

My Approach to Assess Cardiac Sympathetic Activity

Adriana Soares Xavier de Brito,^{1,2} Jessica Costa Leite,³ Simone Cristina Soares Brandão⁴

Instituto Nacional de Cardiologia,¹ Rio de Janeiro, RJ – Brazil

Instituto D'Or de Pesquisa e Ensino,² Rio de Janeiro, RJ – Brazil

Faculdade de Ciencias Medicas da Paraiba,³ Joao Pessoa, PB – Brazil

Universidade Federal de Pernambuco,⁴ Recife, PB – Brazil

Abstract

Sympathetic innervation plays a crucial role in regulating blood flow, chronotropism, dromotropism, lusitropism, and myocardial inotropism. In several cardiac and neurodegenerative disorders, the autonomic nervous system (ANS) undergoes alterations. Cardiac neuronal imaging can aid in understanding the pathophysiology, diagnosis, and prognosis of these conditions. This article provides a clear and objective overview of the step-by-step procedure for mIBG-I123 scintigraphy, which assesses cardiac sympathetic activity in primary clinical practice settings.

Introduction

The autonomic nervous system (ANS) is functionally subdivided into sympathetic (SNS) and parasympathetic (PNS) systems, which collaborate to control homeostasis.¹ The control of the cardiac ANS is a dynamic process, and its dysfunction can arise from either intrinsic or extrinsic factors. The first results from diseases directly impacting the autonomic nerves, such as diabetes mellitus and autonomic failure syndromes. The second one manifests as a secondary condition to cardiac or systemic diseases.²

Heart disease can lead to both anatomical (primary) and functional (secondary) changes in the autonomic function of the heart. These changes can contribute to the progression of heart disease and/or be involved in the development of arrhythmias.² Additionally, some neurodegenerative diseases can affect the ANS. In such a context, cardiac neuronal imaging can aid in understanding the pathophysiology, diagnosis, and prognosis of these diseases.^{3,4} This article provides a clear and objective overview of the step-by-step procedure for scintigraphy using metaiodobenzylguanidine labeled with iodine-123 (mIBG-I123) to assess cardiac sympathetic activity in the primary clinical practice scenarios (Central Illustration).

Keywords

123-metaiodobenzylguanidine; Heart Rate; Heart Failure; Parkinson Disease.

Mailing Address: Adriana Soares Xavier de Brito •

Instituto Nacional de Cardiologia. Rua das Laranjeiras, 374. Postal code: 22240-006. Rio de Janeiro, RJ – Brazil

E-mail: adrijssoares@hotmail.com

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Cardiac Scintigraphy with mIBG-I123

The normal heart is densely innervated by the SNS, allowing for the non-invasive assessment of cardiac adrenergic activity through cardiac scintigraphy with mIBG-I123, a false neurotransmitter analog of guanethidine.⁵ mIBG was initially discovered in the early 1980s during research on adrenal gland tumors due to its molecular structure being similar to norepinephrine (NE). Additionally, mIBG utilizes the same uptake-1 and storage mechanisms as NE in the neurosecretory vesicles of cardiac presynaptic nerve endings.⁶

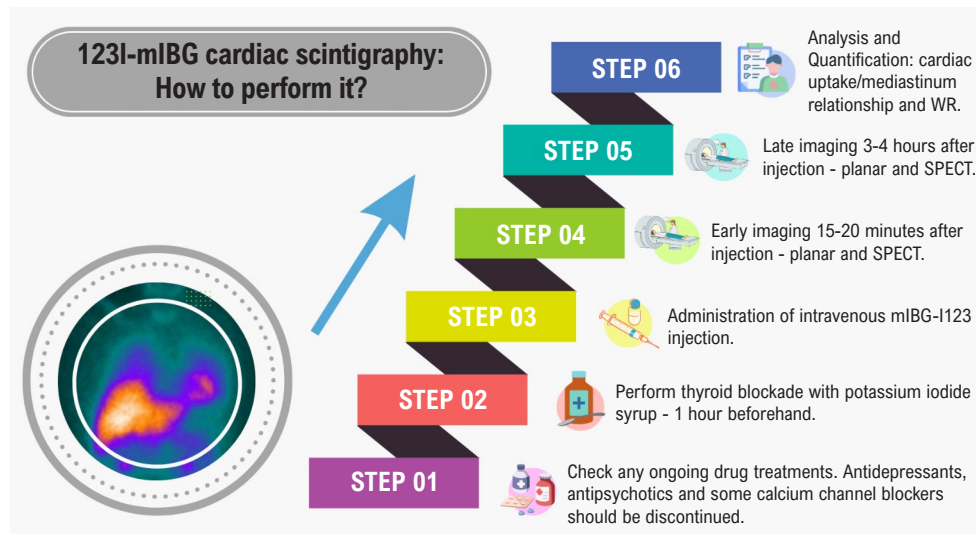
After adrenergic stimulation, mIBG is released into the cardiac synaptic cleft. However, unlike NE, it is not metabolized by monoamine oxidase and catechol-ortho-methyltransferase enzymes, exhibits low affinity for postsynaptic receptors, and lacks pharmacological action (Figure 1). Studies have shown that in vivo cardiac mIBG uptake correlates with NE concentration, reflecting the innervation of the cardiac SNS under both physiological and pathological conditions.⁵ mIBG-I123 enables the visualization of global and regional sympathetic innervation of the left ventricular (LV) myocardium through the acquisition of cardiac scintigraphic images, including planar and tomographic images (SPECT — Single Photon Emission Computed Tomography).

How Is the Exam Performed?

The intravenous administration of mIBG-123I is performed at rest, at least 30 minutes after the oral intake of potassium iodide syrup or an iodine-containing solution, to block and protect the thyroid. Medications that might interfere with catecholamine uptake, such as antidepressants, antipsychotics, and certain calcium channel blockers, should be discontinued before the examination.⁷ However, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors or ACEI), and/or angiotensin receptor blockers do not need to be discontinued.⁸

The procedure is typically conducted using tomographic gamma cameras equipped with high-resolution, low-energy parallel-hole collimators, using a 20% symmetric window centered on the iodine-123 photopeak of 159 keV and a 128 x 128 matrix. Approximately 15 to 20 minutes and 3 to 4 hours after the administration of mIBG-123I (at 185 to 370 MBq or 5 to 10 mCi), planar images in the anterior projection as well as tomographic (SPECT) images of the chest are acquired with the patient lying supine and the left arm raised above the chest.⁷ While not mandatory, SPECT images can aid in assessing regional myocardial sympathetic activity, which can be compared with myocardial perfusion

Central Illustration: My Approach to Assess Cardiac Sympathetic Activity



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SPECT: Single Photon Emission Computed Tomography; WR: washout rate.

scintigraphy images to evaluate perfused but denervated areas (mismatch), which are more susceptible to arrhythmias.⁹

In anterior planar chest images, the relationship of mIBG-I123 uptake between the heart and mediastinum (H/M) and the myocardial washout rate (WR) were evaluated. The early and late H/M ratio is calculated by averaging counts per pixel in regions of interest drawn in the superior mediastinum (7x7 pixels) and over the entire heart (Figure 2). The early H/M ratio represents the integrity of presynaptic nerve terminals and the density of β -adrenergic receptors. The late H/M ratio combines information on neural function, including uptake, NE release and storage in presynaptic vesicles. In turn, the WR reflects cardiac adrenergic tone.¹⁰ The radiotracer WR is calculated using the following formula: $WR = [(H - \text{early } M) - (H - \text{late } M)] / (H - \text{early } M) \times 100 (\%)$, which can be corrected by the iodine-123 decay factor (1.21 factor if the interval time between early and late images is 3 hours and 45 minutes, for example).⁷

Normal values for the H/M ratio range from 1.8 to 2.8, with an approximate average of 2.2 ± 0.3 on late images. The average WR value of normal controls is about $10 \pm 9\%$. The intra- and inter-observer variability of these measurements is less than 5%. It is worth noting that the lower the H/M ratio and the higher the WR, the worse the cardiac sympathetic activity.⁸

Tomographic images (SPECT) are obtained with 60 projections, each lasting 30 seconds, covering a 180° arc and stored in a 64×64 matrix. These images are used for analysis and quantification of the global and segmental distribution of mIBG-I123 in the LV myocardium, of semiquantitative visual form in the three tomographic axes (short axis, vertical long axis and horizontal long axis).

Clinical applications

Cardiac scintigraphy with mIBG-123I can be useful in several clinical settings (Table 1), being most frequently used in cases of heart failure (HF) and to help diagnose neurodegenerative diseases.

Use in HF

In patients with HF, chronic exposure to high concentrations of circulating NE leads to a dysfunction in the response of β -adrenergic agonist receptors.¹¹ This phenomenon can be attributed to several mechanisms, including the downregulation of β -adrenergic receptors, impaired coupling of β -receptor subtypes, upregulation of the enzyme β -adrenoreceptor kinase, increased activity of G proteins, and decreased activity of adenylyclase. Ventricular remodeling, characterized by NE-induced hypertrophy and apoptosis of myocytes, is associated with the re-expression of fetal genes and subsequent downregulation of adult genes. These findings highlight the cardiotoxic effects of direct chronic adrenergic stimulation of β -adrenergic receptors in myocytes and fibroblasts, contributing to various biochemical and structural changes in HF (Figure 3).^{11,12}

Due to these alterations, cardiac scintigraphy with mIBG-I123 in HF shows reduced myocardial radiotracer uptake and accelerated WR compared to healthy individuals.^{5,13} Several studies have shown that the decreased heart-to-mediastinum (H/M) ratio and increased WR are independent predictors of adverse cardiac outcomes, including death, HF progression, and ventricular arrhythmias, in patients with LV dysfunction. These

Sympathetic Nerve Terminal

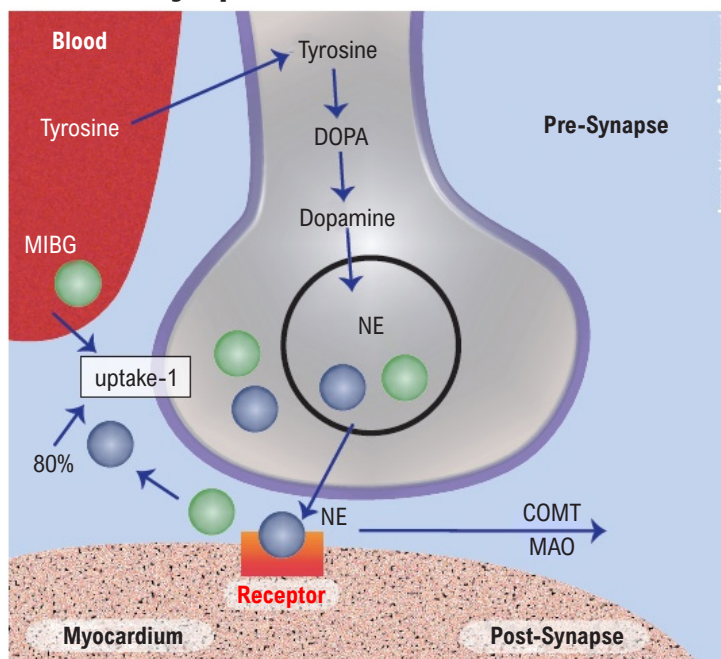


Figure 1 – Representative image of the uptake and release of mIBG in cardiac synaptic nerve terminals by uptake-1 receptors similar to NE

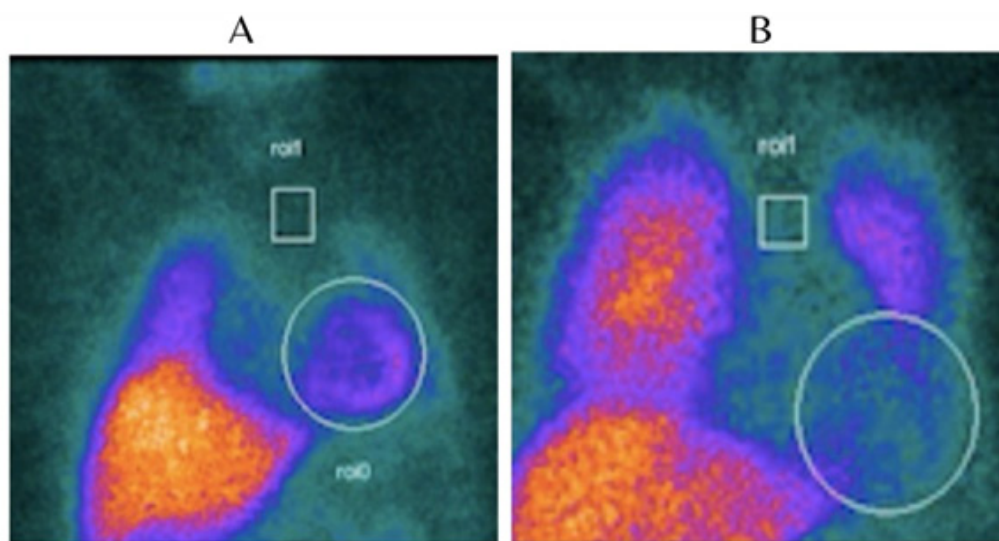


Figure 2 – ¹²³I-mIBG cardiac scintigraphy. In A: late planar image of the anterior chest demonstrating a normal pattern of mIBG-¹²³I uptake in the left ventricular (LV) myocardium, with areas of interest drawn over the LV (circle) and the superior mediastinum (rectangle) to calculate the heart/mediastinum (C/M) ratio; in B: image of a patient with heart failure (HF) with marked reduction in ¹²³I-mIBG uptake in LV topography (circle) and greatly reduced C/M index, indicative of cardiac sympathetic hyperactivity.

predictors are even more significant than LV ejection fraction (LVEF), New York Heart Association (NYHA) functional class, LV size, and plasma NE levels.^{14,15}

The results of a prospective, multicenter ADMIRE-HF trial revealed that patients with HF, NYHA functional class II or III, with an H/M ratio lower than 1.6 had a cardiac death rate of

Table 1 – Main clinical applications of 123I-mIBG cardiac scintigraphy.

Clinical scenarios	Established	Potential
HFrEF	Risk stratification, independent of other parameters, assessment of HF progression, arrhythmic events and total cardiac mortality up to 2 years. Identification of a subgroup at low risk for cardiac events and death. Clinical follow-up of medical therapies indicated in the guidelines.	Identify patients most likely to benefit from CRT or LVAD. Guide the treatment of patients with LVAD: bridge to transplant, possible explant. Surrogate marker to assess the benefit of new medical therapies and devices.
HFpEF	Subanalyses of larger studies show risk stratification capabilities similar to that seen in patients with HFrEF.	Identify patients who may be at higher risk than those clinically apparent.
HF-associated Arrhythmias	Risk stratification for lethal or potentially lethal ventricular arrhythmias up to 2 years. Identification of patients at very low risk of lethal arrhythmic events for up to 2 years.	Refine indication criteria for patients who will benefit from ICD. Help identify patients who will no longer require ICD, who are at the end of their battery life or who are suffering from device infection.
Primary arrhythmic conditions	Identification of patients at risk for worse outcomes, including arrhythmic events and total mortality.	Improve understanding of primary arrhythmic conditions pathophysiology. Guide management of patients with primary arrhythmic conditions.
Heart transplant	Monitor cardiac reinnervation after transplantation.	Identify patients most likely to have complications after transplantation, including rejection and transplantation due to CADs.
Ischemic heart disease	Assessment of the risk area in patients with acute coronary syndromes. Risk stratification of patients with hibernating myocardium.	Guide management of patients with acute coronary syndromes. Guide patient management after an ischemic event. Ischemic memory.
Diabetes mellitus	Identification of cardiac autonomic abnormalities, including patients without extracardiac manifestations.	Identify patients at greater clinical risk than apparent, aiding diagnosis and guiding appropriate management.
Chemotherapy cardiotoxicity	Identify and quantify cardiac injury in patients undergoing these treatments.	Guide chemotherapy conduct. Improve understanding of drug toxicity pathophysiology.
Neurodegenerative diseases	Differential diagnosis of tremors (parkinsonism). Help in the diagnosis of PD and the differentiation between Alzheimer's and Lewy body dementia. Identify and quantify cardiac autonomic injury.	Definition of conduct.
Chagas disease	Identify and quantify cardiac autonomic injury. Identification of patients at risk for worse outcomes, including arrhythmic events and total mortality.	Guide treatment.
Takotsubo syndrome	Identify and quantify cardiac autonomic injury.	Guide treatment. Improve understanding of pathophysiology.
Cardiomyopathies	Early diagnosis. Cardiovascular risk stratification.	Guide treatment. Improve understanding of the pathophysiology.

ICD: implantable cardioverter-defibrillator; CAD: coronary artery disease; LAVE: left ventricular assist device; HF: heart failure; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction; mIBG-123I: metaiodobenzylguanidine labeled with iodine-123; CRT: cardiac resynchronization therapy; PD: Parkinson's disease. Adapted from the JCS Joint Working Group and the Brazilian nuclear cardiology guideline.⁸

19.1% versus 1.8% in the group with values above 1.6, a negative predictive value for these outcomes in two years, reaching 98.8%.¹⁶

Regarding the therapeutic assessment of ventricular dysfunction, numerous studies using cardiac scintigraphy with mIBG-I123 have demonstrated that the use of beta-blockers, ACE inhibitors and spironolactone can significantly improve cardiac SNS activity.^{15,17,18} Studies have also proven that using carvedilol in patients with HF improved cardiac uptake and WR of mIBG-I123, LVEF, LV systolic and diastolic volumes, functional class, and significantly reduced brain natriuretic

peptide (BNP) levels. These results suggest that carvedilol can improve adrenergic dysfunction and ventricular remodeling.¹⁴

Regarding cardiac implantable devices, research has shown that biventricular resynchronization therapy (CRT) resulted in an increased uptake of early and late mIBG-I123, as evidenced by a significant improvement in cardiac SNS activity in HF patients after such device implantation. These findings suggest that such a device can be the potential mechanism behind the observed benefits in large studies on morbidity and mortality with CRT.¹⁹ A Brazilian study has also suggested that cardiac scintigraphy with

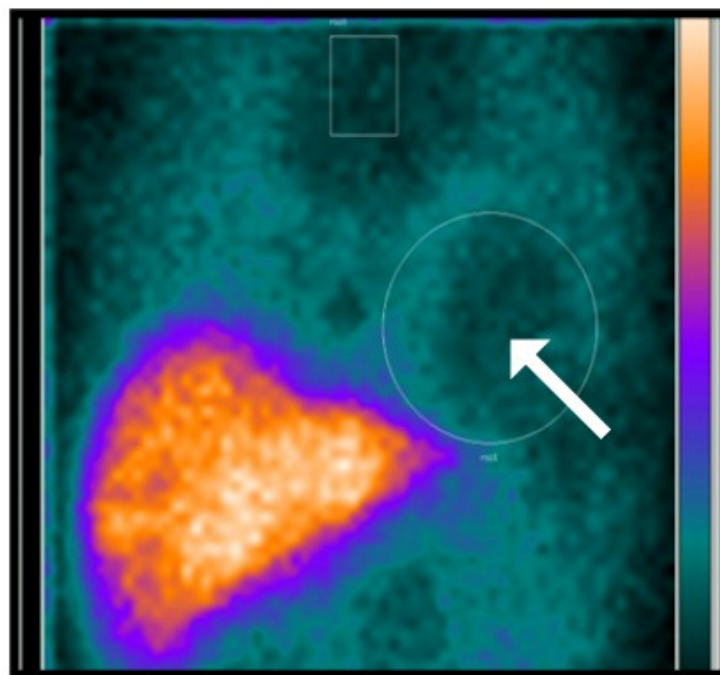


Figure 3 – Late planar images of ^{123}I -mIBG cardiac scintigraphy shows marked low uptake of the radiotracer in the left ventricle (circle). The late heart/mediastinum ratio was 1.21 and the washout rate was 42%, indicating cardiac sympathetic hyperactivity

mIBG-I123 can refine the indication criteria for CRT. Patients with severe HF and a late H/M ratio below 1.36 are less likely to respond favorably to CRT.^{20,21}

Furthermore, some authors have linked adrenergic denervation on scintigraphy with sudden death in patients with LV dysfunction, including those with mild dysfunction and NYHA functional class I. Changes in the SNS were also identified as independent predictors of tachycardia recurrence and ventricular fibrillation in patients with a history of these arrhythmias. This suggests that cardiac scintigraphy with mIBG-I123 could be a valuable tool for identifying patients at high risk of sudden death.^{21,22}

In addition to the indications described above, other applications are outlined in Table 1.

Use in parkinsonism and differential diagnosis of dementia

Parkinson's disease (PD) is the most prevalent neurodegenerative condition leading to parkinsonism. It is characterized by the degeneration of dopaminergic and non-dopaminergic neurons. It is distinguished by the abnormal aggregation of α -synuclein in the substantia nigra, forming intracytoplasmic neuronal inclusions known as Lewy bodies (DLB). Despite the existence of established diagnostic criteria for PD and other neurodegenerative disorders presenting parkinsonism, such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration, accurately diagnosing these conditions remains a significant challenge for neurologists.²³

Studies have shown that cardiac uptake of mIBG-I123 is diminished in patients with Lewy body inclusion diseases like PD^{24,25} and dementia with DLB. Evaluating myocardial sympathetic innervation through cardiac scintigraphy with mIBG-I123 is valuable for distinguishing PD from other causes of parkinsonism, including essential tremors, and for differentiating DLB from Alzheimer's disease.²⁶

The α -Synuclein-dependent neurodegeneration in PD affects pre- and post-ganglionic autonomic neurons, impairing cardiac uptake of mIBG-I123. Meanwhile, in other diseases, such as multiple system atrophy, in which insufficiency autonomic function is predominantly preganglionic, cardiac uptake of mIBG-I123 is preserved. A post-mortem study showed that the number of axons immunoreactive for tyrosine hydroxylase, a marker for sympathetic axons of the heart, was significantly reduced in PD and DLB. This finding supported the results that indicate a reduced cardiac uptake of mIBG-I123 in these diseases, presenting very low values of early and late H/M ratios, and demonstrating high sensitivity and specificity of the method (around 90%), even in the early stages of the disease.^{26,27}

In a Brazilian study, Leite et al. evaluated patients with new-onset sporadic PD without clinically defined dysautonomia, and observed that cardiac mIBG-I123 uptake on SPECT images was low or absent in all patients, concluding that the examination effectively detected changes in cardiac sympathetic neurotransmission in PD patients, even in the absence of dysautonomia symptoms.²⁷

Cardiac scintigraphy with mIBG-I123 is currently recommended (level A) by the European Federation of

Neurological Societies and by the Movement Disorder Society task force for the differential diagnosis of syndromes with parkinsonism.²⁸

Clinical Illustrative Examples

Case 1: Male, 66 years old, HFrEF (NYHA functional class III), ischemic heart disease, reporting tiredness and palpitations. Echocardiogram with LVEF of 37%, BNP of 2180 pg/mL and episodes of non-sustained ventricular tachycardia (NSVT) on the 24-hour Holter monitor. Cardiac scintigraphy was performed with mIBG-I123 (Figure 3), indicating a marked impairment of myocardial sympathetic innervation, which led to worse prognosis and greater risk of fatal ventricular arrhythmias. The patient was referred for implantable cardioverter defibrillator (ICD) implantation and received appropriate shocks from the device six months after its implantation.

Case 2: Female, 42 years old, indeterminate-phase Chagas disease, reporting lipothymia. Echocardiogram with LVEF of

63% (Simpson); 24-hour Holter monitoring showed frequent ventricular ectopias and short episodes of NSVT. Cardiac scintigraphy with mIBG-I123 and myocardial perfusion with sestamibi-Tc99m (Figure 4) were performed, revealing denervated myocardial tissue with normal perfusion (mismatch), suggesting a greater risk of potentially fatal ventricular arrhythmias.

Case 3: Female, 62 years old, journalist, sought the neurologist's attention due to mild morning stiffness in her right upper limb. She did not report any other symptoms or chronic illnesses. Referred for cardiac scintigraphy examination with mIBG-I123 (Figure 5) to investigate PD. The examination revealed severe impairment of myocardial sympathetic innervation, which is a characteristic finding in PD.

Final considerations

The mIBG-I123 scintigraphy provides a comprehensive view of cardiac sympathetic innervation, enhancing cardiovascular risk assessment and enabling early detection

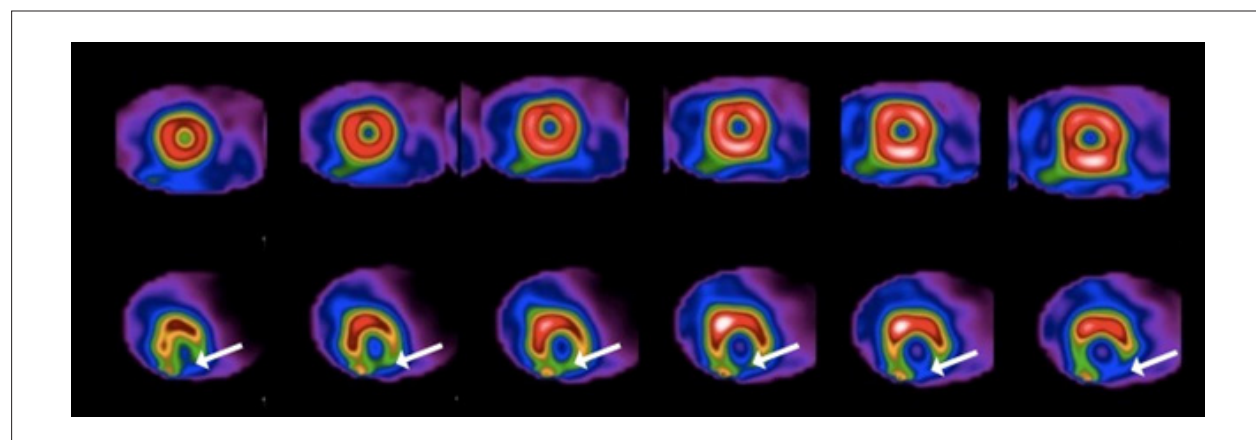


Figure 4 – 123I-mIBG cardiac scintigraphy (lower row) and 99mTc-sestamibi myocardial perfusion (upper row). Short-axis SPECT images show a mismatch perfusion/sympathetic innervation of the left ventricular myocardium, with normal perfusion and marked reduction in 123I-mIBG uptake in the apical, inferior and inferolateral segments (arrows), suggestive of denervated myocardial tissue in these regions.

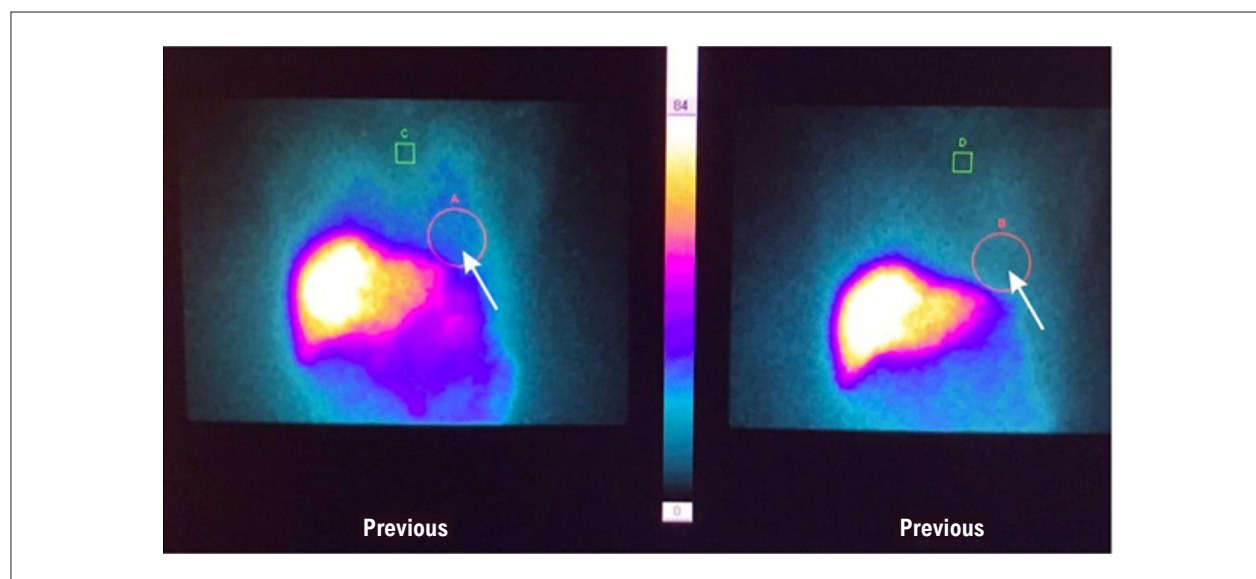


Figure 5 – Planar images of 123I-mIBG cardiac scintigraphy show marked low radiotracer uptake in cardiac topography (arrow). The heart/mediastinum ratio was 1.31 (early) and 1.23 (late). The washout rate was 35%. These data suggest severe impairment of myocardial sympathetic innervation, characteristic of Parkinson's disease.

of heart disease and neurodegenerative disorders. Nevertheless, enhancing clinical expertise is crucial to enhance the positive and negative predictive values of this technique, leading to a more precise differentiation between individuals with low and high cardiovascular risk. Furthermore, the scarcity of cost-effectiveness data and limited availability in clinical settings represent significant challenges for large-scale implementation.

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: Brito ASX, Leite JC, Brandão SCS.

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