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Invited Review

I -123 metaiodobenzylguanidine imaging for predicting ventricular arrhythmia in heart failure patients

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Abstract

Compared to antiarrhythmic drugs, implantable cardioverter defibrillator (ICD) leads to a more significant improvement in preventing ventricular arrhythmia in heart failure patients. However, an important question has been raised that how to select appropriate patients for ICD therapy. I-123 metaiodobenzylguanidine (MIBG) planar and SPECT imaging have shown great potentials to predict ventricular arrhythmia in heart failure patients by assessing the abnormalities of the sympathetic nervous system. Clinical trials demonstrated that several parameters measured from I-123 MIBG planar and SPECT imaging, such as heart-to-mediastinum ratio, washout rate, defect score, and innervation/perfusion mismatch, predicted ventricular arrhythmias in heart failure patients. This paper introduces the current practice of ICD therapy and reviews the technical background of I-123 MIBG planar and SPECT imaging and their clinical data in predicting ventricular arrhythmia.

Keywords: heart failure, ventricular arrhythmia, implantable cardioverter defibrillator, I-123 metaiodobenzylguanidine (MIBG)

INTRODUCTION

Heart failure (HF) is a prevalent, costly, and potentially deadly disease[1]. Around 5.1 million people in the United States had HF in 2009[2]. In developed countries, around 2% of adults suffer from HF[1,3] and about one-third of them are admitted to hospital each year[4]. The most common cause of HF is coronary artery disease (CAD), which is the main cause in nearly 70% of patients[5]. In the United States, more than half of all cardiac deaths are sudden deaths[6] and more than 80% of sudden deaths are caused by arrhythmia[7].

Therapies with antiarrhythmic drugs (AAD) and implantable cardioverter defibrillator (ICD) have been developed to prevent arrhythmias. A number of clinical trials have demonstrated the superiority of ICD over AAD in the prevention of death from ventricular arrhythmias[6,7]. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[8] showed that HF patients with ICD therapy had an all-cause death risk of 23% lower than placebo and an absolute decrease in mortality of 7.2% after 5-year follow-up in the overall population.

Left ventricular ejection fraction (LVEF) is the main criterion used for ICD patient selection[9]. An LVEF of less than 40% may confirm a diagnosis of HF. An LVEF of less than 35% represents an increase of the risk of life-threatening arrhythmia. ICD therapy may be recommended for these patients. The updated

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2009 guidelines of ACC/AHA associated with other institutes suggest[10]: ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in patients with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-myocardial infarction (MI), a LVEF less than or equal to 35%, and New York Heart Association (NYHA) functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year (Class I, Level of Evidence: A).

Although the recommendations based on LVEF provide an important guide in ICD installation, pivot trials and post-hoc studies have demonstrated that this predictor has numerous limitations. On one hand, ICD never discharges in a considerable number of patients who received ICD. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II, only 35% of patients received appropriate ICD shocks within 3-year follow-up. On the other hand, many arrhythmic deaths occur in a population who have a higher LVEF but are not qualified for ICD according to the guidelines. Moreover, the complications of ICD therapy during the surgery and long-term management limitations[8] may cause serious problems, including a 4% post-procedural complication rate[11], infection, device malfunction, worsened quality of life, psychiatric problems and life style restrictions[12,13].

Therefore, selection criteria better than LVEF are needed to improve patient selection for ICD therapy. Abnormalities of the sympathetic nervous system are thought to play an important role in the development of ventricular tachyarrhythmia[14,15]. It was found that the inducibility of ventricular tachyarrhythmia is related to regional cardiac sympathetic denervation as assessed by I-123 metaiodobenzylguanidine (MIBG) imaging[16,17]. Thus, cardiac I-123 MIBG imaging may improve the selection of heart failure patients who are at a high risk of ventricular arrhythmia and may benefit from ICD therapy[18].

This review paper introduces the recent advances in I-123 MIBG imaging for the prediction of ventricular arrhythmias and discusses the clinical value of I-123 MIBG imaging in patient selection for ICD therapy.

I-123 MIBG: AN AUTONOMIC TRACER TO ASSESS THE SYMPATHETIC NERVOUS SYSTEM

The neurohormonal system plays an important role in HF[19-22]. Initially, neurohormonal feedback mechanisms tend to compensate the hemodynamic consequences of cardiac dysfunction via positive inotropic and chronotropic effects. Consequently, these chronic neurohormonal effects may cause cardiac hypertrophy and fibrosis, thereafter remodeling. Moreover, down-regulation of myocardial-adrenoceptors and alterations in postsynaptic signaling lead to further decline in cardiac function, creating arrhythmias.

In addition, a dysfunctional cardiac autonomic nervous system may also be related to the development of ventricular arrhythmias[23]. The regions with impaired innervation may be viable and hypersensitive to catecholamine, resulting in increased automaticity and enhanced triggering. In particular, the border zone of myocardial scar tissue may be predisposed to the development of re-entrant circuits because these regions are viable but may have damaged sympathetic nerves. The viable peri-infarct region can be partially denervated because sympathetic nerve fibers are more vulnerable to ischemia than cardiomyocytes. Consequently, important clinical and prognostic information in HF patients can be provided by assessment of cardiac sympathetic innervation.

MIBG, an analogue of norepinephrine, has been extensively applied to investigate sympathetic innervation[23]. After administration, MIBG is primarily transported into the pre-synaptic nerve terminal by sodium- and ATP-dependent transporters, referred to as uptake-1. In the nerve terminal, MIBG does not-degrade, resulting in an accumulation of MIBG with high signal intensity. The signals of MIBG labeled with I-123 permits visualization of myocardial sympathetic neuronal uptake. Thereafter, cardiac sympathetic nerve innervation can be analyzed by analyzing I-123 MIBG images, including review of planar images for global cardiac tracer uptake and tomographic images for regional cardiac trace uptake.

I-123 MIBG PLANAR IMAGING

Imaging protocols

I-123 MIBG planar images are usually obtained at approximately 15 minutes after MIBG administration (early scan), and again 3-5 hours later (late scan). There were several slightly different I-123 MIBG planar imaging protocols. In the pivot study by Kasama et al.[18], patients were injected intravenously with I-123 MIBG (111 MBq) in a supine position. At 15 min and at 4 h after injection, static data were acquired in the anterior view with a single-head gamma-camera. In the study by Boogers et al.[17], patients were pretreated with 120 mg of sodium iodide to block uptake of free I-123 by the thyroid gland. Sodium iodide was given orally 1 h before intravenous administration of 185 MBq I-123. I-123 MIBG planar imaging was

performed in the supine position. A planar image was acquired for 10 minutes from an anterior thoracic view 10 to 15 min after tracer administration. Planar imaging was repeated after 3 to 4 hours of tracer administration. In both studies, 128×128 planar images were acquired with a 20% energy window centered around the 159-keV energy peak of I-123 MIBG.

Image processing and analysis

The standard parameters of I-123 MIBG planar imaging are heart-to-mediastinum ratio (HMR) and washout rate (WR)[9,16-18]. Using regions of interest (ROI) of the entire heart and upper mediastinum on planar images, the HMR is computed by dividing the mean pixel value within the myocardium by the mean pixel value within the mediastinum as shown in ***Fig. 1***.

A high HMR value denotes greater tracer uptake and indicates normal heart conditions, while lower value signifies reduced adrenergic density and may have abnormal condition. HMR can be calculated for both early and late planar images, respectively. WR indicates the capability of the myocardium to retain tracer uptake. High WR is associated with increased risk. WR was calculated using the following equation[18]:

$$\mathrm{WR} = \frac{HMR_{early} - HMR_{delayed}}{HMR_{early}} \times 100\%$$

The HMR and WR in the planar image are considerably influenced by imaging systems, and location and size of the selected cardiac and mediastinal ROIs[24-27]. The normal HMR has been reported to be quite different in recent studies. A questionnaire survey is shown in ***Table 1***. Taking into account the variation of these HMR, careful consideration should be taken when investigating HMR and WR with varied imaging systems and observations. A semi-automated method would be beneficial to reduce the inter-observer variability. In a study by Okuda et al.[24], the only step requiring manual operation is specifying the center of circular cardiac contour. Automatic threshold and search of cardiac ROI and mediastinal ROI showed high reproducibility of this new method when tested in 37 patients.

Clinical results

I-123 MIBG planar imaging may be useful for making decisions about patient selection for ICD therapy. A few studies evaluated the association of HMR with ICD discharges. Arora et al.[28] performed a pilot study in 17 advanced HF patients with ICD therapy. Patients with a recorded ICD discharge showed significantly greater early HMR than those without an ICD discharge. Nagahara et al.[29] evaluated 54 HF patients with an ICD. During a mean follow-up of 15 months, late HMR was independently associated with appropriate ICD discharge.

Recently, AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF)[30], a multi-center clinical study was completed to confirm

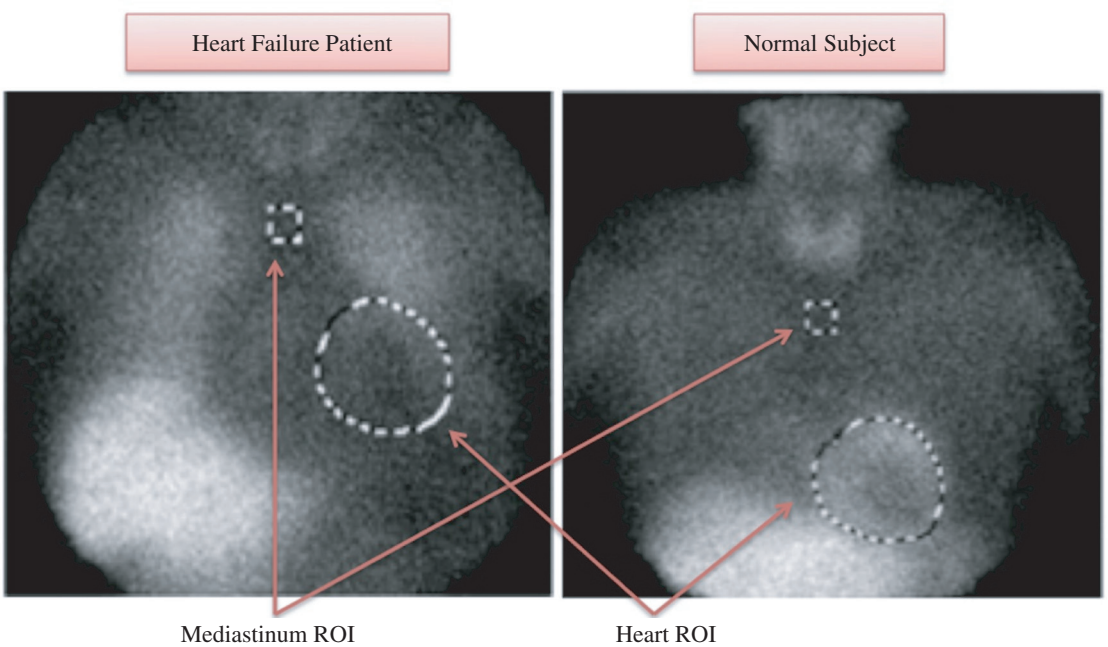

***Fig. 1* ROI selection and HMR calculation by I-123 MIBG planar imaging.** The normal subject has prominently higher MIBG uptake in the heart than the heart failure patient, as compared to the corresponding mediastinal MIBG uptakes. ROI: region of interest; HMR: heart-to-mediastinum ratio

the findings of extensive single-center trials and assess the prognostic role of I-123 MIBG imaging. A total of 961 subjects with NYHA class II/III HF and LVEF $\leqslant$ 35% were enrolled. Time to occurrence of the first cardiac event (NYHA class progression, potentially life-threatening arrhythmic event, or cardiac death) was compared in patients with HMR $\geqslant$ 1.6 vs. HMR< 1.6. The ADMIRE-HF study reported that patients with HMR $\geqslant$ 1.6 had significantly lower cardiac event risk than patients with HMR<1.6. The 2-year event rates were 38% vs. 15% for these two groups. Noteworthy, a total of 86 subjects had either non-fatal arrhythmic events or sudden cardiac deaths. These combined arrhythmic events were significantly more common in the subjects with HMR <1.6 (76 of 790, 10.4%) than in the subjects with HMR $\geqslant$ 1.6 (7 of 201, 3.5%).

Some groups also evaluated WR in HF patients. In the study by Kasama,[18] WR in HF patients was significantly lower in the non-cardiac death group than in the cardiac death group. The cardiac death-free rate was significantly higher in patients with WR< 25% than in those with WR $\geqslant$ 25%. Furthermore, the sudden death-free rate was significantly higher in the patients with WR< 22% than in those with WR $\geqslant$ 22%. Kioka et al.[31] also reported that abnormal WR could predict sudden cardiac death in patients with mild-to-moderate HF.

I-123 MIBG SPECT IMAGING

Imaging protocols

I-123 MIBG SPECT images were usually acquired immediately after the completion of the I-123 MIBG planar imaging. Important imaging parameters include collimator choice, energy window and reconstruction algorithms[32]. The largest clinical trial of I-123 MIBG, ADMIRE-HF, used low-energy/high-resolution collimators, with a symmetric 20% energy window peaked at 159 keV, and the projection images were reconstructed using filtered back-projection algorithm[30].

The denervated but viable myocardium, causing innervation supersensitivity, is considered to create dangerous ventricular arrhythmias; therefore, I-123 MIBG SPECT imaging was usually acquired in conjunction with myocardial perfusion imaging (MPI). In the ADMIRE-HF trial[30], patients underwent resting ^{99m}Tc tetrofosmin SPECT MPI on a separate day. The SPECT MPI was acquired at a minimum of 15 minutes post administration with a conventional protocol[30]. All the projection images were also reconstructed using filtered back-projection algorithm.

Image processing and analysis

A commonly measured parameter in I-123 MIBG SPECT imaging is defect score[17,18], which is calculated by assessment of patient´s segmental I-123 MIBG tracer uptake using 17 segments as recommended by the American Heart Association. Each myocardial segment is scored according to a 5-point tracer uptake scale from 0=normal tracer uptake to 4=no tracer uptake[17,18]. Subsequently, the I-123 MIBG SPECT defect score is obtained as the summation of all the segmental tracer uptake scores. Both early and late SPECT imaging can generate defect scores.

The other important parameter is innervation perfusion mismatch score. An innervation/ perfusion mismatch that creates innervation supersensitivity indicates the risk of ventricular arrhythmias[33]. A similar method based on the 17-segment model is usually used to calculate a perfusion defect score from supercriptTc SPECT MPI images. Then, a MIBG-perfusion mismatch score can be calculated by subtracting the perfusion defect score from the MIBG defect score to represent the size of mismatch, i.e., myocardium with abnormal MIBG uptake but normal perfusion uptake.

I-123 MIBG SPECT images can also be used to measure HMR. Similar to the definition of ROIs in planar imaging, volumes of interest (VOIs) of the heart and mediastinum are drawn on reconstructed SPECT transaxial images, and then the ratio between mean counts within and the two VOIs is measured as HMR. Chen et al.[32] demonstrated that SPECT imaging produced more accurate HMR than planar imaging. In another further quantitative SPECT study[34], they measured HMR of 67 pilot patients and 1,051 validation patients, and found that SPECT HMR has similar capability to planar HMR to differentiate HF patients from normal controls.

Clinical results

I-123 MIBG SPECT imaging has been used for prognosis in HF patients by a number of clinical

Table 1 **Normal HMR values**

Data source	Early HMR	Late HMR	Number of investigated subjects
JSNM I-123 MIBG[36]	2.39 $\pm$ 0.21	2.49 $\pm$ 0.25	36
Parthenakis et al[37]	2.08 $\pm$ 0.20	2.05 $\pm$ 0.02	15
Somsen et al[38]	1.89 $\pm$ 0.14	1.93 $\pm$ 0.16	25

HMR: heart-to-mediastinum ratio.

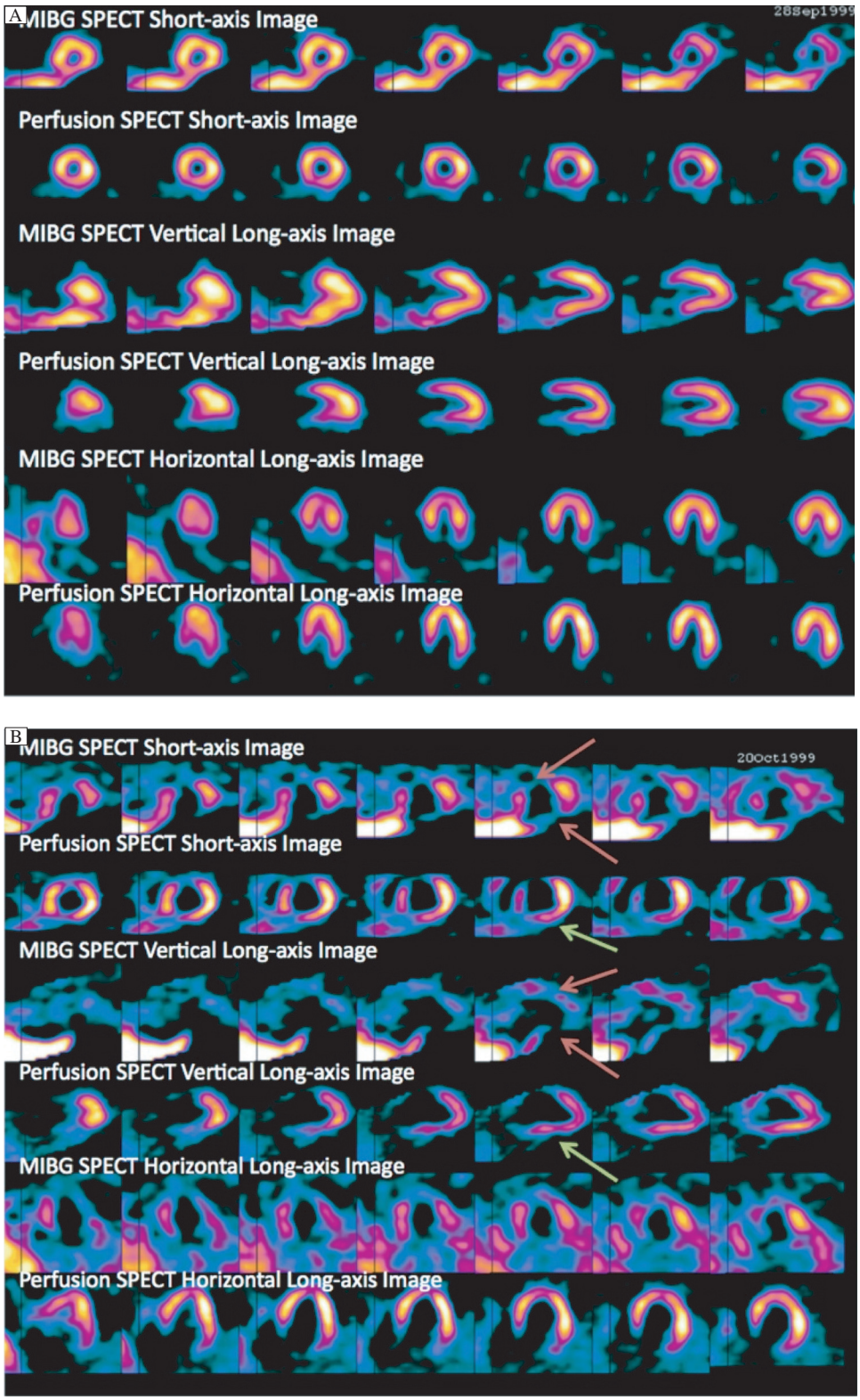

***Fig. 2* MIBG and perfusion SPECT images of two HF patients with ICD. (Courtesy of Mark I. Travin, MD, Montefiore Medical Center, Bronx, NY, USA).** A: A representative HF patient with ICD, but not experiencing ICD shocks. Both MIBG and perfusion SPECT images show good myocardial uptakes of the MIBG and perfusion tracers, respectively, indicating a low risk of ventricular arrhythmia in this patient. B: A representative HF patient with ICD, and experiencing ICD shocks. The MIBG SPECT images show low myocardial uptakes of MIBG in the anterior and inferior wall (red arrows). Good myocardial perfusion is observed in the inferior wall as shown by the perfusion SPECT images (green arrows). Therefore, this patient has large MIBG defects in both anterior and inferior walls and prominent MIBG/perfusion mismatch in the inferior wall, indicating a high risk of ventricular arrhythmia.

studies. Boogers et al.[17] measured the innervation/perfusion mismatch score in 50 patients with LV systolic dysfunction referred for electrophysiologic testing. The study showed that innervation/perfusion mismatch score was associated with the occurrence of ventricular arrhythmias in univariable analysis; however, no significant association was found in multivariable analysis. On the other hand, it revealed that regional cardiac denervation was significantly higher in patients with positive electrophysiologic tests than patients with negative electrophysiologic tests. Mitrani et. al.[35] reported that patients with ventricular tachycardia showed significantly more regional sympathetic denervation as compared to patients without ventricular tachycardia. This study also demonstrated that regional cardiac sympathetic denervation derived from late I-123 MIBG SPECT was significantly associated with ventricular arrhythmias causing appropriate ICD therapy. ***Fig. 2*** shows case examples, where the HF patient with ICD discharges had more extensive MIBG defect as well as MIBG-perfusion mismatch.

SUMMARY

The selection of HF patients for ICD therapy is a challenging clinical problem. The current methods are mainly based on LVEF, which has many limitations. I-123 MIBG imaging provides a useful tool for the assessment of the sympathetic nervous system. Several parameters given by I-123 MIBG planar and SPECT imaging, such as heart-to-mediastinum ratio, MIBG defect score, and MIBG-perfusion mismatch score, have been shown to predict ventricular arrhythmia and are promising in selecting HF patients for ICD therapy. Further studies are needed to establish these clinical applications of I-123 MIBG planar and SPECT imaging.

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