

My Approach to Nuclear Medicine in the Assessment of Microvascular Disease in Women

Lara Cristiane Terra Ferreira Carreira,¹ Livia Carreira,² Adriana Soares Xavier de Brito^{3,4} 

Cardiologia Nuclear de Curitiba (CNC),¹ Curitiba, PR – Brazil

PUC Paraná,² Curitiba, PR – Brazil

Instituto Nacional de Cardiologia,³ Rio de Janeiro, RJ – Brazil

Instituto D'Or de Pesquisa e Ensino,⁴ Rio de Janeiro, RJ – Brazil

Abstract

Coronary microvascular dysfunction (CMD) is a condition that has been increasingly recognized as a cause of angina, with prognostic importance in multiple cardiovascular processes, especially in women. It results from abnormalities in the structure and/or function of the coronary microcirculation. Even in the absence of obstructive coronary artery disease (CAD), CMD is associated with worse prognosis, greater morbidity, impaired quality of life, and recurrent hospitalizations due to angina and heart failure, posing a challenge for diagnosis and treatment. In this article, we briefly review CMD and how nuclear medicine can assist in its assessment.

Introduction

Coronary microvascular dysfunction (CMD) results from abnormalities in the structure and/or function of the coronary microcirculation that occur in a variety of cardiovascular conditions (Central Figure). It has been increasingly recognized as a cause of angina, with prognostic importance in multiple cardiovascular disease processes, including its association with adverse outcomes in patients with signs and symptoms of ischemia with non-obstructive coronary arteries (INOCA).¹

Although the diagnostic and therapeutic focus in patients with suspected ischemic heart disease (IHD) has traditionally been on obstructive atherosclerosis in the epicardial coronary arteries, there is currently a greater understanding of the impact of disorders affecting the microcirculation.

This condition has been increasingly diagnosed, especially in women, accounting for almost 60% to 70% of women and 30% of men undergoing coronary

angiography.² This population presents greater morbidity, impaired quality of life, and recurrent hospitalizations due to angina and heart failure, with repeated non-invasive tests and coronary angiograms, posing a challenge for diagnosis and treatment. The majority of women with CMD also have cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, or family history of premature coronary artery disease (CAD), and evidence of non-obstructive coronary atherosclerosis. CMD is an important factor in the observation of similar or worse outcomes of atherosclerosis in women, notwithstanding a lower rate of obstructive epicardial CAD.¹

Pathophysiological mechanisms of CMD

Notably, the epicardial arteries represent only 10% of the volume of coronary circulation, while the microcirculation accounts for the remaining 90%, and it is the site responsible for most of the resistance to coronary blood flow and its regulation.¹

In INOCA, mismatch between blood supply and myocardial oxygen demands may be caused by CMD and/or epicardial coronary artery spasm, typically in the context of non-obstructive coronary atherosclerosis. Ischemia can be caused by transient or sustained impairments in myocardial perfusion that can be structural and/or functional, involving the epicardial coronary arteries and/or their microcirculation.³

Structural factors implicated in CMD include decreased capillary density, luminal narrowing of arterioles/capillaries related to edematous endothelial cells, proliferated smooth muscle cells, and external compression.

Functional mechanisms include endothelial and/or smooth muscle cell dysfunction, mainly at the arteriolar level. Endothelial dysfunction leads to an attenuated response to typical triggers for microvascular dilation, such as exercise or acetylcholine exposure. Furthermore, endothelial dysfunction can even lead to a vasoconstrictor response to these triggers, thus resulting in vasospasm. In addition to the endothelium, the myogenic response of the microvasculature is abnormal in CMD. This can be observed in the attenuated response to vasodilators, such as adenosine, which directly target smooth muscle cells.¹

There are also myocardial factors, such as left ventricular hypertrophy, diastolic dysfunction associated with interstitial and perivascular fibrosis, and increased intramyocardial and intracavitary pressure that substantially contribute to microvascular dysfunction (Figure 1).⁴

Keywords

Microvascular Angina; Myocardial Ischemia; Nuclear Medicine.

Mailing Address: Lara Cristiane Terra Ferreira Carreira •

Cardiologia Nuclear de Curitiba (CNC). Rua Desembargador Hugo Simas, 322 A. Postal code: 80520-250. Curitiba, PR – Brazil

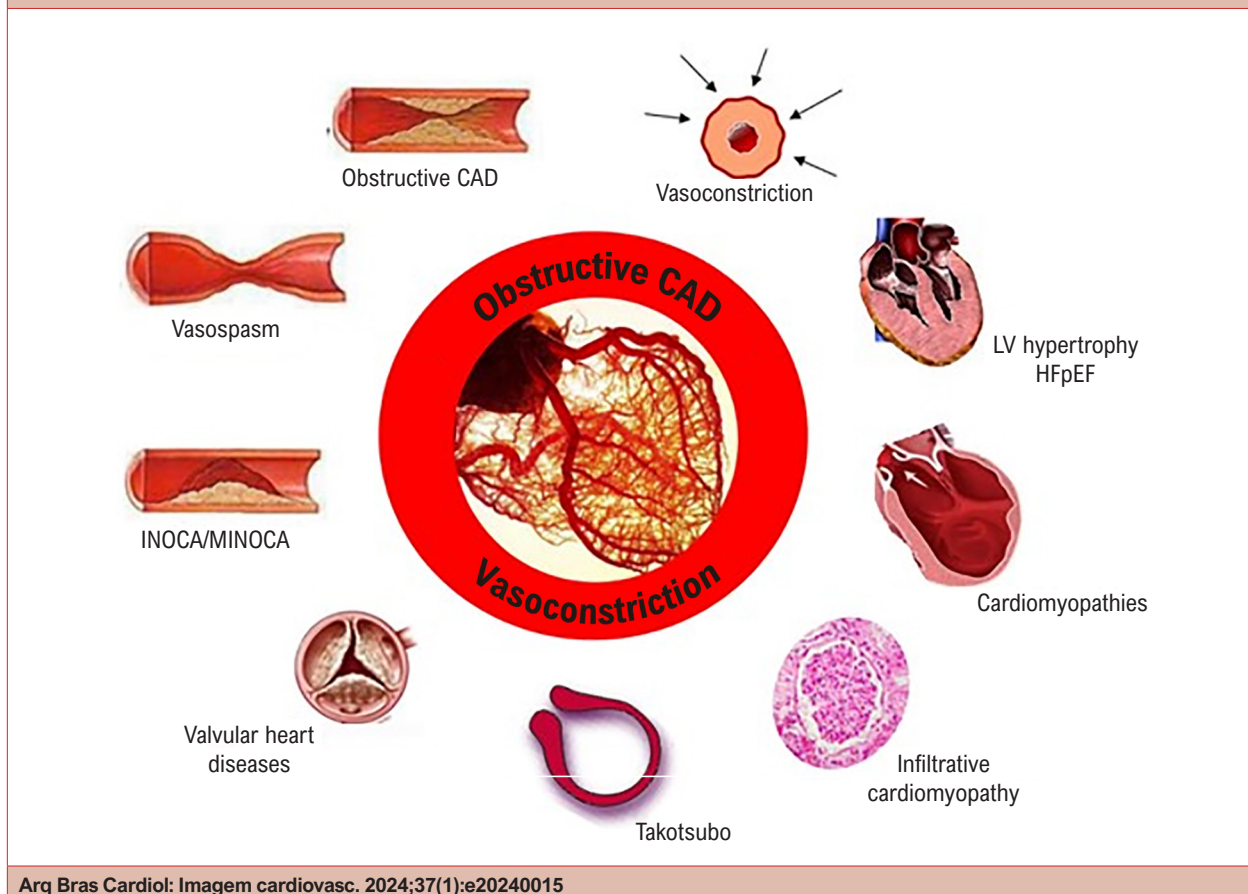
E-mail: lara_carreira@yahoo.com.br

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Central Illustration: My Approach to Nuclear Medicine in the Assessment of Microvascular Disease in Women



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Role of coronary microvascular dysfunction in different cardiovascular diseases. CAD: coronary artery disease; HFpEF: heart failure with preserved ejection fraction; INOCA: ischemia with non-obstructive coronary arteries; LV: left ventricular; MINOCA: myocardial infarction with non-obstructive coronary arteries; CMD: Coronary microvascular dysfunction. Source: Authors' archives.

Patients with CMD present a spectrum of symptoms, similar to patients with obstructive epicardial CAD, including typical angina pectoris, atypical chest pain, and anginal equivalent symptoms, such as dyspnea on exertion. Compared to patients with angina due to obstructive CAD, patients with microvascular angina tend to respond less to nitrates.

Diagnosis of CMD

Diagnosis of CMD should be suspected, and additional tests should be considered when there are symptoms of angina and/or objective signs of ischemia on non-invasive testing, without explanatory obstructive epicardial CAD.

The Coronary Vasomotor Disorders International Study (COVADIS) Group was established in 2012 to develop international standards for the diagnostic criteria for microvascular and vasospastic angina (Table 1).⁶

In the initial evaluation, these patients often present electrocardiographic alterations on the exercise test, although there may or may not be hypoperfusion in

traditional myocardial perfusion imaging methods (Clinical Case 1).

Historically, the methods available for assessment of CMD were based on the quantification of coronary blood flow in response to vasoactive stimuli and the angiographic assessment of myocardial blush, such as invasive tests that measure coronary flow reserve (CFR) in response to adenosine and acetylcholine using a flow catheter with intracoronary Doppler or thermodilution.⁷

However, invasive assessment of coronary function is rarely performed as a routine procedure. The advent of non-invasive techniques such as positron emission tomography (PET), myocardial perfusion scintigraphy (MPS), cardiac magnetic resonance imaging, and stress echocardiography have increased the feasibility of diagnosing reduced myocardial flow reserve indicative of CMD.^{8,9}

Nuclear imaging is able to evaluate the entire spectrum of IHD, from ischemia resulting from obstruction of the epicardial arteries to CMD. National and international

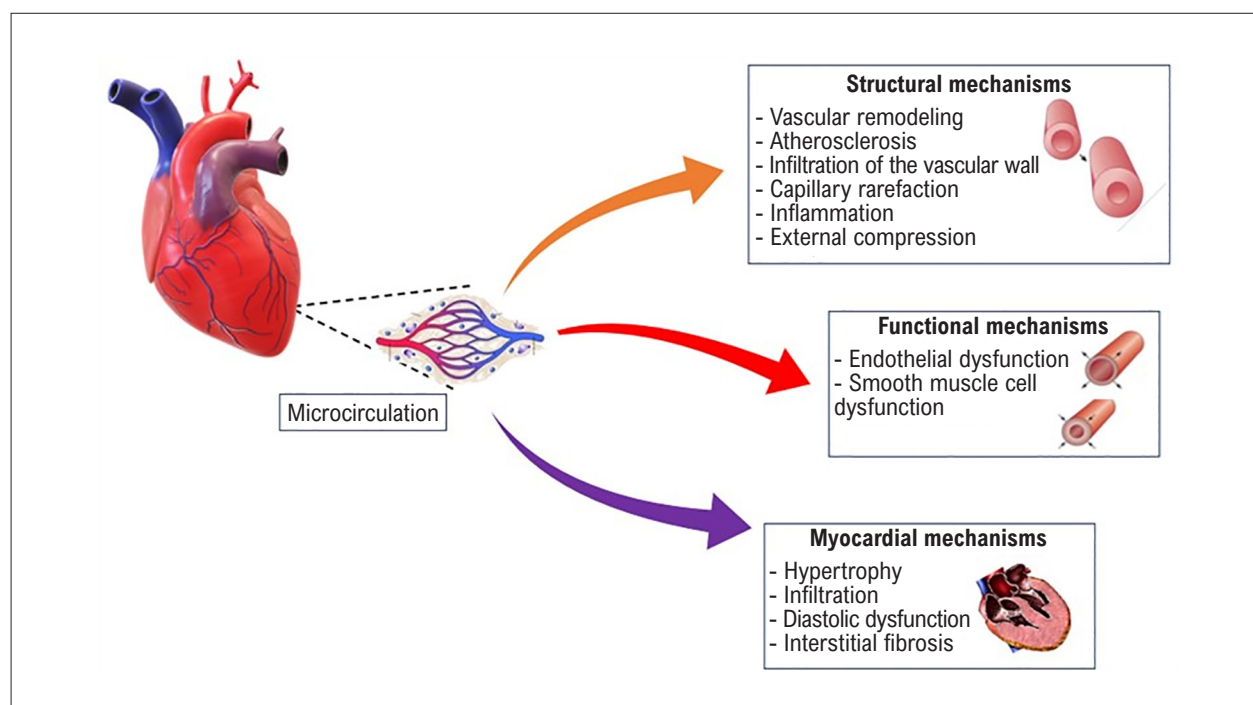


Figure 1 – Mecanismos da disfunção da microcirculação (adaptado de Rehan et al.).⁵

guidelines emphasize, when evaluating IHD, the use of MPS, which can be performed on all patients, regardless of renal function, presence of arrhythmias, obesity, or intracardiac devices.¹⁰ The techniques used are SPECT and PET. For more than three decades, MPS using SPECT has been used extensively in clinical practice due to its wide availability and to the extensive literature supporting its value in the diagnosis and risk stratification of IHD. It is the most commonly used non-invasive imaging study in the evaluation of women at intermediate to high risk of IHD with stable ischemic symptoms.

Patients who present altered perfusion, whether using SPECT or PET, have a greater risk of cardiovascular events. However, in CMD, perfusion defects may not be evident, or they may not have a typical regional distribution corresponding to an epicardial artery. Contractile abnormalities are not normally observed.

The difficulty in observing myocardial ischemia using traditional imaging methods may be related to a non-uniform distribution of microvasculature dysfunction.¹

Definitive non-invasive clinical diagnosis of CMD depends on the identification of impaired CFR in the absence of flow-limiting CAD. Impaired CFR, calculated as the ratio of hyperemic coronary blood flow to resting coronary blood flow, reflects flow abnormalities in the epicardial coronary arteries and microvasculature.

Cardiac PET examination is currently considered the gold standard for non-invasive assessment of myocardial blood flow (MBF), both at rest and in hyperemia, and it represents a crucial tool for evaluating CFR, reflecting microvascular dysfunction, with a significant prognostic

value. Murphy et al. demonstrated that $CFR < 2.0$ was associated with an annual rate of major adverse cardiac events of 7.8% and 5.6% among symptomatic men and women without obstructive CAD versus 3.3% and 1.7%, respectively, for those with $CFR \geq 2.0$.¹¹

Despite the enormous known advantages in terms of diagnosis and risk stratification (Figure 2), cardiac PET cannot yet be integrated into the clinical routine in Brazil, due to the unavailability of PET perfusion tracers in our country.

In the last decade, nuclear cardiology has witnessed a major advance, due to the introduction of cameras with solid-state cadmium-zinc-telluride (CZT) detectors, which allow the assessment of MBF and CFR using SPECT. In view of its advantages in spatial, temporal, and energy resolution over standard gamma camera systems, MBF quantification is feasible, and it has good consistency with coronary flow values based on PET/CT.¹³

Another benefit of dynamic SPECT-CZT is the wide availability of tracers labeled with technetium-99m. It has also demonstrated good reliability in the diagnostic and prognostic assessment of patients with suspected or known CAD, with a potential role in identifying CMD.¹⁴

Although very promising, it is important to highlight that most studies to date are from single centers, and they have small samples. However, this technology arouses a great deal of interest on the part of the scientific community, since the radiopharmaceuticals used are widely available, and the equipment has a lower cost when compared to PET/CT.

Table 1 – COVADIS (Coronary Vasomotor Disorders International Study) diagnostic criteria for microvascular angina and vasospastic angina in patients with INOCA

Criteria	Microvascular angina	Vasospastic angina
1 Symptoms of myocardial ischemia	Angina at rest or during exertion	1. Nitrate-responsive angina during spontaneous episode, with at least 1 of the following: A. Resting angina, especially between night and early morning B. Marked diurnal variation in exercise tolerance, reduced in the morning C. Hyperventilation can precipitate an episode D. Calcium channel blockers suppress episodes
2 Absence of obstructive CAD (< 50% diameter reduction or FFR > 0.80)	Coronary CT angiography Invasive coronary angiography	Coronary CT angiography Invasive coronary angiography
3 Objective evidence of myocardial ischemia	Presence of reversible defect, abnormalities in flow reserve on functional imaging tests	Transient ischemic ECG changes during spontaneous episode, including any of the following in at least 2 contiguous leads: A. ST segment elevation ≥ 0.1 mV B. ST segment depression ≥ 0.1 mV C. New negative U waves
4 Evidence of coronary dysfunction	Coronary flow reserve decreased (≤ 2.0 or ≤ 2.5 depending on the methodology used), determined invasively or non-determinant. Microvascular coronary spasm, defined as reproduction of symptoms, changes ischemic on ECG but without epicardial spasm during acetylcholine test. Coronary microvascular resistance index decreased (e.g. IMR ≥ 25) Slow coronary flow phenomenon, defined with TIMI > 25.	Coronary artery spasm defined as total or subtotal coronary artery occlusion (> 90% constriction) with angina and ischemic ECG changes, either spontaneously or in response to provocative stimuli (typically acetylcholine, ergot, or hyperventilation)

"Definitive" diagnosis: all 4 criteria present; "Suspicious" diagnosis: criteria 1 + 2 present, but only criteria 3 or 4 present or equivocal. CAD: Coronary Artery Disease; FFR: Fractional Flow Reserve; IMR: Microcirculatory Resistance Index; TIMI: thrombolysis in myocardial infarction.

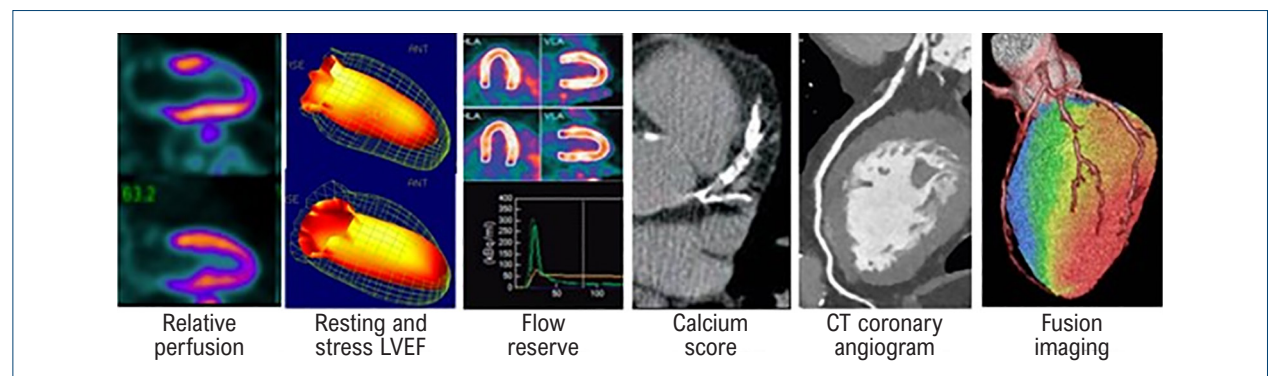


Figure 2 – CT: computed tomography; LVEF: left ventricular ejection fraction; PET: positron emission tomography. PET/CT perfusion images – comprehensive data Adapted from Al-Mallah et al, J Nucl Cardiol 2010; 17:498-513.¹²

My approach

Given the diagnostic and prognostic importance of coronary flow measurements obtained non-invasively in CMD, it has become vital to introduce new methods that make it possible to quantify them. Studies that standardize and validate protocols for obtaining MBF and CFR using CZT gamma cameras are necessary for the method to be widely available and reproducible in the investigation of CMD.

The exam is performed at rest and under pharmacological stress with a vasodilator (dipyridamole or adenosine), in a protocol that lasts 1 or 2 days. Patients are advised to suspend caffeine and methylxanthines for 24 hours before the exam.

Images are acquired dynamically on a CZT gamma camera, to allow the quantification of MBF and CFR in

specific commercial software, coupled to the perfusion image acquisition protocol. The protocol usually begins with the intravenous injection of 0.5 to 1 mCi of sestamibi-^{99m}Tc to position the heart in the field of view of the gamma camera, through a rapid acquisition of 60 seconds.

The resting phase involves the acquisition of dynamic images, simultaneous with the beginning of intravenous administration of the radiotracer sestamibi-^{99m}Tc, immediately followed by perfusion imaging. With the patient still positioned in field of view of the gamma camera, the pharmacological stress phase is carried out with intravenous injection of dipyridamole at a dose of 0.56 mg/kg or adenosine at 140 mcg/kg/min for 4 or 6 minutes. At peak stress, a second dose of sestamibi-^{99m}Tc is administered, with triple the activity value of the dose injected at rest. Both stages are acquired coupled with electrocardiogram monitoring to evaluate the function and volumes of the left ventricle using gated SPECT.^{15,16}

The dynamic data from acquisitions are processed using a dedicated workstation, with specific commercial software.

Clinical cases from clinical practice

Clinical case 1: Woman, 73 years old, sedentary, with grade III obesity, systemic arterial hypertension, glucose intolerance, and dyslipidemia, complaining of palpitations, oppressive chest discomfort associated with fatigue on minor exertion, and hypertensive peaks. MPS (SPECT) at rest and under pharmacological stress with a vasodilator demonstrated a significant area of reversible hypoperfusion compatible with ischemia in the anterior, anteroseptal, and inferior apical walls (Figure 3A).

Coronary angiography revealed coronary arteries without obstructive lesions. She became asymptomatic after 10 months of treatment, with changes in lifestyle habits, supervised exercise, a low-calorie diet, and optimization of medications. MPS was repeated, which demonstrated a significant reduction in the area of radiotracer hypoperfusion, without evidence of ischemia, and improved left ventricular function (Figure 3B).

Clinical Case 2: Woman, 62 years old, former smoker, with hypertension and dyslipidemia, complaining of recent onset of fatigue. History of breast cancer and mastectomy 7 years prior, with recurrence of the disease 2 years prior, undergoing radiotherapy and chemotherapy. She experienced a transient reduction in left ventricular ejection fraction while taking trastuzumab. Coronary CT angiography showed no obstructive lesions. She was referred for MPS at rest and under pharmacological stress with vasodilator and analysis of coronary flow reserve (SPECT-CZT) to investigate CMD, which demonstrated preserved myocardial perfusion (Figure 4A), but with significant changes in coronary flow reserve in the territory of the 3 coronary arteries (Figure 4B).

Conclusion

CMD has a high prevalence and significant clinical implications in daily practice, especially in women. Functional and/or structural microcirculation abnormalities can lead to ischemia in the absence of significant epicardial stenosis or worsen concomitant atherosclerotic CAD.

The recognition of microvascular angina reinforces the importance of functional nuclear techniques, as well as the fact that assessment of IHD should be more comprehensive, beyond the detection of obstructive epicardial CAD.

Cardiac PET is currently the gold standard for assessing MBF and CFR. Nonetheless, the method's low availability and high costs make widespread use difficult. The development of new technologies, such as CZT gamma camera equipment, with good accuracy and agreement with PET in evaluating CFR, has been promising in this context, making diagnosis of CMD possible. However, standardization of acquisition and post-processing protocols, as well as updates to available software, are necessary to reduce variability between centers and increase the clinical robustness of SPECT-CZT results, with improved risk stratification, better therapeutic approach, and consequent changes in the prognosis of CMD.

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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, critical revision of the manuscript for intellectual content: Carreira LCTF, Carreira L, Brito ASX.

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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.

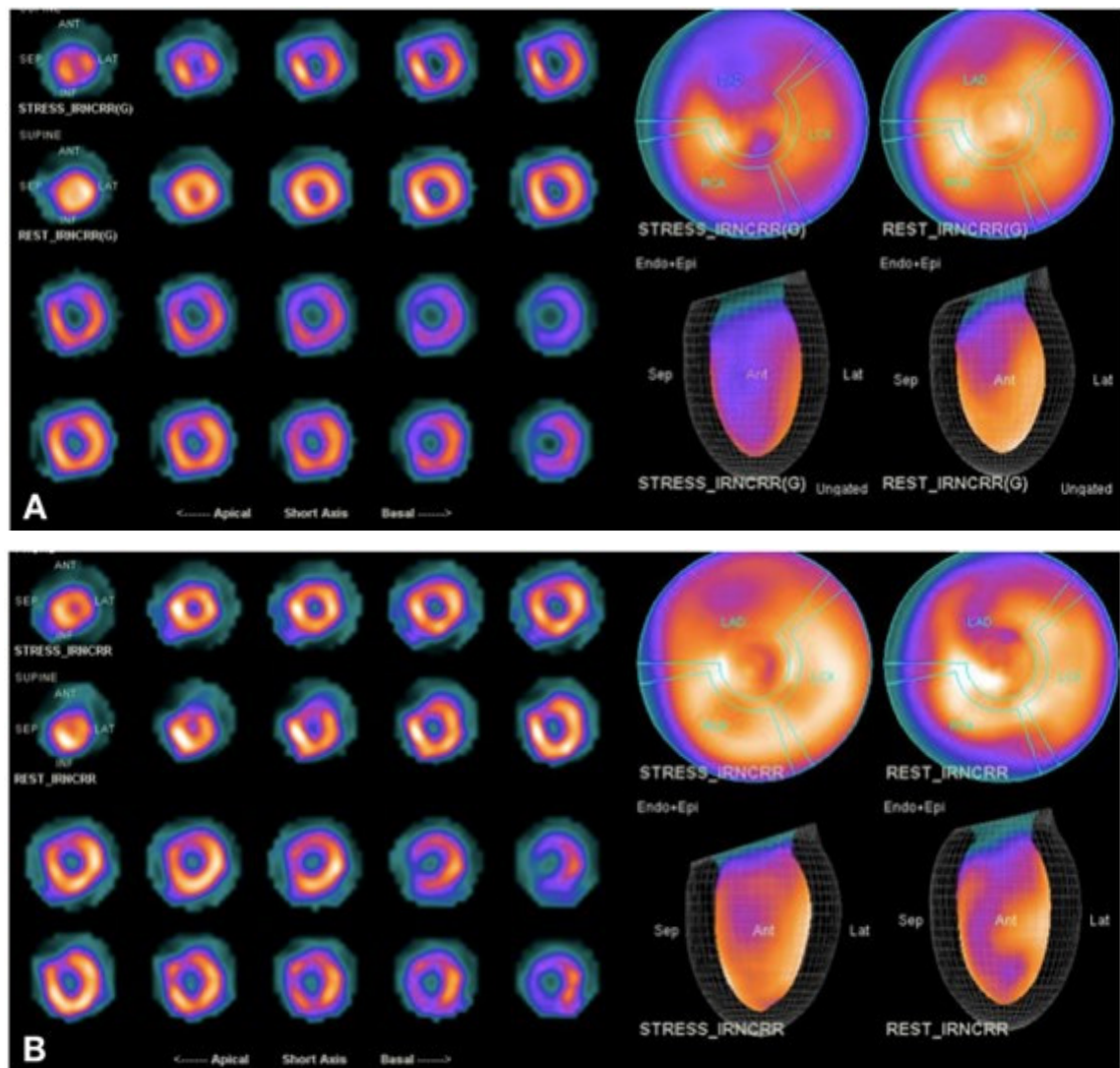


Figure 3 – A) CPM (SPECT) with 99mTc-Sestamibi: moderate hypoperfusion of the radiopharmaceutical is observed in the anterior wall, anteroseptal region, and inferior apical region of the left ventricle in the stress images (lines a and c), which normalize in the rest images (lines b and d). **B)** CPM (SPECT) with 99mTc-Sestamibi: normal distribution of the radiopharmaceutical is observed in the walls of the left ventricle, with no evidence of ischemia.

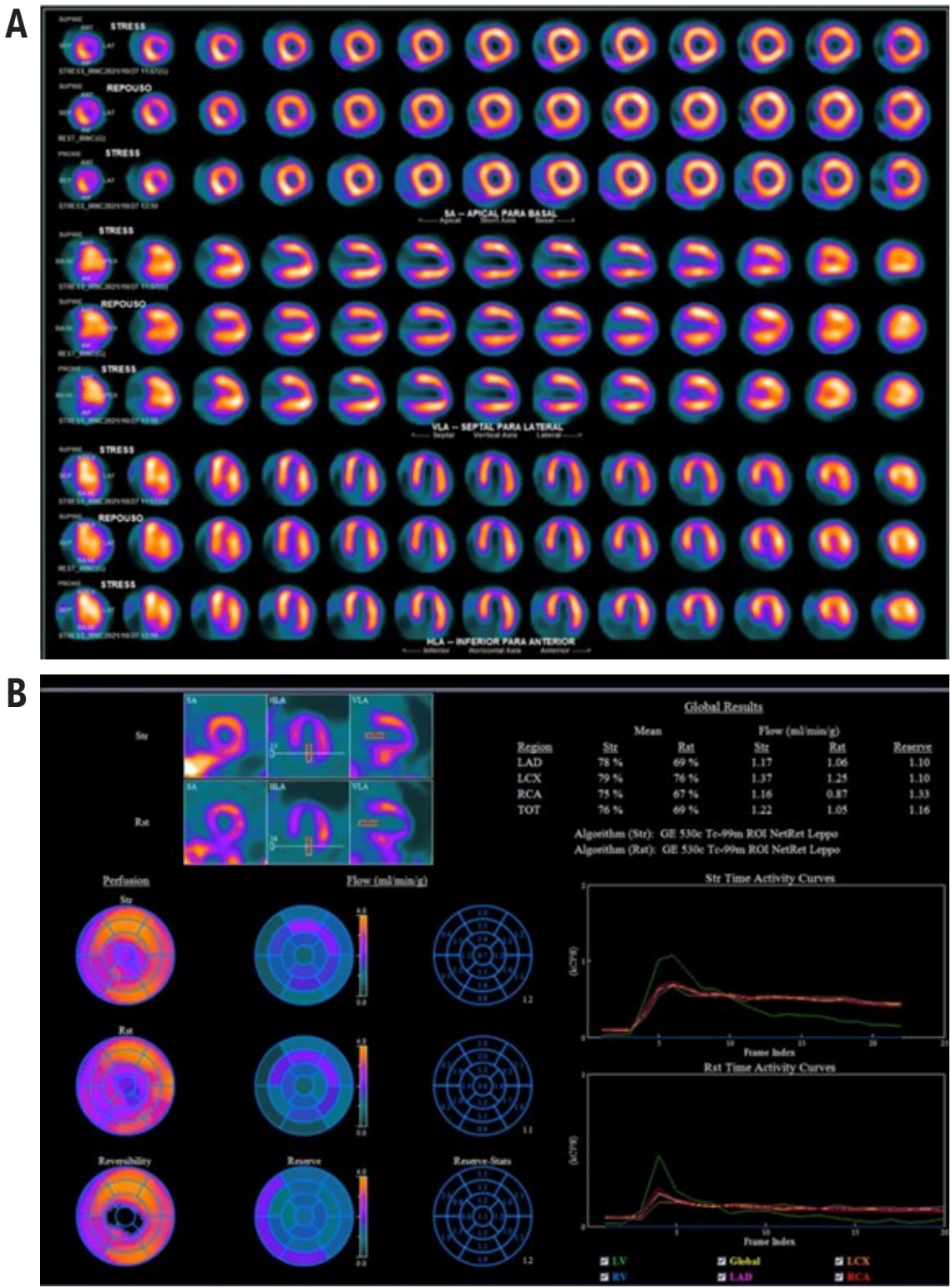


Figure 4 – A) CPM (SPECT-CZT) with ^{99m}Tc -Sestamibi at rest and pharmacological stress: homogeneous distribution of the radiopharmaceutical is observed in the walls of the left ventricle. **B)** CPM (SPECT-CZT) with ^{99m}Tc -Sestamibi at rest and pharmacological stress: significant reduction in myocardial perfusion in the territory of the three coronary arteries is observed.

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