Significance of ^{123}I -mIBG SPECT cardiac imaging in heart failure

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^{123}I -meta-iodobenzylguanide (^{123}I -mIBG) scintigraphy assesses the integrity and activity of cardiac sympathetic neuronal innervation.¹ Jacobson et al published the data from Phase III clinical study involving 961 patients with heart failure in 2010: AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF). This study provided prospective validation of the independent prognostic value of ^{123}I -mIBG scintigraphy to assess the patients with heart failure (HF).² Pontico et al. discuss the prognostic value of ^{123}I -mIBG single-photon emission computed tomography (SPECT) cardiac imaging in HF patients in this issue of the journal (3). After a literature search, the authors selected 16 publications dealing with the prognostic significance of ^{123}I -mIBG SPECT imaging in patients with HF.³ In their research, summed defect score, regional wash-out, and regional myocardial tracer uptake demonstrated to have potential prognostic implications in patients with HF and predictive of an increased risk of an arrhythmic event and sudden cardiac death.

In HF, several mechanisms interact in a complex manner to contribute to the pathophysiology of dysfunctional myocardium. These mechanisms include abnormalities in myocardial perfusion; alterations in

cellular metabolism and contractility; hypertrophy and remodeling of the myocytes and the interstitium; and an impairment of the sympathetic nervous system (SNS) innervation, electrical impulse conduction, and ectopic electrical activity of the myocardium. Regardless of the underlying pathophysiologic mechanisms, the SNS and renin-angiotensin-aldosterone systems are activated in patients with HF. The activated sympathetic systems act favorably in the early phase by positive inotropic, chronotropic, and dromotropic effects. But they become detrimental in the long run as they induce myocardial hypertrophy, fibrosis, electrical instability, and left ventricular dysfunction.⁴ Nuclear imaging techniques can be used to obtain information about myocardial perfusion, flow reserve, regional and global contractility, myocardial metabolism, and sympathetic neuronal activity of the myocardium. Nuclear imaging can be used to study the tissue characteristics of the failing heart.⁵ mIBG is an analog of norepinephrine that tracks myocardial kinetics of norepinephrine (NE): its initial uptake, release, reuptake, and wash-out from the myocardium. Radiolabeled mIBG can be used to image the cardiac sympathetic neuronal activity. Uptake of ^{123}I -mIBG into neurons is achieved mainly through the uptake-1 mechanism, a homeostatic system responsible for the reuptake of NE. Unlike NE, mIBG is not metabolized in the myocardium, allowing it to be imaged.⁶ Through the ^{123}I -mIBG imaging, the myocardial uptake and distribution are visually assessed. Cardiac ^{123}I -mIBG uptake can be defined semiquantitatively by calculating the uptake ratio between the heart and a reference region in the mediastinum [heart to mediastinum (H/M) ratio]. The mIBG wash-out rate from the myocardium can be derived by comparing early and delayed activities. It provides a parameter that reflects the retention of NE by sympathetic neurons.⁷ ^{123}I -mIBG imaging can be carried out by planer or

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SPECT imaging. The SPECT images of the heart allow evaluation of the regional sympathetic activity. Polar maps of the myocardium can be constructed from the SPECT images, and it allows assessment of the defect extent and severity. Ischemia damages sympathetic neurons (probably earlier and more severely than cardiac myocytes), which may take a long time to regenerate and recover, and the episodes of ischemia result in decreased ^{123}I -mIBG uptake in the region of ischemia. The sympathetic nerve trunks course along the same path as the coronary arteries. Damage to the nerve has the potential of a neuronal defect being present distal to the site of myocardial injury. The extent of the SNS damage can reflect the myocardial damage in ischemic heart disease. Even in non-ischemic HF, the global changes in myocardial ^{123}I -mIBG uptake have been found to have predictive value for adverse cardiac events.^{2,8}

Interestingly recent studies have shown the strong prognostic value of nuclear imaging in HF patients. Verschure et al. have shown ^{123}I -mIBG scintigraphy to better identify HF patients, who can benefit from Implantable Cardioverter Defibrillator (ICD) implantation to improve their prognosis.⁹ A recent retrospective multicenter European study, which included 290 patients with ischemic and non-ischemic HF, showed ^{123}I -mIBG imaging to be an independent predictor of appropriate ICD therapy and cardiac death.¹⁰ Pontico et al. discuss all major studies showing the prognostic value of ^{123}I -mIBG scintigraphy in chronic HF patients. The authors also point out potential factors that can cause biases in the results. The medication used by the patients can affect the neurotransmitter uptake in the nerve endings. They also highlight heterogeneous patient populations in these studies. Perhaps, a subgroup analysis of the population may give a clearer idea.³ We agree with them that these are the areas to explore in future. ^{123}I -mIBG imaging is a potent tool to evaluate the neuronal and myocardial damage in a failing heart. Studies have shown ^{123}I -mIBG image findings in stable New York Heart Association (NYHA) class II and III patients. However, it is potentially possible to assess cardiac remodeling at an early phase and to determine if a particular individual is at risk for further progression of left ventricular dysfunction.⁴ Further studies on the SPECT imaging with ^{123}I -mIBG are required to standardize the technical aspects and image interpretation in HF patients. SPECT imaging is better than planar imaging alone, but SPECT images of ^{123}I -mIBG are more challenging to process and interpret compared to the planar images.¹¹ It can be difficult to define the left ventricular contour in patients with severely impaired myocardial radiotracer uptake and large areas of abnormalities. More studies on HF patients with

objective parameters to measure cardiac muscle damage will be helpful in the future. Another important point is the sample size. We need to use the SPECT technique in a larger sample size to understand the data reproducibility in different patient population subsets. Overall ^{123}I -mIBG scintigraphy is a highly reproducible technique to assess cardiac SNS activity and has a small inter-and intra-observer variation. Inter-institutional differences in image acquisition and post-processing can also affect the interpretation. Therefore, active efforts should be made to standardize cardiac ^{123}I -mIBG scintigraphy imaging parameters. Institutions should follow a standard protocol for patient preparation, the optimum dose of ^{123}I -mIBG administration, imaging parameters, and data analysis.¹² As mentioned before, sympathetic nerve fibers are more susceptible to ischemia than myocytes. The junction of infarct tissue with viable myocardial tissue with distorted anatomy of the SNS predisposes to develop arrhythmogenic foci.¹² Studies have shown a “bell-shaped” curve for the early and late H/M ratio in relation to appropriate ICD therapy. The patients with intermediate abnormalities in H/M ratio are more likely to have appropriate ICD therapy compared to patients with very low and those with preserved H/M ratios.^{9,12} The reason for this “bell shape” may be explained by the fact that the part of the myocardium that is already damaged may not induce further arrhythmia as no more nerve endings are left there. As mentioned in a study by Iqbal et al. assessing the regional distribution of the SNS with the SPECT may help predict the arrhythmia risk in the heart with damaged myocardium.⁵ ^{123}I -mIBG may support the use of ICD in HF patients in a cost-effective way.

^{123}I -mIBG imaging can also help detect the late cardiotoxic effect of chemotherapeutic agents by assessing sympathetic activity.¹³ Boogers et al. described the possible future use of ^{123}I -mIBG imaging in evaluating the potential role of gene and stem cell therapy in HF patients. ^{123}I -mIBG imaging can be useful in monitoring the effectiveness of this therapy by detecting the location and survival of delivered cells.⁴

Despite an impressive array of studies establishing the potential role of ^{123}I -mIBG in the risk-stratification of patients with HF, this imaging modality remains under-utilized in clinical practice. Pontico et al. have not discussed the possible reasons for this anomaly in their manuscript. An ultimate endorsement of the value of any imaging or diagnostic modality is its acceptance by the clinical community and, ultimately, its incorporation into the clinical pathways, treatment algorithms, and guidelines. Limited availability and high cost of I-123, lack of uniform protocols for imaging, and standardized parameters of image interpretation may have contributed to a lack of clinical use of this imaging modality. More

importantly, this may also highlight a complex intersection of multiple and diverse pathophysiological derangements and physiological compensatory mechanisms that ultimately manifest as HF with a very wide spectrum of symptoms and outcomes that cannot readily be represented by any single imaging, physiological or biochemical parameter. Perhaps, an approach that can evaluate the incremental value of a new investigational parameter over a combination of a multitude of established parameters can address this void. However, transforming this approach into a clinical trial with its budgetary and logistics constraints remains a daunting task. Unfortunately, the ultimate outcome of these complexities is an underutilization of potentially highly useful new molecular imaging modalities in clinical practice.

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Diwakar Jain serves as a consultant for GE and also serves on the speakers' Bureau of Astellas and Pfizer. The remaining authors have no conflicts.

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