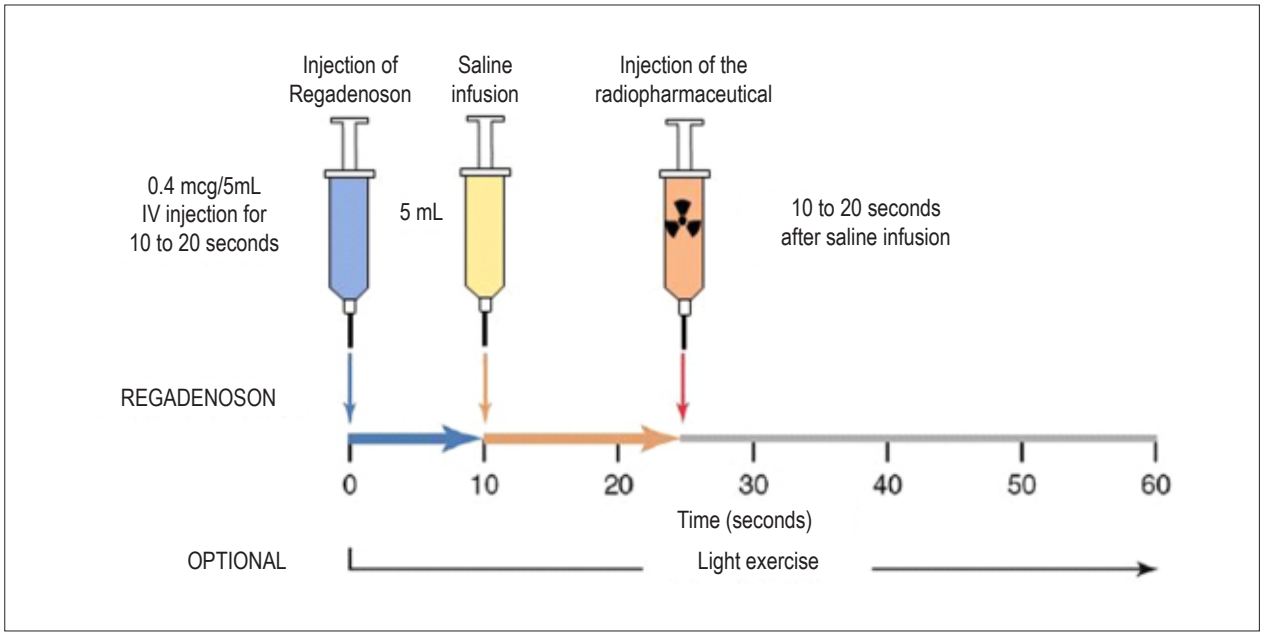

Figure 7 – *Myocardial perfusion scintigraphy associated with intravenous administration of regadenoson, a specific agonist of adenosine A_2A receptors in the cellular membrane. Activation of the receptor produces coronary vasodilation with a consequent increase in flow, similar to dipyridamole and adenosine. Maximum plasma concentration is reached 1 to 4 minutes after injection, with a biological half-life of 2 to 4 minutes during the first phase. The intermediate and the late phases follow, with approximate duration of 30 minutes (loss of pharmocodynamic effect) and 2 hours (decline in plasma concentration). The radiopharmaceutical, MIBI-^{99m}Tc or Tetrofosmin-^{99m}Tc, is injected at the moment of maximum hyperemia, close to 30 seconds after injection of regadenoson.*

Table 17 – Serious adverse events related to cardiovascular stress methods (rate of events observed per 1,000 individuals)[79]

Serious events	ET	Dobut	Dipy	Aden	Regad
Any event	0.1 - 3.46	2.988	0.714 - 2.6	0.97	CR
Death	0 to 0.25	CR	0.5	CR	CR
VF/VT	0 to 25.7	0.6 - 1.35	NR	NR	NR
AMI	0.038	0.3 - 3	1	0.108	CR
Cardiac rupture	Unk	CR	NR	NR	NR
High-grade AVB / ASY	Unk	NR	CR	CR	CR
Bronchospasm	Unk	NR	1.5	0.76	CR
Stroke/TIA	Unk	CR	NR	NR	CR
AF	Unk	5 - 40	NR	NR	CR
Seizure	Unk	CR	NR	1.5	CR

Aden: adenosine; AVB: atrioventricular blockage; AF: atrial fibrillation; AMI: acute myocardial infarction; ASY: asystole; CR: case report; Dipy: dipyridamole; Dobut: dobutamine; ET: exercise testing; NR: not reported; Regad: regadenoson; TIA: transient ischemic attack; Unk: Unknown; VF/VT: ventricular fibrillation/ventricular tachycardia.

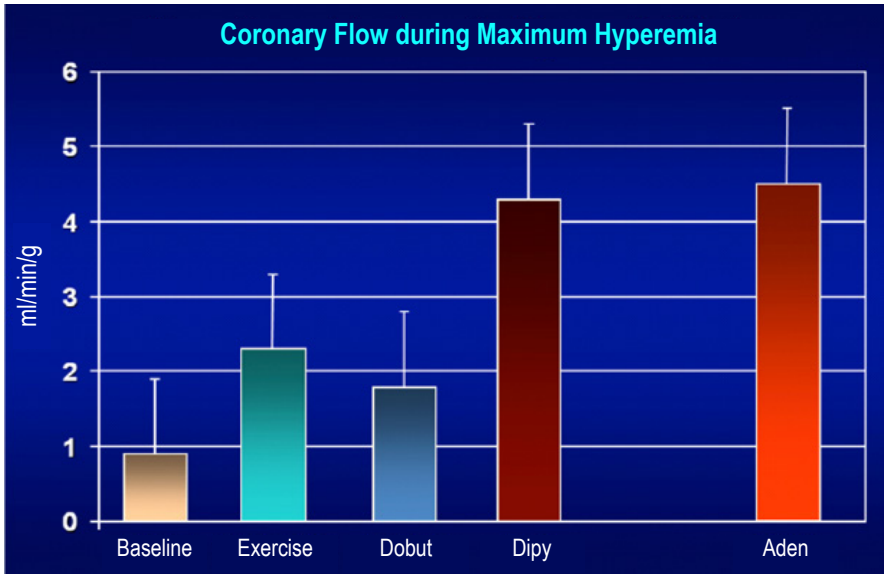

Figure 8 – *Effects of different types of stress methods on coronary flow elevation and values reached during maximum hyperemia. Baseline: resting coronary flow, 1 ml.min.g-1; Exercise: reaching values 2.5 to 3.5 times baseline coronary flow value; Dobut (dobutamine): reaching values around 2.0 to 2.5 times baseline coronary flow value; Dipy (dipyridamole) and Aden (adenosine): reaching values as high as 5.0 times baseline coronary flow value.[28]*

the short, long vertical, and long horizontal axes (Figure 9). Characterization of uptake of the radiopharmaceutical MIBI-^{99m}Tc or Tetrofosmin-^{99m}Tc during both exam stages (resting and stress, 1 day protocol) and thallium-201 during the stress and redistribution phases focuses on the anterior, septal, inferior , lateral, and apical regions of the LV (Figure 9). The short-axis projection uses transverse tomographic slices of the LV, sweeping from the apex or distal portion, through the middle of the cavity, to the basal portion. All regions and subdivisions are numerically identified, in accordance with the established scoring system, with the aim of standardizing segmentary analysis of the LV myocardium for perfusion study. Division into 17 segments has consensually been accepted, resulting in less interpretation subjectivity (Figure 10 and Table 18). Different radiopharmaceutical uptake and retention patterns allow for differentiation of normal, ischemic, and fibrotic tissues. The normal myocardium has similar uptake during both the stress and resting/redistribution phases, whereas the ischemic myocardium shows reduced relative uptake in stress images and normal uptake during resting/redistribution. Fibrotic tissue, on the other hand, shows reduced relative uptake during both study

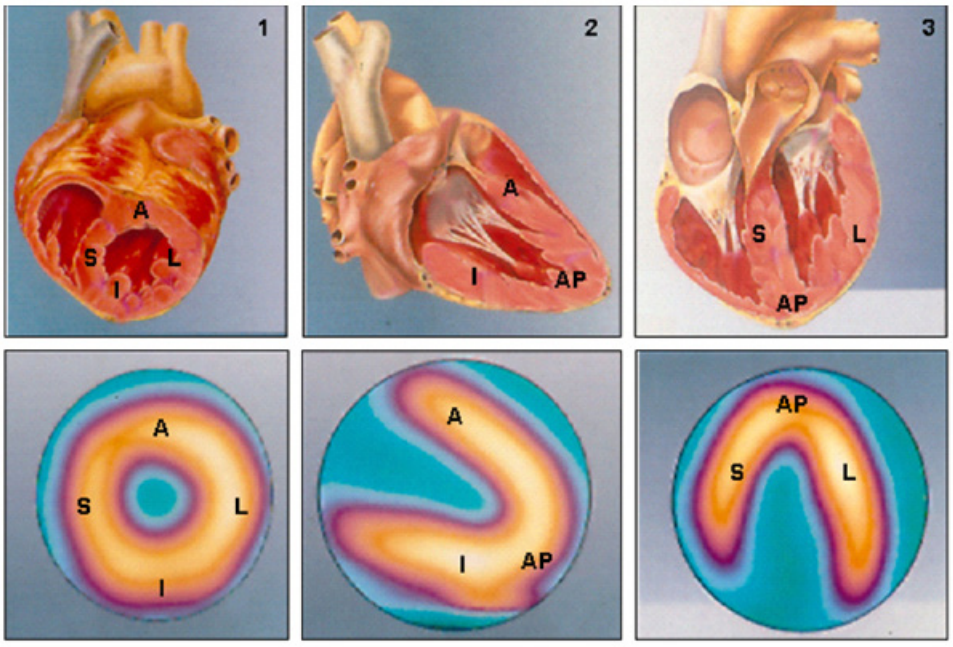

Figure 9 – *Two-dimensional reconstruction of scintigraphy images representing normal perfusion patterns (lower images), in line with minor axis (1), vertical long axis (2), and horizontal long axis (3) cross sections and their respective corresponding anatomical cross sections (upper images). A: anterior; AP: apical; I: inferior; L: lateral; S: septal. Adapted from Mastrocola LE.*[195]

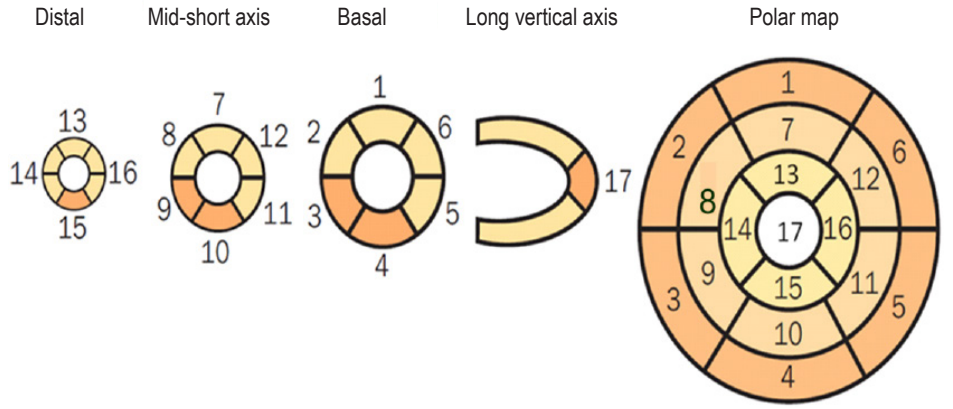

Figure 10 – *Numerical segmentation model of the left ventricular myocardium in 17 parts, considering tomographic slices of the minor and long vertical axes (distal or apical, middle, and basal or proximal portions), representing the myocardial regions; furthermore, correspondence of segments may be seen as presented in the polar map, which represents radiopharmaceutical distribution throughout the left ventricular myocardium in the form of a polar map, whose center corresponds to the apex and whose peripheries correspond to the basal portions. The correspondence between the numerical classifications and their respective segments is described in Table 18.*

phases. If fibrotic tissue coexists with an ischemic yet viable myocardium, reduced relative uptake will be observed during the stress phase, with partial improvement during the resting/redistribution phase. Hibernating myocardium will also show persistent reduced uptake, or be it, reduced uptake that is similar in both the stress and the resting phases. To differentiate it from fibrotic tissue, it is possible to perform assessment of viable myocardium with thallium-201, in

Table 18 – Numerical classification of segmentary division of the left ventricular myocardium into 17 parts, in cross sections (slices ?) of the minor and long-vertical axes

Regions/walls	Distal/apical portion	Middle portion	Proximal/basal portion
Anterior	13	7	1
Anteroseptal	–	8	2
Inferoseptal	–	9	3
Septal	14	–	–
Inferior	15	10	4
Inferolateral	–	11	5
Anterolateral	–	12	6
Lateral	16	–	–
Apex	17	–	–

Obs: apical region includes the apex and distal or apical portion of all walls (13,14,15,16).

which case it is sometimes necessary to add another phase or stage, namely that of late redistribution or reinjection, interpreted in the same manner.

Semiquantitative analysis: With the aim of numerically assessing the intensity of radiopharmaceutical uptake (perfusion), within the established standards (17-segment model), specific scores have been developed: **a) perfusion –** considers the following numerical scale: **0 =** normal; **1 =** mildly reduced radiopharmaceutical uptake; **2 =** moderately reduced uptake; **3 =** severely reduced uptake; **4 =** absence of radiopharmaceutical uptake. Scores of 3 or 4 are normally associated with coronary stenosis of > 90%. Therefore, the higher the number of affected segments is; the more extensive the process; the higher the summed scores, and the greater the severity will be. This has an unquestionable prognostic value for patients with CAD. The following calculations are achieved by the sum of values attributed to each segment: the sum of the values attributed to each segment during the stress phase is known as the "summed stress score" (**SSS**); this is repeated during the baseline or redistribution phase to obtain the "summed rest/redistribution score" (**SRS**). The difference between the SSS and the SRS is known as the "summed difference score" (**SDS**). According to Hachamovitch et al.[56,57] numerical **SSS** values **< 4** are considered *normal*; between **4** and **8**, *mildly abnormal*; between **9** and **13**, *moderately abnormal*; and **> 13**, *severely abnormal*. It is worth emphasizing that **SSS** values **< 4**, which may not necessarily be zero, are understood as normal, because there are myocardial regions which show lower radiopharmaceutical concentrations in and of themselves and may, consequently, receive values other than zero.

Quantitative analysis: *Polar maps* are two- or three-dimensional reconstructions of the LV, initially elaborated with the proposal of encompassing relative radiopharmaceutical distribution throughout the heart in a single image. They are shown in circular form, resembling a target, for which reason they are also known as "bull's eye plots." Radiopharmaceutical uptake, which is representative of perfusion, is shown on a color scale, with the LV apex occupying the center of the target, while basal regions of the heart are represented by the outermost circle of the target (Figure 10). Programs capable of reconstructing these images also allow for percentage quantification of areas with reduced uptake by comparing the images to a databank of normal individuals of the same age and sex. Perfusion defects may also be quantified by the number of pixels in a determined region and by existing standard deviations in relation to normal perfusion areas.

We may also obtain polar maps with parameters relative to ventricular function, such as LV wall motility and systolic thickness. These methods of quantitative analysis serve as complements to assist in qualitative or semiqualitative visual analysis.

Evaluation of ventricular function with perfusion agents: In a manner analogous to that described for perfusion study, segmentary contractile analysis of the LV makes use of motility and systolic thickness scores for each segment, also considering division into 17 segments, visualized in the cross sections of the minor axis (distal, mid-cavity, and proximal regions) and the long vertical axis (anteroapical and inferoapical regions). Numerical values are attributed. Analysis of motility of LV walls is performed directly on the computer monitor, making the subendocardial contour visible. Analysis of systolic thickness should be directed to the color scale chosen for a group of images. When thickness is within normal limits, the color increment is observed toward the bottom of the scale. Furthermore, it is possible to obtain percentage of thickness in each region. For distal and middle slices of the minor axis, as well as for the apex, average normal thickness is around 40%, with a **score of zero (0)** Thicknesses between 30% and 40% are interpreted as borderline; those between 20% and 30% receive a **score of 1** (mild reduction); 10% to 20%, a **score of 2** (moderate to severe reduction); and less than 10%, a **score of 3** (absence of thickness)**.** In the proximal (or basal) cross section of the minor axis, thickness of around 20% is considered normal. A *score of 1* is not used, but rather only scores of 2 and 3. Abnormalities in motility and thickness generally go hand-in-hand, with slight differences in gradation between the two (Table 19) and in the resulting sums. In some cases, we may observe discrepancy between results, for instance, following revascularization surgery and in the presence of left bundle branch block, in which the motility of the interventricular septum is compromised, whereas thickness is not.

Whenever possible, analysis of ventricular function should be performed at the baseline phase and after stress, with the purpose of detecting additionally indicative alterations in stunned or hibernating myocardium. The validated scores, which have been previously described, are recommended. Regarding the effect of global analysis of LV systolic function, LVEF is the parameter with the best reliability, and scores predominantly concentrate on segmentary analysis.

Furthermore, the subjective or qualitative assessment of images regarding results related to myocardial perfusion study, which have been previously described (*homogenous*

Table 19 – Segmentary analysis of left ventricle motility and systolic thickness by single photon emission computed tomography synchronized with ECG (Gated-SPECT)

Score (points)	Motility	Thickness
0	Normal	Normal
1	Mild hypokinesis	Mild reduction
2	Moderate hypokinesis	Moderate/severe reduction
3	Severe hypokinesis	Absence of thickness
4	Akinesis	–
5	Dyskinesis	–

distribution or normal uptake of the radiopharmaceutical in the myocardium; transient low uptake suggestive of ischemia; fixed low uptake suggestive of fibrosis; partially reversible low uptake suggestive of ischemia associated with fibrosis), should take the presence of the following types of artifacts into account:

- Technical artifacts, resulting from inadequate image processing.
- Motion artifacts.
- Attenuation artifacts, due to interposition of mammary or diaphragmatic tissue (intestinal handles), which are factors that interfere with the specificity of the exam.

6. Current Utilization of Myocardial Perfusion and Ventricular Function Studies with Radiopharmaceuticals as Part of the Medical Decision-Making Process

MPS with the injection of radiopharmaceuticals associated with ET or the administration of coronary vasodilators is an established method for diagnosis and risk stratification of obstructive CAD,[91-100] with the aim of guiding more effective clinical management of patients as part of the medical decision-making process.[101,102] It currently integrates other non-invasive cardiovascular imaging techniques, such as Doppler echocardiography with color flow mapping, CS, coronary angio-CT, PET, and cardiac magnetic resonance (MR), to characterize risk and functional expression of atherosclerotic disease.[103] Accuracy of method was, until recently, based on invasive coronary cineangiography, considered the standard for this comparison. The following stand out as highly relevant aspects, considered of paramount importance to the modality:

- Obtaining variables and parameters that are fundamental to incremental prognostic characterization of CAD, such as electrocardiographic response to exercise, functional capacity , chronotropic response, blood pressure, et al. Of all forms of stress associated to MPS, the exercise testing is, without a doubt, the one that adds the greatest amount of information.[104-106]
- When analyzing perfusion images, the possibility of quantifying area of myocardial ischemia or myocardium at risk has advanced a great deal over the past decades, undoubtedly participating in risk stratification and medical decision making for stable CAD, where it provides assistance for the choice between maintaining clinical treatment and interventional treatment.[107] Even in the absence of randomized studies published to date, which might reaffirm this information (the Ischemia Study - report to the Addendum of this guideline),[108] the evidence which has currently been accumulated and made available documents better evolution in patients with severe ischemic burden who undergo myocardial revascularization.[109-112]
- When analyzing ventricular function images, indirect observation of thickness and motility of the LV walls and comparison of resting and exercise ejection fractions greatly improve the method's specificity for characterizing true ischemia and aggregate incremental prognostic value with the definition of markers of severity, such as transient ischemic dilatation (TID), representing ventricular dysfunction and / or subendocardic ischemia induced by applied stress.
- The ability to infer coronary flow reserve under applied stress or stimulus with elevated accuracy, superior to other conventional methods, with the exception of PET, is the most important physiological parameter for characterization of ischemia and the medical decision-making process, currently available in clinical practice with direct invasive measures of FFR and instantaneous wave-free ratio (IFR). Software currently in development for calculating coronary reserve in association with SPECT methodology and other non-invasive methods will likely aggregate unquestionable value to appropriate clinical or interventional treatment choices, in the near future, encompassing not only obstructive atherosclerotic disease, but also physiopathological conditions, including microvascular disease and endothelial dysfunction in the scenario of ischemic heart disease.[85,113-115]

The main applications with the best cost-effectiveness are shown in patients with intermediate pre-test probability of CAD, estimated based on the integration of clinical variables which have been established and documented in Brazilian and international guidelines, with their respective recommendations and levels of evidence (Tables 20 and 22 and Figure 11). Ideal diagnostic and prognostic capacities have for decades been considered with regard to severe coronary lesions. Nonetheless, exercise testing are indicated as the ideal and preferred association for myocardial scintigraphy, considering the physiological nature of the form of applied exercise and the established clinical value of the variables obtained during and after work.[116-120]

Pharmacological tests performed in nuclear cardiology represent good alternatives for assessing patients with physical limitations or clinical limitations to undergoing efficient exercise testings. They include approximately 20% to 30% of all cases referred for scintigraphy and approximately 50% of elderly patients.[121] In these circumstances, the drugs utilized are dipyridamole, adenosine,[69,122,123] and regadenoson.[124] (Additional details described in Methodology.)

Similarly, in practice, when comparing conventional algorithms used for established the probability of CAD

Table 20 – Recommendations for cardiovascular risk assessment, considering the presence or absence of known risk factors. European Guidelines on cardiovascular disease prevention in clinical practice[119]

Recommendations	Class of recommendation	Level of evidence
CV risk assessment in individuals with family history of premature CV disease, family history of dyslipidemia, major risk factors (smoking, HBP, DM, raised lipid levels), or specific comorbidities that increase CV risk.	I	C
Repeat risk assessment every 5 years; repeat more often in individuals with risks close to levels which treatment is mandatory	I	C
Consider CV risk assessment in men > age 40 and women > age 50 or post-menopausal with no known risk factors	IIb	C
CV risk assessment in men < age 40 and women < age 50 with no known risk factors is not recommended	III	C

C: level of evidence based on consensus of expert opinion and/or small studies, registries, or retrospective studies; CV: cardiovascular; DM: diabetes mellitus; HBP: High blood pressure; I, IIb, and III: class of recommendation.

Table 21 – Percent probability of obstructive coronary artery disease, considering the presence of chest pain, sex, and age. Adapted from Diamond GA, Forrester JS and the Brazilian Cardiology Society's Third Guidelines on Exercise Testing[117,118]

Age	Non-anginal chest pain		Atypical angina		Typical angina	
	Men	Women	Men	Women	Women	Men
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

Table 22 – Percent probability of obstructive coronary artery disease, considering the presence of chest pain, sex, and age. Comparison between LR and HR patients. Adapted from Gibbons RJ et al. and the Brazilian Cardiology Society's Third Guidelines on Exercise Testing[117,119]

Age	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR
35	3	35	1	19	8	59	2	39	30	86	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

CAD: coronary artery disease; HR: high risk (smoking, diabetes, or dyslipidemia); LR: low risk (without smoking, diabetes, or dyslipidemia).

and major adverse events in stable chest pain patients or asymptomatic patients, such as Framingham Risk Score (FRS), PROCAM, SCORE, Diamond Forrester,[125] or Global Risk;[126] the estimated prevalence (EP) of the disease is observed to be significantly higher than the observed prevalence (OP), when coronary angio-CT is used to characterize luminal obstruction, ≥ 50% and ≥ 70%, respectively. In this situation, an international multicenter study (CONFIRM)[127] of 14,048 consecutive patients with clinical suspicion of coronary obstructive atherosclerosis who underwent angio-CT showed that, in all age and sex categories, guidelines for calculating probability overestimated prevalence in the general population (51% EP × 18% OP for lesions ≥ 50% and 42% EP × 10% OP for obstructions ≥ 70%, $p < 0.001$), directed by accentuated differences between patients with typical angina (86% EP × 29% OP for lesions ≥ 50%) and atypical angina (47% EP × 15% OP for lesions > 50%). Considering this information to be true, more evidence has arisen within the literature in the search for new markers which might aggregate value and assist in more objective and realistic restratification of cardiovascular risk, with specific guidelines[128] dealing with critical questions regarding, for instance, what types of evidence will contribute to risk assessment or reclassification when new markers are added to traditional scores, with emphasis on functional capacity and CS (Table 23).

6.1. The Application of Bayes' Theorem to Analysis of Myocardial Perfusion Images with Radiopharmaceuticals

Even when isolated analysis of images is used to describe perfusion findings, interpret data, and write reports, medical comments and conclusions should be the result of the

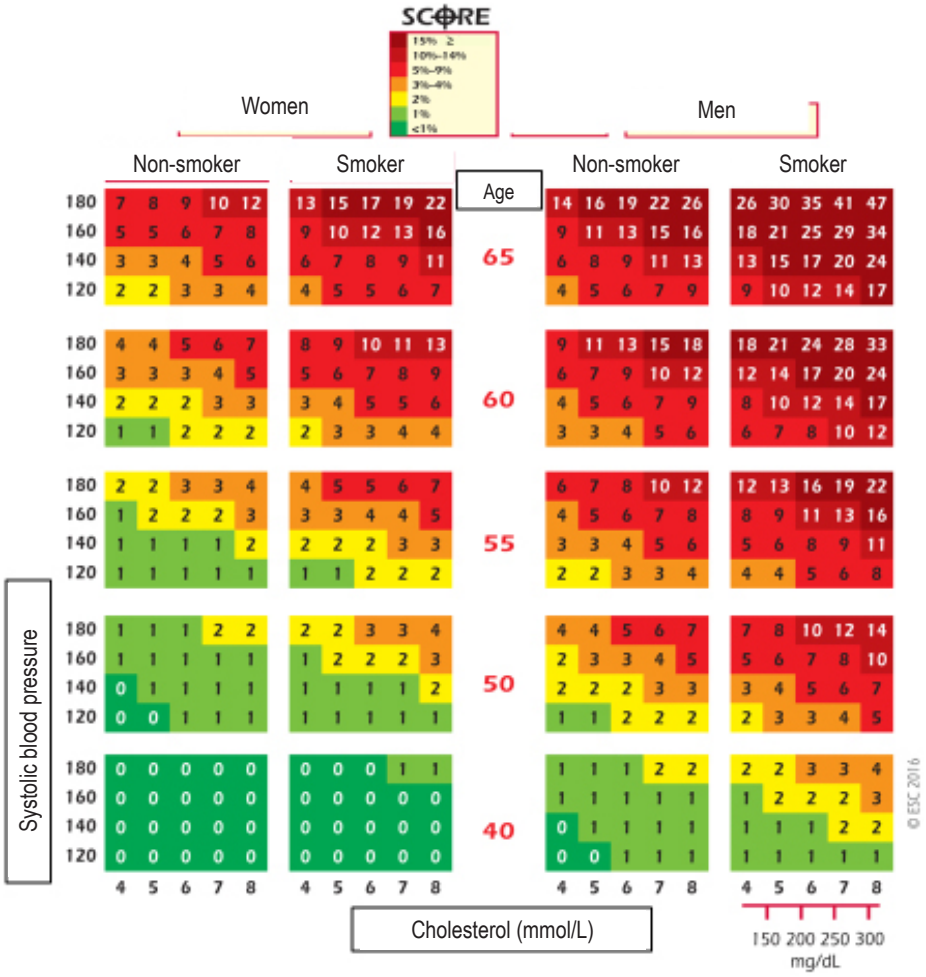

Figure 11 – *Calculation of 10-year risk of fatal cardiovascular event, in populations of countries with high cardiovascular risk, considering the risk factors of age, sex, smoking, total cholesterol, and systolic blood pressure. Cart from the SCORE (Systematic Coronary Risk Evaluation) Study. The color scale varying from red to green corresponds to percent risk over 10 years, described in the upper part of the Table. Adapted from Piepoli MF et al.*[120]

Table 23 – New markers for cardiovascular risk stratification

• High-sensitivity CRP
• Apolipoprotein B
• Glomerular filtration rate
• Microalbuminuria
• Ankle-brachial index
• Family history
• Functional capacity
• Mean carotid intima thickness
• Coronary calcium score

CRP: C-reactive protein.

integration of all available pretest clinical data and data obtained during the performance of the stress or associated stimulus test within the denominated incremental prognostic value. In this sense, Bayes' theory of conditional probability or the application of Bayesian principles assists in decision making by establishing that the risk of an event occurring after a test is influenced by the sensitivity and specificity of an applied method, as well as the pretest prevalence of the disease, all of which are incorporated into the estimation of post-test probability for characterization of myocardial ischemia and, consequently, CAD (Figure 12).[129,130]

In this way, the diagnostic ability of a test is related to the population type selected, and it is may create tendencies or biases. For example, the selective referral of patients with

$$Post.Test.Prob. = \frac{Sensitivity \times Pre.Test.Prob}{Sensitivity \times Pre\text{-}Test.Prob + (1 - Specificity) \times (1 - Pre\text{-}Test\ Prob)}$$

Figure 12 – *Formula for calculating post-test probability of a disease according to Bayes' theorem.*

"positive," "altered," or "ischemic" results for coronary cineangiography studies, in conjunction with few referrals of individuals with negative results, increases the chance of false-positive results with respect to true-negative results. This would be an equivocal methodology for evaluating the accuracy of a test, artificially decreasing the method's specificity or its ability to select healthy individuals within a population.[131,132] On the other hand, sensitivity will expressively increase in patients referred with a high prevalence of symptoms.

Many possibilities may be present for medical management within different prevalences of clinically estimated CAD, emphasizing that the diagnostic power of conventional exercise testing or tests associated with MPS is at a maximum when the pretest probability of CAD is intermediate. However, for a given pretest probability, the post-test probability increases progressively with the severity of the alterations found, such as the amount of myocardium at risk or the sum of extent and intensity (ischemic burden) of perfusion modifications in the perfusion images with radiopharmaceuticals. In the extreme case of a study with severe abnormalities, post-test probability will be elevated regardless of pretest probability (Figure 13).[130]

Furthermore, not only Bayesian analysis, but also statistical techniques that use multivariate analysis to estimate post-test risk may also provide important diagnostic information, with the following advantages: they do not require the tests to be independent of each another or the diagnostic indexes (sensitivity and specificity) to remain constant in populations with different disease prevalences. Thus, in the condition of continuous-scale diagnostic tests, changes in percentages of sensitivity and specificity should be taken into consideration when cutoff values for classifying individuals with and without a disease vary. Some results may even be expressed as the sum of sensitivity and specificity for an "optimal" cutoff value. However, owing to the fact that an optimal cutoff value is not relevant to a specific application, it is recommendable to plot these indexes under a range or scale of values of interest, generally distributed under a receiver operating characteristics (ROC) curve, expressed in a 2-axis graph, where the y axis represents sensitivity and the x axis = 1 − specificity, for variable cutoff values (Figure 14).[133]

6.2. Value of the Diagnosis-Prognosis Binomial to Integrated Assessment of Perfusion Images

The presence of transient or reversible defects in radiopharmaceutical uptake reflect ischemia, which is in itself associated with greater incidence of future events, when comparing normal images or images with persistent perfusion defects. Thus, in patients with suspected or proven chronic coronary disease, estimation of the quantity of myocardium at risk as assessed by semi-quantitative and quantitative analyses, extent, intensity, and degree of reversibility of existing defects, as well as measures of LVEF following physical or pharmacological stress, have prognostic value, indicating risk of events during clinical follow up.[134-138] Other scintigraphy markers of severity may stand out, such as apparent transient dilation of the LV, induced or accentuated by exercise or pharmacological tests,[139,140] which may translate to extensive subendocardial ischemia, in addition to high pulmonary uptake, translating to LV dysfunction. Furthermore, increased uptake in the walls of the right ventricle (RV) in multi-arterial patients whose lesions are predominantly in the left coronary territory, may suggest an imbalance in perfusion between ventricles.[141,142]

Considering the scope and accumulated experience of MPS with radioisotopes in diverse clinical scenarios relating to CAD, guidelines and consensuses have suggested the main applications based on levels of evidence in the literature, and created scores that numerically classify indications as inappropriate; possible, but questionable; and appropriate[143,144] (additional details described in the *Indications* section).

6.3. Radiopharmaceuticals for Performance of Myocardial Perfusion Scintigraphy and Image Generation and Perfusion Defects

Nuclear cardiology is connected to the assessment of cardiovascular physiology, currently encompassing metabolism, innervation, myocardial perfusion, ventricular function, and synchronism. It has a capability for early detection of cardiovascular physiopathological alterations, allowing for interventions which may interrupt or revert the disease condition before structural alterations are established in a definitive, evolutive, and irreversible manner. To represent cardiac physiology, images are formed using the principle of radiotracers or tracers,[29] in which the exchange of stable atoms with their isotopes does not alter the biological properties of the organism where the images are being obtained.

Radioactive labeling is performed with minimal quantities of chemical substances, resulting in a radiopharmaceutical that may be used to truly represent physiological or biochemical state of unlabeled molecules . In this manner, alterations to the physiology being evaluated and toxicity effects do not occur. These characteristics are different from other imaging methods which use elevated concentrations of chemical substances to create sufficient contrast and, consequently, obtain images of the functional situation and anatomical aspects of the organ under study.[145] The images in this specialty are digital; they

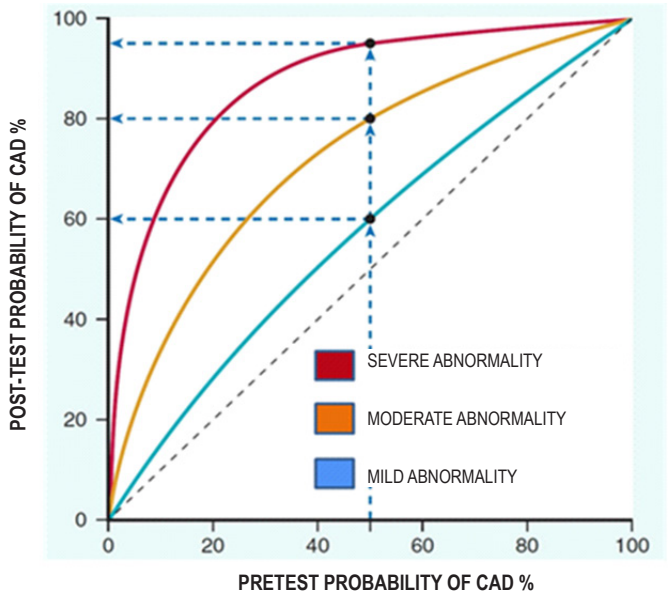

Figure 13 – *Importance of amount of myocardium at risk (extension and intensity of ischemia) on myocardial perfusion imaging with radiopharmaceuticals (^{99m}Tc-sestamibi or thallium-201) to post-test probability of coronary artery disease (CAD). For a given pretest probability (50% indicated in the graph), the post-test probabilities will be significantly higher according to imaging findings. With the condition of high-risk ischemia or > 20% extent of ischemic myocardium, the clinical implications for decision making become practically independent of pre-test probability of CAD. Source: Adapted from Udelson JE et al.*[130]

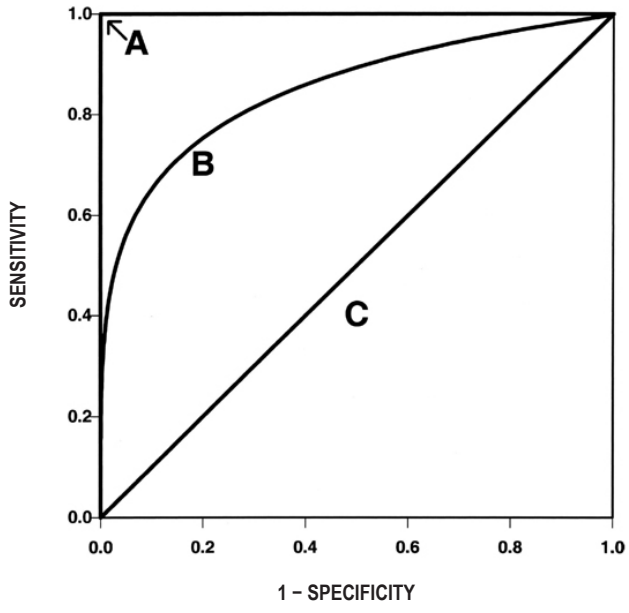

Figure 14 – *Hypothetical examples of ROC curves, with: the area under the curve representing maximum or perfect diagnostic accuracy of the standard utilized (curve A; AUC = 1); "real" area under the curve representing good efficiency of the method used, often found in clinical practice (curve B; AUC = 0.85); the 45-degree diagonal line corresponding to random chance (curve C; AUC = 0.50), with the area under the ROC demonstrating the averages of diagnostic accuracy across a spectrum of cutoff values. On rare occasions, the estimated AUC is less than 0.5, indicating that the test being evaluated performs worse than random chance. Adapted from Zou KH et al.*[133]

either use "pixels" as units of measurement for resolution or are transformed into a digital matrix, emphasizing that "pixel" values of images of the ventricular myocardium are directly proportional to physiological cardiovascular properties. Physical phenomena such as the "Compton scattering effect," the "photoelectric effect," and geometric distortions should, however, be considered,[146] given that they tend to interfere with direct proportionality, in a manner that is decreasing as equipment and image reconstruction techniques technologically evolve. Furthermore, another factor related to acceptance and preference of nuclear cardiology for detecting myocardial perfusion defects is the elevated, superior resolution contrast (allowing for differentiation between normal and decreased perfusion) in comparison with other imaging methods,[147,148] even considering lower spatial resolution. There is also a peculiar aspect, namely, that the myocardium (organ of interest) appears emphasized due to the greater brightness in comparison with underlying structures (background) and, consequently, provides excellent signaling, which facilitates the development of integrated, computerized algorithms for SPECT and PET techniques. These programs, which automatically process and objectively quantify images, have good comprehension, and they are well validated and internationally utilized.[149-151] From the conceptual point of view, it is necessary to grasp that scintigraphy image generation is based on relative uptake of the radiopharmaceutical in the myocardium of the LV, when it is injected intravenously during physical exercise or pharmacological tests. The comparison of radiopharmaceutical uptake between ventricular walls is expressed in images based on a color scale, created by specific computer programs which, in addition to allowing for subjective analysis of perfusion, make it possible to conduct semi-quantitative and quantitative evaluation of affected myocardial area. During visual evaluation of scintigraphy images, the following are taken into consideration: homogenous distribution patterns or normal radiopharmaceutical uptake in the myocardium, transient low uptake suggestive of ischemia, fixed low uptake suggestive of fibrosis, and partially reversible low uptake suggestive of ischemia associated with fibrosis[24,152] (Examples are provided in the *Methodology* and *Tutorial Cases* sections).

7. Evaluation of Patients with Potential Acute Coronary Syndrome – Algorithms in the Chest Pain Unit

7.1. Introduction

Continuous chest pain is one of the most common symptoms in emergency units, accounting for approximately 8 million annual visits in the USA.[153] Although approximately 50% of patients are admitted for diagnostic definition, only 30% of visits will correspond to the condition of acute coronary syndrome (ACS), 2% to 4% of whom will be inappropriately discharged from the hospital (Figure 15), leading to serious risks of severe events, in addition to legal-medical problems. Considering these implications, as well as hesitation to discharge patients with acute myocardial infarction (AMI), assessment of patients with atypical chest pain in emergency unit has emphasized admission for posterior clarification and risk stratification. With the development of more sensitive cardiac biomarkers in conjunction with more precise non-invasive exams and validated clinical parameters, early

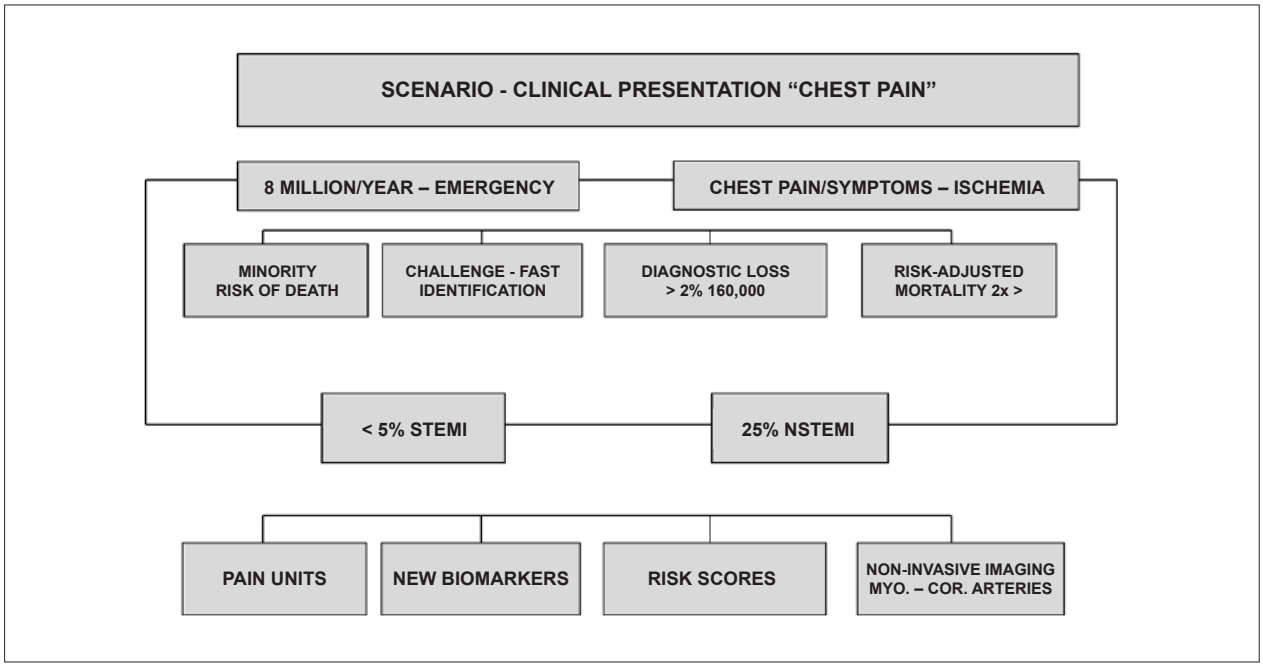

Figure 15 – *Chest pain spectrum in emergency units, with clinical implications, forms of presentation of acute coronary syndrome and available methods for investigation and risk stratification. Cor: coronary; Myo: myocardium. NSTEMI: non-ST-segment-elevation myocardial infarction; STEMI: ST-segment-elevation myocardial infarction. Source: Adapted from Amsterdam EA.*[154]

identification of low-risk patients has been carried out more rapidly. In this process of diagnostic and prognostic assessment, the following play an important role: resting ECG, cardiac enzymes, and non-invasive exams such as ET, MPS, Doppler echocardiogram, and coronary angio-CT, in addition to cardiac resonance in specific cases. The choice of recommended imaging method should be based on the procedures available, local institutional experience, and present clinical situation. The exam with the highest diagnostic accuracy and negative predictive value (NPV) will offer more precise risk stratification, which is fundamental to decision making regarding need for hospital admission or safe discharge from the emergency unit.

In addition to the 2 physiopathological conditions described (Non-ST segment Elevation Myocardial Infarction – NSTEMI and ST segment elevation myocardial infarction – STEMI), unstable angina also stands out, which does not feature myocardial necrosis as an initial consequence.[155,156] Nevertheless, unstable plaque and evolutive phenomena of erosion and rupture may progress to infarction and related complications, such as severe arrhythmias, ventricular dysfunction, and death. Conditions of vasospasm, in epicardial coronary arteries or with microvascular disease, have additionally been implicated in ACS without thrombosis and myocardial infarction, in the absence of obstructive lesions.[157-159] It is, finally, important to emphasize that, in patients with documented ACS and intermediate- to high-risk patients, invasive coronary cineangiography and percutaneous revascularization represent the most frequent forms of initial assessment, and non-invasive imaging methods are reserved for clinically stable situations and low- to intermediate-risk patients, with the aim of reclassifying risk, diagnosis, and stratification in the post-event phase.[160,161]

7.2. Goals for Evaluating Acute Chest Pain and Participation of Non-invasive Methods in Assessing ACS[154,162,163]

- Precise diagnosis for appropriate conduct in UA or AMI, whether with clinical treatment or invasive strategy via catheterization and angioplasty.
- Early, safe discharge from the hospital if clinical data and exams show no abnormalities. Probability of severe cardiac events < 1% over 30 days of evolution following discharge from the emergency unit or hospital.

Following serial evaluation of ECG, without modifications, in addition to normal cardiac enzymes and clinical situation characterized as low- to intermediate-risk, non-invasive functional exams may play an important role in risk stratification of patients with acute chest pain. The choice of MPS, cardiac resonance, or angio-CT will depend on the objective and the clinical question to be answered.

Exercise testing: constitutes an important strategy for assessing patients with suspected ACS following stabilization, and it aids prognosis and medical management . Patients with chest pain in the emergency room, once they have been identified as low-risk, may undergo ET, a normal result of which confers low annual risk of cardiovascular events, allowing for earlier and safer discharge from the hospital.[164] Brazilian and international guidelines recommend ET as a first-choice exam for risk stratification in patients who are able to exercise, as the procedure is low-cost and widely available, and it has a low rate of complications, similar to that of tests conducted in normal conditions.[165] A treadmill or a cycle ergometer may be used, following appropriate protocols for the patient's clinical conditions, such as the ramp protocol or the modified Naughton or Bruce protocol. Logistics related to performing ET in the emergency unit may, however, be compromised as a result of unavailable operational personnel or infrastructure during certain periods (e.g. weekends or night shifts).

Summary of indications for ET in ACS (characterize low-risk after initial clinical stratification)

- Baseline ECG and biomarkers (necrosis) without alterations.
- Absence of symptoms (precordial pain or dyspnea).
- Hemodynamic stability and adequate conditions for physical effort.

If ET results are normal and the patient has shown good functional capacity, other procedures may be unnecessary, in virtue of the test's high NPV.[165]

Summary of Recommendations and Evidence

Class of recommendation I. Level of evidence: B

- Low-risk (clinical and ECG) patients with normal biomarkers should be referred for exercise test after 9 to 12 hours. Within the routines of chest pain units, these exams may be used as discharge criteria.

If it is not possible to perform ET or if ECG is uninterpretable, the patient may undergo provocative tests for ischemia associated with non-invasive imaging.

Doppler echocardiogram (ECHO): This is fundamental for evaluating patients with acute chest pain[166-168] and evolving ACS, initially considering LVEF, segmentary contractile alterations, and the presence of thrombi, in addition to mechanical complications (rupture of interventricular septum or papillary muscles) that result in severe events, such as cardiorespiratory arrest. Moreover, this method may also evaluate chest pain with non-coronary etiology, such as pericardial disease, hypertrophic cardiomyopathy, aortic dissection in the presence of renal insufficiency that makes it impossible to perform angio-CT, and others. In addition to assessing the presence and extent of ventricular dysfunction, it is able to quantify severity of valvular abnormalities that may be present and associated with ischemic etiology.

Summary of Recommendations and Evidence

Recommendation class I

- Transthoracic ECHO is indicated when there is clinical suspicion of aortic and pericardial diseases, pulmonary embolism, and valvulopathies (*level of evidence: C*).
- In cases with complications resulting from unstable ACS, such as interventricular communication and mitral insufficiency (*level of evidence: C*).
- Stress echocardiography is considered an alternative to exercise testing in patients who cannot exercise (*level of evidence: B*).

Recommendation class IIa

- Patients suffering from chest pain – resting ECG to determine whether or not pain is of ischemic origin (*level of evidence: B*).
- Patients with uncomplicated anterior wall AMI, with the objective of determining the exact size of the ischemic lesion (*level of evidence: B*).

In stable patients with evolving ACS, echocardiography associated with pharmacological stress before hospital discharge may identify induced ischemia and assist in risk stratification and medical management of immediate follow-up (6 to 12 weeks), especially if LVEF values are below 40%.

Coronary angiotomography: Many studies have shown that coronary angio-CT is an important tool for evaluating acute chest pain, especially in low- to intermediate-risk patients.[169-172] It is a safe procedure for diagnosing ACS, and it is able to reduce intra-hospital follow-up time and contribute to cost reduction. In the Rule Out Myocardial Infarction by Cardiac Computed Tomography II (ROMICAT II) Study, duration of hospital stay was significantly lower in patients stratified via angio-CT in comparison with the group submitted to conventional evaluation (23.2 ± 37 hours *vs*. 30.8 ± 28 hours).[173] There was also a significant increase in percentage of patients discharged from the emergency unit in the group stratified with this method (46.7% *vs*. 12.4% $p < 0.001$), in spite of higher costs associated with angio-CT and the greater tendency to refer patients for catheterization and revascularizations.

Based on recent publications, low- to intermediate-risk patients with acute chest pain, non-diagnostic ECG, and negative markers of necrosis have Class-I recommendation and level of evidence A for undergoing angio-CT, especially considering the method's NPV. There are, nevertheless, limitations in the presence of STEMI and NSTEMI (Figure 16) (with the exception of coronary dissection) and known CAD or prior revascularization where the existence of intracoronary prostheses (stents) and calcium may negatively influence the exam's specificity for its proposed aim, leaving the possibilities of functional evaluation and global repercussion. Finally, it is necessary to consider exposure to elevated doses of radiation and lower image quality for the exclusion of pulmonary embolism, aortic dissection, or ACS (triple rule-out).[174]

Myocardial perfusion scintigraphy (MPS): Within the scope of its applications (*See the Indications chapter*), the following stand out: indirect evaluation of coronary reserve

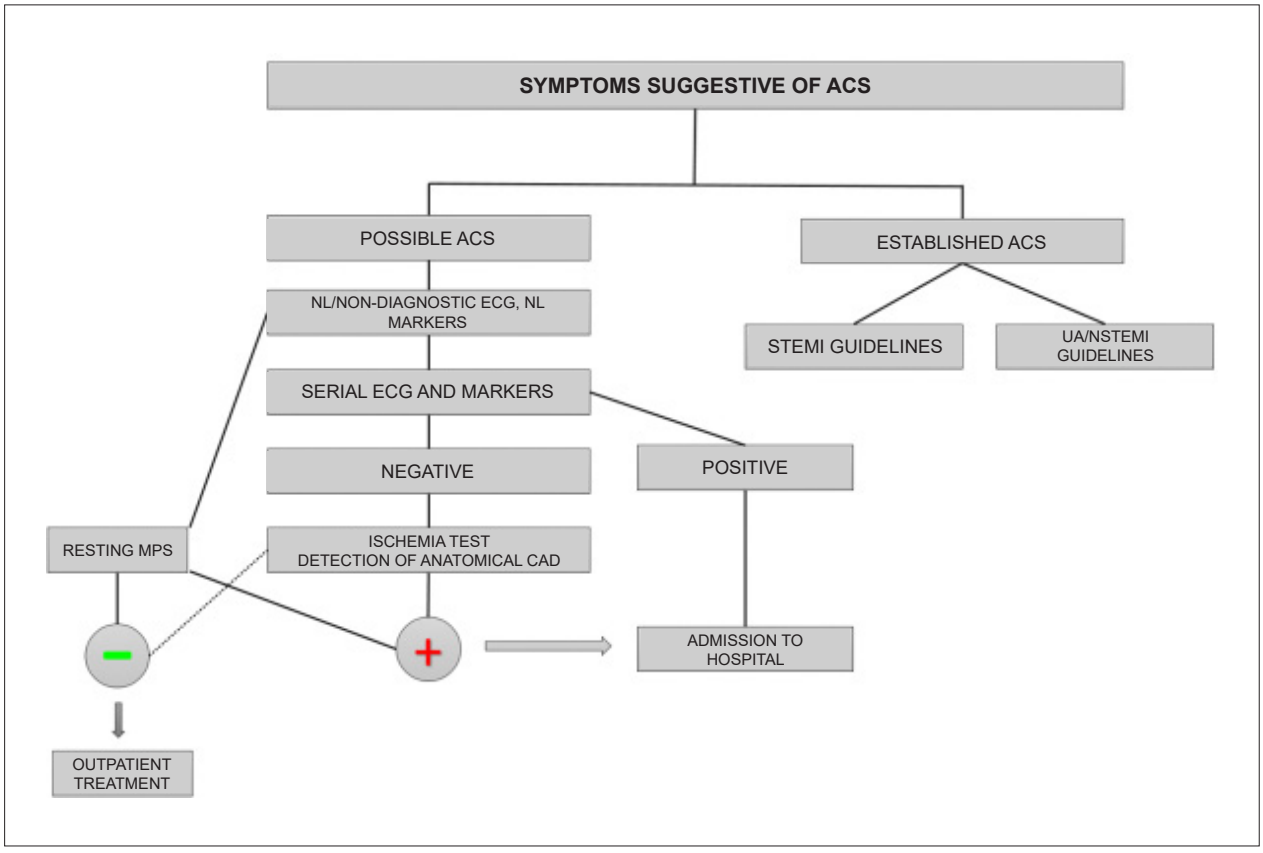

Figure 16 – *Clinical scenarios of patients who present with chest pain at emergency units. Situations of ACS diagnosed as STEMI and UA/NSTEMI correspond to orientations established by pertinent guidelines. In the condition of possible or suspected ACS, the previously described sequences of diagnostic investigation and stratification are recommended. ACS: acute coronary syndrome; CAD: coronary artery disease; MPS: myocardial perfusion scintigraphy; NL: normal; NSTEMI: non-ST-segment elevation acute myocardial infarction; STEMI: ST-segment elevation acute myocardial infarction; UA: unstable angina.*

and consequent estimation of functional significance of coronary stenoses, evaluation of the efficacy of therapeutic interventions, and stratification of ACS risk. One of the principal indications for MPS during the first 12 hours of symptom onset is to decide whether or not to hospitalize a patient with chest pain and suspected CAD, when ECG was normal or had non-specific alterations. Resting MPS, when it is performed in an early phase of attendance and considered low-risk, determines a low index of future cardiac events. Recent studies have demonstrated that, when ACS is suspected, the use of resting perfusion images with radiopharmaceuticals[175,176] is also associated with shorter hospital stays and lower costs, and it is additionally able to reduce unnecessary hospitalizations.[177,178] Furthermore, numerous observational studies have demonstrated a high NPV for normal resting perfusion images, with the objective of ruling out AMI or short-term cardiac events.[179] In a study by Schaeffer et al.,[180] 479 patients underwent resting MPS and were followed for 16 months. Of these patients, 434 had "normal" resting MPS, and 45 had "abnormal" resting MPS. In the normal group, only 3 patients (0.7%) had severe cardiac events, showing a NPV of 99.3%.[180] Equally, multiple evaluations have demonstrated the efficacy and safety of MPS with SPECT for assessing patients with chest pain in the emergency unit.[181-183] Population samples involved, however, were more heterogeneous and had higher numbers of risk factors for CAD. MPS effectively foresaw which patients would require coronary angiography. Nabi et al. related that 38.3% of patients with abnormal MPS underwent revascularization, while 0.9% of patients with normal MPS subsequently underwent coronary intervention. Of patients with myocardial area at risk (ischemia) involving > 10% extent in perfusion images, 55% underwent revascularization.[182,183]

The study known as the PREMIER trial by N Better et al.[184] evaluated the performance of resting MPS in investigating chest pain in the emergency room with 356 low- to intermediate-risk patients, from 8 developing countries, including 2 Brazilian centers. The primary outcome considered included the compound events of death, non-fatal AMI, recurring angina, and coronary revascularization over 30 days, and the results reaffirmed the association between normal images and a good NPV (99.3%) for severe events (death or AMI).[184] Moreover, it is worth highlighting that the presence of resting perfusion alterations (abnormal scintigraphy) was the only variable independently associated with the primary outcome (adjusted OR = 8.19, 95% CI: 4.10–16.40, p = 0.0001), with even higher expression when only patients who received injections during episodes of pain were considered (adjusted OR = 17.35). On the other hand, results considered high-risk indicated worse prognoses for future cardiac events (death, AMI, myocardial revascularization surgery, or percutaneous intervention).[185,186]

The Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE) Study, which evaluated patients with ACS and normal or non-diagnostic ECG who were still in the emergency room, observed admission rates of 54% in patients who underwent MPS and 63% in other patients, suggesting that the initial strategy of resting scintigraphy is satisfactory, based on the fact that it demonstrates good risk stratification capability.[184,186]

International guidelines recommend the use of resting myocardial perfusion images for acute chest pain as a class I recommendation with level of evidence A for risk stratification of patients with suspected ACS and non-diagnostic ECG.[187,188]

Time of radiopharmaceutical injection: The main applications of MPS within the first hours of a patient's arrival at the hospital are:

- *Radiopharmaceutical injection* (technetium-99m-labeled sestamibi / MIBI or tetrofosmin, also known as ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin), *while resting, during an episode of chest pain, with normal or non-specific ECG*, with the objective of rapid diagnostic definition.
- *Radiopharmaceutical injection while resting, in the absence of chest pain, with normal or non-specific ECG*, when the symptom has ceased less than 6 hours prior, but preferably within the 2 preceding hours. Wackers et al.[179] have demonstrated that, in cases where injections are administered up to 6 hours after pain, in ACS, there is an 84% incidence of perfusion abnormalities; this decreases to 19% when intravenous radiopharmaceutical administration occurred between 12 and 18 hours after the last episode of pain. Kontos et al.[176] found no reduction in sensitivity for identifying patients who evolved to AMI or revascularization when the injection was administered during the moment of pain or up to 6 hours after the cessation of the symptom.

Taken as a whole, perfusion imaging with radiopharmaceuticals for evaluation of acute chest pain does not present any formal contraindications; it is well tolerated by most patients, and the quantitative assessment of information about ischemia is of special importance to the clinical decision-making process.

PET: In a retrospective study conducted with more than 7,000 patients who presented at the emergency unit with chest pain,[189] 92.5% of patients with positive stress or resting PET were diagnosed with ACS, by cardiac catheterization, electrocardiographic alterations, or positive cardiac biomarkers. In patients with reversible perfusion defects while resting or under stress (positive PET) who underwent cardiac catheterization, 87% were considered to have significant CAD. For patients without reversible perfusion abnormalities whose exams were classified as negative, no deaths were informed during the 30-day follow-up period. PET has a significantly better spatial resolution and higher sensitivity when compared to MPS. In Brazil, the elevated costs and low availability of this technology for patients with ACS are, however, limiting factors to its routine use.

UA and NSTEMI: Patients whose clinical conditions indicate a high risk of AMI or UA should undergo hemodynamic study. For those with low to intermediate risks whose unstable angina (UA) has been clinically stabilized, MPS has shown an important value for risk stratification.[190] Additionally, it assists in diagnosis and medical management. It is recommended within the first hours of the patient's arrival at the hospital. Cases with a history of chest pain, whose biochemical markers, nevertheless, show no alterations, with normal or non-diagnostic ECG are considered candidates. When

patients are symptomatic or immediately following cessation of symptoms, intravenous administration of Sestamibi-^{99m}Tc or Tetrofosmin-^{99m}Tc occurs, preferably while resting, followed by image acquisition directly after or up to 6 hours following radiopharmaceutical injection. To perform MPS associated with physical stress or vasodilator drugs in appropriate patients (those with low to intermediate risks), symptoms should be under control or angina should be stabilized for at least 48/72 hours.[191] Patients without ischemia or infarction and preserved LV function have good prognosis and they may be managed conservatively, while patients with significant ischemia induced during associated tests should be referred for invasive exams.

The simultaneous information provided by myocardial perfusion and ventricular function via scintigraphy synchronized with ECG (Gated-SPECT) is of fundamental importance, given that both the absolute LVEF value and the extent and intensity of perfusion defects have prognostic value for the occurrence of future cardiac events.

Finally, with the advent of chest pain units and emergency units for the evaluation of patients with suspected ACS and with new tools which have become available, such as clinical risk scores, biomarkers, or multimodalities (non-invasive exams), algorithms have been proposed to support investigation and treatment of different clinical presentation scenarios (Figure 16). Their implementation aims to improve cost-effectiveness and to lower morbidity and mortality in the management of this subpopulation, within the spectrum of ischemic heart disease.

Recommendations and Evidence

Class I

Stress and resting MPS as an alternative to cases with limitations to ET (level of evidence: C).

Class II

Patients suffering from chest pain may be evaluated via resting MPS to determine whether the pain is of ischemic origin or not (level of evidence: A).

STEMI: Coronary cineangiography is a priority indication for initially attending patients with ACS and ST-segment elevation, seeing that coronary reperfusion is the primary objective. However, in cases in which clinical condition, ECG, and biochemical markers are inconclusive, MPS may aggregate incremental diagnostic and prognostic value. These situations are generally characterized by atypical clinical conditions in patients with non-specific electrocardiographic alterations in the ST segment, left bundle branch block, and, mainly, in those who are attended before or after the onset of the condition, while they are already outside of the ideal period for dosage of biochemical markers.

Recommendations and evidence for stress and resting MPS following STEMI

Class I

- Before being discharged from the hospital, in stable patients who have not undergone coronary cineangiography for risk assessment and therapeutic decision making (level of evidence *B*).
- Complementary evaluation following coronary cineangiography, in cases where there are doubts, with the aim of defining and quantifying ischemia for eventual myocardial revascularization (level of evidence B).

8. Positron Emission Tomography in Cardiology

8.1. Introduction

Myocardial perfusion defects evaluated with the use of radiopharmaceuticals and induced by stress are well established as a technique with diagnostic and prognostic capability for the identification of flow-limiting coronary diseases. In MPS, interpretation has mainly been qualitative, semiquantitative, and quantitative, assessing regional perfusion in relative terms.[95,102,121,192-196]

8.2. Basic Principles of Positron Emission and Main Indications

PET consists of a specific method in nuclear medicine. It is different from the widely used gamma camera or Anger camera employed in MPS for the technique commonly known as SPECT. PET, differently from SPECT, uses emitters of positrons, particles similar to electrons (except for the fact that they have a positive electric charge), with very short half-lives. The principle of PET consists of the detection of 2 photons (gamma rays) that are emitted in diametrically opposite directions to occasion annihilation of the positron upon encountering an electron in the periphery of the atom. This detection occurs through a series of crystals arranged throughout the 360 degrees of a ring-shaped detector surrounding the patient. The detection of the 2 photons emitted in diametrically opposite directions, at exactly 180 degrees, with an existing coincidence circuit in the PET equipment, making it different from SPECT, which uses single photons.[197]

Since PET cameras have incorporated electronic collimation, mechanical collimators made of lead have not been made necessary, allowing for greater sensitivity than in SPECT systems. The sensitivity of current 3D PET systems is 5 times greater than of the older 2D PET ones. On the other hand, there is more attenuation in PET studies than in SPECT, making attenuation correction necessary to the reconstruction of PET images. The most current systems, which have a resource known as time of flight (TOF), are based on the speed of light to localize the annihilation event in a much smaller directional ray than in conventional PET cameras, resulting in increased spatial resolution.

This method has already been established as the standard for assessing myocardial viability (*See the Myocardial Viability section*), with the use of a glucose analogue labeled with fluorine-18 (^{18}F-FDG), a technique which, although it is not widely used in Brazilian clinical practice, is widely viable in most nuclear medicine centers where PET is available in Brazil. Its use for the assessment of myocardial perfusion is not necessarily a new technique, as it dates back to more than 30 years ago and has since been evolving.[198-200] Nonetheless, its clinical use has remained restricted for many years owing

to its methodological complexity, high operational costs, and low availability of devices and tracers. Recent technological advances have reduced the costs, and its increasingly frequent use in oncology has resulted in increased equipment availability. Nowadays, non-invasive estimation of absolute coronary flow and flow reserve with this technique has become possible and has been validated.[197] The scenario is contrary in Brazil, however. In spite of a small amount of experience using research protocols, this method is not available in clinical practice. Even though PET cameras are distributed throughout the country, there is a lack of other radiotracers for the modality as well as a lack of economic viability.

8.3. Radioactive Tracers for Use in Positron Emission Tomography

Different available radiotracers make it possible to identify vasoactive, metabolic, or neurological processes that are present in diverse cardiomyopathies and atherosclerosis, on the molecular level. The images acquired allow for evaluation of the cardiovascular system on different levels, including: perfusion,[201-203] metabolism,[204-207] sympathetic innervation,[208,209] and inflammation;[210-212] depending on the tracer utilized. Myocardial perfusion studies using PET may be performed using different tracers, each of which possesses specific characteristics, advantages, and disadvantages (Table 24).

Rubidium-82 (^{82}Rb) and ammonia labeled with nitrogen-13 ($^{13}NH_3$) have been approved for clinical use by the Food and Drug Administration (FDA), and they are the most commonly used in the USA. On the other hand, water labeled with oxygen-15 (^{15}O-H_2O) has been used mainly for research in the USA, as it diffuses freely between blood and the myocardium, which makes it ideal for quantitative flow measures. In South America and Brazil, associated costs, especially with tracers, have limited their use. Initial experience with myocardial perfusion using PET and ^{82}Rb have been conducted at the Heart Institute of São Paulo (InCor, acronym in Portuguese).[213] As ^{82}Rb is the only one of these tracers produced in a generator system, from strontium-82, it has an advantage in relation to the others whose production depends on a cyclotron. These generators may be transported, and, specifically in case of Brazil, they may be imported especially for this purpose. Their short physical half-life of 76 seconds constitutes another favorable aspect, given that it implies very low dosimetry for the patient, with estimated exposure lower than 2 milliSieverts (mSv), in a stress and resting protocol, including tomography for attenuation correction. On the other hand, stress with exercise becomes unviable, considering the elevated costs, making it possible only in high-volume centers that perform around 40 exams weekly.[214] Payment tables for medical procedures in Brazil, to date, restrict the payment of PET for oncological indications, which complicates its use for cardiology. The use of $^{13}NH_3$ requires a cyclotron, the installation of which has extremely high costs, but it provides high contrast images, due to its high first-pass extraction fraction. It offers good accuracy for absolute measure of myocardial blood flow (MBF), and its relatively long half-life of approximately 10 minutes, makes physical exercise viable.[215]

^{18}F-flurpiridaz is a new tracer. Although its production requires a cyclotron, its labeling with fluoride-18 makes it possible to utilize the production and distribution systems that are already widely available for oncological use of PET. Due to its relatively long half-life of 110 minutes, it is appropriate for associated use with an exercise testing, and its high first-pass extraction fraction also makes it ideal for flow quantification. Its use is currently being evaluated in a phase-III study.[216-220]

8.4. Use of PET for Assessment of Myocardial Ischemia

PET has advantages over conventional SPECT, including higher spatial resolution and contrast rate, higher sensitivity than the tracers classically used in MPS (thallium-201 and technetium-99m-labeled radiopharmaceuticals), and higher specificity, considering the attenuation correction system based on coupled CT, which results in better capability to differentiate true perfusion defects from attenuation artifacts.[201,221-223] These advantages are notably applied to some special populations, such as obese patients and women with voluminous breasts, in whom gamma ray attenuation in soft tissue may be a factor of greater importance to the final quality of cardiac images.

Table 24 – Main characteristics of perfusion myocardial radiotracers labeled with positron emitters

	Rubidium-82 (^{82}Rb)	Ammonia labeled with Nitrogen-13 ($^{13}NH_3$)	Water labeled with Oxygen-15 (^{15}O-H_2O)	^{18}F-Flurpiridaz
Physical half-life	1.27 min	9.97 min	2.04 min	110 min
Extraction fraction (flow)	40% to 70%	94% to 98%	95% to 100%	> 90%
Means of production	82-strontium/rubidium (^{82}Sr/Rb) generator	Cyclotron	Cyclotron	Cyclotron
Advantages	• Commercially available in the form of a generator • Capable of evaluating flow quantitatively • Short half-life for quick tests • Low radiation	• High contrast resolution • Capable of evaluating flow quantitatively • Potential for use with exercise	• Ideal for quantification of flow • Short half-life for quick tests • Low radiation	• High contrast resolution • Capable of evaluating flow quantitatively • Potential for use with exercise • May be distributed by central production
Disadvantages	• Short half-life does not allow for exercise • Lower resolution	• Requires a local cyclotron • Heterogeneity of distribution	• Requires a local cyclotron • Short half-life does not allow for exercise	• Not commercially available

The objective of evaluating myocardial perfusion via PET is to detect physiologically significant coronary stenoses, aiding clinical management of patients with known or suspected CAD and patients who, although they have no known diseases, possess risk factors, in order to evaluate atherosclerosis progression. Other objectives include determining the cause of ischemic symptoms to recommend clinical treatment or revascularization, estimating potential for future adverse events, and improving patient survival. One of its strengths is that it is the non-invasive modality of choice for accurately quantifying MBF. It allows for quantification in absolute terms of ml.min per gram of myocardium in stress and resting phases. The ratio between the 2 flows is known as the myocardial flow reserve (MFR), a valuable parameter that makes it possible to overcome one of the currently existing limitations to conventional perfusion imaging with SPECT when evaluating patients with multivessel CAD.

Results of invasive studies (FAME-1 and FAME-2) that analyzed FFR demonstrated its value in evaluating functional significance of single-vessel stenoses.[224,225] Some studies have provided evidence of a correlation between regional MFR and FFR measured invasively without comparing them directly, however.[113,226]

Quantitative PET measures of MBF in absolute terms represent a paradigm change in the evaluation and management of patients with CAD, with a disassociation from the anatomical gold standard of coronary cineangiography, which had previously been established for decades, and a return to functional assessment. These measures additionally make it possible to expand the use of perfusion imaging within the current scenario, with the aim of detecting flow-limiting epicardial lesions, for earlier stages of atherosclerosis, microvascular dysfunction (Figure 17), and evaluation of balanced flow reductions in triple-vessel disease. They also offer an opportunity to monitor responses to changes in lifestyle or risk factors and therapeutic interventions.[227,228]

Two recent meta-analyses evaluating methodology have indicated that PET has superior accuracy in comparison with SPECT. The first meta-analysis compared PET with SPECT synchronized with ECG and associated with attenuation correction. In analysis with a ROC curve, the area under the

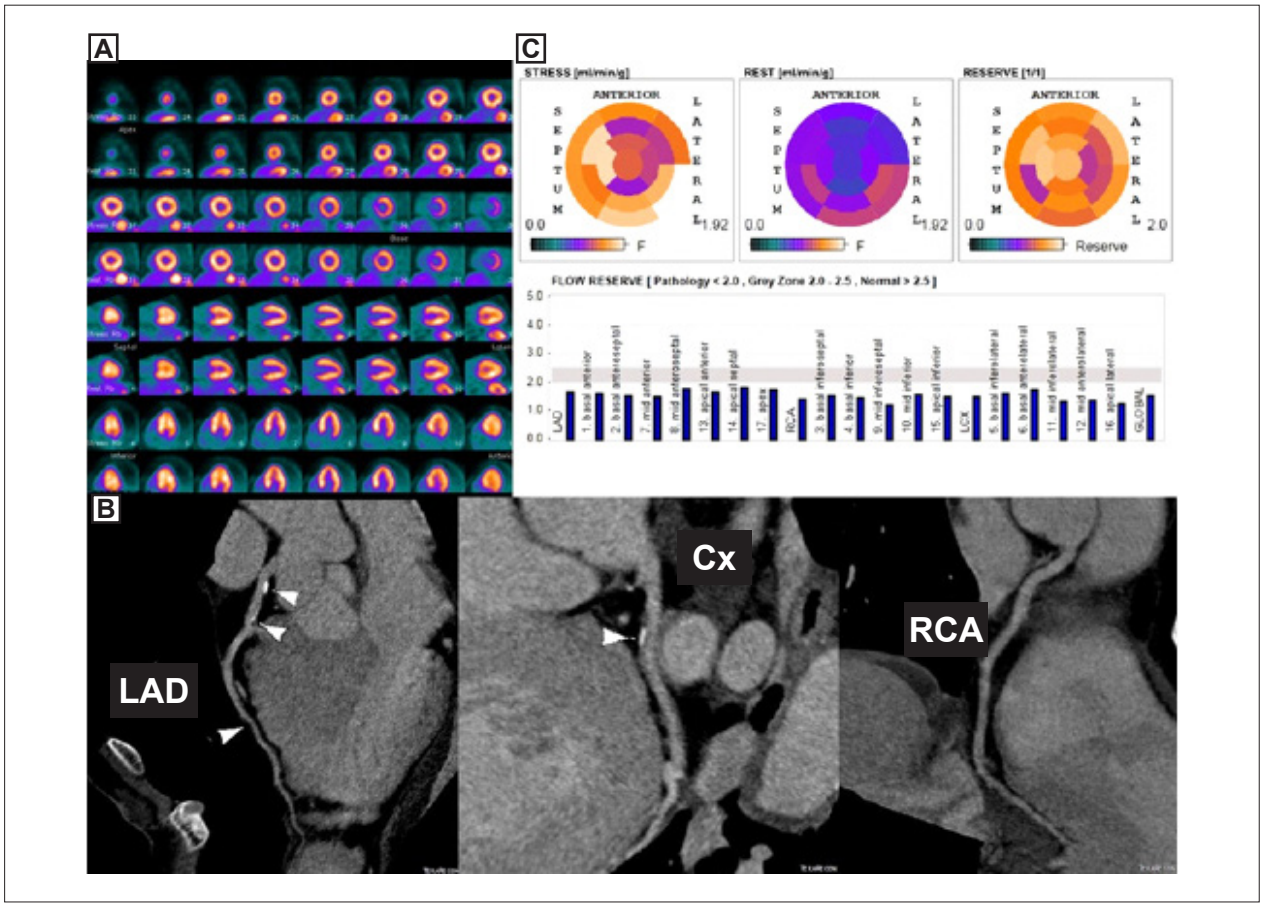

Figure 17 – *A 53-year old patient, of pardo race, with chronic renal insufficiency, undergoing hemodialysis, and left ventricular hypertrophy. Pre-renal transplant evaluation. Counterclockwise: A) PET perfusion with rubidium-82 with no segmentary defects in uptake between different walls of the left ventricle. B) Coronary tomography with evidence of parietal calcium in the anterior descending and circumflex arteries, but no obstructive lesions. C) Quantification of myocardial blood flow and flow reserve, widely reduced throughout all coronary territories (In the bar graph, coronary flow values < 2.0 ml.min-1.gram-1 of myocardium are considered abnormal; values between 2.0 and 2.5 ml.min-1.gram-1 are considered in the gray zone; and values > 2.5 ml.min-1.gram-1 are considered normal), notwithstanding the absence of obstructive epicardial disease, are indicative of microvascular disease. LAD: left anterior descending; Cx: circunflex; RCA: rigth coronary artery. Source - INCOR - FMUSP - SP.*

curve for PET and SPECT was, respectively, 0.95 and 0.90 ($p < 0.0001$), showing a small superiority for PET. The second meta-analysis indicated ^{82}Rb as the most used tracer, resulting in higher sensitivity for PET. Specificity, on the other hand, although superior, was not statistically significant.[222]

Regarding prognosis, similarly to SPECT, for which data are abundant, robust, and well established, normal myocardial perfusion with PET is indicative of good prognosis, with cardiac events varying between 0.09% and 0.9% during 1 year of follow-up, depending on the population analyzed. On the other hand, adverse events increase with the extent of perfusion defects on PET. A recently published register including more than 7,000 patients demonstrated that the hazard ratio of cardiac death increased with every 10% increment of extent of perfusion defects, classified as mild, moderate, and severe, respectively, hazard ratio: 2.3 (95% CI: 1.4–3.8; p = 0.001); hazard ratio: 4.2 (95% CI: 2.3–7.5; $p < 0.001$), and hazard ratio: 4.9 (95% CI: 2.5–9.6; $p < 0.0001$), in relation to a normal exam.[221]

8.5. Patient Preparation, Types of Stress, and Dosimetry

Preparations include a 6-hour water-only fast. Patients should avoid caffeine and foods or medications containing xanthines (theophylline, theobromine) for at least 24 hours. Generally speaking, stress protocols are generic for all types of perfusion agents, bearing similarities to those of MPS with SPECT, with specific differences in accordance with acquisition protocols.

Current dosimetry for studies with rubidium-82 (^{82}Rb) in adults, considering maximum administered activity per 60-mCi dose, may vary from 1.1 to 3.5 mSv of total effective dose. With the current advances in instrumentation of PET cameras, studies with good diagnostic quality may be acquired with injected activities that vary from 20 to 40 mCi per resting and stress dose, resulting in even lower exposure. In studies with ammonia labeled with nitrogen-13 ($^{13}NH_3$), the habitual activity is 10 to 20 mCi per dose (which corresponds to 1.48 mSv per dose). Doses of up to 25 to 30 mCi may be used in patients with high body mass index (BMI), with relatively lower dosimetry as a function of its shorter half-life and the low energy of its positron.

The evolution of imaging systems has allowed for the development of PET/CT capable of performing hybrid imaging, or be it, using CT not only for attenuation correction but also for quantification of CS and acquisition of coronary angio-CT, in addition to allowing for the fusion of these images, facilitating the integration of anatomical and functional information. Another great advance is that of PET systems incorporated to PET/MR. This new hybrid imaging modality has enormous potential for structural-functional evaluation, tissue characterization, and reduced exposure to radiation.[229-231] This, thus, amplifies the possibility of developing new studies, with the aim of expanding data on clinical applications and diagnostic and prognostic benefits of PET in studies of more diverse cardiovascular conditions.

Objective measures of coronary flow reserve will certainly be able to be extended to the MPS-SPECT method, providing evidence of nuclear medicine's ability to carry out quantifications of MBF and allowing for additional parameters for evaluating perfusion, as well as myocardial reserve, with a resulting impact on clinical management of patients, which will objectively orient decisions about revascularization (Figure 18).[232]

Provided that availability barriers are overcome and costs of both imaging systems and tracers are reduced, especially in developing countries such as Brazil, the growing application of this new methodology has a promising outlook in cardiology.

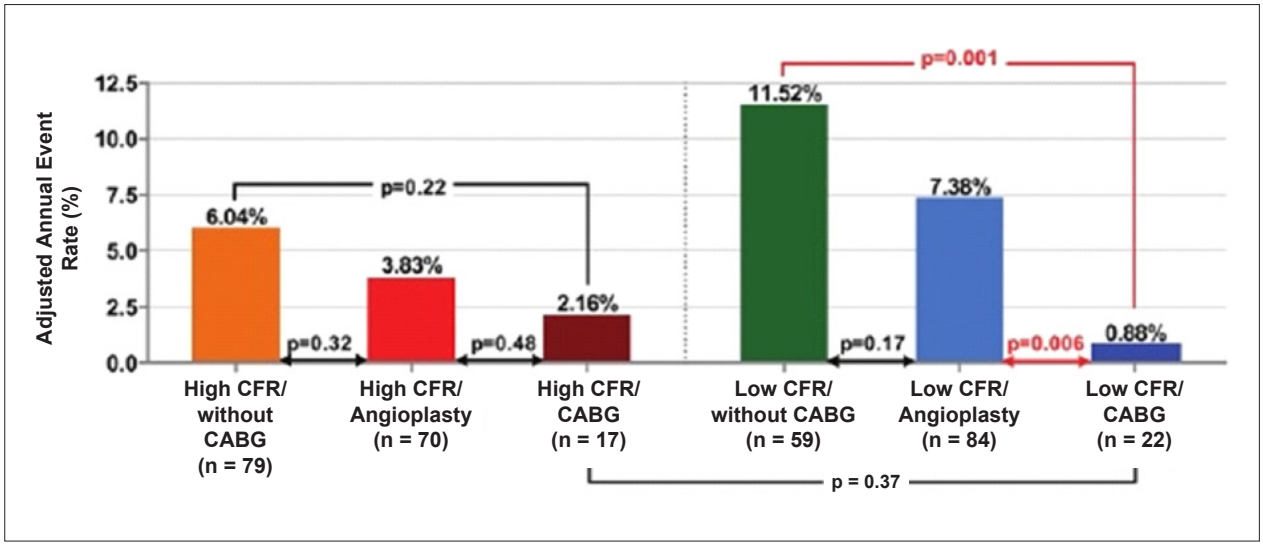

Figure 18 – *Coronary flow reserve (CFR). Left: In patients with high CRF, there were no statistically significant differences in adjusted rates of annual events, notwithstanding apparent reduction observed in patients who underwent angioplasty or coronary artery bypass graft (CABG). Right: In patients with low CRF, both procedures showed significant benefits in reducing events. Source: Adapted from Taqueti VR et al.*[232]

9. Integrating Diagnostic Modalities in Cardiology – Tutorial Cases

9.1. Introduction

Technological evolution has facilitated the development of excellent tools for both establishing diagnosis and estimating prognosis of CAD. These advances allow us to evaluate different aspects of anatomy and physiology of the heart non-invasively, with great accuracy. Most importantly, today we are able to rely on methods which help establish the best course of treatment in the most diverse clinical situations of patients with suspected or known diseases, whether they are symptomatic or asymptomatic. This wide range of alternatives presents an additional challenge to doctors, namely, that of defining the best strategy and the most rational complementary sequence of evaluation possible, regarding use of resources for diverse clinical situations, guaranteeing not only the highest accuracy in evaluation, but also the best benefits, considering healthcare costs. Doctors generally should seek to orient initial investigation with the aim of using the lowest number of diagnostic exams for an effective evaluation. However, in this era of multimodalities, it has become necessary to perform more than 1 exam in order to make the best therapeutic decision. Combined assessment of different phenomena of the heart is often necessary, for instance, to define physiological repercussions of an anatomical lesion.

Two questions linked to the bases of medical semiology and to the essence of medicine ask, **"Who is the patient?"** and **"What information is the doctor looking for?"** In this approach, the application of good techniques, such as anamnesis and complete physical examination, has become clear in clinical medicine, enabling doctors to formulate their initial patient profiles and to establish the most probable diagnostic hypotheses. Joint estimation of the pre-test probability of the disease[233] and knowledge regarding the accuracy of a test to determine post-test probability of a true or false result (Bayes' Theorem) are implicit and no less important. The application of this basic principle, associated with knowledge regarding what different diagnostic tools may offer, allows for the elaboration of better investigation strategies. Confirming or excluding the presence of CAD from the anatomical point of view or, alternatively, investigating the physiological repercussions of myocardial ischemia via stress tests have distinct implications for patient management. Whether to look for one response or another will depend on the patient at hand and the question the doctor wishes to answer.

9.2. Integrating Physiology (Exercise Testing and Nuclear Cardiology) and Anatomy (Calcium Score and Coronary Angiotomography)

Exercise testing (ET), also known as ergometric test, stress or exercise tests, showing evidence of good performance (high workload) with normal results and MPS showing absence of ischemia do not represent absence of CAD indeed . In the presence of CAD, however, these findings are associated with better prognosis in relation to patients with ischemia, given that their use is extremely useful for risk stratification of patients with or without this disease. On the other hand, it is important to know that methodologies based on the anatomy of coronary arteries, such as coronary angio-CT, may also stratify risk, but the presence of atherosclerosis detected by this modality does not necessarily imply poor prognosis or, much less, mean that the patient will necessarily benefit from myocardial revascularization procedures. It may merely represent that prognosis is worse that that of an individual without atherosclerosis. It is, thus, worth reaffirming that it is necessary for doctors to possess global knowledge of their patients and also to delineate clearly the investigation strategy for the question they are seeking to answer. Basic knowledge regarding advantages and disadvantages of available procedures are implicit, making the absolute most of the technological evolutions that have occurred in recent years. Initially speaking, all modalities which have been covered may be used for diagnosis and prognosis. It is, however, evident that they all have strengths and limitations, which are not necessarily uniform for all patients; or be it, there are determined patient characteristics which may make one test superior or inferior to another (Table 25).

Table 25 – Main advantages and disadvantages of exercise testing (ET), myocardial perfusion scintigraphy (MPS), and coronary angiotomography (angio-CT) for assessment of coronary artery disease (CAD)

	Advantages	Disadvantages
ET	• Widely available • Relatively low complexity • Relatively low cost • Does not involve radiation	• Requires ability to exercise • ECG may be uninterpretable • Limited accuracy • Does not detect initial CAD
MPS	• Localizes and quantifies ischemia • Evaluates perfusion and LV function associated with exercise • Evaluates ischemia in patients unable to exercise • Makes it possible to monitor treatment	• Technological complexity • Uses radiation • Attenuation artifacts • Does not detect initial CAD
Angio-CT	• Excludes CAD with great accuracy • Detects CAD in its initial phase • Allows for anatomical evaluation (e.g., anomalous coronaries) • Quick exam	• May overestimate obstructions • Limited use for known CAD • Limited for physiological aspects • Uses radiation

ECG: electrocardiogram; LV: left ventricle. Source: Adapted from Vitola JV.[234]

Once the doctor has answered the 2 initial questions, **"Who is the patient?"** and **"What is the main diagnostic hypothesis?"** he or she needs to answer the third question: "**What is the most appropriate test for this patient and for the question I want to answer?"** To answer this question, it is essential to know the main advantages and disadvantages of the exams, integrating the results of Bayes' theorem and, thus, defining post-test probability. It is, moreover, necessary to identify when continuous or complementary analysis will be required in order to obtain additional information for better patient management (Figure 19).

Of the techniques that have been covered, angio-CT is the most recent, showing great technological evolution, notably over the past 10 years. Data from important clinical studies have consolidated and recognized the value of this modality, as well as how to integrate it with other available tools. Before the advent of angio-CT, studies of patient anatomy presented greater difficulties, as it was mainly obtained via cardiac catheterization, with all the limitations, complications, and costs associated with invasive interventions. The development of a non-invasive, relatively simple and quick imaging technique has, in recent years, made it possible to recover the role of anatomical evaluation of the heart as a diagnostic and prognostic tool, thus integrating angio-CT into the multimodality scenario. Tests that allow for evaluation of cardiac physiology, such as ET and nuclear cardiology with MPS, have been routinely utilized for many decades, and, as they are not invasive, they have been employed for a large number of patients with suspected or known CAD. A great deal has been learned about these tools' capabilities for diagnosis

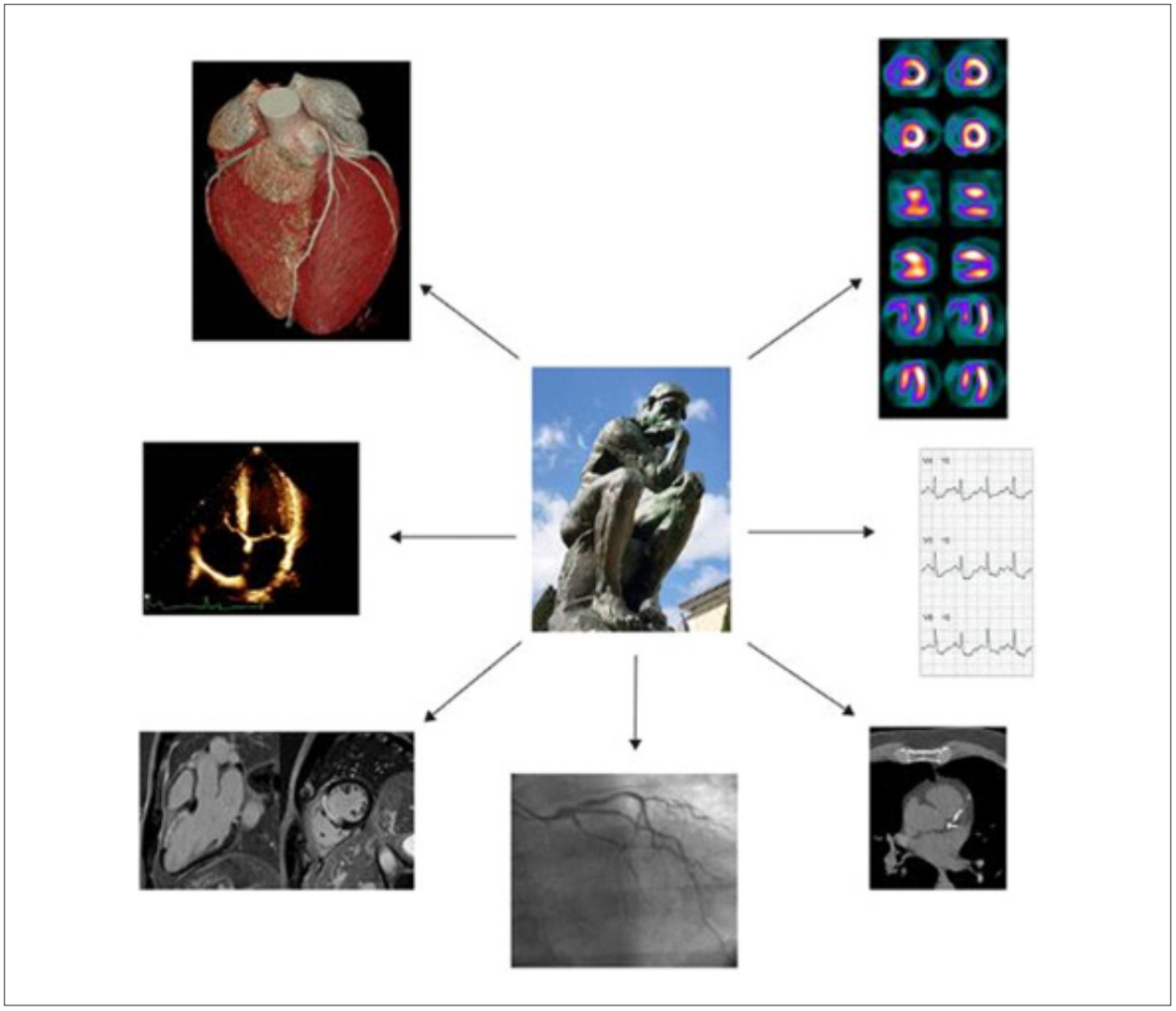

Figure 19 – *The importance of integrating information about different diagnostic modalities in an era of multimodalities. Generally speaking, the diagnostic modalities most used in Brazil are: exercise testing, echocardiogram, myocardial perfusion scintigraphy, angiotomography to evaluate coronary anatomy and calcium score, cardiac magnetic resonance, and, finally, invasive coronary cineangiography (cardiac catheterization). In this scenario, the doctor is central to establishing the best strategy and should ask the following questions: (1) What is my patient's clinical profile? (2) What information am I looking for regarding the clinical hypotheses I have raised? (3) What test will provide this information? (4) Will I need further information to make a decision and manage this patient? Source: Vitola JV.*[234]

and, especially, for establishing prognosis and defining better courses of treatment.

Since the beginning of ET, initially in the 1950's, followed by MPS in the 1970's, information obtained has emphasized the great value of physiology, especially for evaluated coronary reserve flow, with highly consistent data for stratifying risk of cardiac death in patients with known or suspected CAD. Different physiological variables assist in characterizing patients as low-, intermediate-, or high-risk. The results of these tests, however, are not always in agreement, when comparing physiological tests to each another (ET with MPS) or to anatomical tests (angio-CT and catheterization). Potential "disagreements" and situations that may generate doubts are more common when comparing anatomy and physiology, especially at this moment, with the expanded use of angio-CT.

The scope of this text is not to revise details in relation to the variables involved, but rather to integrate information obtained from different available non-invasive tools, especially the interrelations between MPS, angio-CT, and ET. Summarily, the main variables of **ET** that represent *high risk* are: low functional capacity, greater magnitude of ST depression, occurrence in multiple leads, descending ST segment, ST-segment elevation in leads without Q waves, depressed chronotropic response, drop in blood pressure during stress, the presence of complex ventricular arrhythmia, manifestations of angina during low workloads, among others. In MPS, the *principal markers of severity* are: extensive perfusion defects with severe intensity, especially transient defects (transient reduced uptake) in more than 1 territory and mixed fibrosis patterns associated with ischemia (persistent reduced uptake associated with transient reduced uptake), stress-induced LV dilation, tracer uptake in the RV and the lungs, low LVEF, and LV with or without transient dilation associated with stress.

Conversely, aspects associated with *low risk on the ET* are represented by high functional capacity, absence of important ST-segment abnormalities or stress angina, good hemodynamic response with appropriate increase in HR and blood pressure, and absence of complex ventricular arrhythmias. In relation to MPS, markers of *good prognosis* are associated with normal myocardial perfusion and preserved LV ventricular function. Most of the time, especially in the most severe cases, diagnostic modalities are in agreement, or be it, a patient with high-risk ET findings will, likely, show significant MPS defects, corresponding to coronary anatomy compatible with advanced CAD. There are, however, different scenarios in which disagreeing results present challenges to better patient management.

The cases subsequently exposed are intended to integrate clinical data with the use of multimodalities, extending discussions within the medical decision-making process for understanding, interpreting, and suggesting conduct for dealing with agreements and, especially, disagreements. Figure 20 illustrates a concept in which the doctor begins evaluation using medical procedures of

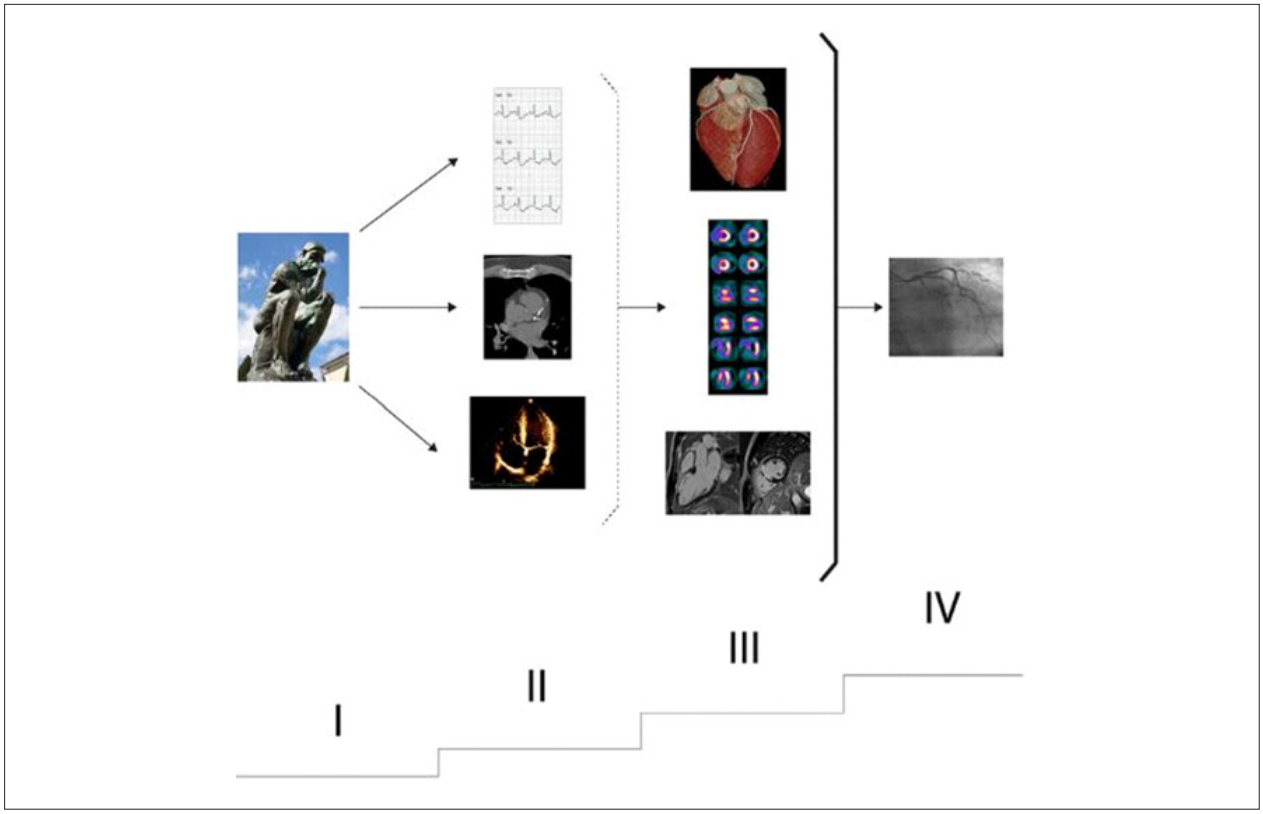

Figure 20 – *Concept of a rational strategy for evaluating and integrating modalities in a logical sequence of investigation of stable patients. It begins with the best rationalization for formulating diagnostic hypotheses (I), going on to the most basic tests (II), such as ECG/ET, ECHO, CS, continuing, as necessary, to more advanced non-invasive imaging methods (III), such as angio-CT, MPS, and CMR. The non-invasive tests, whether basic or advanced, should serve as "filters" for invasive testing, i.e. cardiac catheterization (IV), which should serve in planning advanced treatment only in patients under consideration for myocardial revascularization.*[234]

anamnesis and physical examination during the *initial phase (I)*, formulating the main diagnostic hypotheses, which are fundamental aspects for defining the best investigation strategy. Subsequently, depending on the questions formulated, relatively simple or more *basic* diagnostic tests are obtained *(II)*, such as: resting ECG, ET, resting ECHO and, eventually, CS. Subsequently, in accordance with the need for additional information and depending on the diagnostic hypotheses considered, the doctor may consider the application of more *advanced* non-invasive imaging techniques *(III)*, such as angio-CT, MPS, and, potentially, cardiac magnetic resonance. Applying scientific knowledge regarding diagnostic and prognostic value, to both basic tests and more advanced non-invasive imaging methods, it is possible to establish filters for selecting patients who will really require invasive testing, such as *cardiac catheterization (IV)*, notably with the aim of planning for myocardial revascularization.

9.3. Practical Examples of Integration of Modalities

1. Patient with abnormal ET, Duke score characterizing intermediate risk, and normal MPS

Clinical history: female, age 50, with hypertension, dyslipidemia, atypical symptoms, and borderline ET. Referred for MPS (Figures 21 and 22).

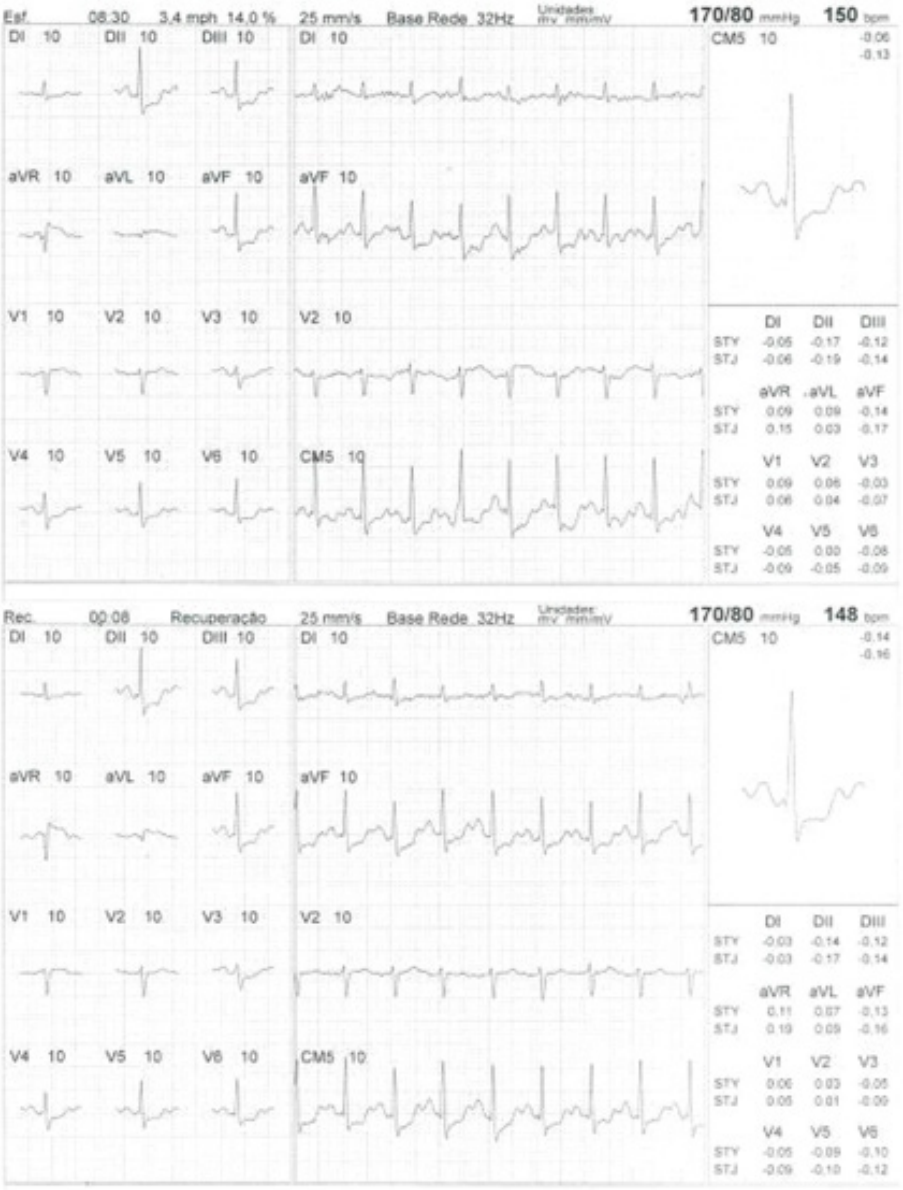

Figure 21 – *Case 1 - Electrocardiogram tracing during peak stress and initial recovery with alterations (explained in the text).*

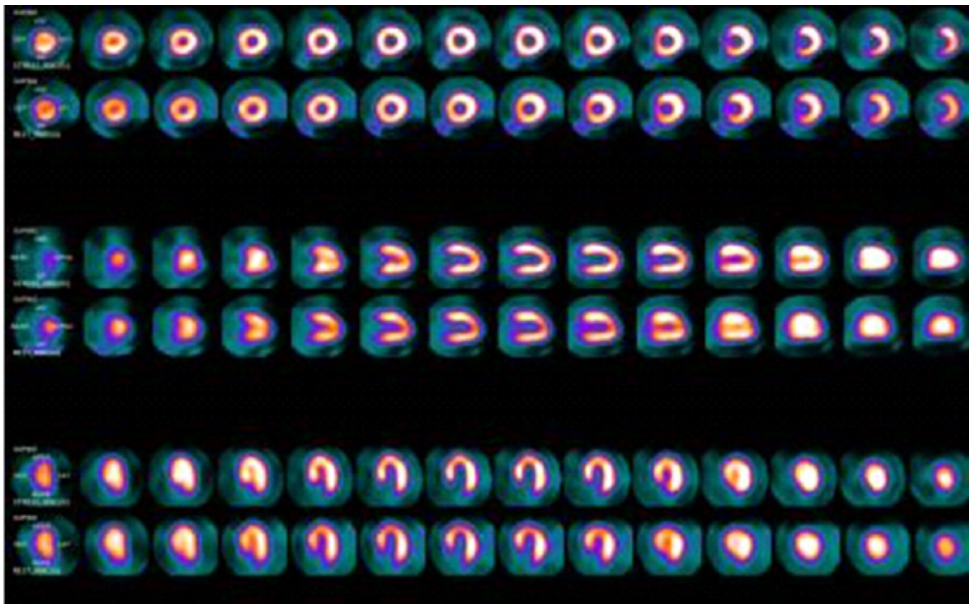

Figure 22 – *Case 1 - Myocardial perfusion scintigraphy within normality. Images acquired with dedicated cardiac equipment (gamma camera), equipped with solid cadmium-zinc-tellurium detectors.*

Findings: The patient exercised for 8.5 minutes on the Bruce protocol, with satisfactory HR and blood pressure responses, reproducing the ET findings that motivated referral for MPS, with ST-segment depression varying from 1 to 1.5 mm after 80 mm on the J point, with aspect varying from slow ascending to horizontal, in multiple leads (Figure 21). She denied having precordial pain, but there was a manifestation of cervical and mandibular discomfort. Calculation of the *Duke Score*, *DS = Time in min. − (5 × ST) − (4 × Angina Index)*, resulted in intermediate risk, both considering the symptom as angina [+ 8.5 − (5 × 1.5) − (4 × 1)] = **−3**] and not considering it as angina [+8.5 − (5 × 1.5) − 4×0] = **+1**]. MPS was within normality.

Comments: This is one of the most common situations in nuclear cardiology laboratories. The first questions to be formulated refer to the risk defined by the ET. Abnormal responses may characterize low, intermediate, or high risks. For MPS, the best indication is for intermediate risk, which was the case with this patient. It should ideally be associated with physical exercise instead of pharmacological alternatives; when this is normal, the patient is stratified as low risk and, in most cases, the exam will indicate a probability of death lower than 1% per year, implying conservative medical management. At this moment, investigation may cease, based on the conclusion that the patient's symptoms are not related to significant myocardial ischemia and that he or she requires prevention with the objective of controlling hypertension and dyslipidemia. Other findings in clinical practice include patients with functional capacity similar to the case described but with higher magnitude of ST-segment depression, resulting in a high-risk Duke score. Due to the absence of angina during stress and good functional capacity, however, the doctor may suspect that the calculation is overestimating the risk via ET. Such findings may be observed more frequently in patients with hypertension, possibly related to myocardial hypertrophy. In Brazil, Vitola et al. studied patients with high-risk Duke scores and MPS results, finding perfusion abnormalities in 70% of these individuals.[235] However, the other 30% showed normal MPS, and it was demonstrated that these patients had excellent prognosis. Thus, in specific cases, even in the presence of high risks characterized by the same score, the application of multimodalities, such as the association of physical stress with non-invasive MPS imaging, are appropriate before proceeding to investigation via catheterization. Furthermore, it may also be possible to utilize angio-CT in some cases, considering its high NPV, with the aim of clarifying diagnosis and excluding important CAD, especially in young patients, where the probability of a "false-positive" result is higher.

2. Patient with normal ET and abnormal MPS

Clinical history: male, age 36, long-standing DM, insulin dependent, obese and hypertensive. Atypical symptoms, notably related to fatigue during stress. Referred for MPS to investigate ischemia, following ET which was normal but which had low sensitivity owing to electric axis deviation to the left, suggestive of left anterior fascicular block (LAFB) on resting ECG.

Findings: Resting ECG characterized LAFB (Figure 23). Time in the Bruce protocol was 10 minutes, with neither angina nor ST-segment alterations (Figure 24). Perfusion images showed transient reduced uptake, with large extension

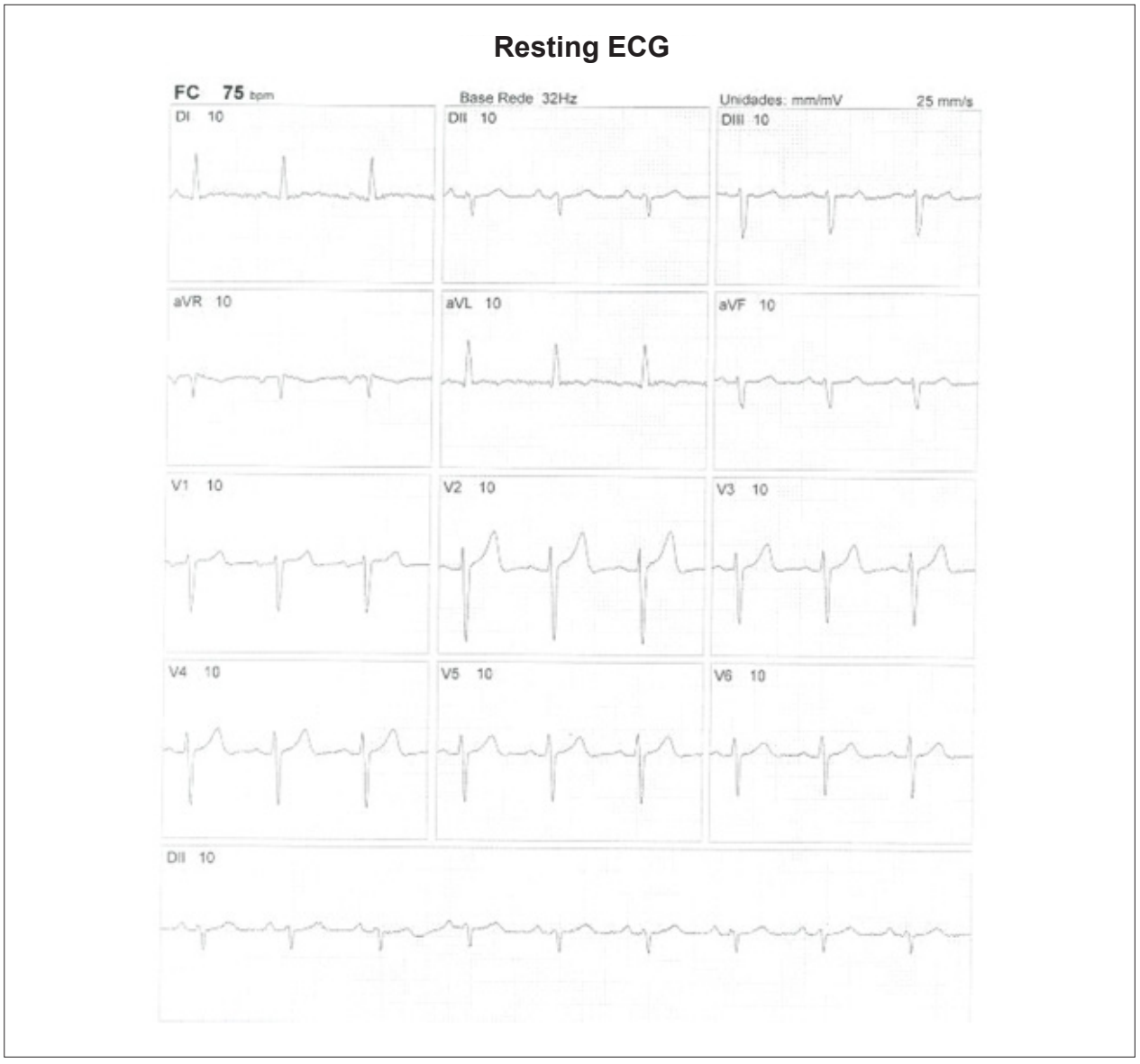

Figure 23 – *Case 2 - Resting electrocardiogram suggestive of left anterior fascicular block.*

and moderate to severe intensity, suggestive of ischemia, involving predominantly the inferolateral, lateral, anterior, and anteroseptal walls of the LV, extending to the apex (Figure 25). Observe how the LV cavity dilate after physical exercise, with the appearance of diffuse hypokinesis and a drop in LVEF from 55% to 45% when comparing both stages.

Comments: Given a normal ET, with a high workload or good performance, with neither angina nor ST-segment alterations, patients are generally considered to have low post-test risk, but this is not always the case, as can be seen here. Nor does a normal ET represent the absence of CAD, as potentially shown by the presence of calcium in the coronary arteries on angio-CT or by ischemia detected by a more sensitive technique, such as MPS. In accordance with the evolution of medical knowledge in this era of multimodalities, restratification, even of patients with low risk on exercise testing, has become possible, as an exception. These possibilities should be considered more frequently in patients with family history of early CAD, DM, or multiple combined risk factors, and especially in those with high clinical risk (Framingham score) or LAFB on resting ECG. The case presented exemplifies precisely this scenario of a clinically high-risk patient (multiple risk factors, including DM), with LAFB on resting ECG and low risks on ET, who was restratified to a higher level of risk via perfusion imaging, due to the presence of important ischemia and LV dysfunction during stress, which are high-risk indicators. In this condition, when these tests are in disagreement, in a young, symptomatic patient (probable ischemic equivalent) with high clinical risk confirmed on

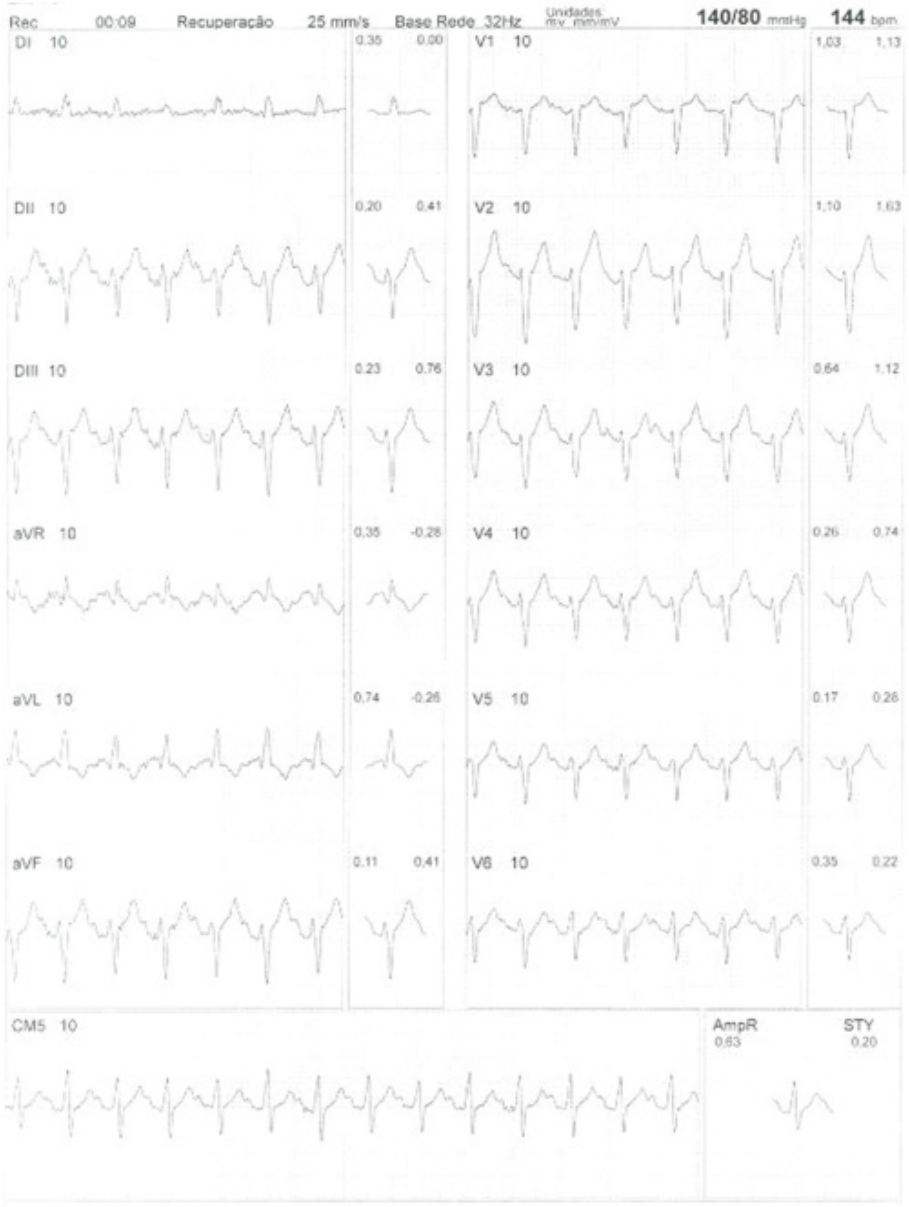

Figure 24 – *Case 2 - Electrocardiogram obtained during immediate recovery, representing peak effort, heart rate of 144 bpm, with total workload performed considered satisfactory, in addition to the absence of ischemic ST-segment alterations.*

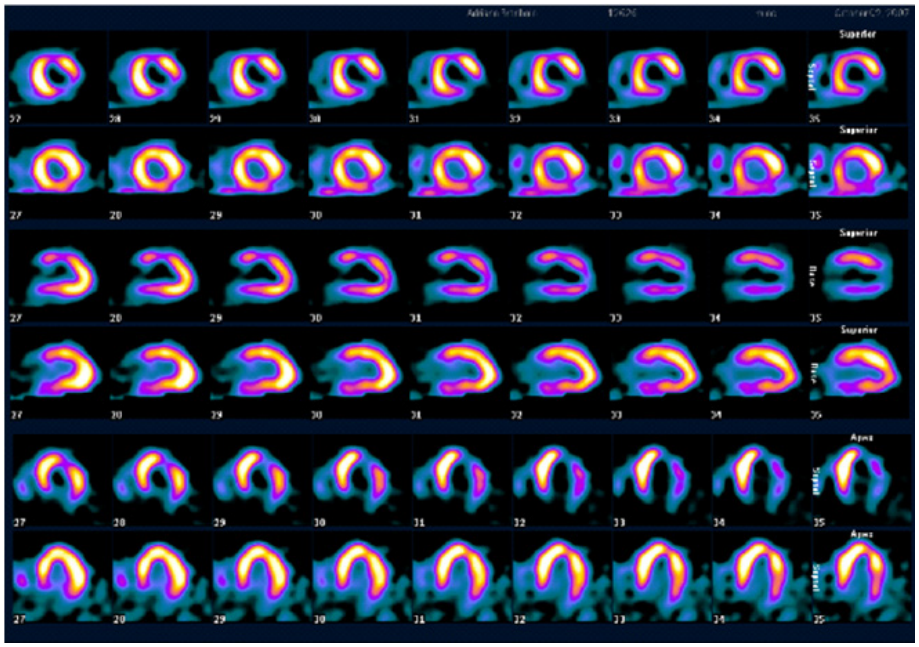

Figure 25 – *Case 2 - Myocardial perfusion scintigraphy showing important myocardial perfusion abnormalities, with multivessel ischemia and transient left ventricular cavity dilatation, representing high-risk indicators. Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

an imaging exam, referral for coronary cineangiography is supported as part of medical management.

3. Patient in pre-operative evaluation for non-cardiac surgery, with mild abnormalities on MPS, high calcium score, and non-obstructive CAD

Clinical history: male, age 65, hypertensive, obese (BMI = 45), stroke 5 years prior, asymptomatic, in pre-operative evaluation for cholecystectomy and bariatric surgery. Interpretable resting ECG, unable to exercise. Referred for MPS with dipyridamole as initial investigation exam.

Findings: ECG tracings show no modification during and after intravenous administration of dipyridamole. Perfusion images reveal mild defects (small extension) in radiopharmaceutical uptake in the inferior and inferolateral/lateral walls and in the LV apex (the latter being transient), with preserved LV function (Figure 26). Considering the 2 protocol series of image acquisition, resting and under pharmacological stimulation, interpretation is limited due to the significant obesity. The finding may even represent an attenuation artifact. With the patient in an asymptomatic conditions, with the reported alterations in perfusion and preserved LV function, additional information is required before making the important decision of approving the patient for surgery, and anatomical evaluation via angio-CT is thus recommended. The findings indicate a CS of 1,621 measured by the Agatston score, corresponding to the 96% percentile, when compared to individuals of the same sex, age, and race.[236] Moreover, there is evidence of non-obstructive lesions (< 30%) in all coronaries and an absence of significant obstructions > 50% (Figure 27).

Comments: In the presence of multiple risk factors, considering the patient's age and stroke history, the probability of CAD is intermediate to high. Pre-operative risk stratification is necessary, and, although the resting ECG was interpretable, the patient was unable to perform exercise. MPS with dipyridamole is well indicated, given that normal results could lead to the patient being approved for surgery. On the other hand, faced with abnormalities in perfusion and/or function, with indicators of high risk, there is a sufficient base of evidence for indicating catheterization. In this case, however, the result showed normal LV function and mild alterations in perfusion, with the possible presence of artifacts or results of small vessel CAD (microcirculation) and/or endothelial dysfunction. The angio-CT findings indicated high CS compatible with a high atherosclerotic burden and poor long-term prognosis,[237] which was not surprising given the profile of this patient whose coronary calcium (CC) was in the 96% percentile, meaning that 96% of individuals of the same age, sex, and race had lower coronary calcification indexes than the case described. Nonetheless, the contrasting anatomical evaluation revealed non-obstructive coronary lesions (< 30%), which reinforces the possibility that the patient might have small vessel CAD, which already bears physiological repercussions, implying more aggressive clinical management. The absence of significant obstructive lesions or high-risk anatomy serves as an additional filters for avoiding invasive examination (catheterization) and confirming that surgical risk would not be prohibitive. The most appropriate form of management for this patient, likewise, appears to gear toward aggressive preventative measures, with risk-factor control and follow up, in addition to medical treatment of CAD, which does

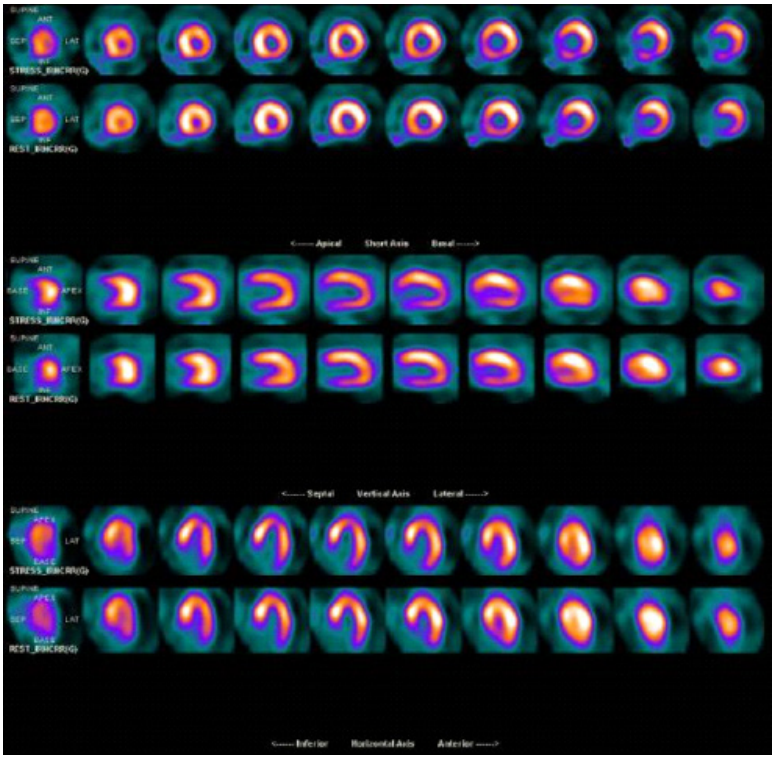

Figure 26 – *Case 3 - Myocardial perfusion scintigraphy showing mild alterations in myocardial perfusion, with analysis limited by significant obesity (grade III). Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

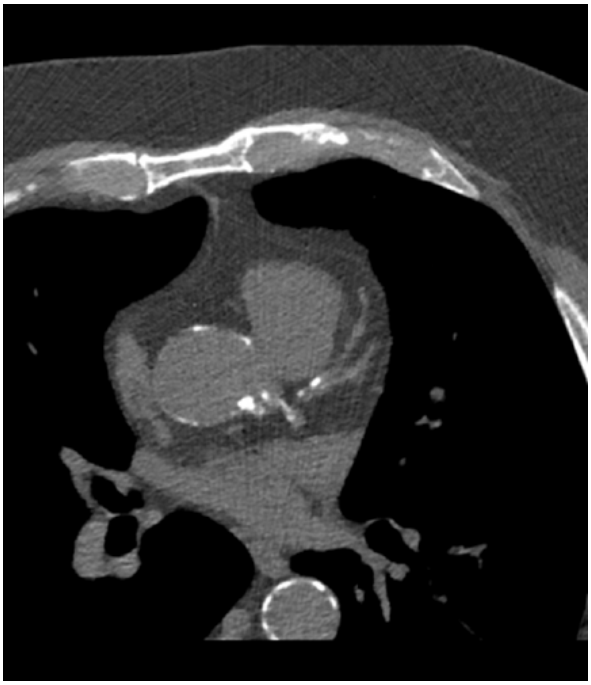

Figure 27 – *Case 3 - Angio-CT showing vascular calcifications involving coronary arteries and ascending and descending aorta.*

not, however, require myocardial revascularization. Bariatric surgery itself may perhaps assist in controlling these risk factors.

4. Patient with elevated CS normal MPS and ET

Clinical history: male, age 52, asymptomatic, diagnosed with DM 5 years prior, hypertensive and dyslipidemic. Calculated CS.

Findings: CS resulted in a high Agatston score of 1,143, in the 99% percentile (Figure 28). MPS with physical exercise was indicated. Patient underwent stress in the Bruce protocol for 10 minutes, reaching HR of 158 bpm (94% of the recommended maximum HR), with no clinical, electrocardiographic, or hemodynamic alterations. MPS (with a CZT camera) showed homogenous radiopharmaceutical distribution in the LV walls (Figure 29), as well as normal LV systolic function.

Comments: This situation has occurred more frequently in clinical practice, to the extent that CS has gone on to be incorporated as a screening method for CAD and risk stratification in the subgroup of asymptomatic patients (DM and intermediate Framingham score). This disagreement between results is understandable given that the presence of atherosclerosis will not necessarily result in ischemia detected by functional methods. For instance, an ET may indicate low risk according to the Duke score in a patient who has performed only 5 minutes of exercise in the Bruce protocol but who showed neither ST alterations nor angina. It is intuitive to grasp that, in the presence of coronary disease (most cases with high CS), this does not represent exactly the same low risks as in a patient without CAD (absence of coronary calcification or zero CS). Regarding these facts, there is extensive literature on the prognostic value of CS, with long follow-up periods (> 15 years).[238] In this manner, it is feasible to expect the group characterized as low-risk by the Duke score to be heterogeneous, and patients should thus be treated individually, considering the intensity of prevention. In the case demonstrated, as the patient has DM, there had already been an indication for statin use, with the very high CS (in the 99% percentile) reallocating the patient into an even higher risk within the group with DM. As part of data revision which has been occurring over the past 20 years, cases have been found which showed normal but which, nonetheless, presented coronary events during medium-term evolution, in a manner similar to the discrepancies recently observed between ET and CT. Likewise, a recent study by Chang et al.[239] observed the same discrepancies in patients with low-risk Duke scores from ET and CS > 400. They evaluated 946 patients with the Framingham score, classifying the majority as intermediate-risk (estimated 11.1% average for events over 10 years) and, basically, asymptomatic, as evaluated by ET and CS. The average Duke score was 8.4, categorized as low-risk (≥ 5). Stress tests were positive or altered in 12.3% of patients, while CS > 100 were found in 54.2% of patients. MPS was abnormal in 10.9% of the same population. It was demonstrated that CS restratified risk for patients with low-risk Duke scores, identifying individuals with atherosclerosis and higher propensity for

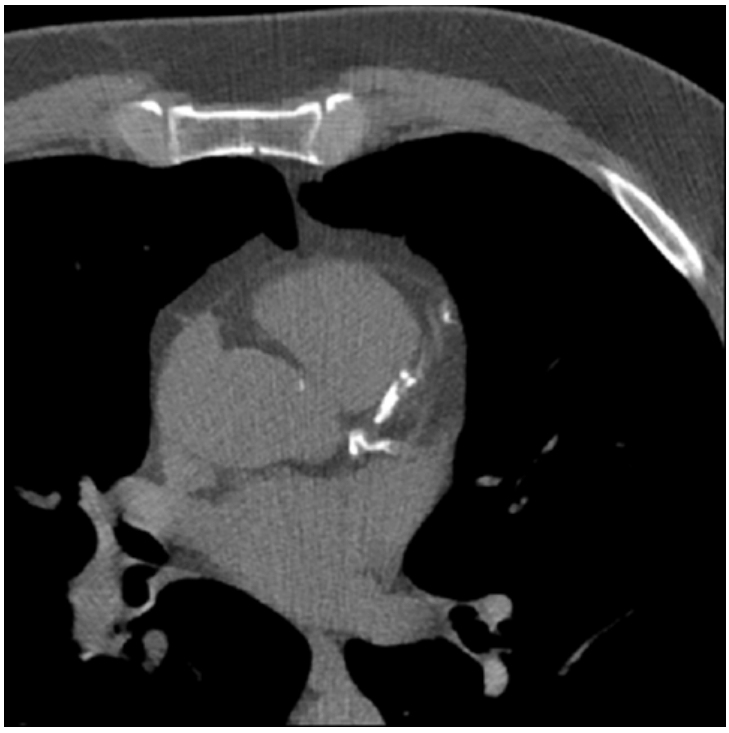

Figure 28 – *Case 4 - Angio-CT imaging shows elevated calcification index in coronary arteries.*

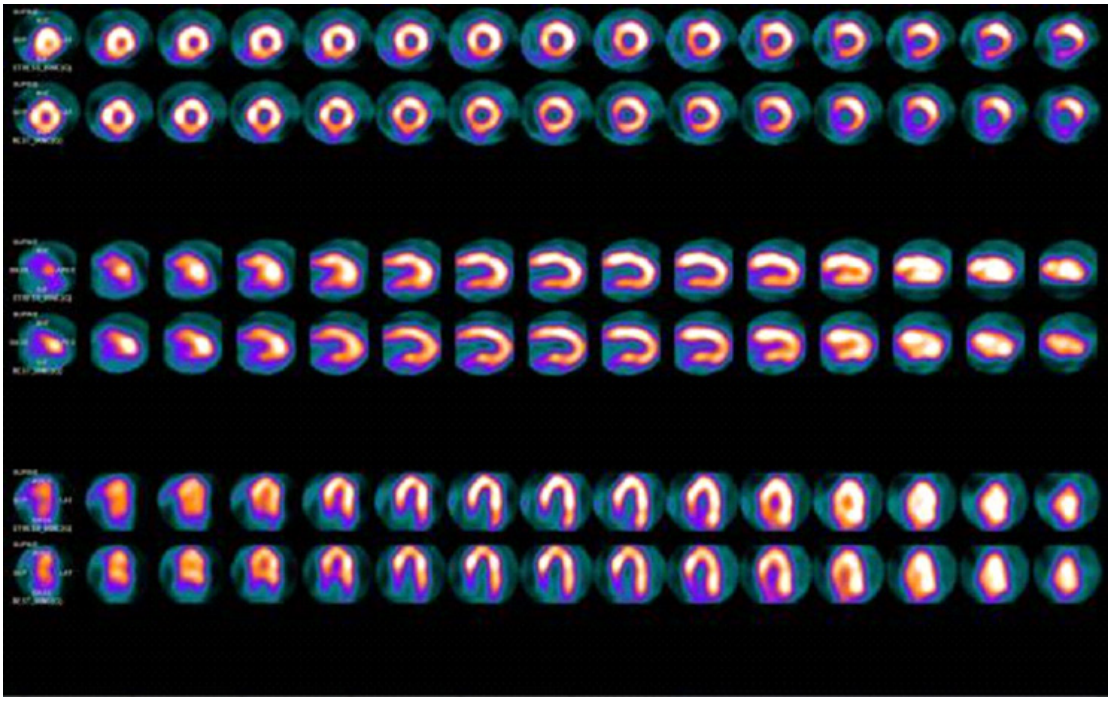

Figure 29 – *Case 4 - Myocardial perfusion scintigraphy within normality. Images acquired with dedicated cardiac equipment, equipped with solid cadmium-zinc-tellurium detectors.*

events. Furthermore, a current register known as CONFIRM has accumulated data that definitively suggest that, in the presence of non-obstructive CAD,[240] evolution may be worse in patients without CAD. It has, thus, become evident that the anatomical technique with angio-CT is identifying coronary atherosclerosis earlier. This set of information definitively represents a change of paradigm in the medical decision-making process. In this situation where CAD is identified, medical management will be geared toward more aggressive prevention of modifiable risk factors and minute observation of possible symptoms that translate to disease instability. In the absence of ischemia, revascularization procedures should not be considered.

5. Patient with high CS and abnormal MPS

Clinical history: female, age 68, asymptomatic, with intermediate-risk Framingham score. Performed CS for risk restratification.

Images: reproduced with permission of Vitola JV.[234]

Findings: The resulting CS was high, at 1,282, according to the Agatston score, placing this patient in the 99% percentile (Figure 30). With this finding, functional evaluation was indicated, using MPS with MIBI-^{99m}Tc associated with exercise. The patient exercised for 7.5 minutes in the Bruce protocol, showing ST-segment depression of up to 3 mm during peak stress, with a varying aspect which tended toward descending in multiple leads, without symptoms (Figure 31). With these findings, the *Duke score* **(DS)** = exercise time in minutes – (5 × ST deviation) – (4 × angina index), or **DS** = +7.5 – (5 × 3) – (4 x 0) = **– 7.5**, resulting in classification as intermediate risk. In the perfusion images, the presence of transient reduced uptake was evidently observed, involving the middle and distal portions of the anteroseptal and anterior walls and apex of the LV, with accentuated intensity and medium extent, compatible with significant ischemia in the territory of the anterior descending artery (Figure 32). Furthermore, mild transient dilation of the LV cavity was observed during stress, in addition to radiopharmaceutical uptake in the RV wall, which are high-risk markers.

Comments: Evidence in the literature has supported the use of CS for risk restratification in patients who have intermediate clinical risks (using, for instance the Framingham or the global risk score), but who are in asymptomatic phases. The higher the CS, the higher the risk will be; not coincidentally, the probability of silent ischemia will also be higher, and this, in turn, increases the patient risks even further. Data have demonstrated that, when CS values are between 400 and 999, the probability of perfusion defects reaches up to 29%, and when values are > 1,000, the probability increases to 39%.[241] Brazilian data from Cerci et al. have reported similar information, with an ischemia prevalence of 34% in patients with CC over 400.[242] Within medical orientation, rigorous preventative measures have shown evident benefits in individuals with high CS. Caution, however, is recommended when indicating revascularization procedures, emphasizing the absence of formal indication,

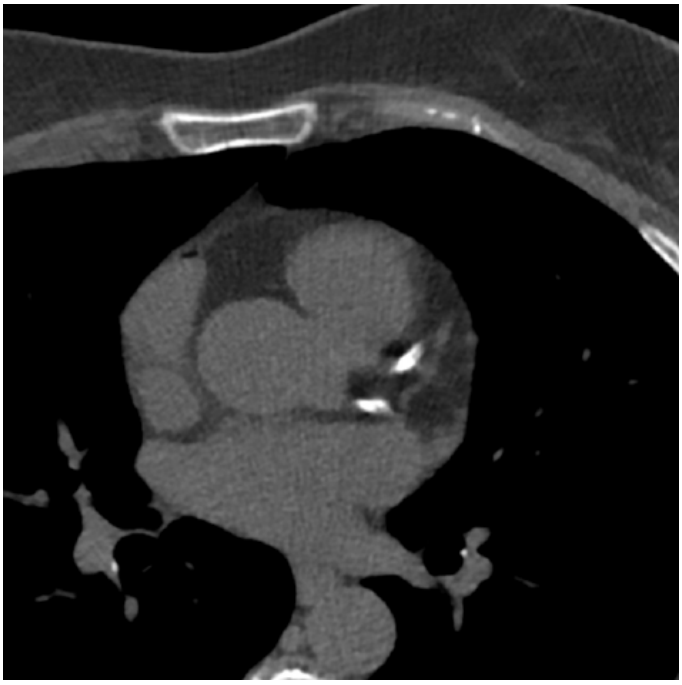

Figure 30 – *Case 5 - Angio-CT revealing severe calcification in coronary arteries.*

consensus, or evidence regarding benefits based solely on CS results. On the other hand, recommendations exist for individuals with high-risk anatomy, at least moderate ischemic burden (in terms of extent and intensity), and the presence of symptoms refractory to clinical treatment.[14] Notwithstanding indications documented in guidelines, levels of evidence demonstrating the benefits of myocardial revascularization with the aim of reducing mortality in patients with stable CAD, based both on information about anatomy[243,244] and ischemia quantification (retrospective data),[245] have been questioned, considering the absence of randomized studies published to date. With this in mind, what is known as the ISCHEMIA study[246] was designed (report to the addendum of thi guideline), randomizing patients who have at least moderate ischemia (more than 10% of the myocardium affected by ischemia of significant intensity or severity) from 400 centers worldwide into 2 treatment scenarios: "optimized clinical treatment" *versus* "optimized clinical treatment associated with revascularization of ischemic territory," excluding patients with left main trunk lesion > 50% on angio-CT. The study objective was to attempt to identify subgroups where revascularization benefits stable patients, filling in this important gap in current scientific evidence. Considering the available information (current evidence and guidelines), it seems appropriate to investigate ischemia in patients with CS over 400 in the attempt to identify individuals with high ischemic burdens (extent and intensity of perfusion defects), who may benefit from invasive strategies.

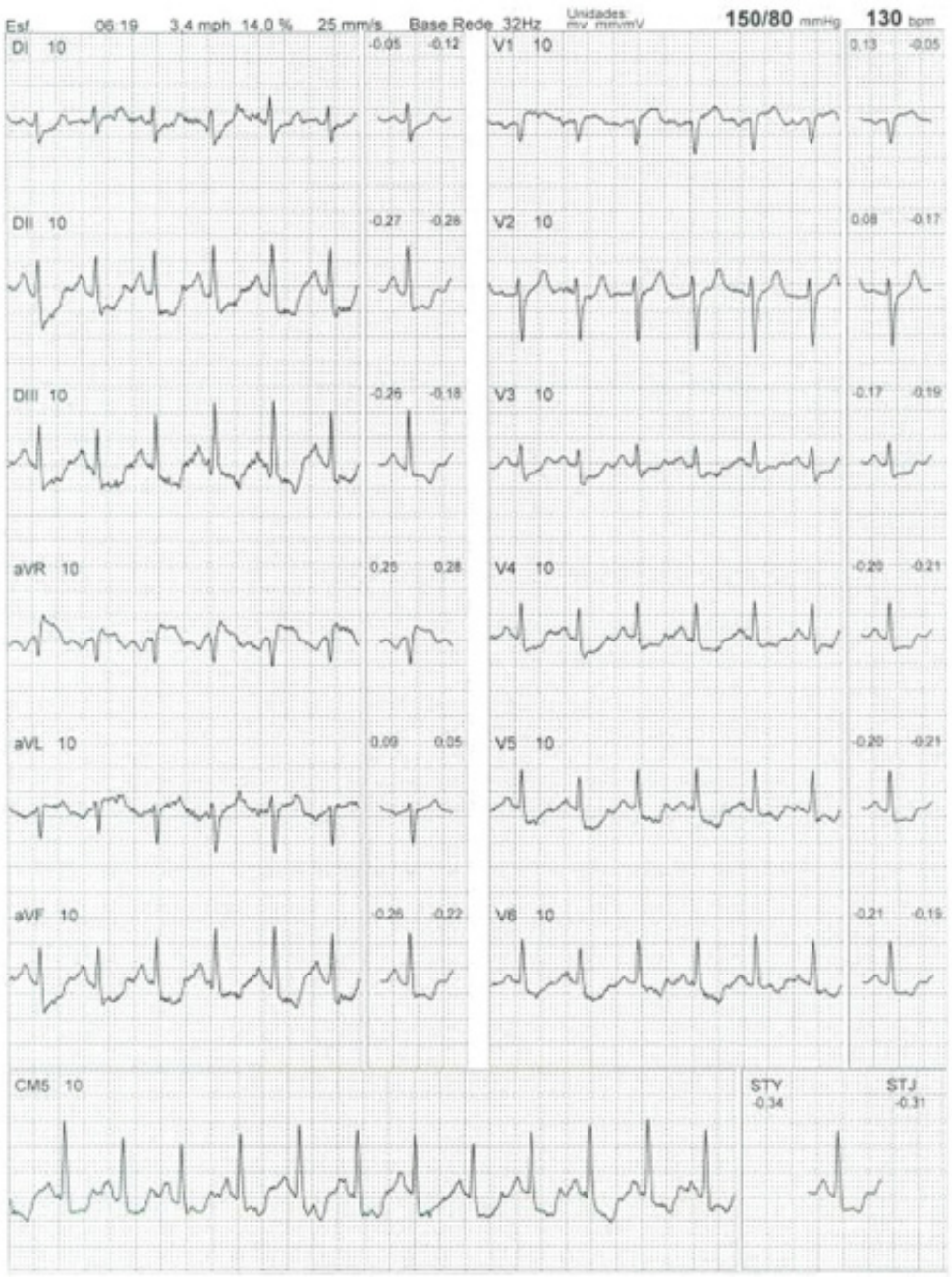

Figure 31 – *Case 5 - Electrocardiogram tracing demonstrating ischemic electrocardiographic alterations in multiple leads, with submaximal heart rate levels. Detailed explanation in the text.*

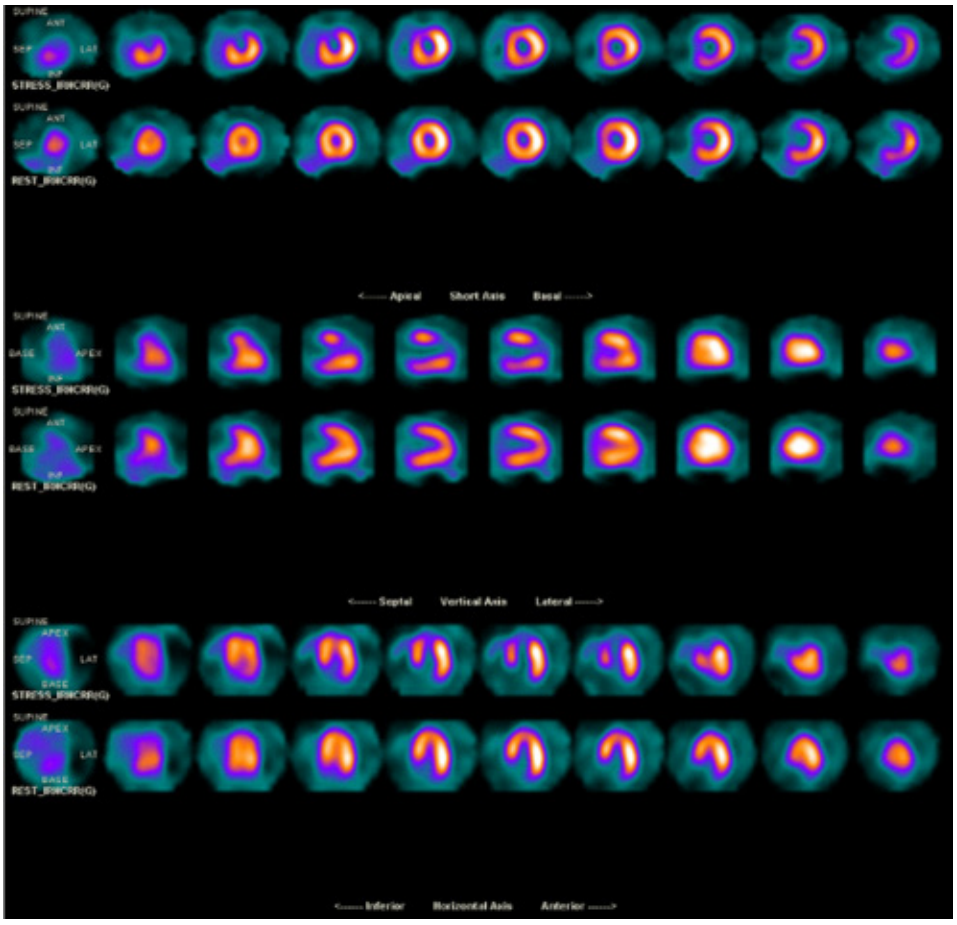

Figure 32 – *Case 5 - Myocardial perfusion scintigraphy demonstrating significant ischemia in the territory of the anterior descending artery. Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

6. Patient with abnormal ET, normal MPS, and normal coronary angio-CT results

Clinical history: male, age 33, atypical chest pain, recent onset of DM, high blood pressure (HBP) and family history of early CAD, ET resulting in intermediate-risk Duke score (+3).

Findings: The stress phase of the ET revealed high estimated metabolic expenditure (11 METs), with 9 minutes in the Ellestad protocol. ST-segment depression of up to 1.5 mm (measured in the J point), with a descending aspect (Figure 33), were observed in multiple leads, during the recovery phase only, and they were sustained until the end of this phase. The Duke score was +3 (intermediate-risk), and MPS showed homogenous radiopharmaceutical distribution throughout the walls of the LV, considered within normal limits (Figure 34). Due to persistence of symptoms during evolution, coronary angio-CT was solicited 2 months later, showing an absence of obstructive lesions and a CS of zero (Figure 35).

Comments: In patients with intermediate probability of CAD, the indicated methods (MPS or angio-CT) are additional possibilities for investigation. At least 2 randomized studies have evaluated these strategies:

I. The PROMISE study,[247] which included 10,003 individuals with suspected CAD, with 25 months of follow up regarding the primary outcome (composed of death, AMI, and hospitalization for UA), showed similar evolution in both randomization groups (A) functional tests, including MPS, 5,007 patients with 3% events *versus* B) angio-CT, 4,996 patients with 3.3% events (p = 0.75). There was, however, a higher number of revascularizations in the group that began with anatomical evaluation.

II. The International Atomic Energy Agency study[248] demonstrated that the initial strategy of angio-CT entails the solicitation of additional diagnostic methods, including MPS itself or direct catheterization. These findings could have been foreseen due to the differences in information between both techniques, as coronary angio-CT is more sensitive for detection of anatomical diseases without

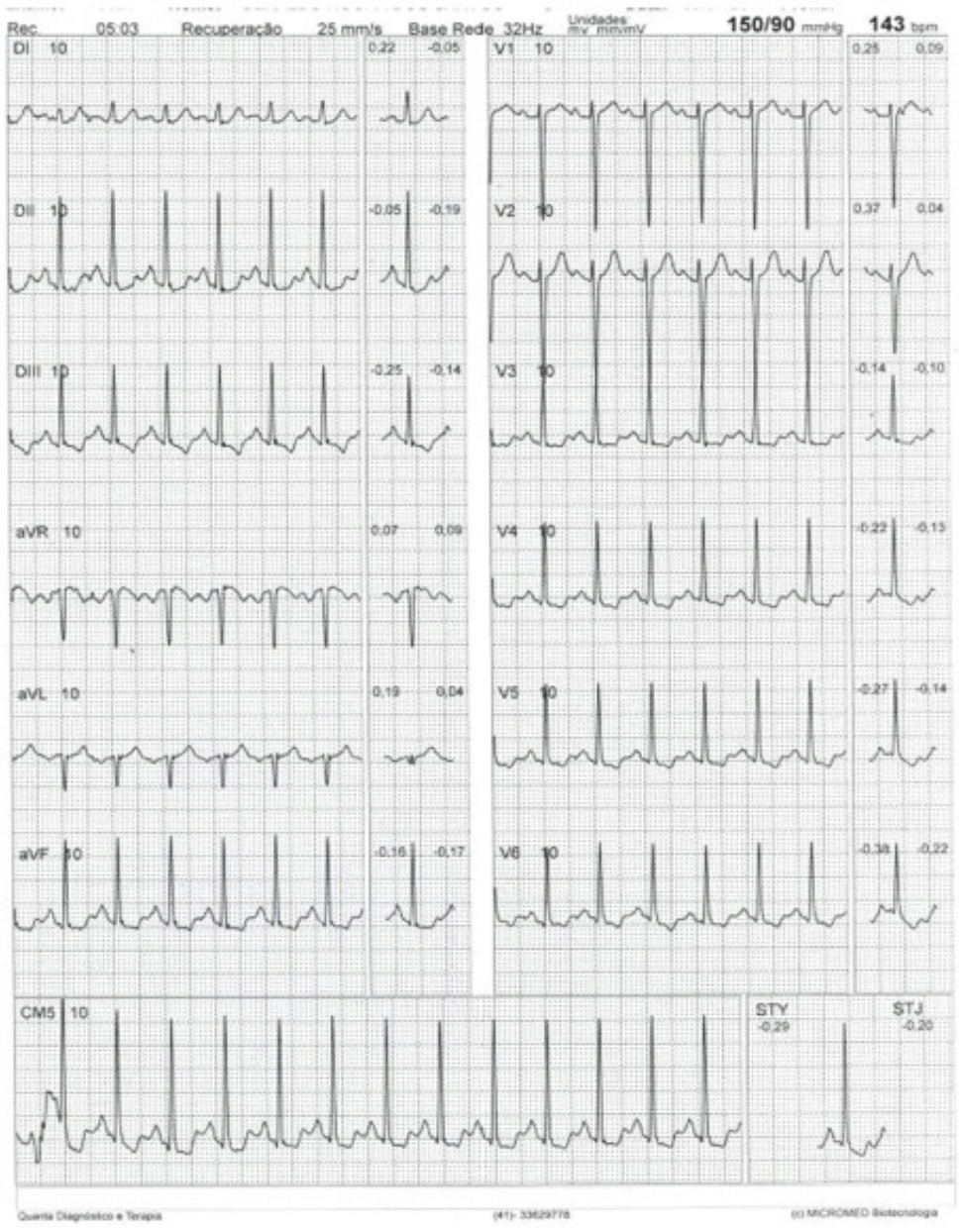

Figure 33 – *Case 6 - Electrocardiogram tracing showing electrocardiographic alterations (ST depression), especially during the recovery phase of the exercise c test.*

important physiological impact. Like *Case 1*, the situation presented in *Case 6* is common in routine coronary angio-CT. In cases where ET shows intermediate or low risk and, especially, in those where the patient has intermediate or low pre-test probability, angio-CT has one of its most precise indications. The main diagnostic virtue of angio-CT is its high NPV which essentially excludes CAD. Thus, if the probability of disease is intermediate or low, the chance of excluding it is greater, and the test shows better benefits. In the case described, as symptoms persisted, complementary evaluation with angio-CT was highly useful to the medical decision-making process. Furthermore, prognosis in a patient without CAD on angio-CT is excellent, with nearly zero risk of AMI and coronary events for up to 5 years,[249] owing to its high NPV and to the fact that characteristic evolution of CAD habitually progresses slowly, with individual variations, and this lowers the chances of an individual developing CAD culminating in a coronary event over a period of 5 years. Integrated analysis of these exams, in the case therefore, infers an excellent prognosis, notwithstanding the altered ET, and its rules out CAD quite safely, in the

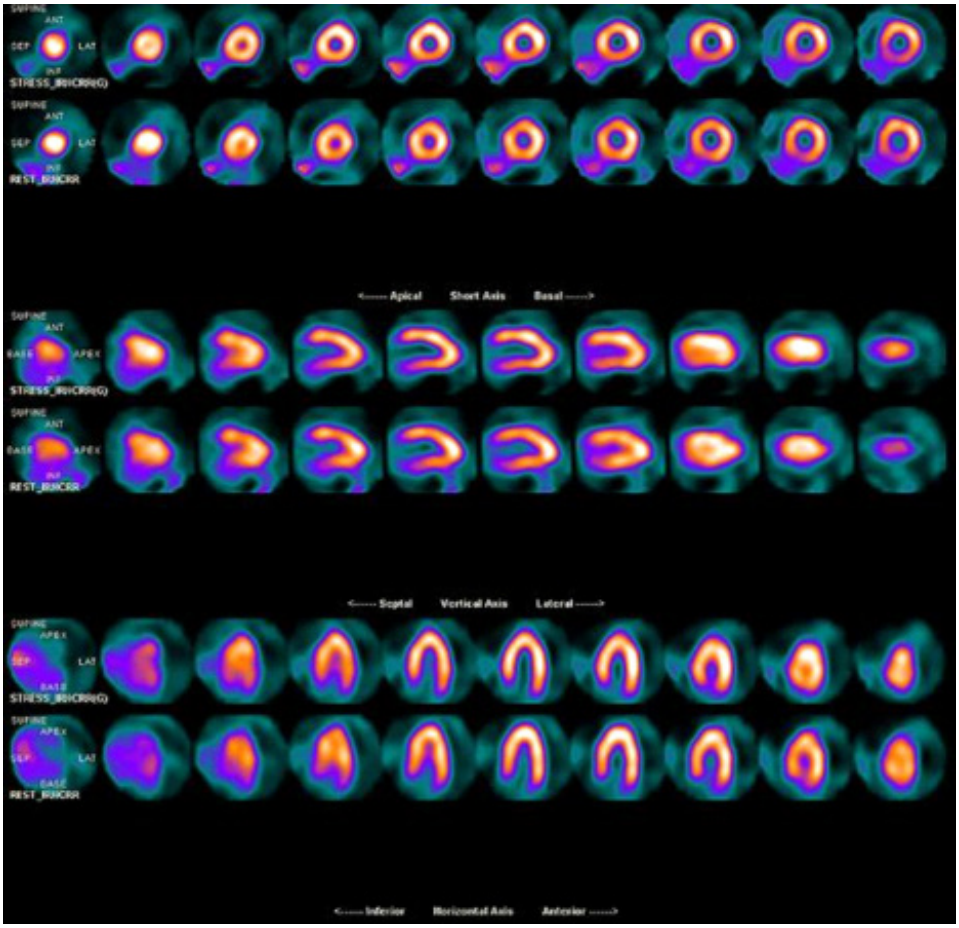

Figure 34 – *Case 6 - Myocardial perfusion scintigraphy within normality, with two image acquisition series, resting and stress, with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

same manner that MPS had already excluded the presence of myocardial ischemia. On the other hand, if the present case had been associated with a high probability of CAD or inadequate technical conditions (e.g. high ventricular response atrial fibrillation), the scenario could have been different, given that, for a patient with high atherosclerotic burden, the positive predictive value of angio-CT is limited. Furthermore, artifacts caused by an unfavorable situation (AF) may severely impair diagnostic accuracy. In these cases, MPS would be a better form of evaluation.

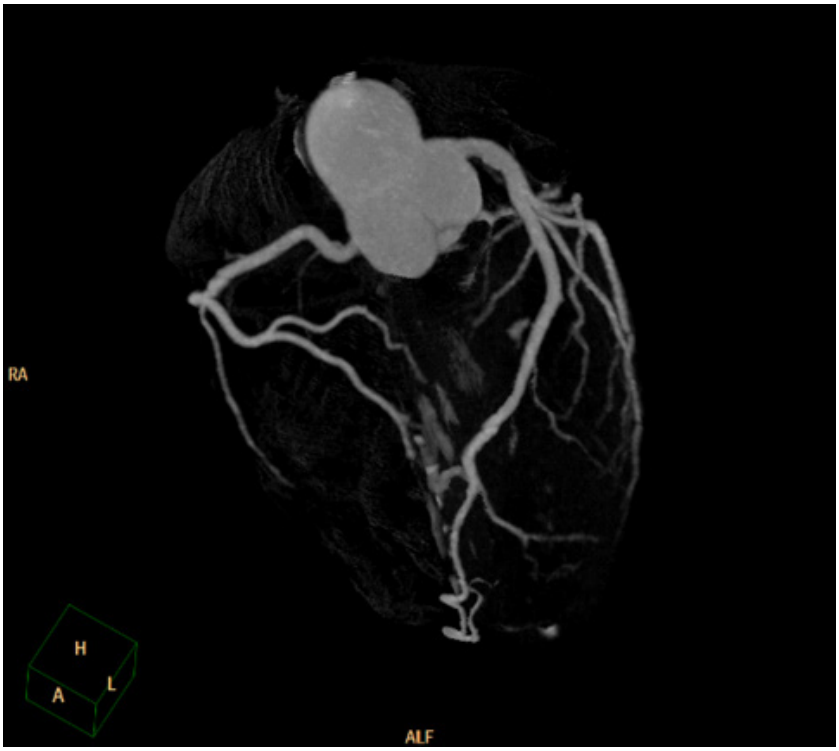

Figure 35 – *Case 6 - Coronary angio-CT within normality.*

7. Patient with artificial electric pacemaker, abnormal MPS and normal angio-CT

Clinical history: female, age 49, diagnosed with Chagas heart disease, using an artificial pacemaker, pain during effort, type II DM, non-insulin-dependent, diagnosed 4 years prior.

Findings: MPS performed with dipyridamole, considering the presence of artificial pacemaker stimulation (Figure 36) suggestive of DDD mode (resting ECG with atrial spikes, without clear visualization of ventricular command). Perfusion defects associated with pharmacological stress were characterized as moderate intensity and medium extent, involving the inferior (mediobasal portion) and inferolateral walls and the apex of the LV (Figure 37), and they were partially transient (predominance of ischemia). Angio-CT showed left dominant coronary circulation, with no signs of atherosclerosis. The presence of atrioventricular pacemaker electrodes limited assessment of the image via angio-CT.

Comments: Returning to the basic and appropriate principles of questions about pre-test probability and characterization of severity based on MPS findings, it is necessary to give special emphasis to the synergy between methods in this case. Symptomatic female patients with DM generally have an intermediate probability of obstructive CAD, mainly depending on the duration and aggressiveness of DM. On the other hand, they also have a high prevalence of endothelial dysfunction and microvascular disease, which may cause alterations in myocardial perfusion.[250] There also exists the condition of Chagas heart disease, which features angina as a manifestation in the absence of obstructive epicardial coronary disease. The doubt which the doctor likely faces upon receiving the MPS results is the following: "What is the chance of obstructive CAD? And of endothelial dysfunction?" This is due not only to the diagnostic question, but also to the therapeutic implications, such as aggressiveness in reducing low density lipoprotein (LDL) cholesterol and the use of acetylsalicylic acid (ASA), for example. Another question is, "Does the perfusion modification in the apex represent an alteration related to Chagas heart disease?" Other questions similarly arise regarding the possibility of silent infarction related to CAD or a defect associated with artificial electrical stimulation resulting in customary atypical movement in the interventricular septum (component of an artifact). In this scenario, a safe and non-invasive way to exclude CAD is to perform angio-CT, which showed normal results in this case. It is important to underline the additional incremental prognostic value of angio-CT in this scenario, given that prognosis for this patient who does not have atherosclerosis, with mild ischemia (likely due to endothelial dysfunction), is considerably better than it would be were there conditions of mild ischemia in a patient suffering from uni- or bi-arterial obstructive CAD, or even in a patient with multivessel non-obstructive CAD.[251] Other considerations refer to the possibility of MPS artifacts, not only related to the pacemaker in this case, but mainly to attenuation artifacts, when attenuation correction is not available, or

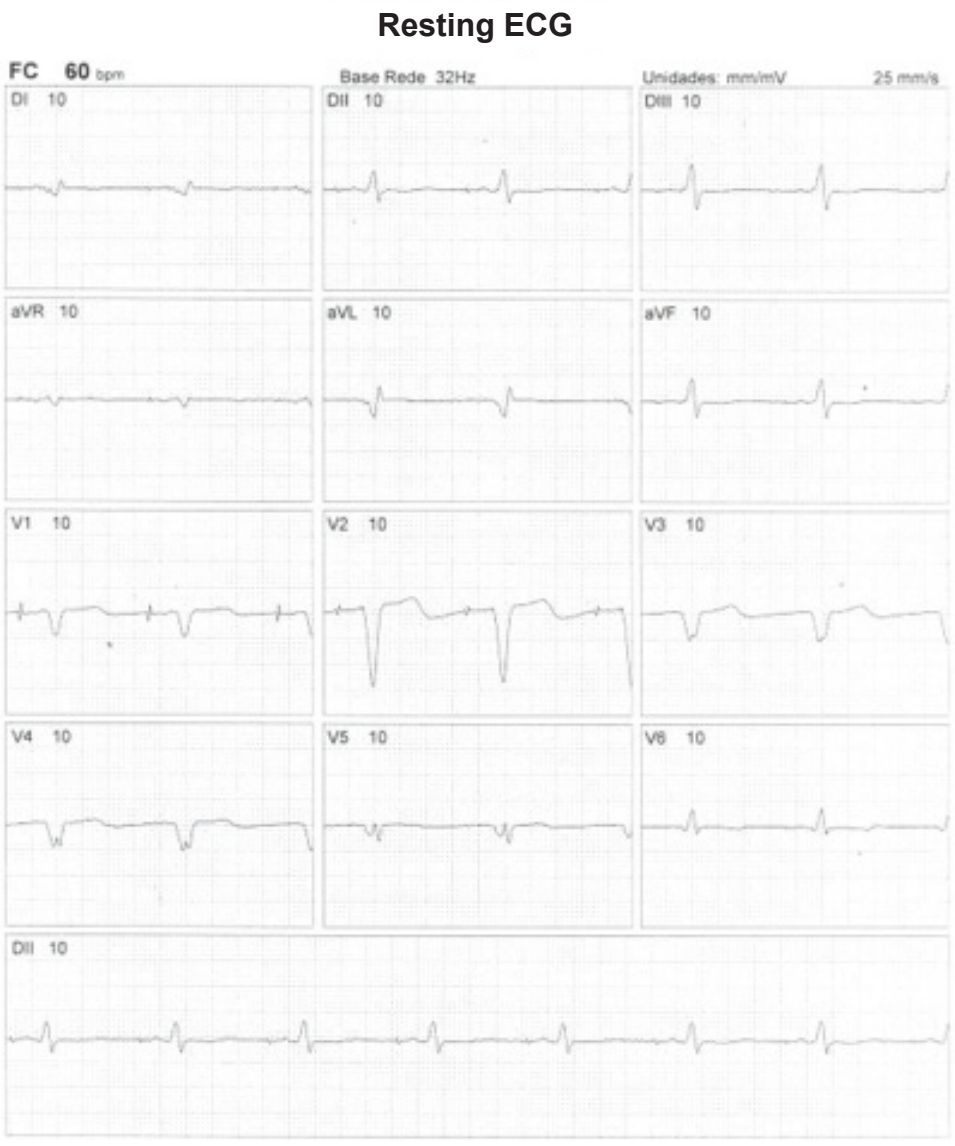

Figure 36 – *Case 7 - Electrocardiogram tracing of patient with artificial pacemaker.*

when the prone position is not routinely used, in addition to the previously described Chagas heart disease. If an artifact is highly suspected, corroborated by the presence of systolic thickness of LV walls without alterations, angio-CT may avoid unnecessary catheterization, even in patients with higher probabilities of CAD. Within Brazilian experience, in a laboratory with a high nuclear cardiology volume, only 24% of patients with mild myocardial ischemia on MPS referred for angio-CT have obstructive CAD. The majority are women (58.8%), 33% of whom have non-obstructive CAD and 43% of whom do not have CAD (International Conference of Nuclear Cardiology – ICNC 2017).[252]

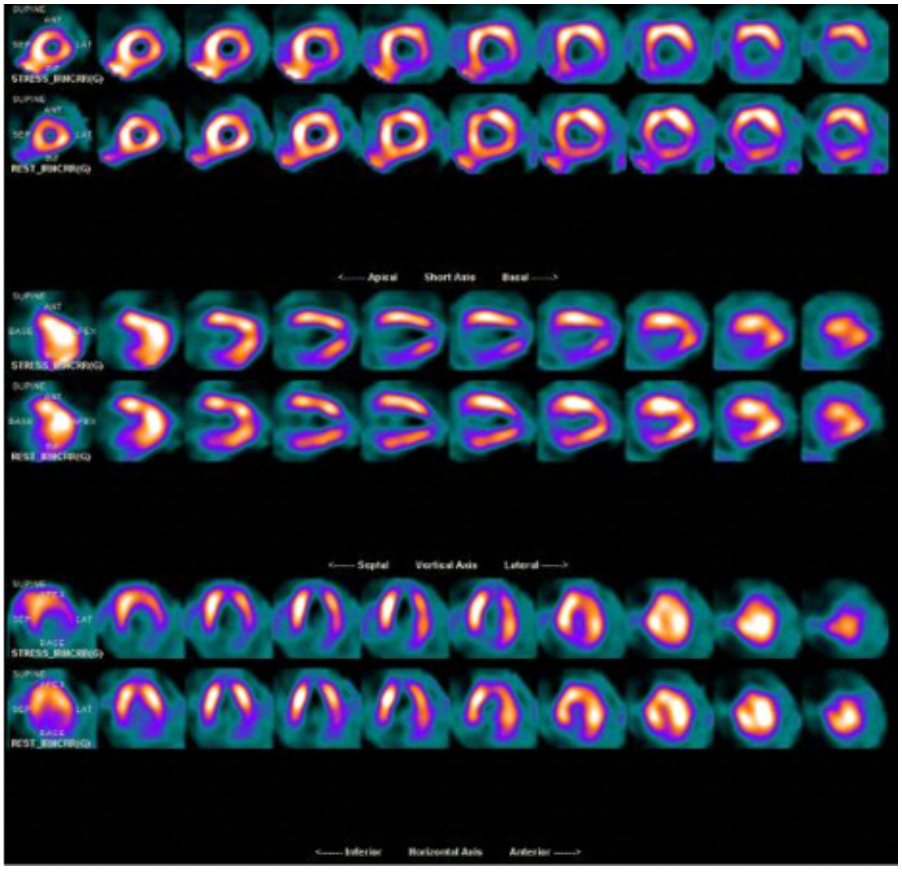

Figure 37 – *Case 7 - Myocardial perfusion scintigraphy showing significant perfusion abnormalities (notably following administration of dipyridamole, with partial improvement while resting) and dilation of the left ventricle. Image acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

8. Patient with abnormal angio-CT and normal MPS

Clinical history: male, age 51, atypical symptoms, active, with positive family history for early CAD.

Findings: Angio-CT showed a CS of 1,445 on the Agatston score (99% percentile); significant obstructive CAD involving the left anterior descending artery in its distal portion (> 70%), with occlusion of the first diagonal branch, which receives collateral circulation; and non-obstructive CAD in the circumflex and right coronary arteries (Figure 38). MPS with perfusion and LV function were considered within normal limits (Figure 39), and ET revealed optimal physical performance (estimated metabolic expenditure of 18 METs) and normal electrocardiographic, clinical, and hemodynamic responses.

Comments: This is a challenging clinical situation, which expresses a fundamental example of integration of non-invasive anatomical and physiological modalities with the goal of avoiding unnecessary revascularization procedures. Performing angio-CT as an initial exam had the objective of excluding obstructive CAD in a young patient with intermediate pre-test probability. Meta-analysis of recent studies has demonstrated a probable benefit of this initial anatomic strategy in this scenario, with reduced AMI, when compared to initial functional test,[253] recently incorporated into guidelines in the United Kingdom.[254] This investigation, however, leads to an increase in the number of invasive procedures and revascularizations, with the risk of these procedures not being appropriate.[245,246] Thus, in the described scenario, with evident anatomy of obstructive CAD, which nevertheless does not meet the criteria for high risk (left main coronary lesion or triple-vessel lesions involving affected areas proximal to the left anterior descending artery), the management considered most appropriate is certainly ischemia quantification, considering that revascularization would be indicated in the presence of at least moderate ischemic burden.[241] In this specific case, the patient should be clinically treated, with an aggressive secondary prevention approach, with close monitoring of modifiable risk factors and special attention to the manifestation of symptoms, postponing revascularization, at least in this moment where there is a lack of evidence regarding its benefits.

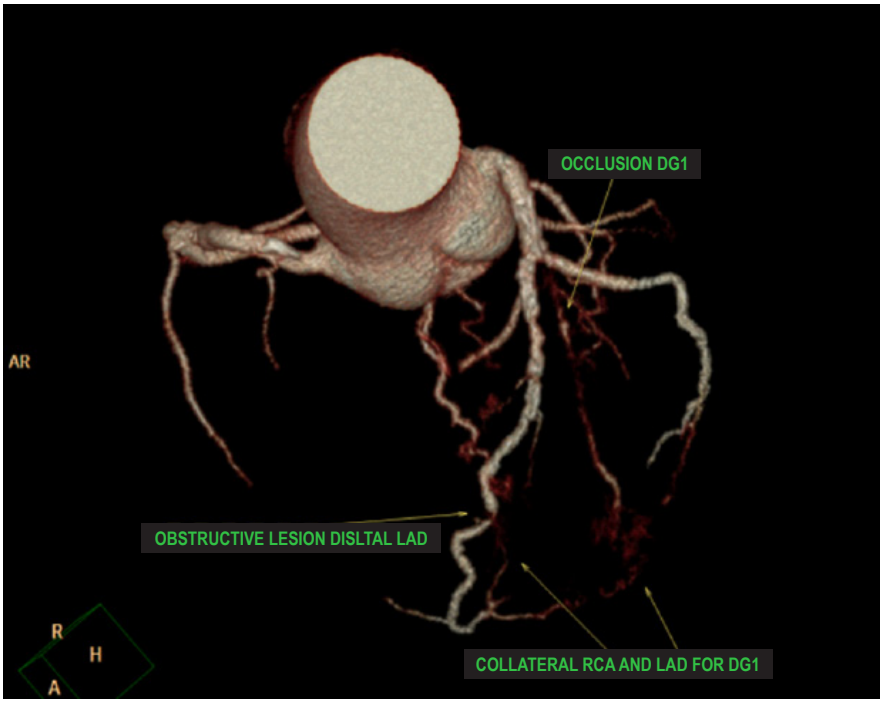

Figure 38 – *Case 8 - Angio-CT showing significant obstructive alterations and evidence of advanced coronary artery disease. DG1: diagonal 1 coronary artery branch; LAD: left anterior descending artery; RCA: right coronary artery.*

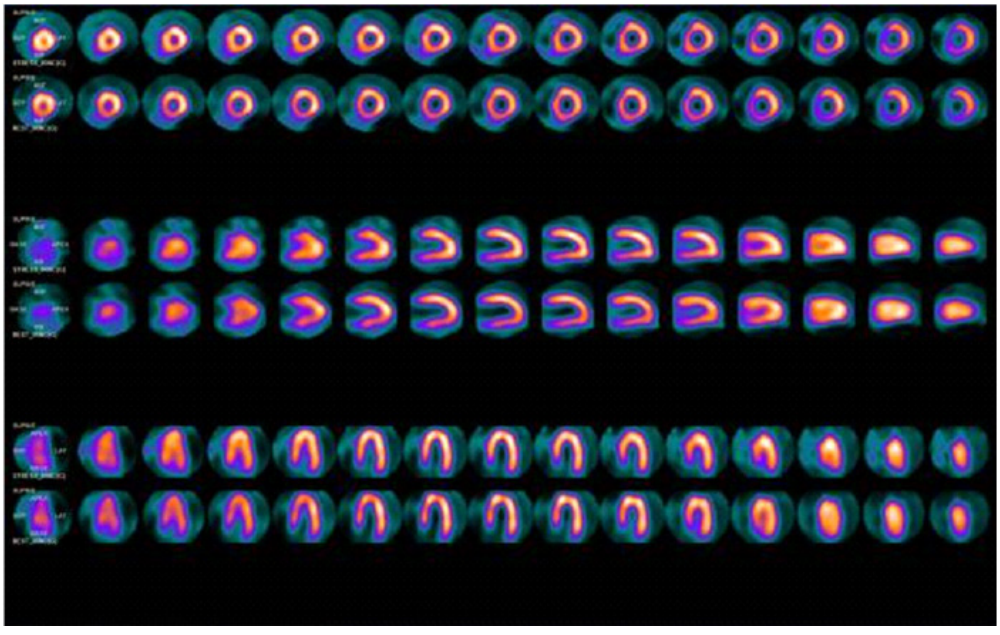

Figure 39 – *Case 8 - Myocardial perfusion scintigraphy within normality. Images acquired with dedicated cardiac equipment, equipped with solid cadmium-zinc-tellurium detectors.*

9. Patient with abnormal angio-CT and abnormal MPS

Clinical history: male, age 51, with atypical chest pain (not always related to effort). Dyslipidemia and family history of early CAD (Both his father and brother had AMI resulting in death at the age of 53). Referred for coronary angio-CT to rule out obstructive CAD as the cause of the symptoms.

Findings: Angio-CT showed a CS of 12.2 (Agatston score, 67% percentile), mild, non-calcified atherosclerosis in the left main coronary and partially calcified atheromatous plaque in the middle third of the left anterior descending branch (Figure 40), resulting in moderate to significant luminal reduction (60% to 70%). The patient was referred for MPS associated with physical stress, exercising for 11 minutes in the Bruce protocol, with no significant ST-segment alterations (Figure 41) and without reproducing the symptoms. MPS images showed mild transient reduced uptake (ischemia) in the anteroseptal and septal walls and the apex of the LV (Figure 42).

Comments: Considering that a male patient with stable chest pain is characterized as having an intermediate pre-test probability of CAD, the routine non-invasive methods for diagnostic and prognostic evaluation are indicated. If the resting ECG is normal and the patient has informed ability to exercise (performing daily activities with estimated metabolic expenditure of > 5 METs), the ET is then the consensual indication, provided that its limitations are taken into account. In the case in question, the early family history of CAD stands out. This fundamental clinical information is not always incorporated into traditional methods of estimating pre-test probability. In this context, coronary angio-CT was chosen, in part to rule out obstructive CAD (high NPV), which is present in only 23% of symptomatic patients within the same probability range, according to the CONFIRM register.[240] This register demonstrates lower observed prevalence of 50% to 70% obstructive lesions on angio-CT, in comparison with the expected prevalence calculated by conventional algorithms, establishing the concept that the routine algorithms for characterizing pre-test or expected probability of events during long follow-up periods, such as the Framingham, PROCAM, Diamond Forrester, SCORE, and Global Risk; overestimate CAD. This is also the case with detection of early, non-obstructive CAD (present in 34% of patients in this register), especially in patients with family history. This investigation strategy has already been shown to be effective and likely to reduce AMI,[252] as previously discussed in this section; it is, however, necessary to be careful with excessive interventions. This was precisely the role of functional evaluation via MPS in this case. Detection and quantification of ischemia are fundamental for determining patient management, given that the presence of moderate to severe ischemia alone would justify a more invasive strategy, such as revascularization, in the absence of refractory angina. This case was thus started on optimal clinical treatment, similar to that of patients included in the COURAGE study.

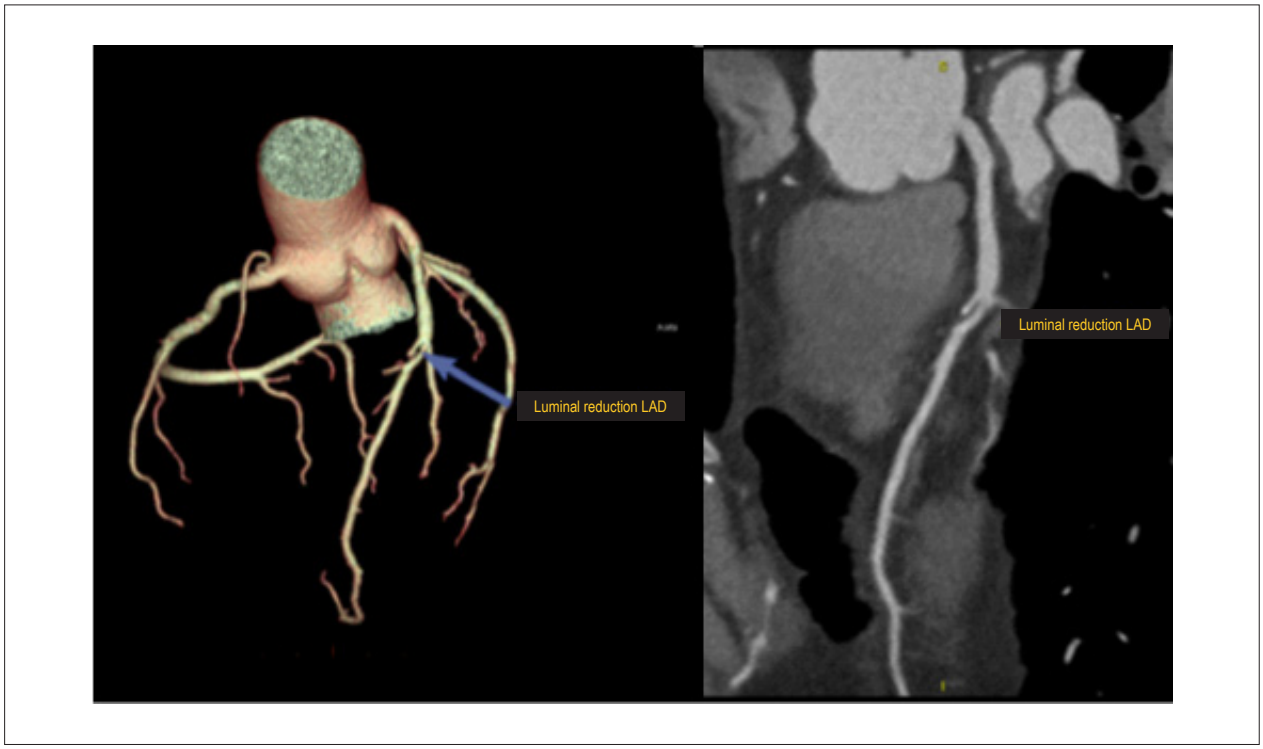

Figure 40 – *Case 9 - Angio-CT demonstrating significant obstructive luminal lesion, with the absence of calcification in coronary arteries. LAD left anterior descending artery.*

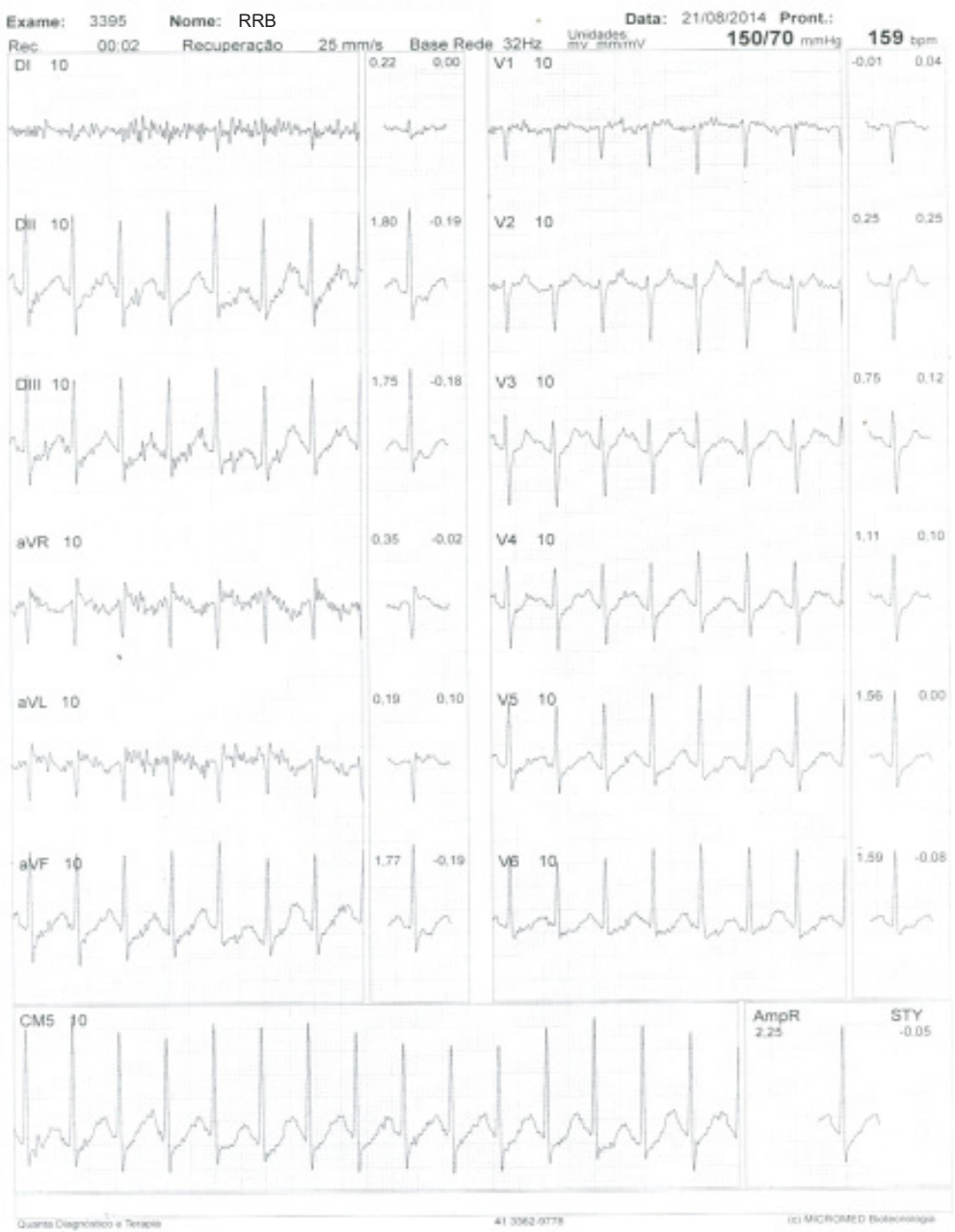

Figure 41 – *Case 9 - Electrocardiogram tracing obtained during immediate recovery period, with no significant alterations.*

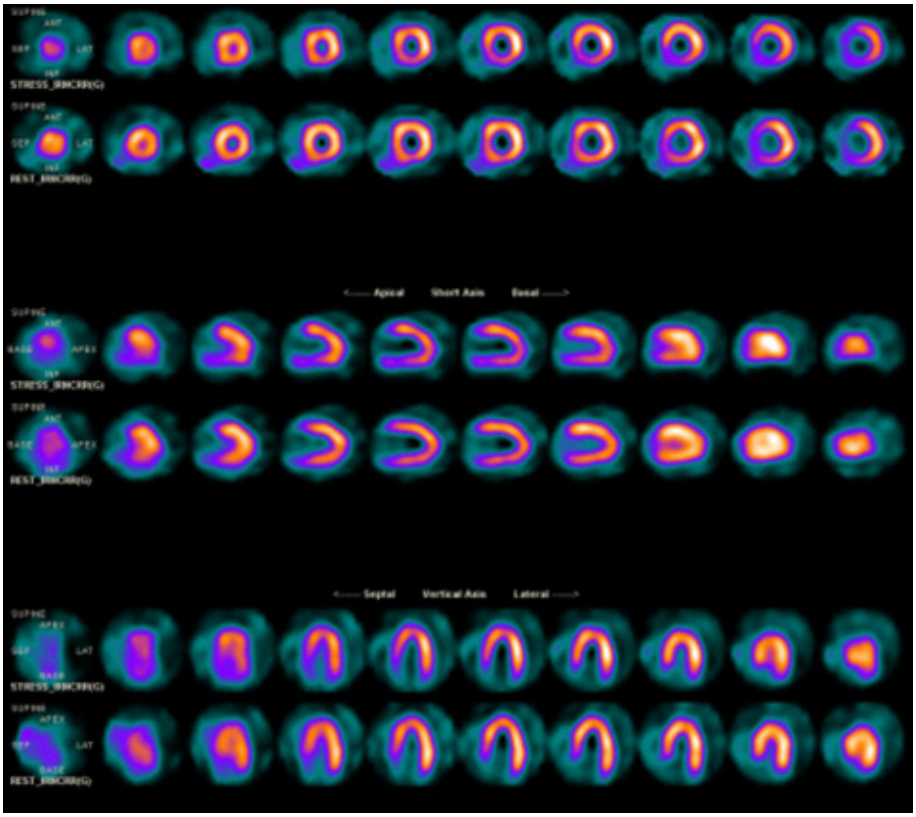

Figure 42 – *Case 9 - Myocardial perfusion scintigraphy demonstrating transient reduced uptake, characterized by mild intensity and small extent, suggestive of ischemia in the anteroseptal and septal walls and the apex. Images acquired with appropriate cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

10. Patient with abnormal ET, normal MPS, and abnormal angio-CT

Clinical history: female, age 67, with fatigue related to effort. Hypertensive ex-smoker, diagnosed with diabetes 1 year prior. Referred for MPS following abnormal ET with intermediate risk.

Findings: The patient exercised for 9 minutes in the Bruce protocol, reaching a HR of 136 bpm (89% maximum HR predicted based on age), triggering stress arrhythmias (ventricular and supraventricular extrasystole, in addition to periods of nonsustained ventricular tachycardia [NSVT]). ST-segment depression reached 3 mm in multiple leads (Figure 43), but the patient was asymptomatic. *Duke Score* = **- 6**, characterized as intermediate risk. On MPS, there was an absence of signs of ischemia (Figure 44). Considering the clinical profile and the finding of complex ventricular arrhythmia (NSVT), concomitant with descending ST-segment depression, in spite of normal perfusion on MPS, the clinical option was to perform an angio-CT, which showed advanced atherosclerosis (Figure 45) with a CS of 829 on the Agatston score (97% distribution percentile) and non-obstructive lesions (< 30%) in multiple vessels.

Comments: In this patient, analysis of ET plays an important role in case management. MPS study with the radiopharmaceutical MIBI-^{99m}Tc showed no abnormalities, which, in itself, determines excellent short-term prognosis. The presence of ventricular tachyarrhythmia during stress, however, adds a risk that is not, in practice, incorporated into risk prognosis by the Duke score. Furthermore, it limits analysis of the ST segment and may give rise to diagnostic doubts. One study which stands out in the literature verified that the inclusion of ventricular arrhythmia as a variable in the Duke score during ET increased its restratification potential in 30% of patients.[23] Once again, questions may arise related to the lower sensitivity of MPS, which was apparently normal in this case (a false-negative result?). Another question is, "Should differential diagnoses such as cardiomyopathy, specific conduction tissue disease, among others, be additionally considered?" Although functionally severe obstructive CAD is improbable when MPS is normal, anatomical data from angio-CT complement and clarify many of these doubts which arose due to the conflicting results of the two functional tests. One alternative would be to perform CS, but, particularly in symptomatic patients, more detailed evaluated of anatomy via angio-CT, which

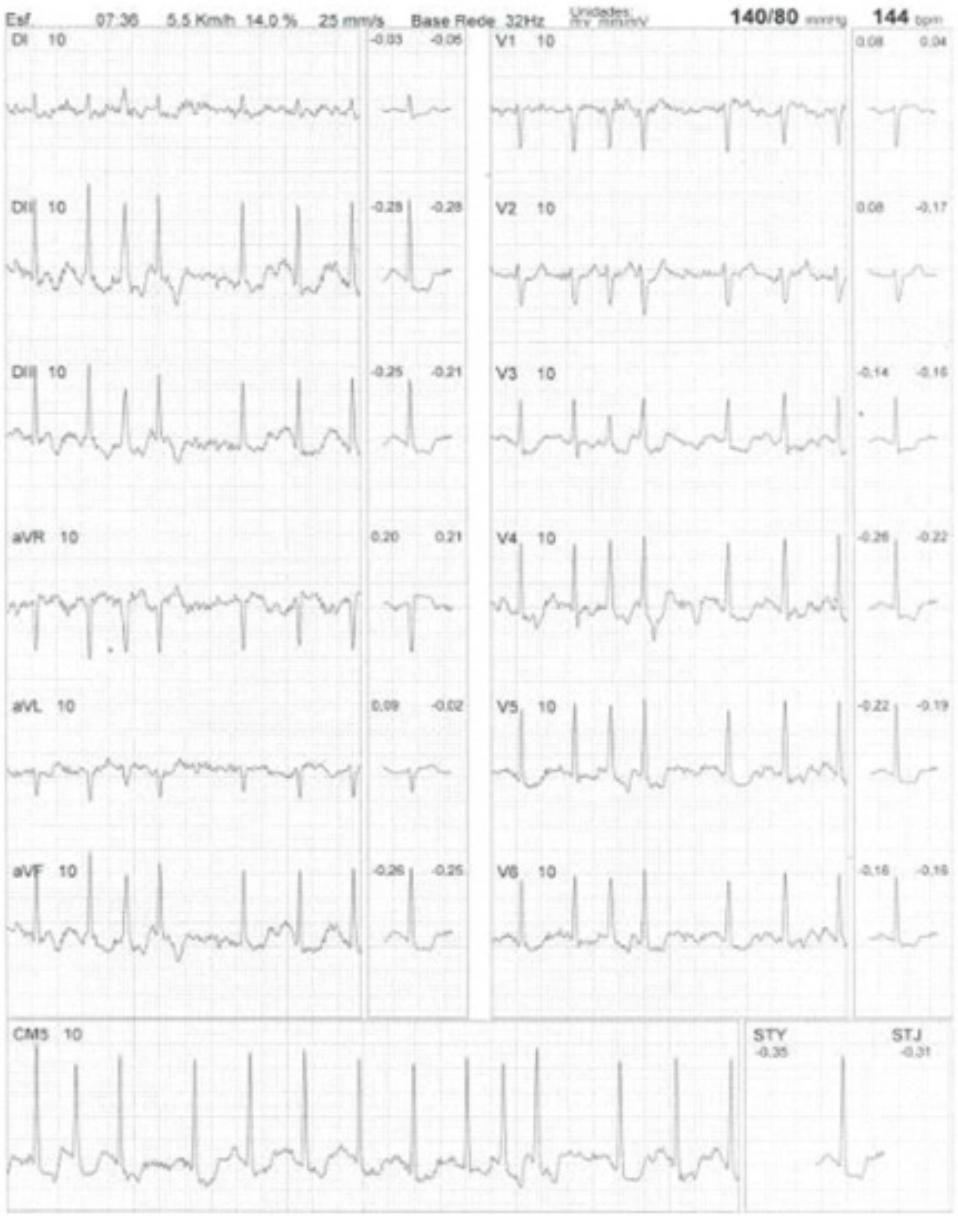

Figure 43 – *Case 10 - Electrocardiogram tracing demonstrates ischemic ST-segment alterations and episodes of supraventricular arrhythmia, in addition to nonsustained ventricular tachycardia.*

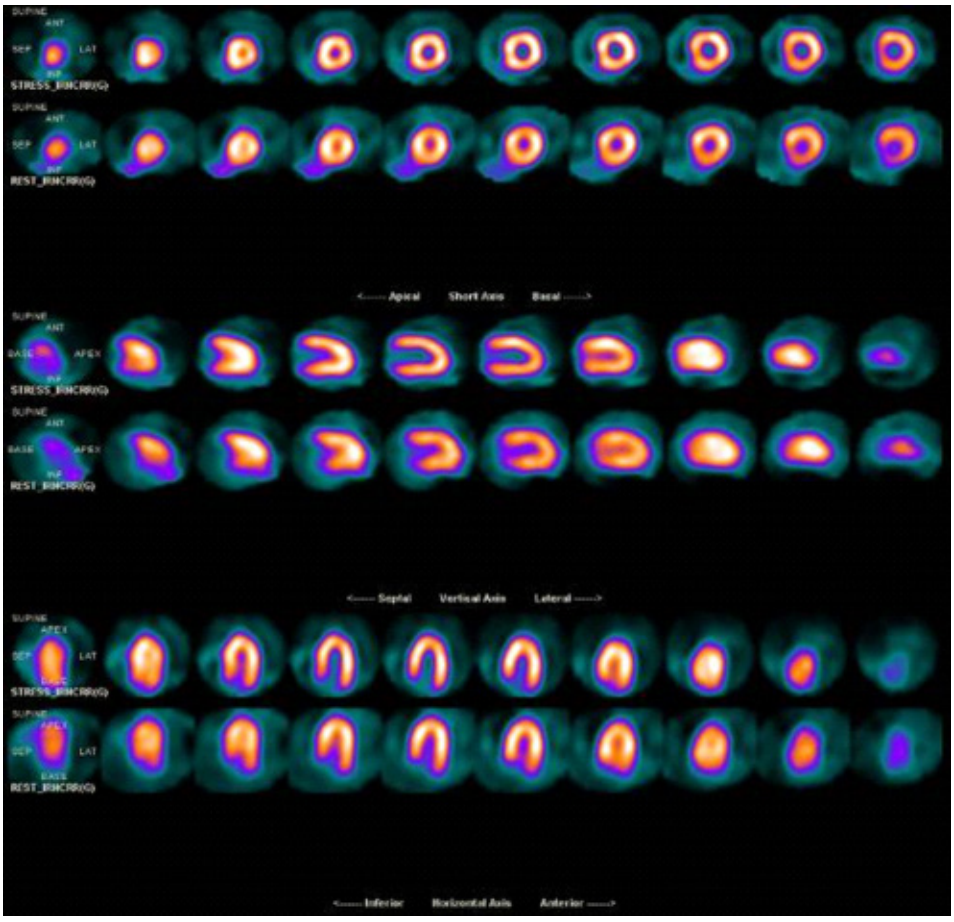

Figure 44 – *Case 10 - Myocardial perfusion scintigraphy with homogenous radiopharmaceutical distribution throughout the walls of the left ventricle, considered within the limits of normal. Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals. Reproduced with the permission of Vitola JV.*[234]

quantifies degree of obstruction and determines the presence and extent of non-calcified atherosclerosis, adds incremental prognostic value.[256] In this specific case, the presence of non-obstructive atherosclerosis, even with normal perfusion, denotes worse prognosis than in patients with normal perfusion and the absence of atherosclerosis.[257] Moreover, the presence of atherosclerosis in multiple segments, as in the present case, confers a prognosis similar to that of uniarterial obstructive CAD.[250] In conclusion, clinical translation of such findings could be resumed in the following manner: there are no indications that the ET alterations are secondary to ischemia, and there are thus no accrued benefits to coronary intervention, whether percutaneous or surgical revascularization. Orientation should be toward aggressive treatment of atherosclerosis to reach lipid goals recommended in current guidelines, in addition to strict control of other modifiable risk factors. The patient's current profile confers medium- and long-term prognosis similar to that of a patient with obstructive CAD in a single coronary artery.

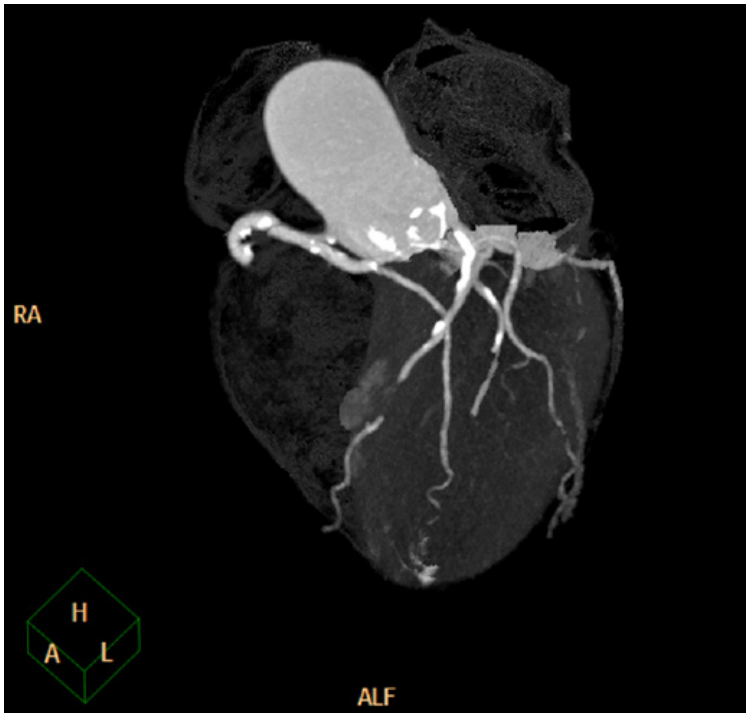

Figure 45 – *Case 10 - Coronary angio-CT showing significant coronary atherosclerosis, with multivascular calcification. Reproduced with the permission of Vitola JV.*[234]

11. Patient unable to exercise, abnormal MPS associated with pharmacological stimulus with dipyridamole and angio-CT showing non-obstructive CAD, ischemia suggestive of microcirculatory abnormalities

Clinical history: female, age 68, with stress fatigue. Hypertensive and obese, diagnosed with diabetes 8 years prior. Referred for MPS due to difficulty performing physical exercise test.

Findings: During the attempted test with physical exercise, the patient exercised for only 6 minutes in the Bruce protocol, with a peak HR of 115 bpm (75.6% the expected upper limit, based on age). The stress phase was discontinued due to fatigue and calf-muscle pain, also establishing suspected chronotropic incompetence. As an alternative, the protocol was initiated with dipyridamole, and it was considered altered due to ST-segment depression of 1.0 mm, in 2 leads, following completion of intravenous administration (Figure 46). MPS was considered abnormal due to transient reduced uptake suggestive of ischemia, involving the anterior and anterolateral (predominantly in the middle distal portion) walls of the LV, with moderate intensity and medium extent, characterized as mild to moderate ischemic burden, in addition to preserved LV function (Figure 47). Considering the high clinical risk profile, the findings of probable chronotropic incompetence, ST-segment alterations with dipyridamole, and ischemia in the anterior descending territory; the option was to complement with angio-CT, which showed non-calcified and non-obstructive atherosclerosis, with a CS of zero and a mild lesion (< 30%) in the anterior descending branch.

Comments: This is a classic example of a symptomatic patient with a combination of factors which, in association, may result in phenomena of endothelial and microcirculatory dysfunction, with the consequent condition of myocardial ischemia. This physiopathological condition, little over a decade ago, would have led to coronary cineangiography study in order to rule out obstructive CAD. As a consequence, "normal" coronary arteries were often observed, in what were known as "white catheterizations." With the findings described in specific populations, especially in female patients, the recent use of the term "ischemic heart disease" has gone on to express the conditions of obstructive atherosclerosis, endothelial dysfunction, and microvascular dysfunction more adequately. A recent review published by Pepine et al. in 2015 [258] described important differences in the CAD spectrum in both sexes, pointing out that symptomatic women have a lower prevalence of obstructive CAD than men with the same symptoms. On the other hand, they tend to have more microvascular dysfunction, plaque erosion, and thrombus formation. In this specific case, the following factors stand out: female sex, obesity, DM, altered functional tests (both the post-dipyridamole ECG and perfusion imaging via MPS), and non-obstructive CAD on angio-CT.

Based on this combination of individual characteristics, especially with endothelial dysfunction and reduced coronary

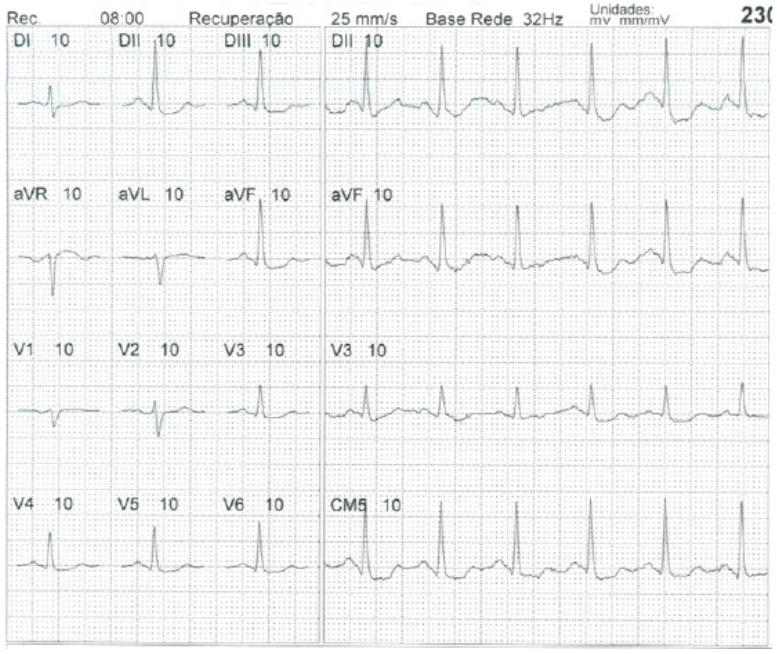

Figure 46 – *Case 11 - Electrocardiogram tracing with ischemic ST-segment alterations following administration of dipyridamole.*

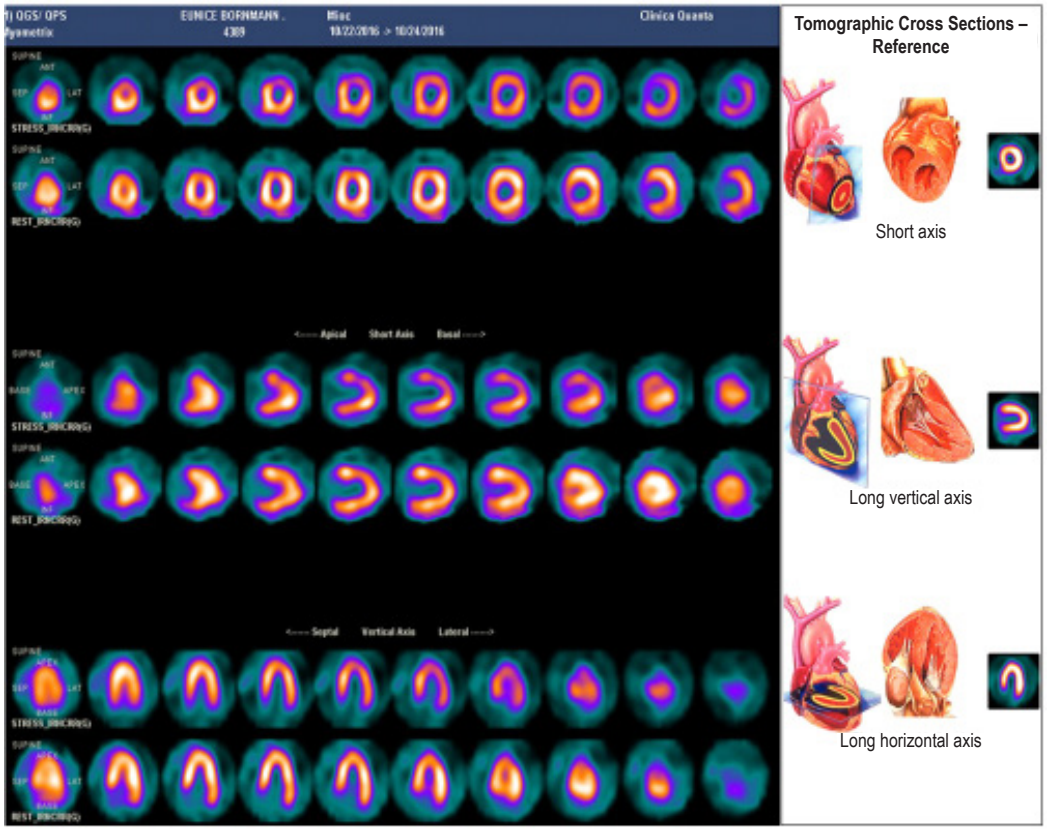

Figure 47 – *Case 11 - Myocardial perfusion scintigraphy (MPS) demonstrating moderate ischemic burden in the anterior wall, extending to the anterolateral wall of the left ventricle. Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

flow reserve (CFR), associated with non-obstructive CAD, the risk of cardiovascular events is significantly higher, and it is similar to that of individuals who have obstructive CAD, but who are not indicated for revascularization.[259] Thus, as the prevalence of obstructive CAD is lower in women, angio-CT has been growing as a preferential diagnostic method for ruling out obstructive CAD in patients with intermediate probability, especially when there are limits to the physical exercise test.[260] In the case in question, the combination of functional (ischemia) and anatomical (non-obstructive CAD) data was essential to the diagnosis of endothelial dysfunction and to guiding therapeutic management.

12. Abnormal ET characterized as intermediate-risk and abnormal MPS with high-risk indicators

Clinical history: male, age 69, with precordial pain during greater efforts for 4 months. Hypertensive, ex-smoker, referred for MPS due to altered ET, with intermediate Duke score.

Findings: patient exercised for 9.5 minutes in the Bruce protocol, reporting non-limiting anginal pain during peak exercise, with descending ST-segment depression of 1.0 mm, measured at the J point, in multiple leads, with prolonged duration, during the recovery phase (Duke score = +0.5) (Figure 48). Perfusion imaging showed transient reduced

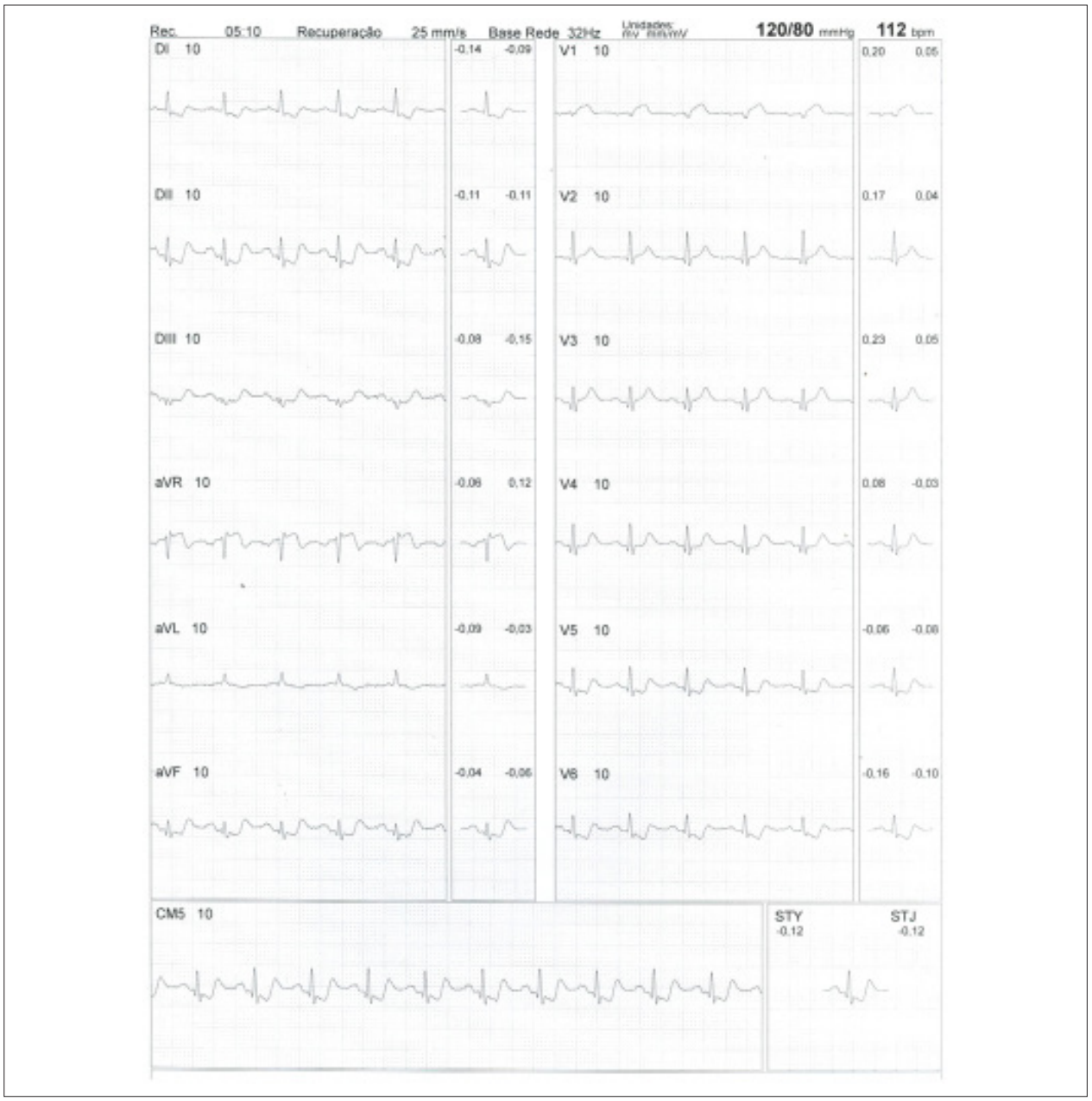

Figure 48 – *Case 12 - Electrocardiogram showing prolonged ischemic alterations during the late recovery phase.*

uptake in the septum and apex of the LV, which was exercise-induced, characterized by severe intensity and medium extent (moderate ischemic burden), associated with the component of persistent reduced uptake in the described territory. Apical and septal akinesis (predominantly distal) were also observed following exercise, as well as apparent transient dilation of the LV cavity and uptake of MIBI-^{99m}Tc in RV walls, which are additional markers of severity (Figure 49).

Comments: This is an example of a case where functional methods are in agreement regarding detection of ischemia. Cardiac imaging, here, provides additional information to the ET (intermediate-risk Duke score), which is known as "incremental prognostic value." Quantification of ischemia via MPS restratifies this patient as high-risk. In this situation, revascularization procedures may be considered based on current evidence, although the results of the ISCHEMIA study (ISCHEMIA study Addendum - report to item 2 of this guideline) have not been yet published. This case is complementary to the discussion elaborated in Case 1, where non-invasive images via MPS added prognostic value and guided patient management.

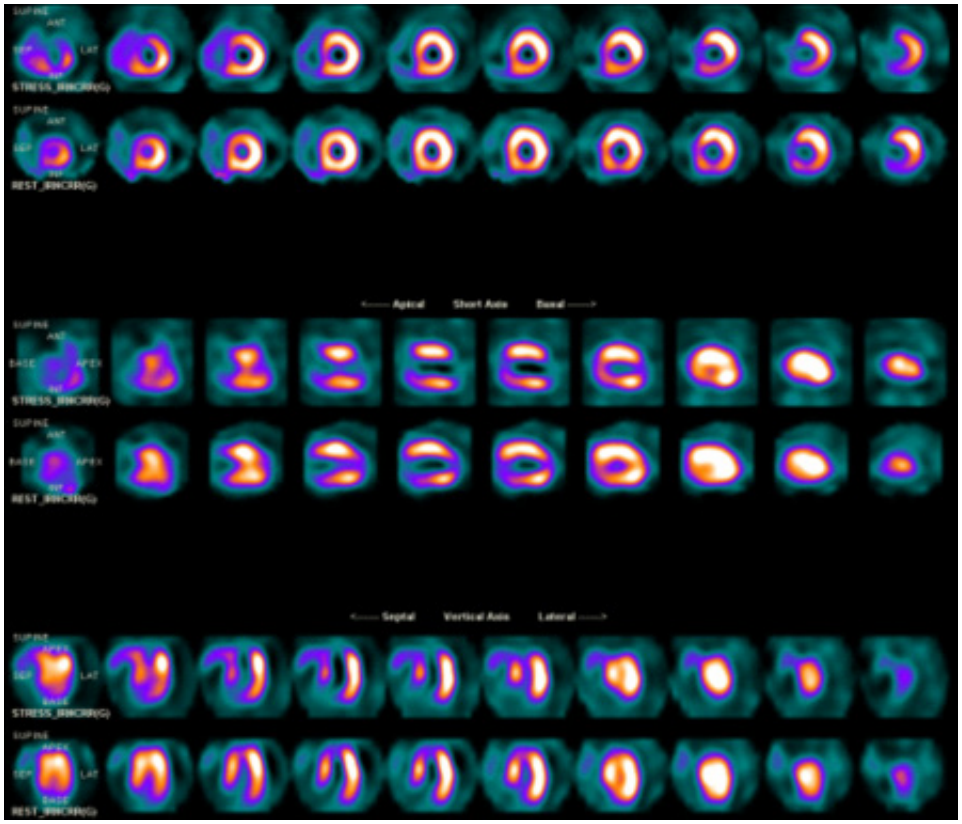

Figure 49 – *Case 12 - Myocardial perfusion scintigraphy (MPS) showing important ischemic findings (transient, stress-induced reduced uptake), with high-risk indicators, involving the territory of the left anterior descending artery (LAD). Images acquired with dedicated cardiac equipment (gamma camera), equipped with conventional sodium iodide crystals.*

10. Evaluation of Myocardial viability via Myocardial Perfusion Scintigraphy

10.1. Introduction

In some patients with chronic CAD and ventricular dysfunction, revascularization may significantly improve symptoms, ventricular function, and mortality. Physiopathological conditions and acute and chronic mechanisms of adaptation to temporary reduction of coronary flow include stunning, hibernation, and preconditioning, either separately or coexisting in the same patient.[261] Evaluation of myocardial viability is, consequently, important to the therapeutic decision-making process for patients with ventricular dysfunction (class of recommendation I, level of evidence B) without angina,[262-266] given that functional improvement will not occur in the presence of fibrosis. Several non-invasive imaging techniques are available for detection of viable myocardium, including stress echocardiography with dobutamine, cardiac resonance, and nuclear imaging with SPECT or PET. These methods evaluate different myocardial characteristics and,

thus, present variations in sensitivity and specificity.[261] In the SPECT technique, the use of thallium-201 (^{201}Tl) is the established method for evaluating myocardial perfusion and the integrity of the cellular membrane. In comparison with other radiopharmaceuticals and available techniques, this has become the choice for determining viability.[267,268]

Additionally and in conjunction with these non-invasive techniques, whose aim is to obtain functional and/or anatomical information, constituting the basis of the physiopathological approach to underlying HF, multiple detector CT is also appropriate.

However, the selection of imaging modalities, whose purpose is to assess CHF and, specifically, viability of a dysfunctional myocardium, depends on the clinical information that is required for adequate patient management (Table 26), with inherent questions and affirmations, such as:

- Is the etiological cause of the cardiomyopathy in question ischemic or non-ischemic?
- In patients considered "ischemic," the need for revascularization should be evaluated with respect to characterization of the quantity of myocardium at risk/viability.
- Evolving assessment of LV function and the possibility of remodeling are mandatory elements for analysis within the clinical decision-making process;[269] other elements include secondary mitral regurgitation,[270] implantable devices, such as defibrillators and/or resynchronization therapy.[271]
- Moreover, when the etiology of LV dysfunction, considered of the utmost magnitude for therapeutic decision making, is mandatorily under discussion, it has been verified that the majority of patients will have ischemic cardiomyopathy. Data from 24 multicenter studies on CHF, published in high-impact periodicals between 1986 and 2005 and summarized in 2006, including 43,568 individuals, showed a 62% prevalence of CAD. This frequency is probably underestimated to the extent that coronary cineangiography was not performed in all patients.[272]

10.2. Morphology

It had initially been established that the recovery of ventricular function, when a hibernating myocardium was revascularized, should indicate that structural changes were absent or minimal, as observed in experimental models of stunned myocardium. However, since the beginning of the 1980's, it has been known that chronically dysfunctional myocardial segments demonstrate distinct morphological changes under microscopy.[273]

There is a combination of normal, atrophic, and hypertrophic myocytes, with or without evidence of necrosis. Electron microscopy shows loss and/or disorganization of myofilaments and alterations in sarcoplasmic reticulum and mitochondria. These structural changes may contribute to slow functional recovery following revascularization.[274]

10.3. Evaluation of Viable Myocardium

The differentiation between the presence and absence of viability is highly relevant in patients under consideration for revascularization. Many patients who demonstrate viability associated with severe LV dysfunction may still be candidates for revascularization, but not for cardiac transplant.[275]

10.4. Physiopathology and Definitions

- The term viable myocardium, regardless of the contractile state of the myocardium, should be understood differently in the context of CHF and viability study, given that the main objective is to predict improvement in LV function following revascularization.
- Persistent contractile dysfunction of the LV may be related to chronic hibernation and/or stunning, and not merely associated with fibrotic tissue. Revascularization may improve function and survival if the dysfunctional myocardium is still viable. Functional improvement will not occur in the presence of fibrosis.
- The initial point for discussion of viability implies regional dysfunction, detected by various non-invasive methods, including echocardiography as an initial line of investigation.
- Differentiation between hibernation and stunning may be established based on blood flow to the myocardium. While resting flow is chronically diminished in hibernation, it may still be preserved in the stunned myocardium, with a compromised flow reserve however.[19]
- Clinically speaking, it may not always be feasible to separate the 2 physiopathological conditions; nor is it always necessary, considering that both entities require revascularization in order for there to be improvements

Table 26 – Clinical situations where nuclear cardiology should be considered a preference for assessing myocardial viability, in the following order of choice: PET with 18F-FDG, resting scintigraphy with thallium-201 and reinjection protocol, and resting scintigraphy with Sestamibi - ^{99m}Tc sensitized with oral nitrite

• Evaluation of extent/localization of dysfunctional myocardium at risk, through significant hypoperfusion (hibernating myocardium)
• Clinical situations in which sensitivity is sought for assessment of viability
• Contraindications to the use of MR: patients with pacemakers or cardiac defibrillators incompatible with resonance, cerebral clips, cochlear implants, metallic fragments in their eyes, or renal insufficiency
• Conditions which limit image acquisition via MR: claustrophobia, irregular cardiac rhythm, dyspnea with inability to remain in dorsal decubitus for prolonged periods
• Availability of the method and local expertise

^{18}F-FDG: fluorodeoxyglucose labeled with fluorine-18; MR: magnetic resonance; PET: positron emission tomography.

in ventricular function. Affected areas are referred to as viable myocardium or myocardium at risk.[276]

- The coexistence of normal myocardium, however, and the formation of subendocardial scarring will not result in improved function, which is now considered "non-jeopardized" area of viable myocardium.
- Most experience in assessing viability has been obtained with nuclear imaging, utilizing SPECT and PET, with assessment of perfusion and metabolism. Moreover, using SPECT, cellular and mitochondrial membrane integrity may be characterized.
- It has been demonstrated that 40% to 50% of dysfunctional segments without contractile reserve may still have preserved perfusion and metabolism, some of which will recover function following revascularization procedures. The loss of contractile reserve is associated with structural damage characterized by greater severity and fibrosis formation.
- Several viability standards have been recognized in areas of contractile dysfunction, for instance: I) any region with > 50% of radiopharmaceutical uptake in resting images; II) any perfusion defect with > 10% increase in uptake of late images.[277] It is, however, necessary to emphasize that areas with > 50% uptake often do not improve in function, given that these regions contain mixtures of normal myocardium and non-transmural scarring.
- Uptake and retention of tracers (sestamibi and tetrofosmin, labeled with technetium-99m) depends on perfusion, cellular membrane integrity, and mitochondrial function, where radiopharmaceutical uptake of > 50% to 60% in dysfunctional areas is frequently used as a sign of viability, when observed in resting images.

10.5. The Most Frequently Used Protocols[24,278,279]

1. **Stress and redistribution – two steps or image acquisition series/one injection of ^{201}Tl:** This is a conventional technique with image acquisition between *2 and 10 minutes* (a maximum of 15 minutes) following injection of ^{201}Tl during peak stress (*first step*). These images reflect initial *distribution* of the radioisotope dependent on blood flow and, thus, regional myocardial flow. Two to four hours after initial intravenous administration of the radioisotope, in the resting condition (*second step*), a new series of images is obtained, representing the "*redistribution phase*," related to the continuous exchange of ^{201}Tl throughout the myocardium and extracellular behavior. This protocol has been designed to study ischemia, and it is not sufficient for characterization of viability, given that viable tissues may not exhibit improvement in radiopharmaceutical uptake (reversibility) within conventional time periods for redistribution images, giving the apparent impression of persistent reduced radioisotope uptake or fibrosis.

2. **Stress/redistribution and reinjection – three steps or image acquisition series/two injections of ^{201}Tl (Figure 50B):** In addition to the conventional protocol, which contains only *1 injection of ^{201}Tl* during *stress* (at a dose of up to 3.0–3.5 mCi), this includes the *reinjection of ^{201}Tl* (generally at a dose of 1 mCi) *immediately after the redistribution phase*, with the aim of elevating blood concentration of the radioisotope, with a new image acquisition series that may vary in terms of time (between 6 to 24 hours). There is evidence that up to 50% of regions with perfusion defects that are apparently "fixed or persistent" improve in terms of relative radioisotope uptake. This information is predictive of improvement in regional function following revascularization. Areas with sustained or severe reduced uptake following reinjection show a low probability of recovering ventricular function. Further variations are demonstrated in **Figures 50 C** and **D**.

3. **Stress/redistribution and late imaging – three steps or image acquisition series/one injection of ^{201}Tl (Figure 50A):** The addition of *late imaging 24 hours* after injection of thallium-201 during the *stress or distribution phase (first step)* allows more time for the phenomenon of redistribution to occur and, consequently, for increase in myocardial uptake of the radiopharmaceutical. This technique shows good predictive value for improvement of ventricular function following revascularization, but suboptimal NPV owing to the technical quality of images obtained after this period, as well as to the fact that some patients do not demonstrate redistribution during very prolonged periods.

4. **Resting/redistribution – two steps or image acquisition series/one injection of ^{201}Tl while resting:** This protocol eliminates the stress phase, based on knowledge of the physiopathology of temporal variations in coronary flow in hibernating myocardium or in unstable patients, leading to perfusion defects that may occur in resting studies, with redistribution in late images. Qualitative studies using the *resting-redistribution* protocol to evaluate efficacy of revascularization have shown that the majority of myocardial regions with reversible defects during pre-operative periods presented post-operative normalization in perfusion and/or improved ventricular function. Some viable regions, however, may not present redistribution, even in images at 24 hours, unless ^{201}Tl blood levels are elevated following reinjection. Practically speaking, most of the clinical information necessary to the medical decision-making process, related to viability study, will have been obtained during the *stress-redistribution-reinjection* sequence, and late images will generally not be necessary. There is no established consensus regarding the accuracy of Sestamibi - ^{99m}Tc while resting for detection of viability, with some studies showing similar uptake for ^{201}Tl and Sestamibi - ^{99m}Tc (quantitative assessment) in patients with UA and LV dysfunction. It has also been observed to have satisfactory predictive value for improvement in contractility in the ventricular walls following revascularization, similar to that of ^{201}Tl.[280] The administration of nitrates before injection of the radiopharmaceutical with the objective of improving resting myocardial flow seems to improve accuracy for detecting myocardial viability.[281]

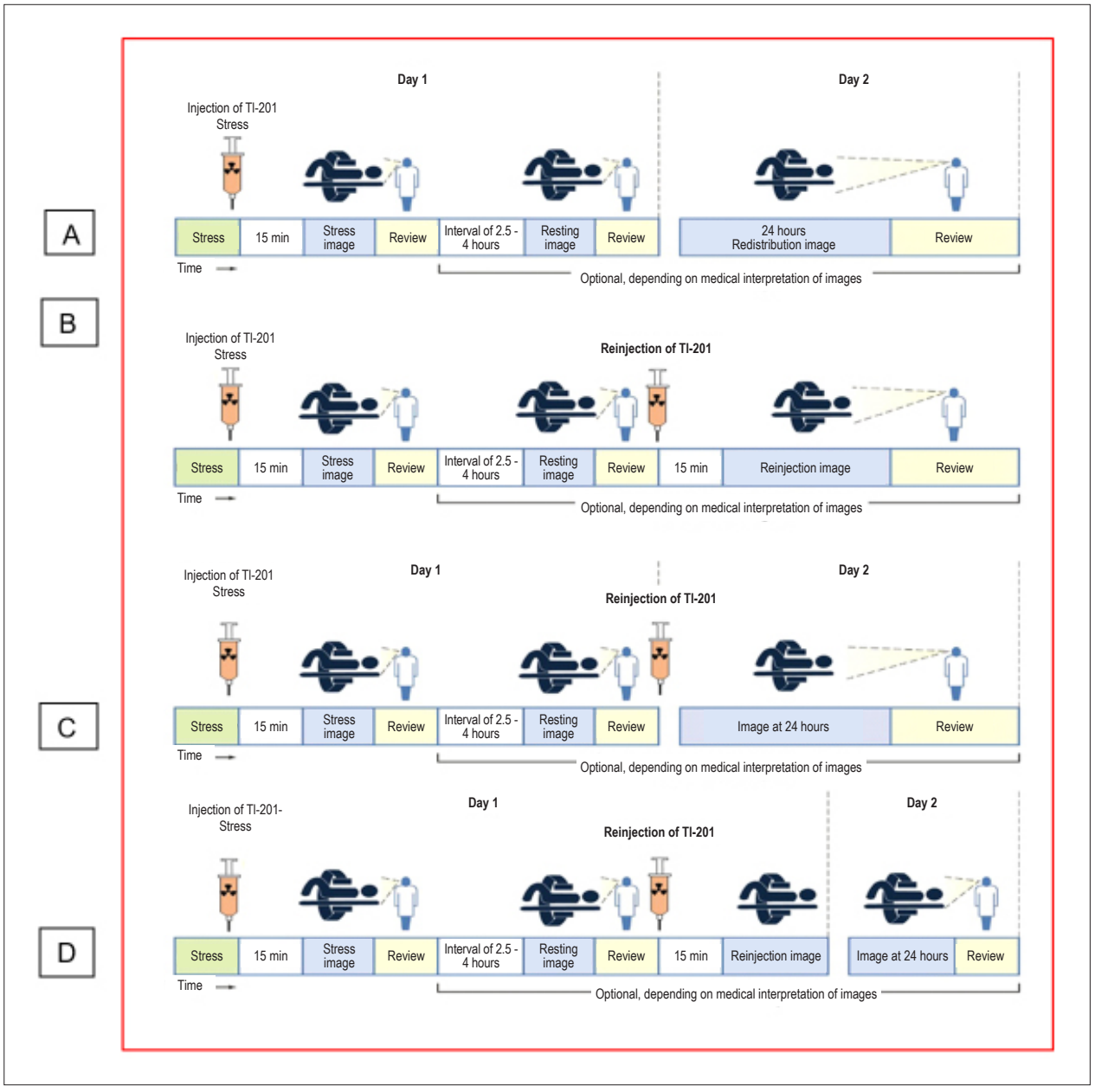

Figure 50 – *Imaging protocols with the use of thallium-201 (^{201}Tl) for characterizing viability of the myocardium. A represents the classic sequence for defining ischemia (Day 1), with the injection of a dose of approximately 3 to 4 mCi during stress, without subsequent reinjection, adding new image acquisition 24 hours later (Day 2); B, C, and D emphasize the need for reinjection of ^{201}Tl with an approximate dose of 1 mCi and sequencing as demonstrated in the proposed protocol.*

10.6. Positron Emission Tomography[282,283]

This non-invasive exam is the reference for detecting myocardial viability, as it simultaneously offers information on myocardial perfusion and metabolism. In normal fasting and aerobic metabolism conditions, while resting, long-chain free fatty acids (FFA) represent around 65% to 70% of energy supply to the cardiac muscle, with a lower participation of glucose (15% to 20%),[21] whereas, in post-prandial conditions, glucose becomes the preferred substrate. In the presence of ischemia, the oxidative metabolism of FFA is diminished and glucose also becomes the preferred myocardial substrate. In this manner, even if the energy produced by anaerobic glycolysis is not enough to maintain myocardial contractility, it is vital for the preservation of cellular membrane integrity, which is characteristic of dysfunctional, yet viable myocardium. Some positron emitters, such as fluorine-18, labeling a glucose analogue or fluorodeoxyglucose (FDG), may be used to evaluate viable (or hibernating) myocardium, which is defined as metabolically active tissue, in the presence of a coinciding perfusion defect. FDG-^{18}F penetrates the cells of the myocardium by the same transport mechanism as glucose and, following phosphorylation to FDG-6-P, remains in the intracellular medium in proportion to the rate of glycolysis, reflecting the

quantity of viable tissue. Patients are typically prepared for imaging with administration of glucose overload and subsequent doses of insulin, prior to intravenous injection of 5 to 15 mCi of FDG-^{18}F. Images are acquired 45 to 90 minutes after the administration of the tracer, lasting, approximately, 15 to 30 minutes. Low-dose CT is required for attenuation correction. The combination of perfusion and metabolism imaging via PET has a sensitivity of 88% and a specificity of 74% for myocardial viability.[284] Some differences exist for patients with diabetes, for whom the preferred form of viability evaluation is with ^{201}Tl or agents bound to ^{99m}Tc. It is also important to remember that the radioisotope fluorine-18 or ^{18}F is produced in a cyclotron, consisting of the bombardment of enriched water labeled with oxygen-18 or ^{18}O and decaying via positron emission, with an energy range of 511 keV. Its half-life is 110 minutes, allowing for the best spatial resolution among radiotracers used for PET.

When using PET for joint analysis of metabolism with FDG-^{18}F and perfusion (positron emitters are not available for this in clinical practice in Brazil), an excellent predictive value for functional recovery has been observed. Measurements of MBF are typically performed with rubidium-82 (^{82}Rb) or ammonia labeled with nitrogen-13 ($^{13}NH_3$). Based on the concept of hibernating myocardium, segments with reduced perfusion, but with preserved FDG uptake (known as mismatches), are classified as viable, with functional improvements following adequate revascularization. However, when perfusion and FDG uptake are diminished or apparently absent (matches), this reflects an absence of viability (areas of fibrosis), which do not show improvements after revascularization. Finally, the combined approach to blood flow-FDG mismatches has been widely document as a predictor of post-revascularization regional improvements in motility, as well as improvements in symptoms of HF, exercise capacity, and prognosis. The PET and Recovery after Revascularization (PARR-2) study,[285] which is still the only randomized prospective study to evaluate the benefits of results of a management strategy assisted by PET in patients with severe LV dysfunction, evaluated 430 randomized individuals for viability study with PET or conventional treatment without the use of PET. Results of primary analysis after 12 months of follow-up have showed a tendency toward improved results in the FDG-assisted PET, which was not statistically significant. On the other hand, post-hoc analysis, including only patients who adhered to the management strategy recommended based on the findings of FDG PET, showed significant improvements in mortality with the PET-assisted approach, when compared to standard care. Di Carli et al.[286] demonstrated that small areas of viable myocardium (more than 5%), identified by PET, stratified patients into subgroups of high-risk of cardiac events in a year. Equally, comparative studies on viability between PET and SPECT with ^{201}Tl demonstrated agreement of results in 80% of cases.

10.7. Additional Information Based on Evidence within the Medical Decision-making process for Patients with Congestive Heart Failure, Decreased Left Ventricular Ejection Fraction, and Viable Myocardium

A classic meta-analysis involving 24 studies and 3,088 patients (Left Ventricular Ejection Fraction – LVEF 32% ± 8%), with the use of different imaging methods, demonstrated that patients with viability had significant reductions in mortality when comparing surgical revascularization treatment and clinical treatment, with no benefits for either group in the absence of viability (Figure 51).[287]

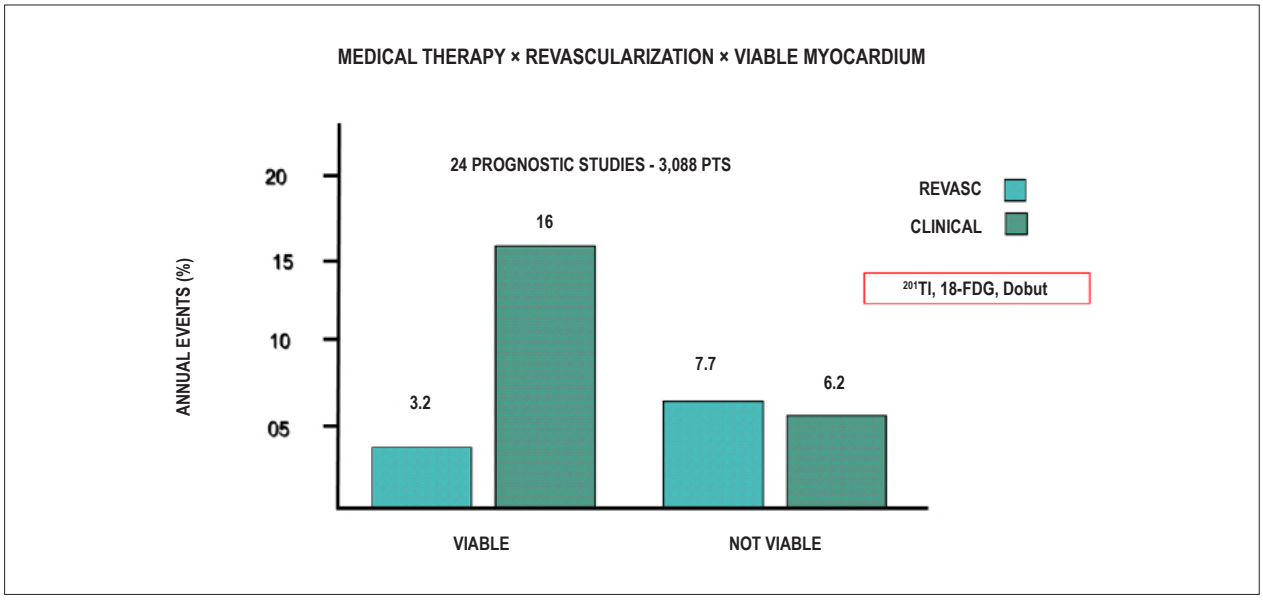

Figure 51 – *Prognostic studies in patients with severe chronic coronary artery disease and ventricular dysfunction evaluating late survival with revascularization versus medical therapy following viability study via non-invasive testing. ^{201}Tl: thallium-201; FDG-^{18}F: metabolic imaging with fluorodeoxyglucose labeled with fluorine-18; Dobut: doppler echocardiography associated with intravenous injection of dobutamine solution; Revasc: myocardial revascularization surgery; Pts: patients; Viable: viable myocardium. Adapted from Allman KC, et al.[287] Note that in the presence of viable myocardium and clinical treatment, the rate of events was > 4 times (16%) higher than in the same situation with surgical treatment via myocardial revascularization (3.2%); however, in the situation of absence of viable myocardium, the comparison between clinical and surgical treatment showed no significant differences in mortality (6.2% vs. 7.7%, respectively).*

In contrast, a recent multicenter prospective randomized study, known as the Surgical Treatment for Ischemic Heart Failure (STICH) study,[288] was unable to show benefits regarding mortality between patients randomized into revascularization surgery (CABG), in comparison with optimized medical therapy (OMT), in primary intention-to-treat analysis, for patients with dilated cardiomyopathy (LVEF ≤ 35%) of ischemic etiology (the first of 2 tested hypotheses, involving 99 centers in 22 countries).

SPECT and/or Doppler echocardiography, associated with a low dose of dobutamine, were used to characterize viability, based on established methodological criteria. Of the 1,212 patients included for evaluation, 601 underwent the aforementioned viability studies, comparing 298 receiving medical therapy and surgical revascularization (CABG Group) to 303 patients with OMT. Of the total of 478 patients with viable myocardium, the outcome of death occurred in 178 (37%), in contrast with 58 (51%) of deaths in 114 patients without viability (hazard ratio: 0.64; 95% CI: 0.48–0.86; p = 0.003). However, after adjusting for other baseline variables, the association with mortality was not significant (p = 0.21). There was significant crossover between the 2 groups and the analysis in question was in favor of better results with CABG.

In spite of these negative findings, recognizing biases in critical analysis of the results in this occasion, it is understood that, in the real world, faced with current evidence,[289-291] viability study may be of assistance when choosing the best treatment in selected populations, leading to better prognosis in evolution.

11. New Technologies and Future Perspectives for Nuclear Cardiology in Studying Ischemic Heart Disease

Established experience and extensive documentation, which has been accumulated over the past decades, have demonstrated that MPS has satisfactory sensitivity and specificity, emphasizing good NPV for ruling out obstructive CAD. Analysis of 32 studies has shown that SPECT has a sensitivity of 87% and a specificity of 73% for detecting significant angiographic lesions (stenosis > 50%).[292] Some limitations to the conventional technique have been observed, such as restricted spatial resolution, reduced counting rates, and attenuation of artifacts. Anger gamma cameras with sodium iodide crystals and photomultipliers, which transform emitted gamma photons into light or scintillation, also have limited temporal resolution in comparison with other imaging methods, such as PET, and they require higher doses of radiotracers, besides to carry out exams with longer image acquisition times. On the other hand, the innumerous advantages of the nuclear method include: **a)** the utilization of radioisotopes that do not alter the biological properties of the organism being studied; **b)** high radioactive labeling with a minimal amount of chemical substances, faithfully representing physiology and cellular biochemistry; **c)** minimal toxicity; **d)** pixel (smallest component of a digital image) values of myocardial images are directly proportional to parameters inherent in cardiovascular physiology, such as perfusion, function, metabolism, and innervation, attributes which are not shared by other modalities, such as angio-CT, cardiac resonance, and echocardiography; **e)** another aspect which stands out is the superior contrast resolution for detecting perfusion abnormalities, differentiating normal and hypoperfusion myocardium with great accuracy, facilitating visual and quantitative image analysis.[29,293]

Evolution of hardware: As exposure to radiation and its long-term deleterious effects have become important concerns on the part of regulatory authorities and scientific societies, new technologies have been introduced to reduce doses of radiotracers in nuclear exams while maintaining image quality and diagnostic accuracy. In this context, new equipment with CZT detectors arose in the first decade of 2000. Differently from traditional Anger gamma cameras, gamma radiation is directly converted to electric pulses upon contact with the CZT detectors, increasing energy resolution and dispensing with photomultipliers, which makes the detectors much finer and lighter. They are also distinct from older conventional cameras in terms of better spatial and energy resolution and the ability to distinguish dispersed radiation, in addition to being more sensitive for detection of emitted photons.[294-296]

Duvall et al.[297] have shown the viability of a reduced-dose protocol and of reduced doses in a study carried out with a dedicated CZT gamma camera (Discovery NM 530c, GE Healthcare), using 5 mCi of ^{99m}Tc as a resting dose and 15 mCi of ^{99m}Tc as stress dose to label sestamibi or tetrofosmin. There was a significant reduction in exposure to radiation in relation to anterior SPECT protocols, and image quality and accuracy for diagnosing CAD were maintained. Gimelli et al.[298] have also evaluated the viability of a stress-resting protocol with a reduced dose, used a CZT camera in a cohort of 137 patients referred for evaluation of CAD, with subsequent coronary cineangiography. Accuracy for identifying coronary lesions was not affected by reduced radioisotope dosage, and high sensitivity and specificity values were obtained. Hindorf et al.[299] showed that the ideal patient position should be established when performing myocardial exams with CZT gamma cameras.

In addition to evaluating diagnostic accuracy, it has become important to evaluate prognostic value of new imaging protocols using CZT cameras. Oldan et al.[300] compared prognostic value between CZT and conventional gamma cameras, observing that prognostic information provided by CZT technology, regarding the outcome composed of all-case mortality and non-fatal AMI, was similar to that provided by traditional equipment (Anger camera). The same dose, however, was administered to both gamma-camera groups. This fact limited the study's ability to evaluate prognostic value with reduced-dose protocols, as previously described.

Brazilian researchers[301] compared the prognostic values of an ultrafast low-dose protocol with a CZT camera and a traditional protocol with a conventional gamma camera with sodium iodide crystals. By means of a propensity score, 2 groups with equal numbers of patients and similar baseline characteristics were compared. The average dose of radiation in the first group (which underwent the exam with a conventional camera) was estimated at 9.5 mSv, whereas the CZT group had an average exposure dose of around 6 mSv. This dose was lower than the effective average SPECT

doses mentioned in previous studies. It was confirmed that the CZT camera protocol showed similar prognostic results when compared to those obtained with traditional SPECT cameras, emphasizing that patients with MPS on CZT had a lower events rate than those who underwent MPS with traditional gamma cameras.

Evolution of software: Filtered back-projection (FBP) is a traditional reconstruction algorithm in LV imaging, which has was used in many SPECT gamma cameras over time. It considers that the radiation emitting object, in this case the heart, is at the same distance from all detectors and that the photons are also uniformly detected at all angles. This supposition, however, leads to a large number of image artifacts, which may be caused by breast attenuation and loss of counting density at higher distance from the heart, for example. FBP, thus, presents limitations that lead to the development of new iterative reconstruction images, which allow for the correction of these inherent artifacts.[302]

New algorithms have been developed, the most widely used of which is known as ordered subset expectation maximization (OSEM). This iterative reconstruction technique is based on estimated projection of the object studied, with additional comparison between the acquired and estimated projections of the object. The projection of proportion is generated, containing the differences between real and estimated projections of the object. These differences are used to modify initial estimation, and every cycle in this chain is called an iteration. Iterations are carried out until a projection more similar to the real object has been achieved. Iterative reconstruction allows for correction of image artifacts, such as dispersion, attenuation, and noise suppression during the reconstruction process, in order to improve image quality and resolution.[303]

DePuey et al.[304] described the use of OSEM for processing exams with different acquisition periods (7 to 15 minutes) performed with a dual-head gamma camera with high resolution collimators. It was demonstrated that, notwithstanding lower time, image quality was maintained or even improved by the use of these reconstruction methods. Additionally, in a Brazilian study, Lima et al.[305] analyzed prognostic accuracy of a new reconstruction algorithm, "Evolution for Cardiac TM," with reduced dose and acquisition time in a dedicated gamma camera (Ventri, GE Healthcare), with an average dosimetry of 6.2 ± 0.3 mSv. The 2,958 patients who underwent exams were followed for approximately 3 years, and their results demonstrated a very low rate of major events (death or infarction), when imaging was normal in comparison with the group with abnormal imaging exams.

New perspectives: MPS may have some imaging limitations in patients with multivessel CAD, due to loss of comparative perfusion parameters between different areas of the myocardium, considering that image generation is based on relative uptake of coronary flow labeled with radiopharmaceuticals between the walls of the LV, as described in the introduction to these Guidelines. Given this situation, quantification of absolute coronary flow and coronary flow reserve (CFR) has arisen as an important alternative for diagnostic and prognostic evaluation of these patients. Falcão et al.[306] demonstrated that evaluation of flow reserve via PET assists in the detection of CAD in patients who have left bundle branch blocks. Patients with apparently normal perfusion and abnormal CFR have higher annual rates of cardiac death, non-fatal myocardial infarction, late revascularization, and hospitalization due to cardiac causes than patients with normal perfusion and normal CFR (6.3% *versus* 1.4%; $p < 0.05$).[307] Ziadi et al.[308] have expanded these results in a prospective study involving 704 patients who underwent injection with rubidium-82 (^{82}Rb) for PET, with the objective of comparing results in patients with reduced or normal CFR and patients with normal or abnormal perfusion exams. Reduced CFR was an independent predictor of major events, including cardiac death and myocardial infarction, adding prognostic value to the perfusion results. Murthy et al.[309] studied the predictive power of CFR in 2,783 consecutive patients, observing a 5.6-fold increase in the risk of cardiac death in patients with lower CFR values, compared to patients with higher values. This variable showed incremental prognostic value in comparison to relative analysis of perfusion and LVEF. The prognostic value of myocardial flow reserve (MFR) as a variable goes beyond CAD. This has been demonstrated in patients with ischemic and non-ischemic cardiomyopathy,[310] hypertrophic cardiomyopathy,[311] and post-cardiac transplant.[312]

The measure of coronary flow reserve using PET is quite accurate, but as it is expensive, it is not widely available in clinical practice, especially in Brazil. However, as SPECT technology is an easily accessible tool, studies show the possibility of acquiring dynamic images and quantifying MFR with this method, with some limitations, however, when using traditional gamma cameras, including limited temporal resolution.[313,314] With the advent of CZT cameras, it has become viable to quantify CFR using this technology.

Wells et al.[315] developed a pig model for measuring absolute myocardial blood flow and flow reserve, using three different radioisotopes, namely, ^{201}Tl, Tetrofosmin-^{99m}Tc and Sestamibi-^{99m}Tc. Following in this research area, Bouallègue et al.[316] obtained CFR in 23 patients with known three-vessel disease using a CZT gamma camera, successfully obtaining good correlation with angiographic findings. New discoveries related to dynamic SPECT image acquisition with measurements of CFR are opening new and exciting research fields that will allow for different applications of SPECT to the extent that their results are better validated.

12. Strategies for Reducing Exposure to Radiation

Ionizing radiation refers to radiation with enough energy to "ionize" atoms and molecules during its interaction with matter, in this case, with elements in the human body. Depending on the type and level of energy used, on the duration of exposure, and on the dose absorbed, damage to the organism may occur. Professionals involved in medical exams or therapies that make use of ionizing radiation should be familiar with the basics of what is known as the "**a**s **l**ow **a**s **r**easonably **a**chievable" (ALARA) principle. This stipulates that an individual's exposure to radiation must be minimized, regardless of reason for exposure. In relation to

nuclear imaging, this means obtaining the principal exam information, most commonly MPS, using the minimum amount of radiation necessary to maintain diagnostic quality. This involves not only the choice of radiotracer, but also the best technique and the best protocol that may be adjusted to minimize radiation exposure.

Furthermore, 2 other important principles guide the application of ionizing radiation for medical imaging: "**justification"** and "**optimization."** *Justification* signifies that a study should be well indicated and justified as adequate, in following with appropriate criteria, as described in these guidelines. The best way to minimize a patient's exposure to radiation is not to recommend an exam that is not appropriately indicated. This situation, however, is often beyond the control of the doctor responsible for performing the exam and should be understood by the referring doctor, who should have a basic grasp on the scientific literature. It is important to emphasize that the risk of a patient dying due to cardiovascular disease (the leading cause of death in Brazil), without undergoing a well indicated exam, is much higher than any eventual risk owing to radiation exposure. The risks of a patient with suspected coronary disease who has an appropriate indication for an exam are not theoretical, but rather real, and they are higher than the risks resulting from radiation use. The other principle which demands our attention is *optimization*, which represents adjustments to protocols, including the use of the best technological resources available (modern software and hardware) to perform an exam. This task is the responsibility of a multiprofessional team, made up of physicians, supervising nurses, nursing technicians, radiology technologists, biomedical specialists, biologists trained to manipulate radioactive material, professionals with training in radiopharmacy, and a team of medical physicists. The risks of deleterious effects of radiation involving patients, provided that the multiprofessional team uses the best technique and consistently observes the principles of justification and optimization, are minimal, and they are, at times, the fruit of theoretical elaboration with no consolidated practical base.

The INCAPS Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS), an important, recently conducted international study coordinated by the International Atomic Energy Agency (IAEA), involving 65 countries, including Brazil, verified that radiation exposure may be different when comparing patients living in different countries, given the diversity of implemented protocols in nuclear cardiology practice worldwide.[317] Innumerous opportunities have been found to improve the application of nuclear cardiology comprehensively worldwide, basically using the principle of *optimization*. It has generally been identified that with simple, low-cost orientations, such as adjusting dose to BMI, it is possible to reduce the administered dose of radiation and patient exposure significantly. Latin America is an example,[318] where there are opportunities to improve protocols. It has been recommended that the majority of patients undergoing MPS have a maximum estimated radiation exposure of 9 mSv. This goal is feasible to reach when applying the recommendations listed in Table 27, which are strategies supported by the IAEA.[24] In the Brazilian centers that participated in the INCAPS study, average doses were observed to vary between 8.4 and 17.8 mSv, thus demonstrating the possibility of optimizing protocols in the country, which has been undertaken since the publication of INCAPS.[318]

12.1. Reducing Radiation Using New Technologies, Image Quality, and Reliability of Findings

Given that exposure to high doses is a source of concern, considering the possibility of biological effects of ionizing radiation, which are known as *deterministic* (those which occur above certain limits of absorbed dose in a determined tissue, including skin erythema, loss of hair, and, possibly, direct cardiac toxicity) and *stochastic* (those whose radiation causes damage that may lead to malignancy which is generally long-term),[319,320] there has been a demand for new technology to reduce doses of radiotracers, maintaining image quality and diagnostic accuracy. In this context, new cameras with CZT detectors have been launched in recent years. Differently from traditional Anger cameras, gamma radiation

Table 27 – Strategies for reducing radiation exposure

1	Divulgate and apply appropriate exam indication criteria
2	Give preference to tracers that result in lower exposure to radiation. It is currently recommended to use technetium-99m (^{99m}Tc), which has a physical half-life of 6 hours, in comparison with thallium-201 (^{201}Tl), whose half-life of 73 hours results in unfavorable dosimetry
3	Avoid protocols that inject both radioisotopes, ^{201}Tl and ^{99m}Tc, in the same study (dual-isotope protocol), also considered an unfavorable dosimetry in combination
4	Avoid injecting any dose of ^{99m}Tc which is > 36 mCi or which results in an exposure dose of > 15 mSv for the complete exam
5	In the event that it is necessary to use ^{201}Tl, avoid doses over 3.5 mCi
6	Attempt to decrease the number of patients who perform both stress and resting phases. In some cases, it is possible to answer the clinical question with the stress injection, provided that images are perfectly normal during this phase
7	Utilize more sensitive equipment which is able to detect lower injected doses of radiopharmaceutical, such as new gamma cameras with solid cadmium-zinc-telluride (CZT) detectors, as well as software which improves imaging quality, even at lower administered doses
8	Apply the dose adjustment table based on patient's size or body mass index (BMI) (Tables 28 and 29)
9	Avoid shine through. This phenomenon occurs in perfusion studies with ^{99m}Tc (one-day protocol, resting and stress phases) when the dose of the second injection is less than 3 times the first dose, and the residual activity in this step may interfere with interpretation of images corresponding to the second injection. This situation may result in a non-diagnostic study, making new investigations necessary and thus increasing the patient's total received dosage.

Table 28 – Suggestions for dose limitation, adjusted to body mass index (BMI), using conventional gamma camera technology[24]

One-day protocol		
BMI	**Dose 1 (mCi)**	**Dose 2 (mCi)**
< 25	8	24
25 to 30	9	27
30 to 35	10	30*
> 35	12	36*
Two-day protocol		
BMI	**Dose 1 (mCi)**	**Dose 2 (mCi)**
< 25	8	8
25 to 30	9	9
30 to 35	10	10
> 35	12	12

**Give preference to the two-day protocol.*

Table 29 – Suggestions for dose limitation, adjusted to body mass index (BMI), using gamma cameras with cadmium-zinc-telluride technology[24]

One-day protocol		
BMI	**Dose 1 (mCi)**	**Dose 2 (mCi)**
< 25	4	12
25 to 30	4.5	13.5
30 to 35	5	15*
> 35	6	18*
Two-day protocol		
BMI	**Dose 1 (mCi)**	**Dose 2 (mCi)**
< 25	4	4
25 to 30	4.5	4.5
30 to 35	5	5
> 35	6	6

**Give preference to the two-day protocol.*

is directly converted into an electric pulse when it comes into contact with CZT detectors, increasing energy resolution and dispensing with photomultipliers, which makes the detectors much finer, lighter, and more sensible to photon detection. Protocols have suggested that it is possible to combine faster exams with lower dosimetry. Owing to high costs, they are still not widely used in Brazil, where there are few more than a dozen gamma cameras with this new technology , which has already begun to contribute relevant publications to the international scenario.[321]

One of the limitations, known as the "Achilles heel" of myocardial perfusion image interpretation is the attenuation which gamma rays undergo when they pass through tissues before reaching the detector. The problem lies in the fact that attenuation may simulate myocardial perfusion defects, and their recognition as cases of "false-positive" results greatly depends on the observer's experience. These defects occur more frequently in the inferior wall in men (especially in patients with abdominal obesity), and they are described as diaphragmatic attenuation. In women, they are most commonly found in the anterior wall, due to attenuation caused by breast tissue. These imaging defects are more common in obese patients, for which reason they require higher injected doses. When the defects found are tenuous, when they occur in a similar way during resting and stress, and when they are accompanied by thickness in the walls of LV without abnormalities, the myocardial perfusion study may frequently be interpreted as normal, thus sparing the patient other investigations, both those that involve radiation and those that do not, and minimizing costs. Another way to lower the attenuation artifacts is to apply specific machines with other sources of radiation, such as an x-ray emitting tomograph, which calculates tissue attenuation factors and applies attenuation correction to the photons emitted by the radioactive tracer, reducing the effects of attenuation by means of software. This equipment, however, adds costs to the exam, and it is difficult in terms of financial viability. Even in the USA, which is the country with the highest volume of myocardial scintigraphy studies, it is estimated that only 20% of medical services routinely apply this method. Finally, another method, which is widely applied in practice to resolve apparent defects in uptake generated by attenuation of gamma photons when they penetrate tissue, is to acquire images in the prone and supine positions , especially during the stress phase, which significantly reduces the artifacts described. Some services have routinely implemented this practice, even considering the increased gamma camera utilization time with a new image acquisition series.

With respect to performing stress exam alone in order to reduce radiation by avoiding the resting dose, the following should be considered:

1. It is possible for the observing doctor to succeed in interpreting a study as "absence of ischemia," based only on stress imaging, thus avoiding the resting injection. In order to do this, the observer must be confident that the image is perfectly normal and free of any perfusion defects, including "attenuation artifacts," which are generally recognized by comparing stress and resting images. The alternative is described above, routinely applying attenuation correction, but this would involve increased costs.
2. Another situation, which is not frequent, but which may occur, is when the patient has homogenous tracer distribution in the LV and apparently normal perfusion, but with an observed transient increase or dilation in the same cavity during the stress phase, when compared to resting images (transient ischemic dilation). The following may, additionally, be observed: **a)** drop in LVEF following stress, compared to resting; and/or **b)** increased uptake in the RV (generally not visualized) during the phase corresponding to stress, in comparison with resting; these are markers of poor prognosis, even in the presence of perfusion which is apparently "normal" owing to homogenous distribution. In these situations, the patient is exceptionally identified as high-risk based on other findings which are not solely

related to tracer distribution in the LV during stress. This analysis and these findings are only possible when comparing resting and stress images. In summary, the doctor interpreting the images should be sure that the stress exam is perfectly normal, in order to dispense with resting image acquisition. Whenever possible, nuclear cardiology should always be performed using exercise as a preferential form of stress instead of pharmacological tests, which serve as alternatives only in patients who are unable to exercise efficiently. In the presence of severe multivessel coronary disease (involving three arteries) and apparent relative homogeneous radiopharmaceutical distribution during stress, it is extremely rare not to observe other high-risk findings during stress testing, in addition to deterioration of LV function induced by stress itself (ischemic myocardial stunning).

In summary, in this section, various ways to reduce radiation exposure in patients undergoing nuclear cardiology exams have been covered. By means of relatively simple adjustments to protocols, injected doses may be optimized, guaranteeing image quality and, most of all, reliability of findings in an exam which is of great clinical importance to orient patient management.

13. Evaluation of Cardiac Sympathetic Activity by Scintigraphy with ^{123}I-MIBG

13.1. Introduction

Autonomic cardiac innervation plays a fundamental role on cardiac performance by regulating myocardial blood flow, HR, and myocardial contractility. In several cardiac diseases, cardiac neuronal function is altered and frequently associated with worse evolution. Dysregulation of the autonomic cardiac nervous system increases the risk of potentially lethal arrhythmias and may be a marker of poor prognosis. Scintigraphy imaging of distribution and cardiac neuronal function facilitates the comprehension of the physiopathology of various diseases that affect the heart and may guide treatment, with consequent improvements to clinical results.[322]

The autonomic cardiac nervous system encompasses sympathetic and parasympathetic innervation, with its norepinephrine (NE) and acetylcholine neurotransmitters, respectively. These work in equilibrium, and they exert *stimulating effects*, via adrenergic receptors, and *inhibitory effects*, via muscarinic receptors, both of which are responsible for electrophysiological and hemodynamic adaptations in the cardiovascular system, in response to bodily demands.[322]

In this way, sympathetic stimuli are controlled by cerebral regulatory centers that integrate signals coming from other parts of the brain and receptors in the body. Efferent signals follow descending pathways in the spinal cord and make synapses with preganglionic fibers that emerge at levels T1 to L3. In this sequence, they establish synapses with the paravertebral stellate ganglion and innervate the RV, in addition to the anterior and lateral regions of the LV. In the heart, sympathetic nerves follow the coronary arteries in the subepicardium and then penetrate the myocardium.[322,323]

Parasympathetic fibers are scarce in number in comparison with sympathetic fibers, and they originate in the marrow, following the vagus nerve. They begin in the epicardium, crossing the atrioventricular groove and penetrating the myocardium. They are located in the subendocardium, predominantly innervating the atria, but they are less dense in the ventricles, with the exception of the inferior wall. They greatly control the function of sinoatrial and atrioventricular nodes.[322]

13.2. Cardiac Scintigraphy with ^{123}I-MIBG

Metaiodobenzylguanidine (MIBG) is a molecule with a structure similar to that of NE, obtained by means of modifications to the molecular structure of guanethidine (a false neurotransmitter, also an NE analogue), which acts selectively on sympathetic nerves, without, however, being metabolized by monoamine oxidase or catechol-O-methyltransferase or exercising a stimulating effect, as NE does. For the objective of diagnosis, MIBG is labeled with iodine-123, forming the radiotracer MIBG-^{123}I,[322-325] demonstrating a good correlation between myocardial uptake of MIBG-^{123}I and NE content in cardiac tissue.[325] After the radiopharmaceutical is injected via intravenous administration, it spreads throughout synaptic space, and is taken up, concentrated, and stored in presynaptic nerve endings in a manner similar to that of NE. MIBG-^{123}I is retained and localized in cardiac sympathetic nerve endings with scintigraphy images obtained by a conventional gamma camera.[322-325]

The radioisotope iodine-123 predominantly emits gamma photons with an energy of 159 keV and a physical half-life of 13.2 hours, making image acquisition easy and well tolerated. MIBG-^{123}I is widely used in Europe and Japan, and it has recently been approved for cardiac use in the USA.[326] In Brazil, this technique is available in some centers. Cardiac scintigraphy with MIBG-^{123}I directly evaluates global and regional sympathetic function of the heart, including uptake, reuptake, storage, and NE release processes in presynaptic nerve endings.[327]

Intravenous injection of MIBG-^{123}I is administered while resting, at least 30 minutes after oral administration of potassium iodide syrup or an iodine-containing solution, in order to block and protect the thyroid. Medications that may potentially interfere with catecholamine uptake, such as antidepressants, and some calcium channel blockers should be suspended for at least 24 hours before administration of the radiopharmaceutical. On the other hand, betablockers, angiotensin converting enzyme inhibitors (ACEI), and/or angiotensin receptor blockers (ARB) do not need to be discontinued.[328] Approximately 15 minutes and 4 hours after administration of MIBG-^{123}I, static images and tomography images (SPECT) of the thorax are obtained in anterior projection, with the patient in dorsal decubitus, with the left arm raised above the thorax. While tomography images are optional, they help evaluate myocardial sympathetic activity and compare with the perfusion study (*see the subsequent topic "Evaluation of arrhythmias"*). Global cardiac uptake of MIBG-^{123}I is evaluated by static imaging of the thorax (Figure 52). The following 2 fundamental parameters are visually and semiquantitatively analyzed: *the relation between cardiac and mediastinal uptake* (heart to mediastinum ratio [HMR])

in *early images* (15 minutes after injection) and *late imaging* (4 hours after injection) and the *myocardial washout rate* (WR) of MIBG-^{123}I.[322-324,327-330]

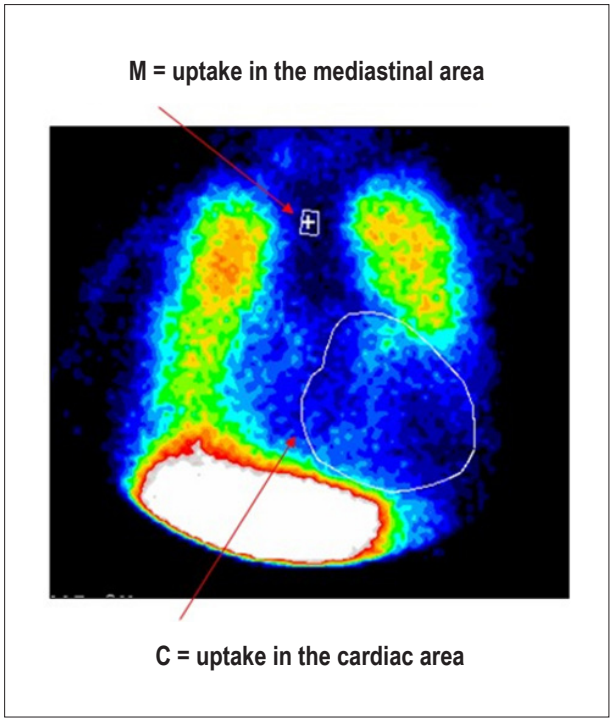

Figure 52 – *Cardiac scintigraphy with MIBG-^{123}I. Colored late imaging of the anterior thorax with the regions of interest (ROI) drawn in the mediastinal (M) and cardiac (C) areas, to calculate the heart to mediastinum ratio (HMR) of MIBG-^{123}I uptake. This index is the measure of the ratio between the statistical count of the rate of average radiation per pixel in the ROI, drawn in the heart and mediastinum.*

Normal HMR values vary from 1.9 to 2.8 with an approximate average of 2.2 ± 0.3 in late images, with results ≥ 1.6 considered predictive of lower risks.[331] HMR reflects the density of receptors and, probably, depicts the integrity of presynaptic nerve endings and of the uptake 1 receptor. This elevated index indicates a predominant localization of the radiotracer in the myocardium, which is expected in normal hearts, to the extent that the finding of reduced HMR indicates lower myocardial uptake of MIBG-^{123}I, translating as reduced density of cardiac adrenergic receptors. Late HMR combines information on neuronal function of uptake and the release of storage vesicles in cardiac nerve endings. Figures 53 and 54 show images of patients with normal and altered HMR, respectively.

Myocardial washout rate (WR) of MIBG-^{123}I is also an important measure of cardiac sympathetic innervation. WR is calculated as the difference in myocardial uptake between the early and late phases and is determined by the percentage of reduction in uptake between these steps, reflecting the amount of catecholamines released in the cardiac synaptic cleft. Cardiac sympathetic hyperactivity is associated with reduced retention of MIBG-^{123}I in late images (reduced late HMR) and increased WR. Normal WR control values are 10% ± 9%.[332] Higher values are predictive of worse prognosis,[333] although there are several methods for determining this ratio in the literature. Intra- and inter-observer variability of these measurements is less than 5%.[328]

13.3. Clinical Applications of Cardiac Scintigraphy with MIBG-^{123}I

Imaging studies of cardiac adrenergic activity may be useful in several clinical scenarios (Table 30), including: HF, ventricular arrhythmias (associated with HR and primary arrhythmias), ischemic heart disease, DM, patients undergoing cardiotoxic chemotherapy, pre- and post-cardiac transplant,

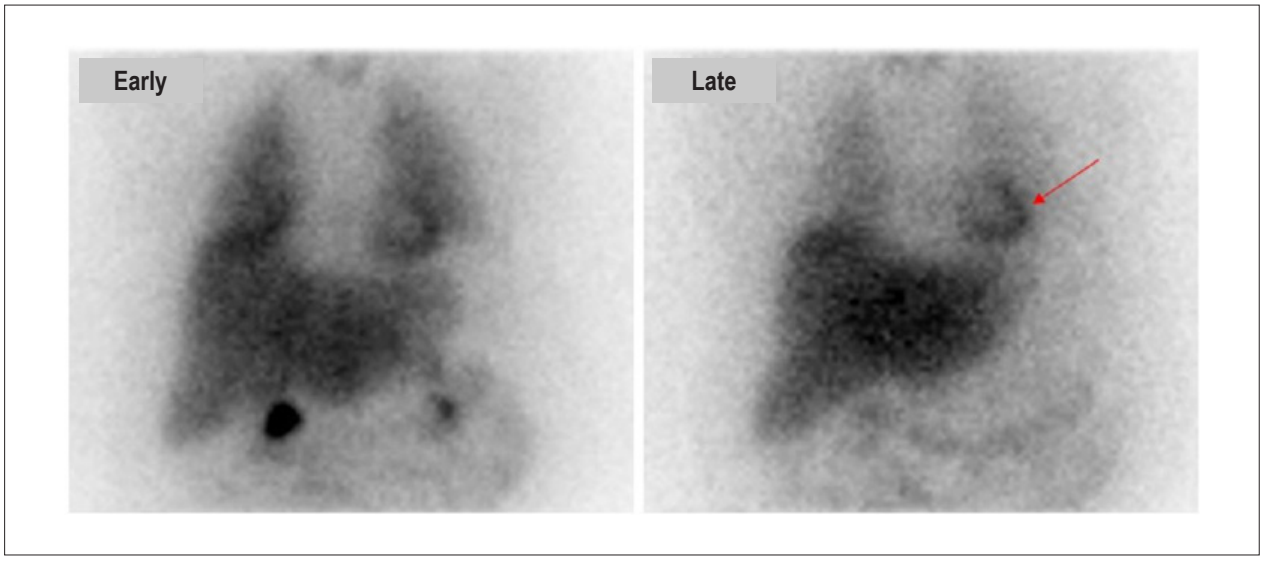

Figure 53 – *Cardiac scintigraphy with MIBG-^{123}I showing normal radiopharmaceutical uptake in the cardiac area (arrow), which denotes preserved cardiac sympathetic activity. Black and white images of the anterior thorax, acquired approximately 15 minutes (early) and 4 hours (late) following intravenous injection of the radiopharmaceutical MIBG-^{123}I.*

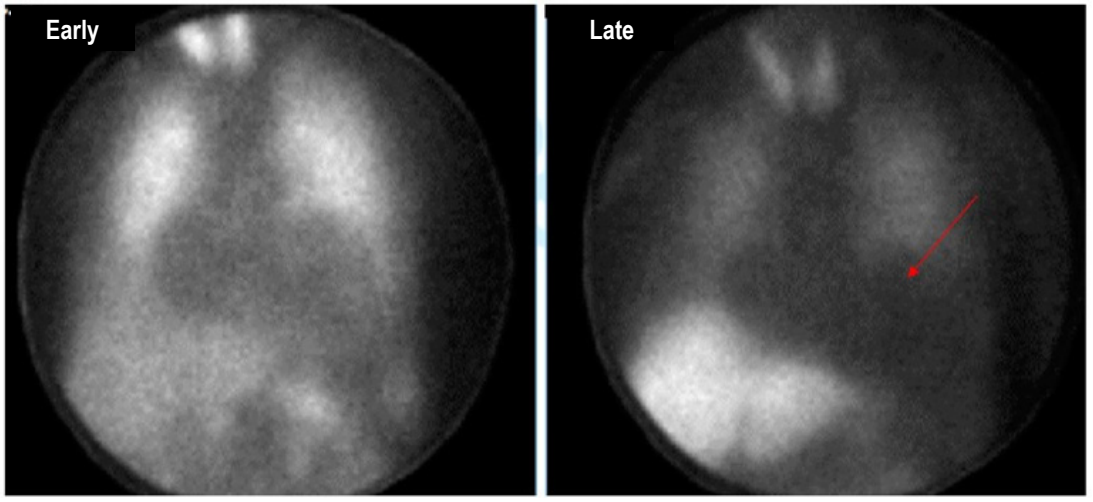

Figure 54 – *Abnormal cardiac scintigraphy with MIBG-^{123}I of a patient with advanced heart failure and highly reduced radiopharmaceutical uptake in the cardiac area (arrow), which denotes cardiac sympathetic hyperactivity. Black and white images of the anterior thorax, acquired approximately 15 minutes (early) and 4 hours (late) following intravenous injection of the radiopharmaceutical MIBG-^{123}I.*

Table 30 – Established and potential indications for cardiac scintigraphy with MIBG-^{123}I

Clinical Scenarios	Established	Potential
HFrEF	• Risk stratification, regardless of other parameters; evaluation of progression of HF, arrhythmic events, and total cardiac mortality up to 2 years • Identification of a low-risk subgroup for cardiac events and mortality • Clinical follow-up of medical therapies indicated in the guidelines	• Identification of patients most likely to benefit from CRT or LVAD • Guiding treatment of patients with LVAD: bridge to transplant, possible explant • Substitute marker for evaluating benefits of new medical therapies and devices
HFpEF	• Subanalyses of larger studies have shown a risk stratification similar to that seen in patients with HFrEF	• Identification of patients whose risks may be higher than clinically apparent
Arrhythmias associated with HF	• Risk stratification for lethal or potentially lethal ventricular arrhythmias for up to 2 years • Identification of patients with very low risks of lethal arrhythmic events for up to 2 years	• Refining indication criteria for patients who will benefit from ICD • Helping identify patients who will no longer need ICD, at the end of battery life or device infection
Primary arrhythmic conditions	• Identification of patients with risks of worse outcomes, including arrhythmic events and total mortality	• Improving understanding of physiopathology of primary arrhythmic conditions • Guiding conduct for patients with primary arrhythmic conditions
Heart transplant	• Following post-transplant cardiac reinnervation after	• Identification of patients who are more likely to have complications following transplant, including transplant rejection and transplant by CAD
Ischemic heart disease	• Evaluation of area at risk in patients with acute coronary syndromes • Risk stratification in patients with hibernating myocardium	• Guiding conduct for patients with acute coronary syndromes • Guiding conduct for patients following ischemic events • Ischemic memory
Diabetes mellitus	• Identification of cardiac autonomic abnormalities, including patients without extracardiac manifestations	• Identification of patients whose risks may be higher than clinically apparent, assisting in diagnosis and orienting appropriate treatment
Cardiotoxicity due to	• Identification and quantification of cardiac lesions in patients undergoing these treatments	• Guiding conduct of chemotherapy • Improving understanding of the physiopathology of toxicity due to drugs

MIBG-^{123}I: metaiodobenzylguanidine labeled with iodine-123; CAD: coronary artery disease; CRT: cardiac resynchronization therapy; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter defibrillator; LVAD: left ventricular assist device. Adapted from JCS Joint Working Group.[339]

Takotsubo syndrome, and cardiac involvement due to systemic conditions, as in Parkinson's disease. Generally speaking, this exam has been established to have an effective capacity for risk stratification of patients with the previously described conditions, but the utility of this information in improving clinical results of patients has not yet been demonstrated.[331]

13.3.1. Heart Failure

In this condition, altered cardiac adrenergic innervation is strongly correlated with mortality, and reduced cardiac uptake of MIBG-^{123}I (late HMR) confers independent and additional long-term prognostic value to other established markers, such as LVEF and B-natriuretic peptide (BNP).[334-336] Some studies have demonstrated that abnormalities in cardiac uptake of MIBG-^{123}I may be predictive of increased risk of ventricular arrhythmia and sudden cardiac death,[322,337] with attempts to standardize the procedure for the sake of routine clinical application.[328-330] Cardiac scintigraphy with MIBG-^{123}I has been approved for use in clinical practice in cardiology since 1992 in Japan,[338] and it is considered a class I indication for evaluation of prognosis and severity of HF, with level of evidence B (Table 31).[338] Studies with higher numbers of patients have recently been published in Europe and the USA. The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF)[336] multicenter, prospective, international study involving the use of MIBG-^{123}I in HF independently validated the prognostic value of cardiac scintigraphy with MIBG-^{123}I for the evaluation of patients with chronic HF.[337] They included 961 patients with HF, NYHA HF functional class II–III, and LVEF ≤ 35%, undergoing cardiac scintigraphy with MIBG-^{123}I, followed for an average of 17 months. Approximately 25% of patients (n = 237) had cardiac events, with approximately 70% of the first events being progression of chronic HF; 20% potentially lethal arrhythmic events (sustained VT > 30 seconds, heart arrest with cardiac arrest with resuscitation and appropriate ICD firing; and approximately 10% cardiac death; with 22% of patients presenting multiple events. Lower risks of the compound outcome were observed in patients with HMR ≥ 1.60 *versus* HMR < 1.60 (38%; hazard ratio: 0.40; p < 0.001) with a highly significant risk ratio for each individual component of the primary compound outcome evaluated. It is worth highlighting that total mortality over 2 years was around 5 times higher (16.1% *versus* 3.0%) in patients with late HMR < 1.60 compared to those with HMR ≥ 1.60, respectively.[337]

Considering this information, the FDA has approved MIBG-^{123}I (*AdreView*^{R}), in 2013, for evaluation of cardiac sympathetic innervation in patients with New York Heart Association (NYHA) *HF class II-III* and LVEF < 35%.[326]

In addition to prognostic evaluation of HF,[333-339] other applications which stand out include the following: evaluation of therapeutic response to medication;[340,341] indication and evaluation of response to cardiac resynchronization therapy (CRT);[342] indication for implant and explant of mechanical left ventricular assist device,[343,344] and implantable cardioverter defibrillator (ICD); and evaluation of reinnervation following cardiac transplant.[345]

Late HMR of MIBG-^{123}I in patients with severe chronic HF, in accordance with traditional classification criteria (LVEF, BNP, functional class), may help reclassify patients into a category of lower risk for events. Patients with late HMR ≥ 1.6 (even with very low LVEF and elevated BNP) have a low probability of severe cardiac events during a period of up to 2 years. This information may lead to changes in treatment.[331] This marker may, also, help refine indication criteria for high-cost invasive therapies for HF, such as CRT[342,346] and ICD implant.[347,348] A Brazilian study carried out by Nishioka et al.[342] has shown that HMR was the only independent predictor of therapy response. Patients with HMR < 1.36 had a lower chance of benefitting from CRT, suggesting that these patients with rather elevated cardiac sympathetic activity have terminal HF.[342,346]

The autonomic nervous system plays an important role in *cardiac arrhythmias*. Scintigraphy with MIBG-^{123}I has the potential to select patients for ICD implant more accurately, in addition to identifying those at higher risks of sudden cardiac death, who would not be selected in accordance with current guidelines. Arora et al.,[347] in a pilot study of 17 patients with advanced chronic HF and ICD, divided patients into groups according to the presence or absence of previous ICD firing. In cases with late HMR of MIBG-^{123}I < 1.54, they observed a higher frequency of ICD firing and a positive predictive value of 71%, at the same time that increased HMR was observed to have a NPV of 83%.

The etiology of HF is frequently classified as ischemic (I) and non-ischemic (NI). Although the physiopathology and the initial lesion are different, investigation studies have suggested that, as the disease progresses, autonomic cardiac abnormalities are characteristic and common, regardless of etiology. Cardiac scintigraphy with MIBG-^{123}I thus continues to be a strong prognostic marker. Wakabayashi et al.[349] showed that, for both groups, late HMR was the strongest independent predictive factor for sudden cardiac death, although the cutoff points for HMR index values were different, namely 1.50 for ischemic cardiomyopathy and 2.02 for non-ischemic cardiomyopathy. For patients with LVEF < 40% and late HMR lower than the identified cutoff values, the rate of cardiac death was higher in the ischemic group (18.2% annually) than in the non-ischemic group (11.9% annually).

Table 31 – Recommendations for cardiac scintigraphy with MIBG-^{123}I in accordance with the Japanese Circulation Society Guidelines[339]

Indication	Class of recommendation	Level of evidence
Evaluation of severity and prognosis of patients with heart failure (HF)	I	B
Evaluation of the effects of HF treatment	IIa	C
Arrhythmogenic disease	IIb	C

13.3.2. Ventricular Arrhythmia

Sudden cardiac death continues to be one of the leading causes of death worldwide. Scarring and/or non-revascularized/ischemic myocardium provide important substrates for the occurrence of potentially lethal ventricular arrhythmias.[350] Furthermore, the presence of clinical HF

increases the risk of ventricular arrhythmia. The sympathetic nervous system is an important trigger of major arrhythmic events by means of global cardiac adrenergic hyperactivity and heterogeneity of regional myocardial sympathetic activity.[322] Evaluation of the autonomic nervous system via myocardial scintigraphy (MS) with MIBG-^{123}I may be useful in diverse clinical situations. The presence of denervated yet viable myocardium and the magnitude of denervation are potential markers of an individual's susceptibility to triggering of severe arrhythmias. Several studies have demonstrated the ability of scintigraphy with MIBG-^{123}I to identify patients at higher risks of developing spontaneous ventricular tachyarrhythmia, appropriate ICD shock,[351,352] and sudden cardiac death.[353-356]

When analyzing the possibilities of scintigraphy imaging results, the finding of a *mismatch* between perfusion and myocardial innervation characterizes a scenario of higher risk for ventricular arrhythmia.[350,351] The denervated regions respond to sympathetic stimuli differently than normal myocardium. This electrophysiological heterogeneity may serve as a substrate for VT and ventricular fibrillation (VF). In the same manner, tomography images (SPECT) of cardiac scintigraphy with MIBG-^{123}I are useful for recognizing increased arrhythmogenicity. A prospective study of 50 patients with antecedents of myocardial infarction who underwent SPECT imaging with MIBG-^{123}I and perfusion SPECT perfusion with Tetrofosmin-^{99m}Tc showed, via multivariate analysis, that a late MIBG-^{123}I SPECT defect score of ≥ 37 was the only parameter capable of differentiating the group of patients who presented VT induced by electrophysiological testing, with a sensitivity of 77% and a specificity of 75%.[357] There were no significant differences in late HMR and the mismatch scores obtained by subtraction of perfusion and sympathetic innervation between the groups with positive and negative induced VT.[356]

Moreover, the Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) study evaluated quantification of denervated myocardium in 204 patients with ischemic heart disease (LVEF ≤ 35%), by means of PET imaging with ^{11}C-meta-hydroxyephedrine (HED-^{11}C), labeled with carbon-11. Perfusion and myocardial viability have also been characterized with ^{13}N-ammonia and ^{18}F-fluordeoxyglucose, respectively. The primary study objective was to observe the occurrence of sudden cardiac death, defined as arrhythmic death or ICD firing due to VF or VT > 240 beats/minute. After 4.1 years of follow-up, sudden cardiac death of 16.2% was registered. The quantification of infarction volume and LVEF were not factors predictive of sudden cardiac death. However, patients with higher volumes of *denervated* myocardium (33 ± 10% *versus* 26 ± 11% of the LV; p = 0.001) showed sudden arrhythmic death more frequently. The authors of this study concluded that, in ischemic cardiomyopathy, sympathetic denervation evaluated by HED-^{11}C PET predicts sudden arrhythmic death regardless of LVEF and infarction volume. This information may improve identification of patients who will most likely benefit from ICD implant.[358] One of the most peculiar aspects of the natural history of chronic Chagas cardiomyopathy is the occurrence of severe ventricular arrhythmia in individuals with preserved LV global systolic function which may evolve to sudden death during early phases of the disease.[359,360] In 43 patients with chronic Chagas cardiopathy and LVEF ≥ 35%, the correlation between extent of sympathetic denervation, myocardial fibrosis, and severity of ventricular arrhythmias was investigated. Patients were divided into 3 groups, according to the presence of sustained VT, non-sustained VT, and the absence of VT on 24-hour Holter. Sympathetic denervation was evaluated via SPECT imaging with MIBG-^{123}I and myocardial fibrosis via SPECT with ^{99m}Tc-sestamibi. The sums of perfusion scores (quantity of fibrosis) were similar in the 3 groups. The summed difference score between MIBG-^{123}I and Sestamibi-^{99m}Tc, which evaluated the extension of denervated yet viable myocardium, was significantly larger in the group with sustained VT on Holter (score of 20.0 ± 8.0), when compared to the group without VT (2.0 ± 5.0; p < 0.0001) and NSVT (11.0 ± 8.0; p < 0.05). In conclusion, the occurrence of ventricular arrhythmias with different degrees of severity is quantitatively correlated with the extension of cardiac sympathetic denervation, but not with the extension of fibrosis, suggesting that myocardial sympathetic denervation plays a role in the generation of ventricular arrhythmia related to chronic Chagas cardiopathy.[361]

Sympathetic denervation may also occur in patients with stable angina in the absence of infarction. Cardiac scintigraphy with MIBG-^{123}I may show inervation defects in these cases, in the absence of perfusion defects. Sympathetic nervous fibers are more susceptible to oxygen privation than cardiomyocytes and the occurrence of myocardial ischemia may thus lead to transient sympathetic denervation.[362] The fact that recovery of inervation may be a slower process also makes it possible to use myocardial scintigraphy with MIBG-^{123}I as a marker of ischemic memory in patients whose chest pain has resolved few hours or days prior.

Regional alterations of cardiac sympathetic activity may also be seen in primary arrhythmic conditions, in the absence of CAD,[363] in Brugada syndrome,[364] in hypertrophic cardiomyopathy,[365,366] and in arrhythmogenic RV dysplasia.[367] These findings in patients with primary arrhythmias support the potential use of cardiac scintigraphy with MIBG-^{123}I for identifying patients at a risk of sudden cardiac death, who may benefit from ICD implant.

13.3.3. Cardiotoxicity Due to Chemotherapy

Over the past decades, there have been great advances in cancer diagnosis and treatment, offering oncology patients reduced mortality, increased survival, and better quality of life. On the other hand, progress in oncological treatment results in higher exposure to the cardiotoxic effects of chemotherapy. Screening for the occurrence of cardiotoxicity (CTX) is highly recommended before, during, and after the completion of chemotherapy. Several methods and diagnostic indexes have been suggested for the detection of CTX and therapeutic strategy planning. Although serial measure of LVEF by conventional echocardiogram is the most utilized strategy for monitoring myocardial damage, it does not appear to be sensitive enough to detect patients with risks of developing significant CTX in early phases of chemotherapy administration.[323] The potential use of cardiac adrenergic imaging for monitoring the cardiotoxic effects of chemotherapy has been debated.[368-370] There is evidence that reduced cardiac uptake of MIBG-^{123}I precedes ejection fraction deterioration.[371]

A recent study has shown that, following 1 year of treatment with anthracyclines, late HMR was the strongest parameter of scintigraphy with MIBG-^{123}I. This index correlates with conventional echocardiography variables and global indexes of radial and longitudinal strain, in addition to doses of galectin-3 in patients with breast cancer treated with anthracyclines. Altered late HMR was a predictor of abnormality in the global radial strain index on ECG.[369]

Cardiac scintigraphy with MIBG-^{123}I was performed in 20 women with breast cancer and normal LVEF who had undergone treatment with anthracycline derivatives, associated and not associated with trastuzumab. It was observed that anthracycline use with trastuzumab promoted higher frequency and intensity of cardiac adrenergic hyperactivity.[367] Carrió et al.[371] identified abnormal MIBG-^{123}I uptake in patients who used anthracyclines, where HMR of MIBG-^{123}I decreased as the cumulative dose of this medication increased.[371]

The degree of cardiac uptake of MIBG-^{123}I may thus be an early marker of CTX. However, multicenter studies with higher case numbers and standardized exam protocols comparing the evaluation of cardiac sympathetic activity with MIBG-^{123}I before and after treatment need to be carried out in order to clarify these findings further.

13.3.4. Cardiac Autonomic Dysfunction in Diabetes Mellitus (DM)

In patients with DM, there is evidence of cardiac denervation in the absence of clinical manifestations.[372] Diabetic autonomic neuropathy has been implied to be a cause of sudden cardiac death, with or without associated myocardial ischemia. Patients with DM and reduced HMR of MIBG-^{123}I have an increased risk for clinical progression of HF.[373] It is, however, not yet clear whether cardiac adrenergic imaging may improve clinical outcome in patients with diabetes.

13.3.5 Cardiac Transplant

Cardiac scintigraphy with MIBG-^{123}I may be useful for evaluation of reinnervation in transplanted hearts. It identifies ventricular sympathetic reinnervation,[345] which slowly develops from the cardiac base several months following surgery, and it is observed in 40% of patients 1 year following transplant.[374] Even though the clinical implications and the mechanisms of cardiac reinnervation have yet to be completely made clear, restoration of cardiac sympathetic innervation probably increases physical capacity, due to improved HR and contractile function during exercise in patients with heart transplants.[374] Evaluation of the process of cardiac reinnervation via scintigraphy with MIBG-^{123}I seems to be useful for outpatient treatment of patients with heart transplants for the prescription of appropriate exercises, evaluation of the effect of physical training, and prediction of long-term survival.

13.3.6. Takotsubo Syndrome

Takotsubo syndrome, also known as neurogenic cardiomyopathy, stress-induced cardiomyopathy, or broken heart syndrome,[375] is characterized by transient left ventricular dysfunction, electrocardiographic alterations similar to those present in AMI, and minimal alterations in cardiac enzymes in the absence of obstructive CAD. It was described in 1991 in Japan[375] and denominated "Takotsubo" owing to the similarity of the morphological aspect which the LV assumes to a type of trap used to capture octopuses in Japan (round in the bottom and narrow in the upper part). It has recently been recognized as a new entity within the spectrum of acute coronary syndromes.[376-378] Its real frequency is unknown, but it is estimated that it represents 1% to 2% of cases that present at the emergency room with acute coronary syndrome.[377,379-381] It generally affects post-menopausal women (95% of cases occur in women between the ages of 60 and 80), and it is rarely (< 3%) seen in women under the age of 50 or in men. In up to 80% of cases, the syndrome is associated with previous events which produced strong physical or emotional stress, such as separations, financial loss, conflicts, loss of a loved one, illness of a loved one, severe disease, surgery, etc. In some cases, however, no preceding physical or emotional stress may be identified.

Several physiopathological mechanisms have been proposed as participants in generating the syndrome, such as occult atherosclerotic disease, multiple coronary spasms, endothelial dysfunction, and microvascular disease. Nevertheless, the most accepted hypothesis is an excess of sympathetic stimulation, with elevated circulating catecholamines causing dynamic obstruction of LV outflow and resulting in short periods of ischemia and ventricular "stunning."[377,379,380,382-384] In fact, excessive sympathetic activity with pronounced plasma elevation of catecholamines has been found in almost 75% of patients with Takotsubo syndrome.[379]

The reason why Takotsubo syndrome occurs much more frequently in women after menopause is unknown. Several explanations have been proposed, such as the influence of sexual hormones on the sympathetic neurohumoral axis[379,385] and coronary vasoreactivity;[379,386] higher vulnerability of women to myocardial stunning, mediated by the sympathetic system;[379,387] and alterations in endothelial function following menopause, in response to reduced estrogen levels.[388]

Clinical presentation is characterized by intense, acute chest pain (similar to that of infarction), dyspnea, ischemic ST-segment alterations (ST-segment elevation and/or inversion of T waves and pathological Q waves), mild increase in cardiac enzymes, and segmental systolic dysfunction in the apex and middle third of the LV, with base hyperkinesis, in the absence of obstructive epicardial coronary disease.

The most accepted criteria for diagnosis are currently those proposed by the Mayo Clinic in 2008:[389,390]

- Transient hypokinesis, akinesis, or dyskinesis in LV mid-segments, with or without apical involvement.
- Regional abnormalities that extend beyond epicardial vascular distribution, often with a precipitating factor.
- Absence of CAD or evidence of acute plaque rupture.
- New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or mild elevation in cardiac troponin (disproportional to the degree of LV dysfunction).
- Absence of pheochromocytoma and myocarditis.

Evaluation via myocardial scintigraphy with MIBG-^{123}I shows defects in the uptake of MIBG generally in the apex, with normal myocardial perfusion observed on perfusion scintigraphy with Sestamibi-^{99m}Tc (Figure 55). Semiquantitative analysis has also demonstrated reduced HMR and increased washout of MIBG-^{123}I. Abnormalities on myocardial scintigraphy with MIBG-^{123}I may be detected hours to days following ischemic injury.[391] For this reason, alterations observed on myocardial scintigraphy with MIBG-^{123}I suggest a physiopathological explanation for this syndrome.[392,393] Prognosis of affected patients is generally favorable. In the vast majority of cases, the LV dysfunction is transient, and complete recovery commonly occurs in around 8 weeks. In rare cases, dysfunction may be accentuated, evolving to cardiogenic shock, ventricular arrhythmia, and death (< 1% intra-hospital mortality).[394]

13.4. Final Considerations

The diagnostic and prognostic potential for evaluating the autonomic nervous system with nuclear cardiology is great. A growing amount of evidence has shown that cardiac scintigraphy with MIBG-^{123}I may assist in selection of patients for more sophisticated HR treatments, such as CRT, as well as new medical approaches, and ICD implants for primary prevention. It is also a valuable tool for cardiovascular risk stratification (potentially lethal ventricular arrhythmias, progression of HF, and cardiac death). Due to the high sensitivity of autonomic nervous system fibers to ischemic injury and delayed recovery, myocardial scintigraphy with MIBG-^{123}I is also useful as an ischemic memory marker or for the recognition of Takotsubo syndrome. Greater clinical experience with this method will, however, be necessary, with the aim of improving positive and negative predictive values, for the sake of greater differentiation of patients with low and high risks, thus contributing to more effective use of medical resources. Japan is the only country where the utility of this imaging technique has been characterized in guidelines. Data related to cost-effectiveness are still limited, and low availability in clinical practice make it difficult to use on a large scale.

14. New Applications of Nuclear Cardiology

14.1. Introduction

The applications of nuclear cardiology go beyond MPS for ischemic heart disease. Some of the indications which will be discussed are not relatively recent in the literature, but they are still little utilized within our context. In comparison to conventional investigation methods, new non-invasive methods of nuclear medicine in cardiology have the potential to improve early detection of affected myocardium, allowing for quantification of disease activity, orienting therapeutic interventions, and monitoring success of treatment.

14.2. Endocarditis

Early diagnosis of infectious endocarditis (IE) continues to be challenging. The pathology should, essentially, be suspected in the presence of fever of unknown origin, especially in association with laboratory signs of infection, anemia, microscopic hematuria, or manifestations of septic embolism. The modified Duke criteria, which are considered a reference,

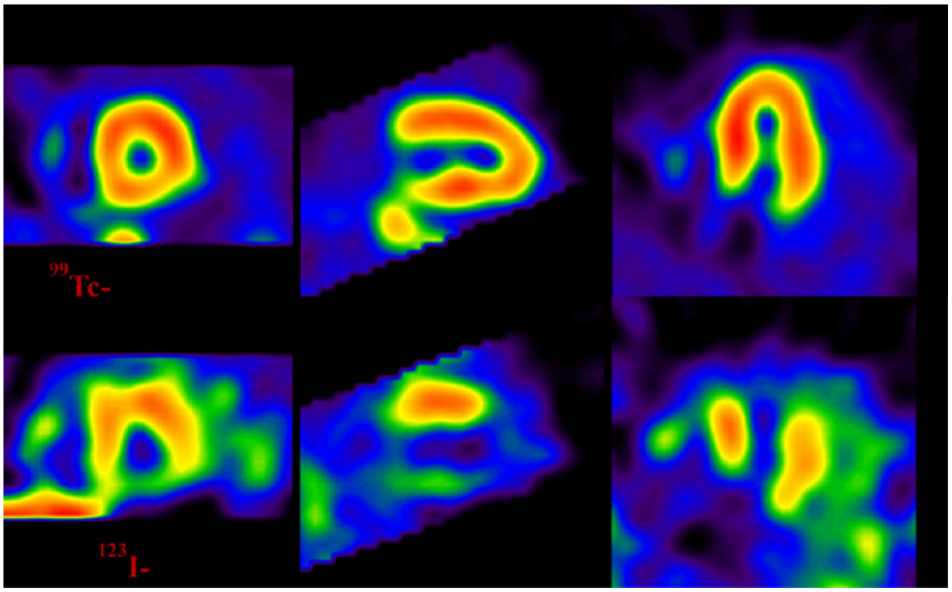

Figure 55 – *Patient with acute coronary syndrome (ACS). Normal myocardial perfusion scintigraphy (MPS) with Sestamibi-^{99m}Tc (top row). Myocardial scintigraphy (MS) with MIBG-^{123}I (bottom row) demonstrates uptake defects in apical segments, suggestive of Takotsubo syndrome. Reduced tracer uptake is additionally observed in the inferior wall. Personal source.*

include clinical, microbiological, and echocardiography findings, resulting in a general sensitivity around 80%.[395] Some limitations, however, stand out, especially in patients with prosthetic valves (PV) and cardiac implantable electronic devices (CIED),[396] implying inadequate classification of up to 24% of patients with proven IE.[395] Advanced imaging techniques for early, sensitive diagnosis of IE are, in fact, valuable tools in clinical practice. The combination of both evaluation of myocardial metabolism of glucose via PET/CT using a glucose analogue labeled with ^{18}F, fluorodeoxyglucose (FDG) (FDG-^{18}F - PET/CT), and modified Duke criteria resulted in increased sensitivity, without large alterations in specificity.[397] Although FDG-^{18}F - PET/CT is not reliable for evaluation of native valve endocarditis,[398] it may accurately diagnose endocarditis in valve prostheses and its systemic complications.[399] In recognition of its utility, FDG-^{18}F - PET/CT was included in the European Society of Cardiology Guidelines, in 2015, as a diagnostic criterion (class of recommendation IIb) for IE in patients with valve prostheses.[400] One option for further improving FDG-^{18}F - PET/CT imaging is the incorporation of angio-CT (PET/angio-CT), resulting in sensitivity, specificity, positive predictive value, and negative predictive values of 91%, 91%, 93%, and 88%, respectively.[401] As a more specific alternative to FDG-^{18}F - PET/CT, guidelines on IE include scintigraphy using marked leukocytes with SPECT/CT imaging. SPECT/CT is the combination of nuclear medicine tomography imaging (SPECT) and anatomical imaging via CT, greatly increasing diagnostic accuracy. However, notwithstanding the proven value of this technique for detecting endocarditis[402,403] (Figure 56), its widespread application is compromised due to limited sensitivity and the difficulty of locating inflammatory foci, but the very high specificity of scintigraphy with marked leukocytes for infection, when using SPECT/CT imaging, may be particularly useful in cases where diagnosis remains uncertain following echocardiography and FDG-^{18}F - PET/CT, especially in patients who have undergone cardiac surgery over the past 2 months.[404-407] As an additional possibility, the simultaneous combination of scintigraphy with marked leukocytes and MPS, acquired to improve localization of infectious points in relation to the valve plane defined by perfusion. Limitations to performing SPECT/CT with marked leukocytes are: the need for a specific structure with laminar flow, the manipulation of blood components, procedure duration, and inferior spatial resolution in relation to PET/CT.[400]

Furthermore, new bacteria-specific tracers have become available, such as carbohydrates, which are metabolized exclusively by bacteria or antibodies directed against components of the bacterial cell membrane. For example, the protein component of the pilin structure of *Enterococcus faecalis* is being developed.[408] This recent study has demonstrated the superior quality of images and another possibility for differentiating between infectious and inflammatory causes of endocarditis.

CIED have been increasingly used over recent years,[400] with elevated rates of infection (1% to 3%), and they are associated with 1-year mortality over 10%.[409] Doppler echocardiography is the first line imaging method for evaluation of suspected CIED infection, but its use is limited for investigating infection in extra-cardiac leads and device pockets. Both FDG-^{18}F - PET/CT and SPECT/CT scintigraphy with marked leukocytes have demonstrated additional value for diagnosis of infections related to CIED or pacemaker. FDG-^{18}F - PET/CT has been shown to be especially useful for diagnosing device pocket

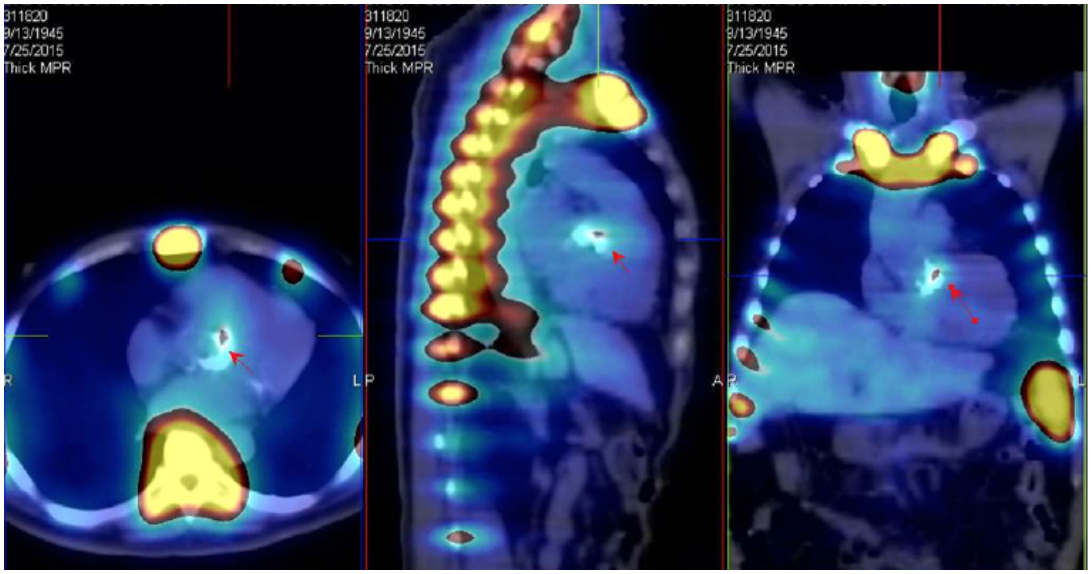

Figure 56 – *Images from scintigraphy with labeledleukocytes with SPECT/CT demonstrate anomalous accumulation in the area of the percutaneously implanted aortic valve (arrows). Transesophageal echocardiogram was inconclusive, and blood culture was positive for* Staphylococcus aureus. *The patient was diagnosed with prosthetic valve infective endocarditis. Personal source (courtesy of Dr. Alan Chambi).*

infections, but it is less reliable for diagnosing infections in the metallic device.[410,411] The presence of a focal hotspot is considered the best criterion for infection,[412] (Figures 57 and 58). It is worth noting that exam accuracy depends on patient preparation and post-implant interval, which is the case with applications involving FDG-^{18}F. Mild FDG-^{18}F uptake has been reported to be nonspecific in patients with CIED or pacemaker with no suspicion of acute-phase infection (≤ 2 months) following cardiac surgery.[410] Moreover, attenuation correction artifacts due to metallic implants should be avoided by means of close evaluation of images without attenuation correction.

Both FDG-^{18}F - PET/CT and scintigraphy with marked leukocytes via SPECT/CT seem to be beneficial in diagnosing infections related to ventricular assist devices (VAD).[413,414] FDG-^{18}F - PET/CT is especially sensitive to infection in these devices. In a small retrospective study, sensitivity to VAD infection was 100%, and specificity was 80%. Furthermore, in 85% of cases, PET imaging had an impact on clinical management of patients.[415]

The role of FDG-^{18}F - PET/CT in investigating extracardiac complications of infection was also studied. In a retrospective analysis of patients with suspected CIED infection, the performance of full body PET also identified septic embolism or infection disseminated into other sites in 28% of cases.[416] These results were confirmed in a prospective study on known device endocarditis.[417] In this cohort, FDG-^{18}F - PET/CT found septic embolism in 10 patients (29%), including 7 cases of spondylodiscitis, 4 of which were not clinically visible and which resulted in significant modifications to therapy.

Guided myocardial biopsy may be another application of FDG-^{18}F - PET/CT, as shown in other diseases.[418] Furthermore, MR and PET/CT seem to be complementary in nature.[419] Investigation of the incremental value of PET/MR, a new integrated imaging modality, may have great potential for diagnosing endocarditis.

14.3. Myocarditis

The most common causes of myocarditis are viral infections. Other causes include other types of infections, autoimmune disorders, or drug interactions. Clinical manifestations of myocarditis are highly variable, ranging from subclinical disease to sudden death. This spectrum also reflects the extent to which this histological disease's severity, etiology, and stage of clinical presentation may vary. Inflammation of the myocardium may be focal or diffused, involving any of the cardiac chambers. Endomyocardial biopsy is currently the gold standard for diagnosis, but it has a low sensitivity (20-30%) and significant associated risk.[420] MR is considered the imaging method of reference for non-invasive diagnosis of myocarditis, given that it allows for detection of several characteristics such as inflammatory hyperemia and edema, necrosis, and myocardial scarring, alterations in ventricular size and geometry, regional and global abnormalities in the movement of walls, and identification of pericardial effusion.[421] MR criteria for diagnosis of myocarditis have been summarized in what are known as the Lake Louise Criteria.[422] MR, however, has limitations that are particularly evident in chronic myocarditis, with low diagnostic precision (50% accuracy).[423]

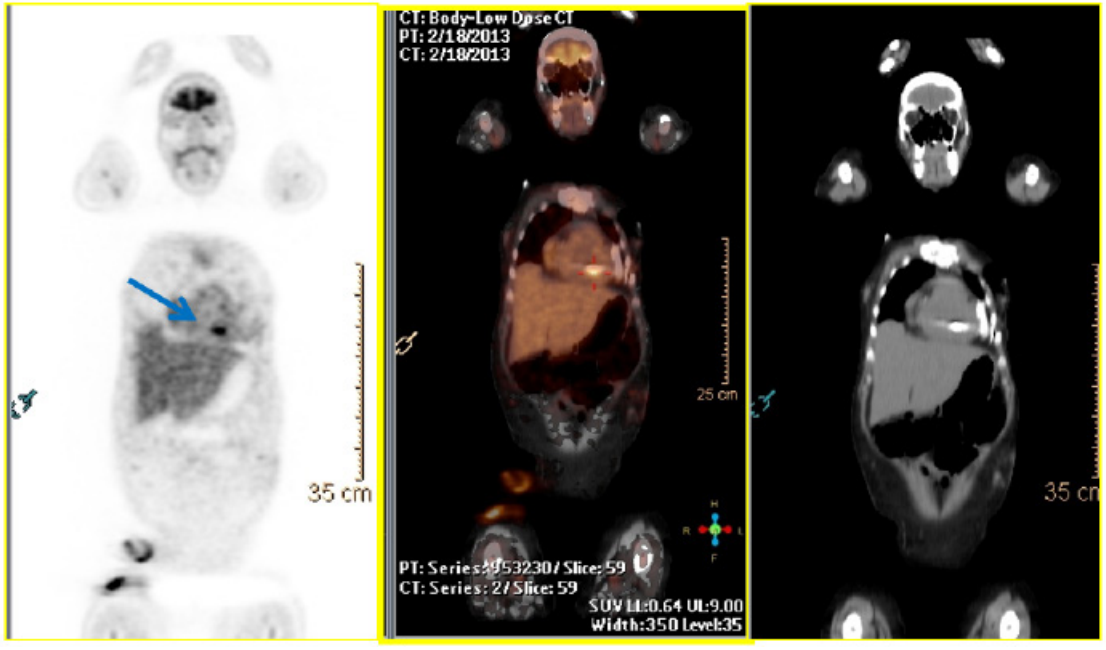

Figure 57 – *Male patient, age 65, with pacemaker implant 4 months prior (removed due to subcutaneous pocket infection); new implantation with the distal end of the right chambers. He evolved with dyspnea and fever 20 days prior; blood culture was positive for S. aureus. FDG-^{18}F - PET/CT study was positive for endocarditis in the implant site; maximum standard uptake value (SUV) = 8.1. Source: INCOR, FMUSP, SP.*

Figure 58 – *Male patient, age 19, with biological prosthesis in the aorta and mitral annuloplasty for 45 days. He evolved with fever, bacteremia, and blood culture positive for* S. Epidermidis. *FDG-^{18}F - PET/CT study was positive for infection in the aortic prosthesis; maximum standard uptake value (SUV) = 9.7. Source: INCOR, FMUSP, SP.*

Using FDG-^{18}F - PET/CT, following adequate patient preparation with a carbohydrate-free diet, it is possible to visualize acute inflammation suggestive of active myocarditis. PET imaging may help distinguish active and chronic forms of the disease, following established working protocols.[424,425] In a prospective study of 65 patients with suspected myocarditis, FDG-^{18}F - PET was in agreement with MR findings.[426] MR and FDG-^{18}F - PET/CT seem to be complementary in nature.[419] For this reason, cardiac PET/MR has potential as a diagnostic tool for myocarditis and a new field of research.[427-429]

14.4. Pericarditis

There are multiple causes of acute or chronic pericardial inflammation, including infections (viral, bacterial, or fungal), myocardial infarction, trauma, malign diseases (primary pericardial neoplasm, pericardial metastases, or paraneoplastic syndrome), autoimmune or inflammatory diseases, and metabolic disorders (uremia). Pericarditis may also be iatrogenic, as a collateral effect of medication. Radiotherapy or idiopathic causes are other possible origins. Although its etiology is variable, the pericardium's response to different causes is not specific. Inflammation of pericardial layers and increased production of pericardial fluids are the most common, and they often manifest as chest pain. In the same manner, Doppler echocardiography stands out as a priority for diagnosis and therapeutic follow-up of pericarditis, externalizing findings such as pericardial effusion and thickness. Generally, CT and MR also allow for evaluation of pericardial effusion and thickness, allowing for better differentiation of pericardium and pericardial fluid.[430]

The use of FDG-^{18}F - PET/CT in pericarditis is generally complementary, and it demonstrates the ability to detect inflammatory tissue, even in the absence of obvious anatomical changes.[431,432] Non-infectious inflammatory pericarditis shows mild to moderate FDG-^{18}F - PET uptake in the pericardium, with diffuse or focal uptake pattern. The literature is still scarce on the utility of FDG-^{18}F - PET/CT for differential diagnosis of the underlying causes of this pathology. Some studies relate the possibility of differentiating infectious/inflammatory pericardial disease and neoplastic/metastatic disease, given that malignity, generally, presents intense metabolic activity.[433] Constrictive or effusive pericarditis, an uncommon complication of chemotherapy, may also present pericardial uptake of FDG-^{18}F, with mild intensity and wide distribution.[431] Only a few case reports are available in the literature, and larger studies are still necessary to determine the accuracy of FDG-^{18}F - PET/CT for pericarditis.

14.5. Cardiac Sarcoidosis

Sarcoidosis is a granulomatous disease whose etiology is unknown. It most commonly affects the lymphatic ganglia and the lungs, but it may involve any system of organs.[434] The heart is frequently affected,[435,436] and this represents one of the main causes of death due to this pathology in Japan and the USA.[437] Due to its multifocal aspect and the irregular manner in which sarcoidosis affects the myocardium, the

sensitivity of endomyocardial biopsy is extremely low (20% to 30%).[438] In comparison with MR, the advantages of FDG-^{18}F - PET/CT include the value of functional metabolic information, the detection of active inflammation, the potential for identifying cardiac and extracardiac involvement (Figure 59) of sarcoidosis, and the possibility of performing imaging in patients with CIED or renal insufficiency. In order to evaluate extracardiac involvement, it is important to perform full-body imaging.

Sarcoidosis normally manifests as an irregular focal uptake pattern. FDG-^{18}F - PET/CT has demonstrated that it detects active cardiac and extracardiac forms reliably, with sensitivity between 81% and 89% and specificity between 78% and 82%, respectively.[439,440] It is necessary to pay attention to the patient preparation required for image acquisition in these cases. It is essential for the patient's diet to be low in carbohydrates and rich in fat the day before the exam and for the patient to be in fasting conditions in order to guarantee that there is no physiological uptake in the myocardium.

FDG-^{18}F - PET/CT may often be combined with MPS synchronized with ECG (Figure 60), with the objective of ruling out CAD or even identifying resting perfusion defects suggestive of inflammation-induced tissue damage.[441,442]

In addition to this, FDG-^{18}F - PET/CT in combination with perfusion imaging has shown evidence of prognostic capability in patients with sarcoidosis,[443] orienting myocardial biopsy,[418] and demonstrating valor for predicting response and monitoring therapy.[444]

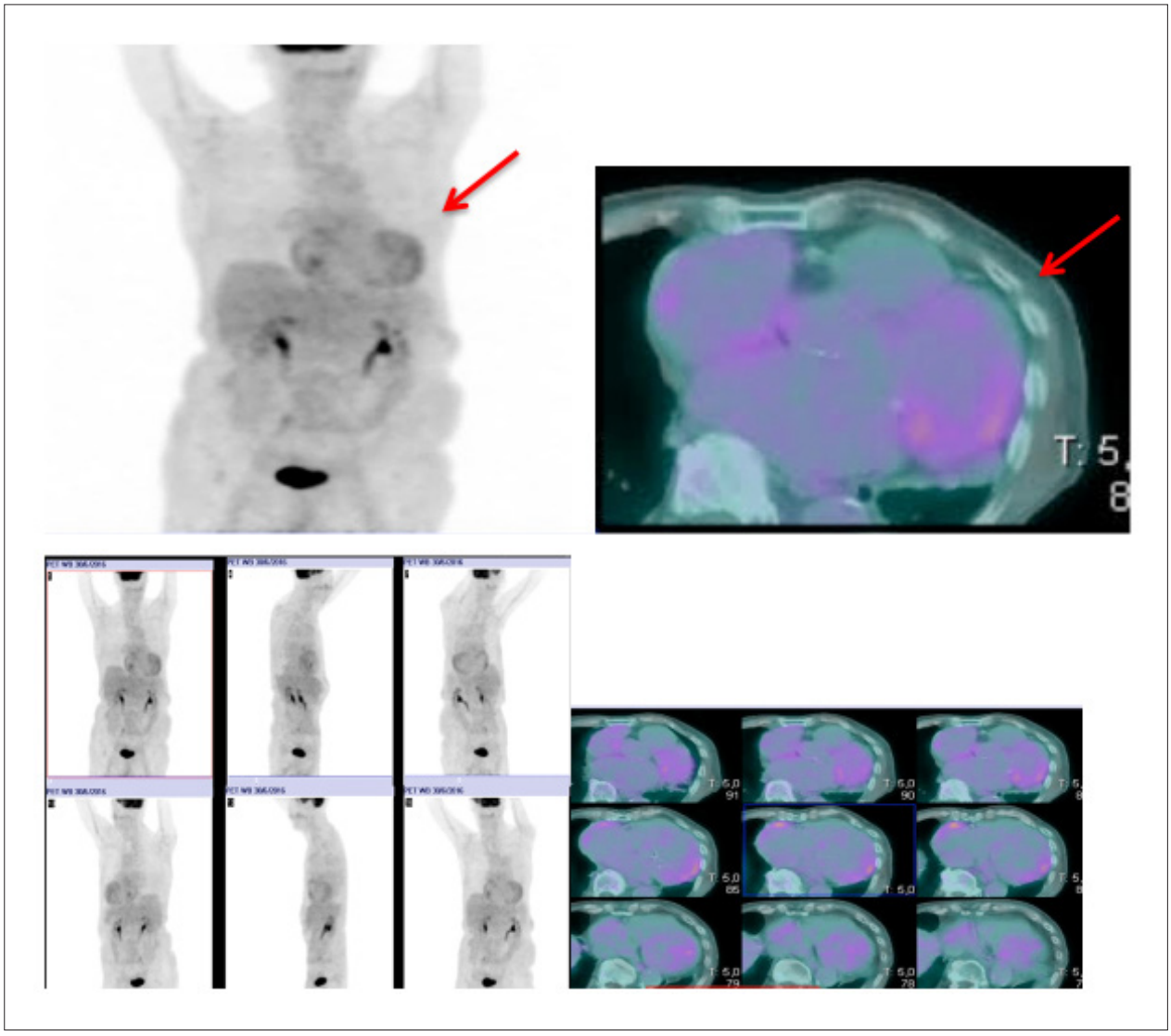

Figure 59 – *FDG-^{18}F - PET/CT with suppression protocol for myocardial glucose uptake (diet), maximum-intensity-projection imaging (left) and coregistration with CT (right). Patient, age 88, with heart failure, reduced ejection fraction, and ventricular tachycardia. Endomyocardial biopsy was compatible with sarcoidosis. Images demonstrated abnormal tracer uptake in the right and left ventricles (arrows). Following immunosuppression, the patient showed clinical improvement and disappearance of abnormalities. Personal source (courtesy of Dr. Evandro T. Mesquita).*

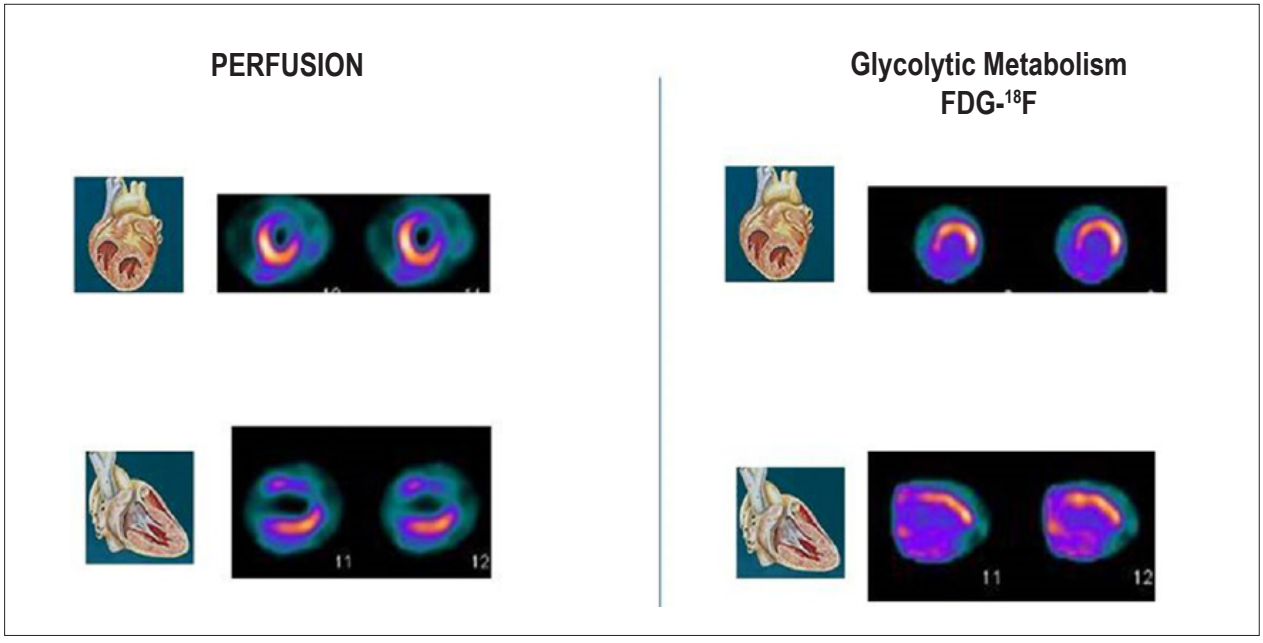

Figure 60 – *Patient with cardiac sarcoidosis. Myocardial perfusion scintigraphy (MPS) with MIBI-^{99m}Tc (left), showing evidence of accentuated persistent hypoperfusion in the anterior and anterolateral walls of the left ventricle; FDG-^{18}F - PET imaging (right) for metabolic study shows that regions with apparent fibrosis were in fact inflammation due to sarcoidosis. Source: INCOR, FMUSP, SP.*

14.6. Cardiac Amyloidosis

The CA is a rare form of cardiomyopathy. Frequently subdiagnosed, it is characterized by extracellular deposition of fibrils, composed of varied serum protein subunits, which have low molecular weight. Although more than 30 different amyloid proteins have been described, the 2 that most frequently infiltrate the heart are: light chain immunoglobulin (AL) and transthyretin (TTR). The AL and TTR forms possess different clinical courses, prognoses, and distinct forms of treatment. In the AL form, fibrils are composed of light-chain immunoglobulins and produced by a population of plasma cell clones located in the bone marrow. In the TTR form, deposits are made up of anomalous monomers or dimers of the hepatic tetrameric protein whose origin may be related to genetic mutations of familial origin (mutated TTR or [mTTR]) or the wild type, formerly known as the senile type (sTTR). More than 100 known mutations are related to mTTR and to autosomal dominant inheritance, which may affect individuals in any age group, especially middle-aged men. The most common manifestation of CA is HF with preserved ejection fraction. In its final stage, it is present as restrictive cardiomyopathy, implying very poor prognosis. Definitive diagnosis requires amyloid deposits on endomyocardial biopsy or, in patients with suggestive cardiac findings, amyloid deposits on histological exams of other tissues (e.g., abdominal fat, rectum, or kidneys).[445]

Echocardiography is the initial non-invasive exam of choice for diagnosing CA, but its specificity is limited.[446] However, complementary sequence with MR, which has satisfactory sensitivity, may suggest a pattern of cardiomyopathy due to amyloid deposition, except in patients with moderate to severe kidney disease.

It has been reported that scintigraphy with intravenous administration of bisphosphonate radiotracers labeled with 99m-technetium (Pyrophosphate-^{99m}Tc is the most used in Brazil) localizes cardiac amyloid deposition. It is considered sensitive and highly specific for TTR CA, identifying the disease early at onset.[447,448] One hypothesis for the binding of these bone markers to amyloid fibers is related to the higher quantity of calcium present in TTR protein, in relation to AL. In a recent multicenter study which included 1,217 patients with suspected CA, the combination of moderate to accentuated increase in myocardial uptake of the radiotracer and the absence of specific monoclonal protein in blood serum or urine, had specificity and positive predictive value of 100% for the TTR form of CA. However, scintigraphy with bisphosphonate radiotracers does not reliably detect other types of CA, and it cannot be used quantitatively for therapeutic monitoring.[418]

The intensity of the concentration of Pyrophosphate-^{99m}Tc in the cardiac area is correlated to the amyloid subtype. Degree of concentration is compared to bone uptake in the ribcage, considering the following: degree 3, greater uptake than the ribs; degree 2, equal to the intensity of concentration in the ribs; degree 1, lower concentration than in the ribs; and degree zero, no significant cardiac tracer concentration. Severely increased concentration (degrees 2 and 3) (Figure 61) is strongly associated with TTR CA, to the extent that some authors suggest dispensing cardiac biopsy in these situations. Less intense increased concentration (degree 1) and absence of increased concentration suggest the AL form, when there is clinical suspicion. Semiquantitative analysis of radiotracer uptake should also be performed (Figure 62).[449]

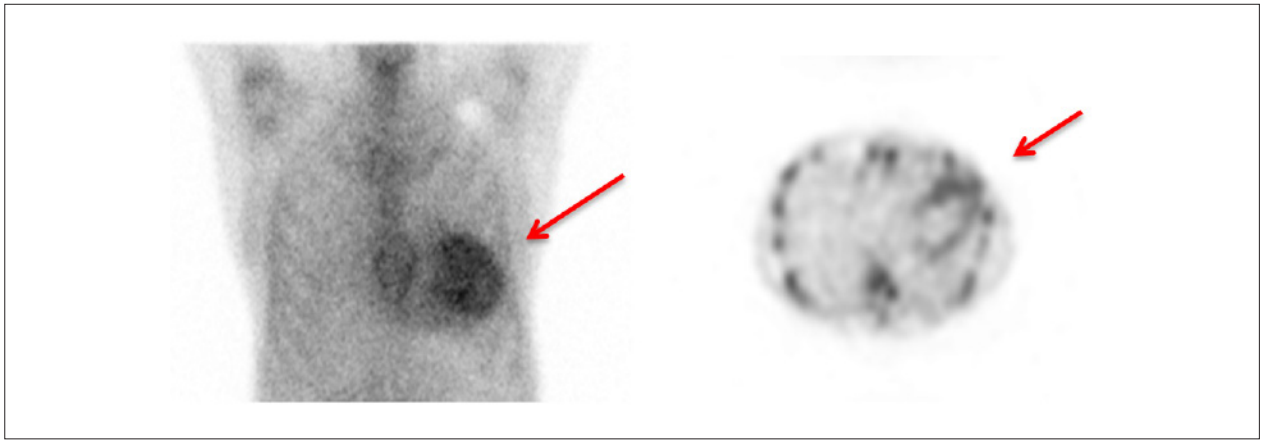

Figure 61 – *Scintigraphy with Pyrophosphate-^{99m}Tc (left: planar imaging of the anterior thorax; right: axial cross section of the tomography image) demonstrated severe radiopharmaceutical uptake in the left ventricle (arrows) in a patient with confirmed transthyretin cardiac amyloidosis. Personal source (courtesy of Dr. Rafael Willain Lopes).*

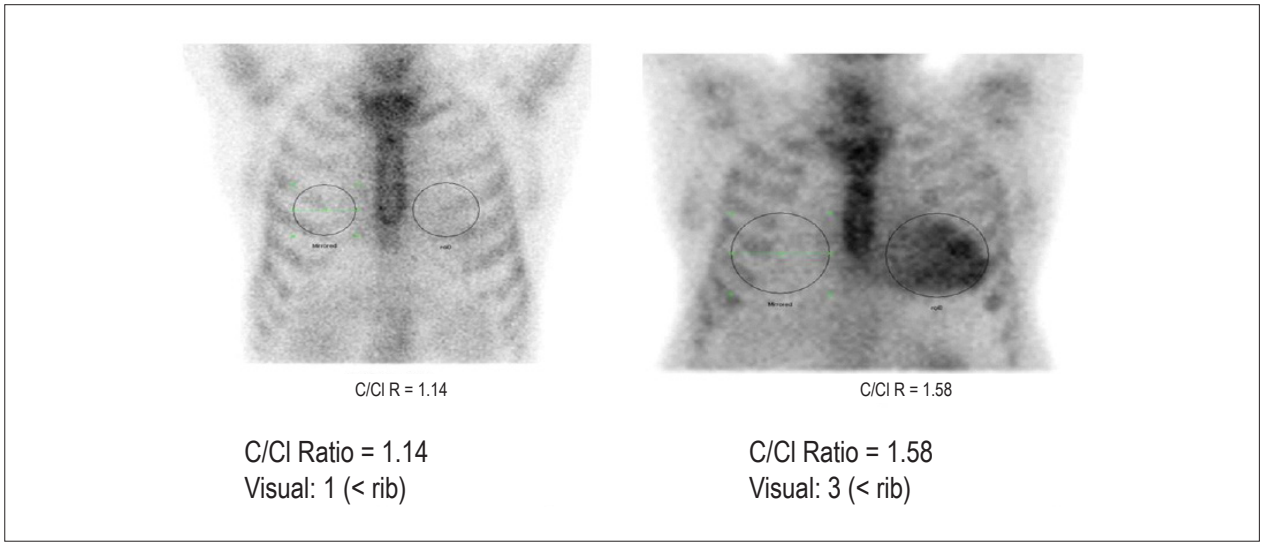

Figure 62 – *Quantification of uptake in planar imaging of anterior thorax scintigraphy with Pyrophosphate-^{99m}Tc. The image on the left represents a negative study, without uptake in the cardiac area. The image on the right represents a study positive for amyloidosis, with accentuated diffuse uptake in the left ventricle. For the purpose of quantification, circular regions of interest (ROI) have been drawn in both hemithoraxes, and the uptake ratio of the radiopharmaceutical between the ROI in the cardiac area (C) and the ROI in the contralateral (Cl) hemithorax. Results over 1.5 suggest TTR amyloidosis. The visual uptake score was equal to 1 in the image on the left and 3 in the image on the right. Source: INCOR, FMUSP, SP.*

A potential bone radiotracer for PET amyloid imaging is sodium fluoride labeled with ^{18}F, or Sodium fluoride-^{18}F. It has been described in single case series, whereas another study identified no increase in uptake of this tracer with TTR CA,[450-452] indicating the need for further studies to investigate the potential value of PET/CT with Sodium fluoride-^{18}F for CA.

A small amount of available data has demonstrated the limited application of FDG-^{18}F - PET/CT for evaluation of CA.[453,454] Up to the present moment, the most promising alternatives include other specific amyloid markers, such as the Pittsburgh B compound labeled with carbon-11 (PIB-^{11}C),[455,456] as well as other compounds labeled with ^{18}F, such as Florbetapir[457,458] and Florbetaben.[459] All studies have reported promising results for diagnosis of CA, given that PIB-^{11}C presents uptake in AC. It has additionally been demonstrated that PIB-^{11}C has lower uptake in patients who have been treated with chemotherapy, in comparison with patients still undergoing treatment. Thus, PIB-^{11}C - PET has the potential to be used for therapeutic monitoring of patients with light-chain CA as a marker of disease activity.[460]

14.7. Final Considerations

New applications of nuclear medicine in cardiology (Table 32) represent an important area which is little explored in

our context. They have the capability to detect functional alterations in these pathologies, indicating whether a disease is or active or not and assisting in therapeutic monitoring. Cardiologists' knowledge of these applications will be essential to their proper use and to the dissemination of these diagnostic methods.

Table 32 – Exam types and main scintigraphy findings of new applications of nuclear cardiology

Pathology	Exam	Main findings
TTR CA (hereditary or wild)	Scintigraphy with ^{99m}Tc-pyrophosphate	Shows moderate to severe radiotracer uptake; high accuracy for detection of TTR form (PPV 100%); allows for early diagnosis; reflects extent of deposit; prognostic marker
Light chain CA	Scintigraphy with ^{99m}Tc-pyrophosphate	Absence of uptake or slight cardiac uptake
Sarcoidosis	FDG-^{18}F - PET/CT	Cardiac hypermetabolism demonstrating active in-flammation
	Myocardial perfusion scintigraphy	Persistent myocardial hy-poperfusion suggestive of tissue damage due to in-flammation
Endocarditis	FDG-^{18}F - PET/CT	Hypermetabolism in areas of infection
	Scintigraphy with marked leukocytes	High uptake in areas of infection

CA: cardiac amyloidosis; PPV: positive predictive value; TTR: transthyretin amyloidosis.

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Update

Erratum

December 2019 Issue, vol.113 (6), page 1138

In Short Editrorial "Admission NT-ProBNP in Myocardial Infarction: an Alert Sign?", consider Luís Beck-da-Silva as the correct form for the name of the author Luís Beck da Silva.

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