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REVIEW ARTICLE−INTERNATIONAL CORNER

# $^{123}$I-MIBG in Latin America

Gabriel Blacher Grossman, MD, PhD[1)], Thais Rossato Arrais, MD[1)] and Ronaldo de Souza Leão Lima, MD, PhD[2)]

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Abstract

**Heart Failure (HF) is a life-threatening disease the incidence of which is increqsing, leading to a considerable increase in disability, mortality and healthcare costs. The actual treatment of HF includes, besides optimal medical treatment, use of resynchronization therapy and implantable cardiac defibrillator. In some developing countries, the cost of these two devices is extremely high, being mandatory the adequate selection of the patients whose will benefit more from these measures. $^{123}$I-MIBG scintigraphy is the only technique approved to provide information of the adrenergic function of the heart, being a powerful risk stratification tool in patients with HF. Multiple studies have shown that the evaluation of cardiac sympathetic nerve activity using $^{123}$I-MIBG imaging, especially the heart-to-mediastinum ratio, can differentiate high-risk from low-risk patients. Cardiac MIBG imaging has still poor availability in Latin America. It is mostly performed in Brazil, where some studies showed the possible benefits and potential uses for MIBG.**

**Keywords: Brazil, Heart Failure, Latin America, MIBG**
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Heart Failure (HF) is a life-threatening disease which incidence is growing over the years, leading to a considerable increase in disability, mortality and healthcare costs (1). It's estimated that heart failure affects more than 15 million people over the world (1) with billions of dollars of cost. In South American population, heart failure is the main cause of hospitalization based on available data (2). Coronary artery disease (CAD), hypertension, diabetes, idiopathic dilated cardiomyopathy and valvular disease are the major etiological risk factors (1). In Latin America, Chagas disease and rheumatic fever are also important causes that lead to HF. Chagas cardiomyopathy is responsible for 41% of the HF cases in endemic areas (2).

The prognosis of the disease is poor, with 25% of mortality at 1 year and 50% at 5 years after the patient become symptomatic (1). In HF patients, the incidence of sudden cardiac death from arrhythmic events remains markedly high, accounting 70% of total mortality in some studies (3).

The actual treatment of HF, includes, beside optimal medical treatment, use of resynchronization therapy (CRT) and implantable cardiac defibrillator (ICD). About 1-3% of patients hospitalized for HF and 15-20% of all patients seen in HF clinics meet eligibility criteria for CRT, and about half of these numbers also meet the criteria for implantable cardiac defibrillator (ICD) implantation, based on ejection fraction (1, 3). However, some patients who receive an ICD never have to deliver therapy and most patients who die from sudden cardiac death don't fill the criteria to receive an ICD based on LVEF (3, 4). Conversely, in some developing countries, the cost of these two devices is extremely high, being mandatory the adequate selection of the patients whose will benefit more from these measures.

## $^{123}$I-MIBG imaging

$^{123}$I-meta-iodobenzylguanide (MIBG) is an analogue of norepinephrine (NE), the neurotransmitter of the cardiac sympathetic system, and was originally developed in the late 1970s at the Michigan University Medical Center for imaging the adrenal medulla and adrenal tumors. MIBG and NE share two uptake systems: specific (Type-1) and non-specific (Type-2). Patients with HF have increased cardiac sympathetic activity with increased release of NE from the presynaptic

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1) Gabriel Blacher Grossman, Thais Rossato Arrais
Hospital Moinhos de Vento, Porto Alegre, Brazil
E-mail: gabriel.grossman@hmv.org.br

2) Ronaldo de Souza Leão Lima
Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

vesicles. The released NE binds to a postsynaptic beta-1, beta-2 and alpha-receptors, amplifies adenyl cyclase activity, producing the desired stimulatory cardiac effects. With the progression of the disease, occurs a downregulation and a decrease in the sensitivity of the B-adrenergic receptors with a decrease in its reuptake, leading to an excess of norepinephrine in the synaptic cleft, and, consequently, in the plasma. Unlike norepinephrine, MIBG is not catabolized after presynaptic uptake, allowing imaging the cardiac sympathetic system (5). This excess sympathetic stimulation leads to increased myocardial stress, ischemia, fibrosis and disease progression, being associated with worse prognosis in patients with HF (6).

$^{123}$I-MIBG scintigraphy is the only technique approved to provide information of the adrenergic function of the heart (1, 3), being a powerful risk stratification tool in patients with HF (1). Cardiac sympathetic imaging with $^{123}$I-MIBG is an important method to evaluate the risk of patients to present arrhythmias or sudden cardiac death (SCD) (4).

The protocol of the $^{123}$I-MIBG imaging includes planar images of anterior view obtained after the intravenous administration of $^{123}$I-MIBG at rest, after 15-30 minutes (early) and after 4 hours (delayed). Single photon emission computed tomography (SPECT) images are used to evaluate regional myocardial uptake patterns. The heart-to-mediastinum ratio (H/M) and the washout ratio (WR) are the common semi-quantitative methods in planar images used to evaluate cardiac sympathetic function. Global cardiac uptake is expressed as a H/M ratio delayed images, which indicates worse prognosis when is under 1,6. Tracer washout between initial and 4h delayed images may also be measured (1). In MIBG SPECT images, the regional innervation/perfusion mismatch is used to evaluate the risk of cardiac death (7).

**Clinical impact**

Multiple studies have shown that the evaluation of cardiac sympathetic nerve activity (CSNA) using $^{123}$I-MIBG imaging, especially the heart-to-mediastinum (H/M) ratio, can differentiate high-risk from low-risk patients, regardless of LVEF, brain natriuretic peptide and NYHA clinical conditions (1, 8). The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) evaluated 961 patients with HF, NYHA functional class II/III, LVEF $<=35\%$ and optimal medical therapy. Events at 2 years were compared (HF progression, arrhythmic events and cardiac death) and occurred in 15% of patients with a H/M value >=1,6 and in 37% in those with a H/M <1,6 (9). This data contributed to incorporate H/M ratio into the Seattle Heart Failure Model (SHFM). By including H/M ratio in the model, there was a 22.7% net reclassification improvement, with 14.9% of patients redirected to a higher risk category than suggested by SHFM score alone and 7.9% of subjects who survived reclassified into a lower risk category (10). Tamaki et al. demonstrated that WR is a powerful predictor of sudden cardiac death in patients with mild to moderate CHF, independently of LVEF, in comparison to signal-averaged electrocardiogram, heart rate variability and QT dispersion (HR 4,79, 95% CI: 1,55-14,76) (11). Kuramoto et al. showed that in this group of patients, MIBG WR increased the prognosis information of the SHFM, with a greater risk of cardiac death in patients with abnormal WR (>27%) for both SHFM score of ≥1 (relative risk 3.3, 95% confidence interval 1.2 to 9.7, $p=0.01$) and a SHFM score of ≤0 (relative risk 3.4, 95% confidence interval 1.2 to 9.6, p=0.004) (12).

**$^{123}$I-MIBG in Latin America**

Cardiac MIBG imaging has still poor availability in Latin America. It is approved only in Brazil and Argentina, but the vast majority of the experience of this method in Latin America is originated in Brazil. Several small studies performed in Brazil showed the possible benefits and potential uses for MIBG.

Grossman et al. demonstrated the H/M ratio and washout differences between HF patients and controls ($1.45 \pm 0.3$ vs $1.95 \pm 0.2$ and $27.2 \pm 6.5$ vs $16.4 \pm 5.5$, $p<0.0001$) (13) (Fig. 1).

**$^{123}$I-MIBG and heart rate recovery**

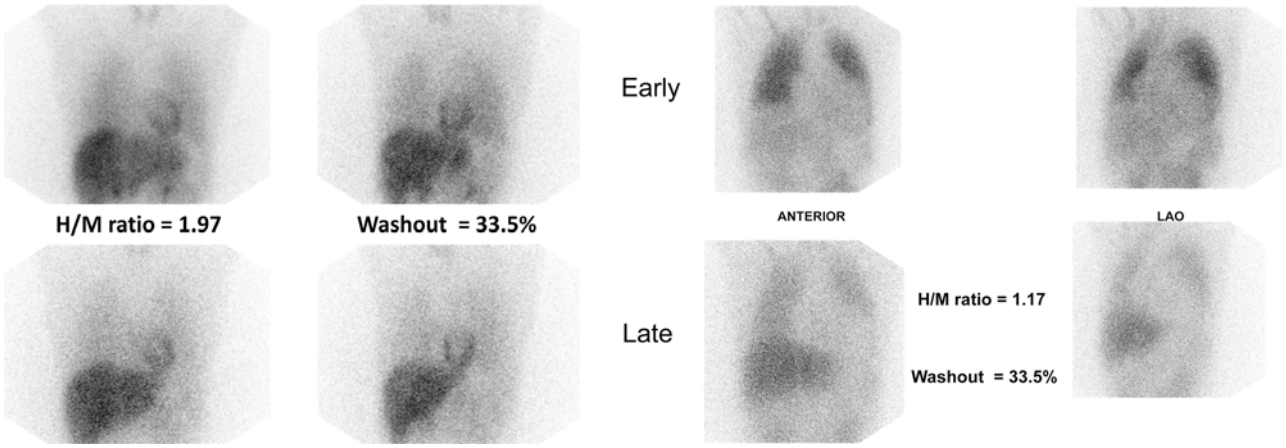
Messias et al. evaluated 25 patients with ejection fraction below 45% in a small observational study, detecting a correlation between high washout ratio and abnormal heart rate recovery (HHR) in exercise, suggesting a potential relation between adrenergic activation and heart rate recovery. The main causes of attenuation of HRR was increased sympathetic activity at rest, with decreased parasympathetic activity and abnormal regulation of the cardiopulmonary baroreflex (14).

**$^{123}$I-MIBG and inflammation**

In a sub analysis of this study, the same investigators analyzed the association of interleukin 1B (IL 1B) levels in this subgroup of patients, demonstrating a relationship between high levels of IL 1B and lower reserve double product, lower functional capacity, slower heart rate recovery at first and second minute and a higher washout ratio, demonstrating that increased sympathetic activity influences the systemic inflammatory response, and probably, this inflammatory response exerts additional deleterious effect in cardiac autonomic disfunction (15).

**$^{123}$I-MIBG and exercise tolerance**

Miranda et al. showed the importance of exercise intolerance as a prognosis marker and its association with MIBG imaging.




**A** MIBG imaging Normal individual **B** MIBG imaging HF patient

**Fig. 1**
・Anterior and left anterior oblique (LAO) planar images of the chest were obtained at 15-30 minutes and 4 hours after intravenous injection of $^{123}$I-MIBG in a normal individual (**A**) with normal H/F ratio and washout and a patient with heart failure with an ejection fraction of 26% and abnormal H/F ratio and washout (**B**).
・H/M ratio: heart to mediastinum ratio; EF: ejection fraction

It was detected that H/M ratio and WR correlates better with gravity of symptoms and NYHA functional class than ejection fraction in patients with HF without previous treatment with betablocker (16).

### $^{123}$I-MIBG and HF with preserved EF

In patients with HF with preserved ejection fraction (HFpEF), Messias et al. demonstrated that the severity of sympathetic disfunction is associated with the degree of cardiovascular impairment during exercise. Twenty-five patients were submitted to MIBG imaging and cardiopulmonary exercise test, with analysis of the VE/VCO2 slope and peak VO2, suggesting that MIBG imaging can contribute to predict the prognosis of this subgroup of patients (17).

### $^{123}$I-MIBG and Chagas disease

In a recent study, Gadioli et al. demonstrated that the occurrence of ventricular arrhythmias of different degrees of severity correlates quantitatively with the extent of cardiac sympathetic denervation, but not with the extent of fibrosis, suggesting that myocardial sympathetic denervation plays a major role in triggering ventricular arrhythmia in Chagas Disease (18). Other study presented evidence that cardiac autonomic sympathetic modulation may be affected in chagasic subjects with preserved ventricular function evaluated by echocardiography, especially in those with “borderline” electrocardiogram (Fig. 2). A total of 40 chagasic patients and 19 control subjects were included in this study. Patients had normal echocardiogram and chest radiography; no arrhythmias or myocardial ischemia; and normal exercise performance for age, gender, and body mass index (19).

### $^{123}$I-MIBG and HF

Finally, De Brito et al. (20) demonstrated that in a population with symptomatic HF patients, LVEF < 40%, NYHA functional class II/III sent to ICD therapy, H/M ratio in 4h was the only independent variable related to the occurrence of cardiac events (appropriate ICD therapy, heart transplant or cardiac death) (Fig. 3A and B).

## Conclusion

Despite the evidence that H/M ratio is a significant risk predictor for arrhythmic events and SCD, especially in patients with heart failure, there are no published data indicating improvement in outcomes in HF patients using this method to make decisions, particularly on ICD implantation (4, 9). Therefore, it is necessary more data to incorporate the use of MIBG scintigraphy in HF guidelines in the future.

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## Conflicts of interest

There is no potential conflict of interest relevant to this article.

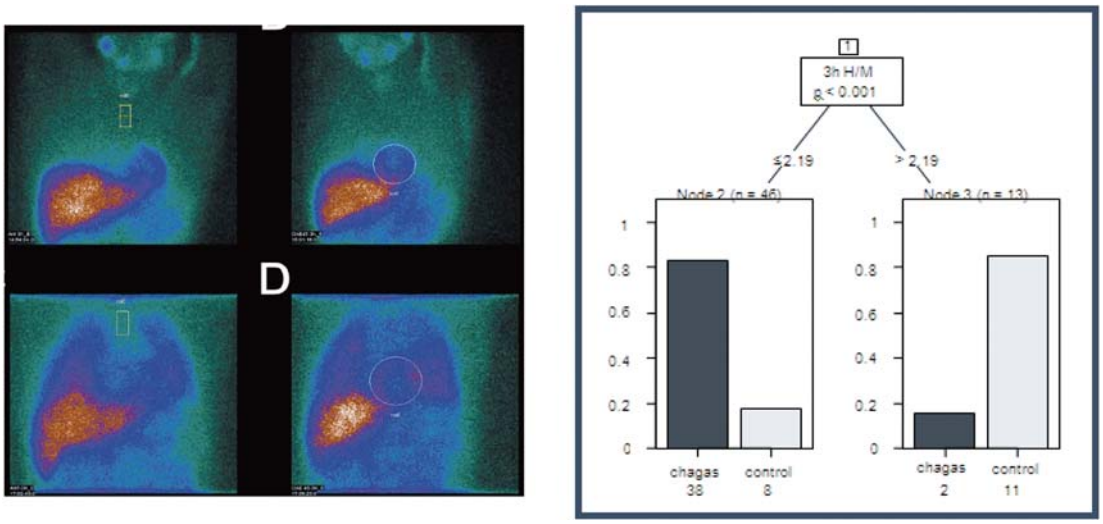


**Fig. 2**

Planar images in anterior and left anterior oblique (LAO) projections illustrate the normal pattern of distribution of $^{123}$I-MIBG in a control subject (top). Planar images in anterior and posterior projections illustrate an altered pattern of distribution of $^{123}$I-MIBG in the heart of a chagasic patient with "borderline" ECG (bottom). In the final tree of the analysis, 3 hours H/M was the only significant variable (P<0.001) to discriminate chagasic patients.

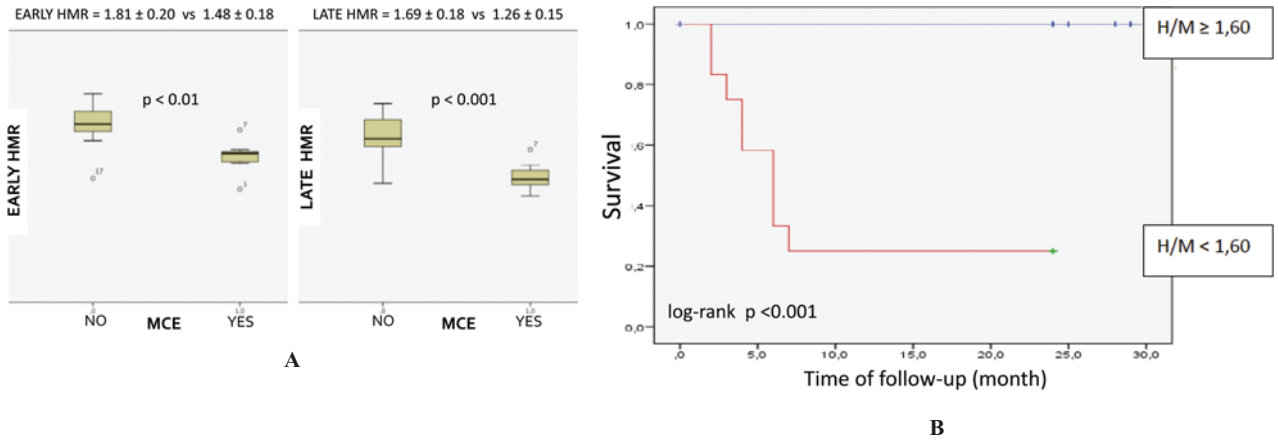


**Fig. 3** A and B.

HMR: Heart/Mediastinum ratio; MCE: Major Cardiovascular Events

Relationship between HMR and MCE. MCE are more frequent in patients with lower HMR in early and late images

Reprint requests and correspondence:
Gabriel Blacher Grossman, MD, PhD
Director of Nuclear Medicine Division, Hospital Moinhos de Vento, Ramiro Barcelos, 910, Porto Alegre, Rio Grande do Sul, Brazil.
E-mail: gabriel.grossman@hmv.org.br

## References

1. Peix A, Mesquita CT, Paez D, et al. Nuclear medicine in the management of patients with heart failure: guidance from an expert panel of the International Atomic Energy Agency (IAEA). Nucl Med Commun 2014; 35: 818-23.
2. Bocchi EA. Heart failure in South America. Curr Cardiol Rev 2013; 9: 147-56.
3. Kasama S, Toyama T, Kurabayashi M. Usefulness of cardiac sympathetic nerve imaging using $^{123}$iodine-metaiodobenzylguanidine scintigraphy for predicting sudden cardiac death in patients with heart failure. Int Heart J 2016; 57: 140-4.
4. Goldberger JJ, Hendel RC. Decision making for implantable cardioverter defibrillator implantation. Circ Cardiovasc Imaging 2015; 8: e004275.
5. Verschure DO, van Eck-Smit BL, Somsen GA, et al. Cardiac sympathetic activity in chronic heart failure: cardiac $^{123}$I-mIBG scintigraphy to improve patient selection for ICD implantation. Neth Heart J 2016; 24: 701-8.
6. Wolinsky D, Hendel R, Cerqueira M, et al. The role of i-123 metaiodobenzylguanidine imaging in management of patients with heart failure. Am J Cardiol 2015; 116 Suppl 1: S1-9.
7. Clements IP, Kelkar AA, Garcia EV, et al. Prognostic significance of $^{123}$I-mIBG SPECT myocardial imaging in heart failure: differences between patients with ischaemic and non-

ischaemic heart failure. Eur Heart J Cardiovasc Imaging 2016; 17: 384-90.
8. Merlet P, Valette H, Dubois-Randé JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992; 33: 471-7.
9. Jacobson AF, Senior R, Cerqueira MD, et al. Myocardial iodin-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010; 55: 2212-21.
10. Ketchum ES, Jacobson AF, Caldwell JH, et al. Selective improvement in Seattle heart failure model risk stratification using Iodine-123 meta-iodobenzylguanidine imaging. J Nucl Cardiol 2012; 19: 1007-16.
11. Tamaki S, Yamada T, Okuyama Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol 2009; 53: 426-35.
12. Kuramoto Y, Yamada T, Tamaki S, et al. Usefulness of cardiac iodine-123 meta-iodobenzylguanidine imaging to improve prognostic power of Seattle heart failure model in patients with chronic heart failure. Am J Cardiol 2011; 107: 1185-90.
13. Santos CG, Grossman GB, Ludwig RTF, et al. Evaluation of cardiac sympathetic dysfunction in heart failure: experience with $^{123}$I-MIBG in Brazil. J Nucl Cardiol 2006; 13: S17.
14. Messias LR, Queiroz Carreira MA, Miranda SM, et al. Is abnormal adrenergic activation associated with abnormal Heart Rate Recovery? Arq Bras Cardiol 2012; 98: 398-405.
15. Messias LR, Carreira MA, Miranda SM, et al. Do interleukin-1$\beta$ levels correlate with MIBG and exercise parameters in heart failure? Arq Bras Cardiol 2013; 100: 395-403.
16. Miranda SM, Moscavitch SD, Carestiato LR, et al. Cardiac I123-MIBG correlates better than ejection fraction with symptoms severity in systolic heart failure. Arq Bras Cardiol 2013; 101: 4-8.
17. Messias LR, Messias AC, de Miranda SM, et al. Abnormal adrenergic activation is the major determinant of reduced functional capacity in heart failure with preserved ejection fraction. Int J Cardiol 2016; 203: 900-2.
18. Gadioli LP, Miranda CH, Pintya AO, et al. The severity of ventricular arrhythmia correlates with the extent of myocardial sympathetic denervation, but not with myocardial fibrosis extent in chronic Chagas cardiomyopathy: Chagas disease, denervation and arrhythmia. J Nucl Cardiol 2018; 25: 75-83.
19. Landesmann MC, da Fonseca LM, de B Pereira B, et al. Iodine-123 metaiodobenzylguanidine cardiac imaging as a method to detect early sympathetic neuronal dysfunction in chagasic patients with normal or borderline electrocardiogram and preserved ventricular function. Clin Nucl Med 2011; 36: 757-61.
20. Brito A, Glavam A, Brito G, et al. Myocardial $^{123}$I-MIBG scintigraphy in heart failure and implantable cardioverter-defbrillator patients: a pilot study results. Eur Heart J Cardiovasc Imaging 2017; 18 suppl 1: i89.