Neuronal Dysfunction and Medical Therapy in Heart Failure: Can an Imaging Biomarker Help to "Personalize" Therapy?

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[123]I-metaiodobenzylguanidine (^{123}I-MIBG) imaging is a tool for evaluating one of the fundamental pathophysiologic abnormalities seen in heart failure (HF), that of an upregulated sympathetic nervous system and its effect on the myocardium. Although this imaging technique offers information about prognosis for patients treated with contemporary guideline-based HF therapies and improves risk stratification, there are neither rigorous nor sufficient outcome data to suggest that this imaging tool can guide therapeutic decision making or better target subsets of patients with HF for particular therapies.

Key Words: heart failure; heart-to-mediastinum ratio; myocardial washout rate; norepinephrine

There have been substantial advances in therapeutics over the past 3 decades for patients with heart failure (HF), with resulting extensive evidence-based recommendations for treatment (1). Although hemodynamic changes dominate the daily clinical syndrome, neurohormonal alterations drive the pathophysiologic progression of HF associated with longer-term outcomes and are the major targets for contemporary drug therapy (1,2). Upregulation of norepinephrine (NE) is associated with a poor prognosis for patients with chronic HF (3). Imaging techniques are now available to evaluate adaptations to the cardiac sympathetic nervous system and thus have the potential to more directly interrogate an important pathophysiologic feature of chronic HF with systolic dysfunction (3,4).

For patients with HF, myocardial synaptic physiology involving NE can be studied by labeling the NE analog guanethidine with radiolabeled iodine. The resulting compound, ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), acts like NE with respect to movement into and out of the synapse. Because it is not catabolized like NE, it is retained within myocardial nerve endings and can be imaged (5). Various measures of ^{123}I-MIBG uptake, such as the heart-to-mediastinum ratio (HMR) and myocardial washout rate, allow investigators to characterize myocardial uptake and thus obtain a noninvasive assessment of cardiac NE receptor density and functional sympathetic innervation (6,7). In general, individuals with healthy hearts have high cardiac uptake of ^{123}I-MIBG, whereas those with HF have lower myocardial uptake, reflecting decreased cardiac adrenergic receptor density.

Seminal work done by Merlet et al. demonstrated the value of ^{123}I-MIBG imaging as a prognostic tool for patients with HF (8). These investigators evaluated ^{123}I-MIBG uptake in 90 patients with HF, a left ventricular ejection fraction (LVEF) of less than 45%, and New York Heart Association (NYHA) class II–IV symptoms and showed that the ^{123}I-MIBG HMR was associated with overall survival during follow-up, which ranged from 1 to 27 mo. During the 20-plus years that have passed since this original observation, treatment and outcomes for patients with HF have improved (9). In response to changing care patterns, there has been great interest in understanding whether the observations of Merlet et al. (8) apply to patients treated with current guideline-based HF therapies.

The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial addressed this topic by prospectively monitoring 961 subjects with HF at 96 centers in the United States, Canada, and Europe after ^{123}I-MIBG imaging (10). Patients had NYHA class II or III symptoms, had an LVEF of less than or equal to 35%, were being treated with guideline-based HF therapies, and were monitored for up to 2 y. The results suggested that the observations of Merlet et al. (8) from 1992 appear to be reproducible in the setting of modern HF therapies. In the ADMIRE-HF trial, the risk of cardiac events (a composite of time to cardiac death, life-threatening arrhythmic event, or NYHA functional class progression) was significantly lower for participants with an HMR of greater than or equal to 1.6 than for those with an HMR of less than 1.6 (hazard ratio, 0.40; 97.5% confidence interval, 0.25–0.64; $P < 0.001$). Although the findings from the ADMIRE-HF trial support the predictive value of this imaging technique for assessing general prognosis, the ADMIRE-HF trial program was not designed to show that clinical decisions can be influenced by the results of ^{123}I-MIBG imaging. Indeed, regulatory authorities recognized this limitation, as the prescribing information for this agent states that its "...utility has not been established for selecting a therapeutic intervention or for monitoring the response to therapy" (11).

Numerous investigators have examined the interplay of HF therapies and ^{123}I-MIBG assessment of the integrity of sympathetic innervation. These studies generally have taken 1 of 2 analytic approaches. One approach investigates the effect of a therapy, such as angiotensin-converting enzyme (ACE) inhibition, on measures of ^{123}I-MIBG uptake evaluated before treatment and

again at a later time (during treatment). This approach attempts to study pathophysiology of the treatment effect, that is, how a treatment (which is known to be clinically effective) affects sympathetic innervation. Many such studies are summarized in Table 1. The other approach involves examining the association between baseline ^{123}I-MIBG data obtained before treatment and some response variable (such as a change in LVEF) resulting from the treatment. This analytic methodology attempts to use ^{123}I-MIBG data to predict which patients might have a "better" response to a treatment. Studies in which this approach was used are summarized in Table 2.

The studies summarized in Table 1 showed that therapies known to be clinically effective in patients with HF, predominantly neurohormonal antagonists, seemed to be consistently associated with improvement in measures of ^{123}I-MIBG uptake or washout. These data, in turn, suggested that such therapies are associated with improvement in functional sympathetic innervation. Whether this change in an underlying physiologic substrate is

part of the causal pathway of the clinically favorable effects of these therapies cannot be determined from such studies. It is conceivable that the observed change in sympathetic innervation is secondary to other, more fundamental effects of the pharmacologic therapies, such as improvement in left ventricular size or function or effects on baroreceptors. Although these studies are of significant interest from a physiologic point of view and raise interesting questions, they do not by themselves illuminate treatment pathways or mechanisms.

Published reviews of ^{123}I-MIBG imaging in HF patients often raise the possibility that ^{123}I-MIBG imaging may be useful in "...judging the likely result of medical or device therapy..." (4). The studies detailed in Table 1 did not address this issue. The idea that an imaging biomarker might be used to "select" patients who may have a greater or a lesser response to a therapy—thereby allowing consideration of the use or nonuse of the therapy—can be potentially informed by studies such as those summarized in Table 2, in which some aspect of baseline ^{123}I-MIBG data

TABLE 1
Effects of HF Therapies on Measures of ^{123}I-MIBG Uptake and Washout

Study	Therapy	No. of patients	Follow-up	Design	Results
Barr et al. (28)	Spironolactone/placebo	42	8 wk	RCT	Improved HMR in spironolactone group
Somsen et al. (29)	Enalapril	23	6 wk	Pre/post uncontrolled	Improved SPECT uptake after enalapril
Fukuoka et al. (30)	Metoprolol	13	3 mo	Nonrandomized, uncontrolled	Patients with change in EF ≥ 5% had more improvement in WOR
Takeishi et al. (31)	Enalapril/control	29	9 mo	Nonrandomized	Improved HMR and WOR in enalapril group
Soeki et al. (32)	Enalapril	10	7 mo	Pre/post uncontrolled	Improved HMR but not WOR in enalapril group
Toyama et al. (33)	Metoprolol/enalapril	24	12 mo	Randomized active control	Improved HMR in enalapril and metoprolol groups
Agostini et al. (34)	Carvedilol	22	6 mo	Pre/post uncontrolled	Improved HMR after carvedilol
Gerson et al. (18)	Carvedilol	22	7 mo	Pre/post uncontrolled	Improved HMR after carvedilol
Kasama et al. (35)	Spirinolactone	30	6 mo	RCT	Improved HMR and WOR in spironolactone group
Toyama et al. (36)	Amiodarone/metoprolol	30	12 mo	Randomized active control	Improved HMR in amiodarone and metoprolol groups
Kasama et al. (37)	Candesartan/placebo	50	6 mo	RCT (in patients with HFpEF)	Improved HMR and WOR in candesartan group

Pre/post = before and after drug treatment; RCT = randomized controlled trial; WOR = washout rate for ^{123}I-MIBG; HFpEF = heart failure with preserved ejection fraction.

TABLE 2
123I-MIBG Uptake or Washout at Baseline as Predictor of Differential Treatment Effect

Study	Therapy	No. of patients	Follow-up	Design	Results
Suwa et al. (38)	Bisoprolol	45	8 mo	Uncontrolled	Baseline HMR associated with "response," defined as both reverse remodeling and improvement in NYHA class
Choi et al. (15)	Carvedilol	11	12 mo	RCT	Inverse correlation between baseline WOR and change in LVEF
Gerson et al. (18)	Carvedilol	22	7 mo	Uncontrolled	No relationship between baseline HMR and change in LVEF
Yamazaki et al. (16)	β-blockers	40	6 mo	Uncontrolled	Lower mean extent and severity uptake scores at baseline in patients with change in LVEF of >10%

RCT = randomized controlled trial; WOR = washout rate for 123I-MIBG.

obtained before treatment is correlated with a measure of response to the treatment. The studies shown in Table 2 are not the result of a formal survey of the literature, as in a formal systematic review; rather, these studies were compiled from an examination of several reviews that have been published in the past 15 y (4,6,12).

Several insights can be gleaned from the studies shown in Table 2. First, there are very few such studies, and they incorporated very few patients. Second, none evaluated true patient-related clinical outcomes. They evaluated surrogates, such as change in ejection fraction or remodeling, that are related to outcomes in a general way (13,14) but are not highly predictive. Third, the data do not resonate with the results of seminal clinical trials. In the study of Choi et al. (15) (Table 2), there was an inverse correlation between the baseline 123I-MIBG washout rate and a change in LVEF over 12 mo of carvedilol therapy; in other words, the higher the washout rate (more abnormal), the lower the change in the LVEF in response to carvedilol. In the study of Yamakazi et al. (16), patients with HF and the least abnormal 123I-MIBG uptake had a better LVEF response to β-blockers. Hence, the patients with the most abnormal 123I-MIBG profiles—who were generally the patients with the most advanced HF—had the least favorable LVEF responses in these 2 studies. However, in the COPERNICUS trial (17), involving 2,289 patients with severe HF symptoms (NYHA class IV) and an LVEF of less than 30%, carvedilol had a very favorable clinical effect. In fact, the effect of carvedilol on survival was so impactful that the COPERNICUS trial was halted early, as the survival benefit exceeded the prespecified monitoring boundaries on an interim analysis. Thus, in rigorously executed clinical trials, patients with very advanced symptoms and left ventricular dysfunction had a very favorable outcome response to carvedilol, inconsistent with the "prediction" of the 123I-MIBG studies.

Finally, the data from the small number of studies shown in Table 2 were not internally consistent. Although 3 of the studies suggested that some baseline measure of 123I-MIBG correlates with a treatment effect of β-blockers on the LVEF, Gerson et al. (18) reported no such relationship. The latter study is actually more consistent with the large clinical trial literature, as none of

the major β-blocker randomized trials, involving thousands of patients, has identified a clinically relevant subgroup of patients in whom there is a clear differential effect on outcomes; that is, there is no subgroup of patients for whom treatment with β-blockers is *not* attempted. Thus, the few 123I-MIBG studies shown in Table 2 provide no indication that imaging with 123I-MIBG might yield clinical information regarding drug selection for patients with HF.

It has also been suggested that 123I-MIBG imaging may assist in the selection of patients for implantable cardioverter defibrillators (ICDs) to better target this expensive therapy. Although it is biologically plausible that a measure of preserved sympathetic innervation might identify a subgroup with such a very low risk for arrhythmic events that an ICD may not be needed, at this point the actual data supporting such a concept are not strong. In the first study to address this issue, Arora et al. (19) reported on a group of 17 patients who had ICDs and were evaluated with 123I-MIBG imaging and heart rate variability analysis. A group of patients who had no ICD discharges (and who, in theory, would not benefit from ICDs) was characterized by both preserved 123I-MIBG uptake and preserved (more normal) heart rate variability, but this group consisted of only 3 patients. In a recent analysis of the ADMIRE-HF trial program, Al Badarin et al. (20) created a risk score for arrhythmic events (the events that would be most directly affected by an ICD) and identified a "low-risk" group of 153 patients in whom only 3 events occurred, for a crude event rate estimate of 2%. The authors acknowledged the absence of external validation but concluded that the data suggested that 123I-MIBG imaging in such patients could have a "... role in individualizing arrhythmic risk assessment and improving decisions for device implantation," by which they presumably meant identifying a low-risk group of patients who may not benefit from an ICD. As pointed out in an accompanying editorial (21), even a risk of 2% may not be low enough to rule out the potential benefit of an ICD. Moreover, authors (such as Al Badarin et al. (20)) often focus on point estimates of risk in a studied population. More important is to examine the confidence intervals around the point estimate, as the *true* risk in the studied population—if it could ever

be measured—might be distinctly higher than 2%, especially given the very small number of events (3) in the small population (153 patients) studied. An estimation of the upper bound of the 95% confidence interval from the data in the study of Al Baradin et al. (20) puts the possible upper bound of risk in this "low-risk" group of patients as high as 4.2%, which is not "low."

The data and level of evidence required for a serum or imaging biomarker to enter clinical use in order to not treat selected patients with an existing guideline-based therapy is very high. Are there any examples in the therapeutic realm of patients with HF? One such example is the evolution of recommendations for cardiac resynchronization therapy (CRT) and the influence of an imaging "biomarker," the electrocardiogram. As recently as 2009, guidelines for HF recommended CRT as a class I indication for patients with symptomatic HF, an LVEF of less than or equal to 35%, and a QRS duration of greater than or equal to 120 ms (22). In the 2013 guidelines, however, the class I CRT indication more specifically (and narrowly) states that patients should have a left bundle branch block configuration as the driver of the wide QRS (1). In other words, a right bundle branch block or non–left bundle branch block driver of a wide QRS is no longer a strong indication for CRT. The data that influenced the change in the recommendation were very strong; they ranged from consistent subgroup analyses of individual large randomized controlled CRT outcome trials (23,24) to metaanalyses of major randomized trials involving more than 5,000 patients and Medicare registry data involving almost 15,000 patients, all with actual clinical outcomes (25,26), not surrogates. The evidence for the use of ^{123}I-MIBG imaging to "narrow" or "target" drug or device therapy is scant relative to the data for CRT.

Since the seminal study of Merlet et al. (8), however, the published data are quite consistent regarding the association of ^{123}I-MIBG imaging results with future risk of various events in patients with HF. Using contemporary analytic approaches to evaluate biomarkers for prognosis, investigators assessed whether ^{123}I-MIBG uptake can improve currently available risk stratification tools. Ketchum et al. determined the incremental value of adding ^{123}I-MIBG uptake data to the Seattle Heart Failure Model (27). Using patient-level data from the ADMIRE-HF trial, they found that the addition of the ^{123}I-MIBG HMR to the calculated Seattle Heart Failure Model score improved risk stratification (the net reclassification improvement was 22.7%; $P < 0.001$). As with most risk stratification studies, however, the clinical value of this observation is unclear because no therapeutic decision is informed by this new information. Ever finer gradations of statistically significant risk stratification or reclassification do not clearly result in any differential clinical decision for most patients with HF, whether the marker is a serum biomarker or an imaging biomarker.

^{123}I-MIBG imaging is a tool for evaluating one of the fundamental pathophysiologic abnormalities seen in HF, that of an upregulated sympathetic nervous system and its effect on the myocardium. Although this imaging technique offers information about prognosis for patients treated with contemporary guideline-based HF therapies and improves risk stratification, there are neither rigorous nor sufficient outcome data to suggest that this imaging technique can guide therapeutic decision making or better target subsets of patients with HF for particular therapies. The lessons from the evolution of CRT indications suggest that it is possible to better target therapies; however, large studies with designs and analyses focused on this topic and appropriate patient populations are essential, and they do not currently exist for ^{123}I-MIBG. Until such a trial or trial program can be conceived and executed and ^{123}I-MIBG

imaging can be shown to identify a new subgroup of patients who have HF and derive (or do not derive) benefit from a given therapy, patients with HF and a reduced LVEF will continue to be treated with "one-size-fits-all" therapies based on clinical trial summary results and guidelines, and ^{123}I-MIBG will continue to be a product approved for use but without clear utility.

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