^{123}Iodo-MIBG in the Study of Patients with Heart Failure and Severe Impairment of Ventricular Function

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Abstract: Increased cardiac sympathetic nerve activity is a prominent feature in the pathophysiology of heart failure (HF) that is associated with progressive left ventricular remodeling, impaired left ventricular function, and worsening of symptoms with progression of functional class. Furthermore, alterations in sympathetic myocardial innervation play an important role in the generation of ventricular arrhythmias and sudden cardiac death (SCD).A high proportion of deaths that occur in patients with HF, especially those with mild symptoms or not in an advanced functional class of the New York Heart Association (NYHA), occur suddenly and unexpectedly. Heart Failure with reduced ejection fraction is a very prevalent entity, which generates significant public health costs each year, extremely high morbidity for those who suffer it, and a large number of deaths, many of them suddenly. In these patients, SCD can be treated, when due to arrhythmic causes, with the implantation of an ICD.This review attempts to demonstrate that evaluation of myocardial sympathetic innervation using the 123I-MIBG scan has prognostic value for predicting cardiovascular events in subjects with heart failure and severe impairment of LVEF.

Keywords: Heart Failure, ^{123}iodine-labeled meta-iodobenzylguanidine (MIBG), Sudden Death.

INTRODUCTION

Increased cardiac sympathetic nerve activity is a prominent feature in the pathophysiology of heart failure (HF) that is associated with progressive left ventricular remodeling, impaired left ventricular function, and worsening of symptoms with progression of functional class [1]. Furthermore, alterations in sympathetic myocardial innervation play an important role in the generation of ventricular arrhythmias and sudden cardiac death (SCD) [2]. Increased neuronal release of norepinephrine (NE) is generally accompanied by a decrease in its reuptake, leading to a higher concentration of NE in the synaptic cleft, with desensitization of beta myocardial adrenoceptors [3]. This is the substrate on which adrenergic receptor antagonists act: they counteract these alterations and improve survival by preventing the progression of HF and tachyarrhythmias [4]. It has been suggested then, that the evaluation of cardiac sympathetic nervous activity could be a very valuable tool in the clinical evaluation and determination of the prognosis of patients with HF. The decrease in NE reuptake has been adequately assessed by images with a NE analog: ^{123}iodine-labeled meta-iodobenzylguanidine (MIBG).^{123}I-MIBG uptake occurs at the sympathetic nerve terminal, mediated by the NA transporter, and since the compound is not metabolized, ^{123}I-MIBG retention after a few hours of injection serves as a reflection of neuronal integrity [5]. The present work sets out to review the most relevant aspects of the study of myocardial innervation with ^{123}I-MIBG, as well as to describe its prognostic value for predicting cardiovascular events in patients with HF.

A Problem: The Selection of Patients with HF Candidates for Electrical Therapy in Primary Prevention

A high proportion of deaths that occur in patients with HF, especially those with mild symptoms or not in an advanced functional class of the New York Heart Association (NYHA), occur suddenly and unexpectedly. The adequate prognostic stratification of this group of patients with HF that allows us to prevent sudden cardiac death (SCD), is one of the greatest challenges of modern cardiology. Many of these deaths are due to electrical disturbances, such as ventricular arrhythmias [6], bradycardia, and asystole, although others are due to coronary, cerebral, or aortic vascular complications. Treatments that improve or slow the progression of cardiovascular disease reduce the annual rate of sudden death, but are not helpful in treating arrhythmic complications when they occur. The implantable cardioverter-defibrillator (ICD) is effective in preventing bradycardia and interrupting life-threatening ventricular arrhythmias. Since the publication of the results of the first cohort of the Framingham study [7], attempts have been made to find parameters that allow for the prediction of sudden death and thus select patients

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with a higher risk of suffering it, so as to be able to apply, in primary prevention, a very effective but at the same time expensive therapy (and not without complications and adverse effects) as is the ICD. Just to mention some of the parameters that have been tested as predictors or risk markers, we can include: electrocardiogram (ECG) disorders such as left ventricular hypertrophy (LVH), repolarization disorders (ST segment and T wave), T-wave alternation, intraventricular conduction disorders, heart rate variability [8]; and also others such as the presence of elevated biomarkers (NT-pro-BNP), the ejection fraction of the left ventricle and the presence and degree of intramyocardial fibrosis evaluated through magnetic cardioresonance. Currently, the left ventricular ejection fraction (LVEF) is the main determinant in the indication of an ICD in primary prevention, being indicated in patients with a LVEF less than or equal to 35%, data obtained from different observational studies and clinical trials and reflected in the indication of the main national and international clinical practice guidelines (CPGs). According to the latter, a NYHA functional class II-III is required, with a life expectancy of at least 1 year [9].

The current experience is controversial regarding the use of the LVEF value for the selection of patients who are candidates to receive an ICD in primary prevention as the sole criterion. One of the first published trials on this area of knowledge was the MADIT study [10]. It included 196 patients post acute myocardial infarction (AMI), with LVEF <35% and who had non-sustained ventricular tachycardia (VT), randomized to receive ICD or a control group. After a mean follow-up of 27 months, a statistically significant difference in mortality was observed: 16% in the ICD group versus 39% in the control group [11].

Three years later, the MUSTT study [12] was published in similar patients, although it compared the absence of antiarrhythmic treatment with treatment guided by electrophysiological studies and with the possibility of applying an ICD to patients in whom pharmacological treatment failed. Again, favorable differences were observed for the use of ICD. Six years after MADIT, the same group of researchers published the MADITT II study. A larger number of patients were included in this trial, with the particularity of eliminating the requirement for unsustained VT and electrophysiological study: depressed LVEF (<30%) was sufficient. After a mean follow-up of 20 months, a significant difference in mortality was observed: 19.8% in the control group and 14.2% in the ICD group. Another relevant study was the CABG PATCH (The Coronary Artery Bypass Graft Patch Trial): this included 900 patients with ischemic heart disease, LVEF less than or equal to 35%, and alterations in the averaged signal ECG who underwent coronary artery bypass grafting (CABG) and were randomized to receive an ICD in primary prevention or not. After a mean follow-up of 32 months, no statistically relevant differences in all-cause mortality were observed between the two groups. Some differences in the selection of patients could explain these dissimilar results: in this study the patients had to have alterations in the averaged signal ECG, while in others such as MADIT, a VT demonstration was required, which seems to be a better predictor of events. Another difference is the treatment of ischemic heart disease: in the CABG PATCH all patients were revascularized, while the proportion of revascularization either by CABG or by angioplasty in MADIT was significantly less. Since the publication of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study, the indication of ICD in primary prevention in patients with HF and LVEF less than or equal to 35% and a longer life expectancy tan a year was further supported, although its evidence in patients with nonischemic dilated cardiomyopathy was not robust. The DANISH study included 1116 patients with dilated heart disease of non-ischemic etiology, with LVEF less than or equal to 35%, in functional class II-III, under optimal medical treatment and were randomized to receive or not an ICD. At a median follow-up of 67.6 months, no significant differences were found in all-cause mortality (21.6% in the ICD arm versus 23.4% in the non-intervention arm) or in the incidence of death from cardiovascular causes, but in the case of SCD: 4.3% versus 8.3%, (HR 0.5, 95% CI 0.31-0.82). In the subgroup analysis, a clear interaction with age was evident: the use of ICD generated a significant decrease in total mortality in patients under 68 years (36%). The DANISH study included a particular population: with a high rate of resynchronizer indication and very well treated pharmacologically (92% with beta-blockers, 97% with inhibitors or antagonists of the renin-angiotensin system, almost 60% of antialdosteronics). Their results imply that the universal use of ICD in primary prevention in patients of non-ischemic etiology under optimal medical treatment does not improve the prognosis, but at the same time it points out that in younger patients and with a less advanced disease, the indication should be considered. Finally, we can conclude that the ICD has an appropriate indication in primary prevention of SCD in

patients with severe HF and reduced LVEF (HFrEF). But is it a sufficient criterion? It seems that it is not. Not only because the appropriate shock rate in patients applying this criterion alone remains low, but also because ICD is a therapy that is not completely safe. If it were devoid of adverse effects, its use would have no more questions than economic ones. However, this is not the case: although serious complications such as death or infection of the device are infrequent (around 1%), other types of complications related to the implant (10%), the generator (6%) or cables (12%), in addition to inappropriate shocks (12%), affect almost a quarter of patients during the first 4 years.

Lastly, to speak in terms of costs, even considering the MADITT II results (which are among the most significantly favorable for the use of ICDs in primary prevention), it would be necessary to implant an ICD in 17 people in order for one of them to benefit and receive an appropriate shock at two-year follow-up [13]. There is no doubt that the LVEF criterion (<35%) in patients with HF is very useful for selecting candidates to receive an ICD in prevention of SCD. But in fairness, it is not enough and it becomes increasingly necessary to improve the selection with new criteria that make it more effective and efficient [14].

Study Techniques with ^{123}Iodo-MIBG

As a first consideration we should know the physical characteristics of the ^{123}iode as a radionuclide. It is a radioisotope of iodine that decays to ^{123}telurium after a half-life of 13.22 hours, with an energy of 159 KeV. The use of a specific modality of collimator, debated in recent years, allows us today to use both medium and low energy, whether for general purpose or high resolution. Some works recommend the use of medium energy collimators due to the presence in the ^{123}iode of photons with a higher energy photopic than the 140 KeV of the ^{99m}Tc, which are those for which low energy is designed. However, the use of medium energy collimators could provide relatively low spatial resolution, altering the correct estimation of activity in small regions, through the effect of partial volume. Nevertheless, although the use of medium energy collimators could present some slight advantage over low energy collimators, many times priority is given to practical issues (for example, having to make frequent changes to collimators) which end up inclining some centers to carry out the study with the low energy ones.

In most clinical trials testing the safety and efficacy of cardiac imaging with ^{123}I-MIBG, low-energy, high-resolution parallel-hole collimators have been used to ensure the best possible quality of images [15]. Before ^{123}I-MIBG injection, it is advisable to perform thyroid block by orally administering Lugol's solution, or 500 milligrams of potassium perchlorate (of choice in patients allergic to iodine). The commonly used intravenous dose of ^{123}I-MIBG is 370 MBq (10 mCi) ± 10% [16]. Planar images were acquired in anterior projection of the thorax, at 15 minutes and late at 4 hours after the injection of the radiotracer, with a duration of 10 minutes per image and on a 256 x 256 matrix [17]. Early uptake reflects the distribution of MIBG in the extraneuronal spaces of the myocardial tissue, translating the integrity and distribution of the presynaptic sympathetic system. In contrast, late uptake translates the neuronal accumulation of MIBG, reflecting the functional status of sympathetic endings [18].

Image evaluation can be done both qualitatively and semiquantitatively. For the first, some groups have classified the uptake into three categories: "normal", "decreased" and "absence of uptake". The discrete heterogeneity in the myocardial distribution of MIBG limits the qualitative assessment of the images and has led to the development of semiquantitative parameters: the ratio of counts between heart and mediastinum is usually used as an index of global MIBG uptake (heart / mediastinum rate, HMR). This is obtained by drawing a region of interest (ROI) in the mediastinum and one in the myocardial region [19]. Care must be taken not to include lung or liver tissue when drawing myocardial ROI, as well as not to include lung or large vessels when obtaining mediastinal ROI. Bateman *et al.* recommend the use of an elliptical ROI over the entire left ventricular myocardium and a rectangular ROI (7 x 7 pixels) in the mediastinum, on an imaginary vertical line that runs from the height of the pulmonary vertices to the diaphragm, taking as center the point or pixel with the least number of counts (Figure **1**) [20]. The HMR is calculated as the ratio between the number of counts per-pixel in the myocardium and the number of counts per-pixel in the mediastinum. The more impaired or decreased myocardial sympathetic activity, the lower your MIBG uptake and the lower the HMR value. On the other hand, the wash out index is obtained with the following formula: (counts per pixel in myocardium at 15 minutes - counts per pixel in myocardium at 4 hours) / counts per pixel in myocardium at 15 minutes. The wash out reflects the tone of the sympathetic nervous system, and it has been suggested that its increase could be an early

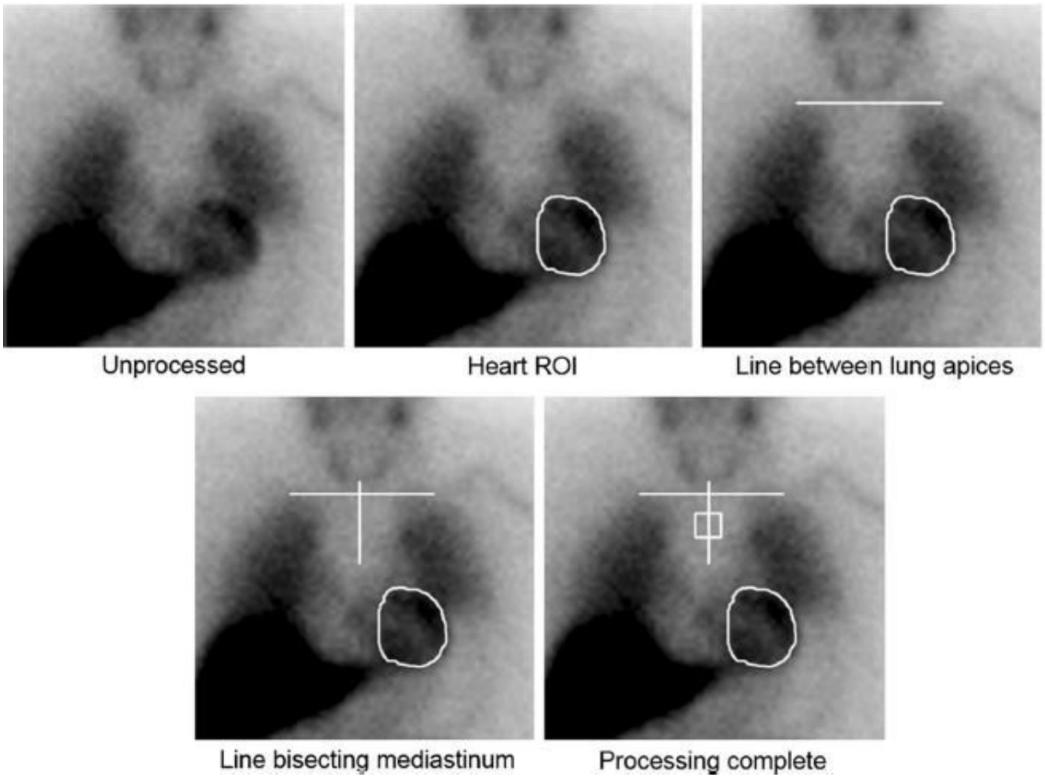

Figure 1: ROI placement steps for anterior planar image. Bateman TM, *et al*. Reliability of the 123I-mIBG heart/mediastinum ratio: Results of a multicenter test–retest reproducibility study. J Nucl Cardiol 2019; 26: 1555-1565.

marker of sympathetic dysfunction. In this way, ^{123}I-MIBG uptake myocardial images have the possibility of evaluating the integrity of the presynaptic nerve terminals and the density of adrenergic receptors, which we know can be modified by pharmacological treatment for HF, thus constituting a image that shows the exact state of adrenergic activation in which the patients are.

Event Prediction with ^{123}I-MIBG

During the decades of the 70s and 80s, studies were carried out to verify the safety and efficacy of ^{123}I-MIBG to show alterations in myocardial sympathetic innervation. Subsequently, during the 90s and 2000s, numerous studies were carried out that sought to prove its usefulness as an event marker in patients with HF, although the small number of patients included and the fact that they were mostly single-center studies, it made their conclusions, although very important and favorable, could not be extrapolated, generalized or reproduced [21]. The year 2010, with the publication of the ADMIRE-HF study (*AdreView Myocardial Imaging for Risk Evaluation in Heart Failure*) marked a before and after in this topic since it definitively validated the prognostic value of the ^{123}I-MIBG scan in the study of patients with HF. This was a prospective, multicenter, international study (which included 96 centers in the US, Canada and Europe), which enrolled 961 patients between July 2005 and February 2008, with a follow-up of up to 2 years. All the patients had HF, in functional class II or III of the NYHA, of ischemic or non-ischemic cause, with LVEF ≤ 35% and optimal pharmacological treatment (according to the current CPG). The patients could be carriers of an ICD, only if it had been indicated in primary prevention. All patients underwent ^{123}I-MIBG scintigraphy according to the previously described technique and were followed up for up to 2 years, with clinical, echocardiographic and laboratory evaluation with biomarkers. Endpoints included: progression of HF and functional class, life-threatening arrhythmic events (sustained ventricular tachycardia, resuscitated cardiac arrest, or appropriate ICD therapy), or death from cardiovascular causes. The authors found that the risk of cardiovascular events was significantly lower (38% versus 15%) for a patient with an HMR ≥ 1.60 (HR: 0.40, 97.5% CI 0.25-0.64, p <0.001). Furthermore, the separate analysis of each of the cardiovascular events showed that this difference was maintained for all types of events considered: progression of HF, arrhythmic event, death due to cardiovascular causes (1.8% versus 11.2%) and including death from all causes (3% versus 16.1%) (Figure **2**). Moreover, treated as a continuous variable, a progressive decline was

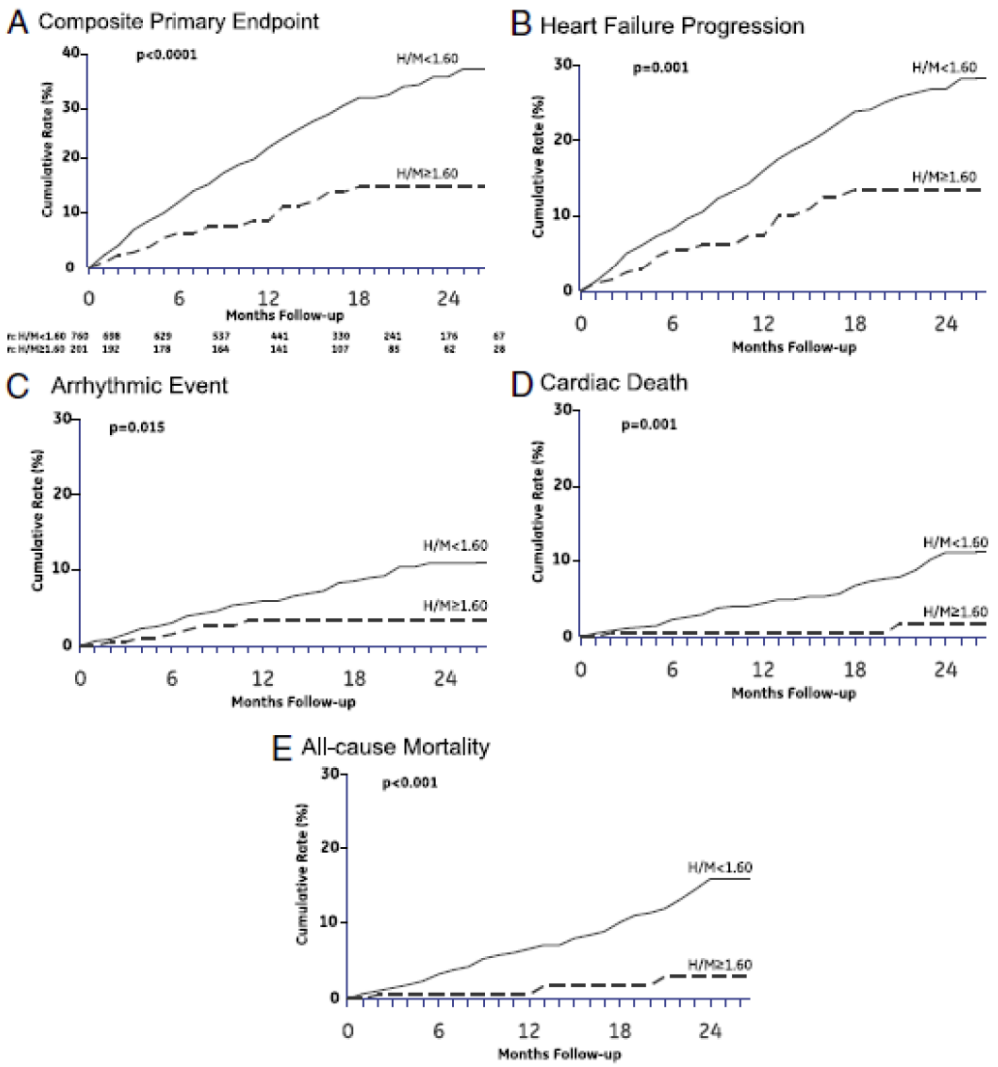

Figure 2: Cumulative Event Curves Comparing Subjects With H/M < 1.6 Versus H/M ≥ 1.6. (**A**) Composite Primary Endpoint; (**B**) Heart Failure Progression; (**C**) Arrhythmic Event; (**D**) Cardiac Death; (**E**) All-cause Mortality. Taken from Jacobson AF, *et al*. Myocardial Iodine-123 Meta-Iodobenzylguanidine Imagingand 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: 2012-21.

observed in both cardiovascular and all-cause mortality from more than 20% for patients with HMR <1.10, to 0% for patients with HMR > 1, 80. Multivariate analysis showed a significant contribution of late HMR to the prediction of events in these patients, together with the LVEF value, the NYHA functional class and the atrial natriuretic peptide (BNP) values. In secondary analysis, the interaction of HMR with LVEF and BNP was evaluated and in all cases a better prognosis and a lower event rate were observed for patients with HMR ≥ 1.60 compared to those with HMR <1.60 [22]. This study thus demonstrated that the evaluation of myocardial sympathetic innervation with HMR using ^{123}I-MIBG scintigraphy has prognostic value in predicting cardiovascular events in subjects with HF and severe LVEF deterioration.

Since the publication of ADMIRE-HF, multiple studies have reproduced the feasibility of the procedure, as well as its results, giving strength and validation to them [15, 16, 23, 24]. Furthermore, the extended version of the ADMIRE-HF study, the ADMIRE-HF-X study, extended the follow-up of its population to 24 months and used mortality as the primary end point. The authors found significant consistency of HMR for the prediction of cardiovascular events and mortality when added to risk prediction models in this population.

CONCLUSIONS

HFrEF is a very prevalent entity, which generates significant public health costs each year, extremely high morbidity for those who suffer it, and a large

number of deaths, many of them suddenly. In these patients, SCD can be treated, when due to arrhythmic causes, with the implantation of an ICD.

Currently, ICD is indicated in primary prevention for patients with LVEF less than or equal to 35%, who are in NYHA functional class II / III, with a life expectancy of at least one year and who are carefully selected. The LVEF criterion less than or equal to 35% effectively allows recognizing patients who have a high risk of suffering from SCD. But in light of the evidence, it is also insufficient. The clinical trials that support this criterion present the problem of having different populations, with different selection criteria and also different treatments, which could explain such dissimilar rates of events observed, as well as the very variable benefits in terms of applying an ICD therapy. It is necessary to have additional criteria that allow selecting more adequately those patients with the highest risk of cardiovascular events and those who will most benefit from the implantation of an ICD, which, on the other hand, is an invasive practice and not without complications, that also has an elevated cost.

We currently have studies with ^{123}I-MIBG that have the ability to assess the integrity and extent of the sympathetic nervous system in myocardial tissue. These methods have demonstrated their safety and reproducibility, as well as their efficacy in predicting cardiovascular events (progression of HF, life-threatening arrhythmic events and death from cardiovascular causes) in patients with HF and impaired LVEF. For all these reasons, the evaluation of these patients through studies with 123I-MIBG could be a central element in the selection of candidates for electrical therapies with ICD in primary prevention, optimizing costs.

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