Cardiac Sympathetic Imaging
With mIBG in Heart Failure

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Cardiac sympathetic imaging with meta-iodobenzylguanidine (mIBG) is a noninvasive tool to risk stratify patients with heart failure (HF). In patients with ischemic and nonischemic cardiomyopathy, cardiac mIBG activity is a very powerful predictor of survival. Cardiac sympathetic imaging can help in understanding how sympathetic overactivity exerts its deleterious actions, which may result in better therapy and outcome for patients with HF. (J Am Coll Cardiol Img 2010;3:92–100) © 2010 by the American College of Cardiology Foundation

Current Challenges in Heart Failure (HF)

The prognosis of HF has improved in the past 20 years, but it remains a serious condition with a markedly increased risk of death in the early period after onset of the syndrome (1). In population studies, there is a 10% mortality by 30 days. For those who survive this early high-risk period, the 5-year mortality is 54% in men and 40% in women (1). Mortality for patients in most recent clinical trials, with a background of appropriate pharmacological neurohormonal blockade, is around 8% to 10% per annum. Device therapy, with cardiac resynchronization with or without an implantable cardioverter-defibrillator further improves the prognosis (2–4), but at a relatively high additional financial cost initially.

In clinical trials of chronic HF therapy, 50% of deaths are due to sudden death, and progressive HF accounts for around 30% of deaths, this latter proportion increasing as symptomatic severity increases (5). In population studies including patients with new-onset HF, progressive HF appears to be the single most common cause of death (52%), with sudden death accounting for only 22% of deaths within the first 6 months of diagnosis (6,7).

Identifying those patients most at risk of death, and those most likely to benefit from currently available treatment technologies, remains a challenge. Identifying the risk of sudden, presumed arrhythmic, death, is particularly difficult. In general, older age, greater functional impairment, poorer systolic function of the left ventricle, lower serum sodium, poorer renal function, broader QRS complex, lower blood pressure, and inability to tolerate disease-modifying drugs such as angiotensin-converting enzyme (ACE) inhibitors are associated with a poorer prognosis and are men-
tioned in guidelines for HF management (8,9). Poorer adherence to evidence-based treatment by the physician has also been shown to be independently associated with a worse prognosis (10). There is a pressing need for improved risk stratification for patients developing HF, with the goal of better identification of those for whom more aggressive therapy is likely to be beneficial.

Pathophysiologic Basis for Cardiac Sympathetic Imaging

Compared with myocardium of healthy controls, the myocardium of patients with chronic left ventricular dysfunction is characterized by a significant reduction of pre-synaptic norepinephrine (NE) uptake and post-synaptic beta-adrenoceptor density (11,12). There is increased sympathetic activity in the hearts of patients with congestive HF, which is a generalized rather than a regional phenomenon and might contribute to the remodeling process of the whole left ventricle. This concept is consistent with the finding that down-regulation of myocardial beta-adrenoceptor density, measured using positron emission tomography (PET) with 11C-CGP-12177, soon after acute myocardial infarction is predictive of the occurrence of left ventricular dilatation at follow-up (13). Myocardial beta-adrenoceptor density appears reduced in patients with HF due to dilated cardiomyopathy (14) and down-regulation of myocardial beta-adrenoceptor is more pronounced in patients with hypertrophic cardiomyopathy who proceed to left ventricular dilation and HF (15). Therefore, myocardial beta-adrenoceptor down-regulation may be a general nonspecific response to stress and could be due to a locally increased amount of NE in the synaptic cleft. The sustained hyperactivity of the sympathetic nervous system observed in HF is the consequence of several mechanisms including increased central sympathetic outflow, altered neuronal NE reuptake, and facilitation of cardiovascular response to sympathetic stimulation by angiotensin II.

As a single-photon emission computed tomography (SPECT) tracer whose use does not require availability of an on-site cyclotron, 123I-meta-iodobenzylguanidine (mIBG) has been the most widely used imaging agent for studying causes and effects of cardiac sympathetic hyperactivity. mIBG was developed through a modification of the potent neuron-blocking agent guanethidine that acts selectively on sympathetic nerve endings. Uptake of 123I-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, allowing it to be imaged. The uptake-1 mechanism is one of the main NE disposal systems, and its malfunction may lead to abnormal catecholamine concentration in the synaptic cleft.

Imaging Techniques and Quantification With mIBG

A complete imaging protocol typically includes planar and SPECT images obtained 15 to 30 min (early) and 3 to 4 h (delayed) after intravenous injection of 111 to 570 MBq (3 to 10 mCi) 123I-mIBG (Fig. 1) (16). Myocardial uptake and distribution is visually assessed. mIBG uptake is semiquantified by calculating a heart-to-mediastinum ratio (HMR) after drawing regions of interest over the heart and mediastinum (Fig. 1). This approach provides a highly reproducible index of cardiac sympathetic activity (16). By comparing early and delayed activities, the mIBG wash-out (WO) rate from the myocardium can be derived, providing a parameter that reflects retention of NE by sympathetic neurons (17).

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 allow assessment of the defect extent and severity. Such polar maps can be easily compared with those of healthy individuals (Fig. 2). 123I-mIBG SPECT images can also be compared with SPECT myocardial perfusion images to examine differences between regional innervation and perfusion. In making such comparisons, it is important to be aware of differences between normal innervation and perfusion patterns, such as lower uptake of 123I-mIBG seen in the posterior inferior wall, especially in elderly persons (18,19).

Imaging With 123I-mIBG in Ischemic Heart Disease

The sympathetic nervous tissue is more sensitive to the effects of ischemia than the myocardial tissue (20). It has been shown that the uptake of 123I-mIBG is significantly reduced in areas of myocardial infarction (21), and adjacent noninfarcted regions (22) as well as in areas with acute and chronic ischemia (23,24). It is likely that ischemia damages sympathetic neurons.
(probably earlier and more severely than cardiac myocytes), which may take a long time to regenerate and that episodes of ischemia result in decreased $^{123}$I-$\text{mIBG}$ uptake. Sympathetic nerve trunks course along the same path as the coronary arteries, with the potential of a neuronal defect being present distal to the site of myocardial injury. Immunohistochemistry has demonstrated good correspondence between $^{123}$I-$\text{mIBG}$ imaging and the presence or absence of sympathetic cardiac nerves (25). Reinnervation may be incomplete as late as 3 months after acute myocardial infarction, but by 12 months after a first infarction, an increase in activity in the peri-infarcted region without a change in perfusion has been observed (26).

Concordance between the extent of $^{123}$I-$\text{mIBG}$ defect at rest and perfusion defect at exercise has been shown in patients with coronary artery disease. This concordance suggests that resting imaging with $^{123}$I-$\text{mIBG}$ combined with resting myocardial perfusion imaging (MPI) may be useful as a marker of reversible ischemia in patients unable to exercise and with contraindications to pharmacological stress (27). Another potential role of $\text{mIBG}$ imaging at rest is the detection of transient ischemia, which has been shown with metabolic tracers of both fatty acid and glucose analogs, termed “ischemic memory,” that may result in regional decrease in $\text{mIBG}$ uptake (28–32). This property of resting $^{123}$I-$\text{mIBG}$ imaging also has promise in the evaluation of the area at risk in the subacute phase of acute coronary syndromes by revealing more extensive defects than MPI.

### Imaging With $^{123}$I-$\text{mIBG}$ for Risk Stratification and Prognosis

Impaired cardiac adrenergic innervation as assessed by $^{123}$I-$\text{mIBG}$ imaging is strongly related to mortality in patients with HF independently of its cause. The prognostic value of $^{123}$I-$\text{mIBG}$ scintigraphy compared with other noninvasive cardiac imaging indices was initially studied in patients with either ischemic or idiopathic cardiomyopathy (33,34). Among all clinical and imaging variables, only the late HMR and left ventricular ejection fraction (LVEF) were independent predictors of mortality, with late HMR being the best predictor of event-free survival. In these studies, a late HMR of $\leq 1.2$ was used to identify reduced $^{123}$I-$\text{mIBG}$ uptake. Using this same threshold, it has been shown that reduced late HMR is correlated with other predictors of prognosis such as LVEF, cardiac

![Figure 1. Quantification of Cardiac $\text{mIBG}$ Activity](image)

(A) Calculation of $\text{meta}$-iodobenzylguanidine ($\text{mIBG}$) heart-to-mediastinum ratio (HMR) and wash-out rate on an anterior view of the thorax. Regions of interest (ROI) are drawn over the heart and mediastinum. (B) Normal cardiac $\text{mIBG}$ activity in a patient with HMR: 1.80. (C) Severely decreased cardiac $\text{mIBG}$ activity in a patient with HMR: 1.10.
index, pulmonary wedge pressure, and peak oxygen consumption, with late HMR ≤1.2 and peak oxygen uptake also predictive of death or cardiac transplantation over follow-up (35).

In other large cohorts of patients (36,37) with HF studied with 123I-mIBG, a reduced late HMR has been the most powerful predictor of cardiac mortality. A late HMR ≤1.74, age >60 years, a history of myocardial infarction, and New York Heart Association (NYHA) functional class III or IV strongly indicated poor clinical outcomes (36). However, 123I-mIBG imaging was the most powerful independent long-term prognostic indicator for ischemic or idiopathic cardiomyopathy patients. Late HMR was the most powerful independent predictor of cardiac mortality in both groups of patients, superior to the early HMR and the WO rate, with an identical threshold for both groups for identifying patients at risk of cardiac death when LVEF <50% (37).

The largest body of prognostic results is based on the late HMR from planar 123I-mIBG imaging (Fig. 3). Further confirmation of the strong prognostic value of this parameter was presented in the results of a recent retrospective multicenter European study (39), which included blind review and prospective quantitative reanalysis of the late HMR of 290 patients with ischemic and nonischemic HF (NYHA functional class II to IV, 262 patients with LVEF <50%) with follow-up data for 2 years. A standardized method for drawing heart and mediastinum region of interests on planar chest images was evaluated by 3 independent blinded readers. The analysis technique was robust, with 95% to 98% agreement among the readers regarding the HMR results obtained. The mean HMR was significantly increased from 22% to 62.5% when diabetes mellitus and chronic renal dysfunction were present with a higher BNP level and low cardiac 123I-mIBG activity.

The extent map displays in black the pixels with counts ≤2 standard deviations or less compared with the normal file. The severity map displays the defect severity, after dividing the total count difference between the black pixels and the normal region by the total number of pixels. The wash-out rate can be estimated for each segment as well as for the whole ventricle. Ant = anterior; Inf = inferior; Lat = lateral; mIBG = meta-iodobenzylguanidine; Sep = septal; SPECT = single-photon emission computed tomography.
Besides the late HMR, the prognostic value of other $^{123}$I-$m$IBG parameters has also been reported. The WO rate was evaluated in patients with LVEF $\leq 40\%$ during a follow-up of 52 months (40). A WO rate $\leq 27\%$ was a strong predictor of survival. In another series of outpatients with HF (mean LVEF 29%), of whom 48 had abnormal WO rate (27%), sudden cardiac death was significantly more frequent in patients with an abnormal WO rate (41). $^{123}$I-$m$IBG WO rate and both early and late HMR were significantly associated with sudden cardiac death. The prognostic value of cardiac $^{123}$I-$m$IBG imaging together with that of time and frequency domain parameters of HRV in patients with mild-to-moderate chronic HF has been prospectively evaluated (42). On univariate analysis, WO rate, late HMR, and normalized very–low-frequency power showed a significant association with the cardiac events at follow-up. Multivariate analysis showed that WO rate was the only independent predictor of cardiac events.

A recent meta-analysis (43) performed on 18 studies with a total of 1,755 patients provided further confirmation that patients with HF and decreased cardiac $^{123}$I-$m$IBG uptake or increased WO rate have a worse prognosis as compared with patients with normal $^{123}$I-$m$IBG parameters.

**Imaging With $^{123}$I-$m$IBG for Assessment of Treatment**

Cardiac $^{123}$I-$m$IBG imaging can demonstrate drug-induced changes in cardiac adrenergic activity. Enalapril improved cardiac sympathetic activity but did
not affect plasma NE levels in a group of patients with HF (44), supporting the concept that restoration of cardiac neuronal uptake of NE is one of the beneficial effects of ACE treatment. Similar increases in cardiac $^{123}$I- $m$IBG uptake have been observed after treatment with other ACE and angiotensin receptor blocker (ARB) (45,46) in patients with chronic HF.

With regard to beta-blocker therapy, patients with improvement of LVEF of $\geq 5\%$ after 3 months of treatment with metoprolol demonstrate a decrease in regional WO rate of $^{123}$I- $m$IBG after 1 month of beta-blocker therapy compared with baseline rates (45). The effect of chronic carvedilol treatment in patients with HF and cardiac sympathetic nerve dysfunction of varying severity due to idiopathic cardiomyopathy has been studied (47–49). Most patients showed a favorable response in left ventricular function to the treatment, regardless of the baseline level of cardiac sympathetic nervous system function, as assessed by cardiac $^{123}$I- $m$IBG imaging. Patients with severely depressed HMR ($<1.40$) had a higher likelihood to achieve an improvement in cardiac sympathetic nervous system function in response to carvedilol treatment. In patients treated with bisoprolol a late HMR $>1.7$ had a sensitivity of 91% and specificity of 92% for predicting response to beta-blocker therapy (48).

The influence of aldosterone treatment on cardiac sympathetic nerve activity has been assessed comparing 2 groups of patients treated with an ACE inhibitor and a loop diuretic, 1 with the addition of spironolactone. After 6 months of treatment with spironolactone, the late HMR of $^{123}$I- $m$IBG and LVEF significantly increased, and the late total defect score as well as the WO rate of $^{123}$I- $m$IBG significantly decreased, with parallel reduction of the left ventricular end-diastolic volume (50). A prospective study comparing amiodarone versus beta-blockers in the treatment of patients with idiopathic cardiomyopathy (51) reported similar improvement in cardiac symptoms, function, and sympathetic nerve activity with both drugs.

$^{123}$I- $m$IBG studies for prognostication in 208 patients under combination therapy and with stabilized mild-to-moderate HF and LVEF $<45\%$, of both ischemic and nonischemic origin have been analyzed (52). $^{123}$I- $m$IBG and echocardiographic studies were performed at baseline and after 6 months of treatment, which included ACE inhibitors, ARB, beta-blockers, loop diuretics, and spironolactone. The variation in the WO rate between the sequential $^{123}$I- $m$IBG studies was significantly lower in the noncardiac death group than that in the cardiac death group and was the only independent predictor of cardiac death.

Newer Multicenter Clinical Trials

Almost all cardiac $^{123}$I- $m$IBG studies reported in the past 20 years represented single-center experiences. However, during the past 5 years, a series of multicenter trials were performed to demonstrate the robustness of quantification of $^{123}$I- $m$IBG cardiac uptake as a prognostic marker in HF patients.

**Prognosis in HF: MBG311 and MBG312.** MBG311 and MBG312 are 2 prospective trials initiated in 2005 to validate the prognostic capability of quantification of sympathetic innervation of the myocardium using $^{123}$I- $m$IBG. These trials have now been designated as part of the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) program. The hypothesis tested was that patients with HF and abnormal HMR ratios have earlier and more frequent events (HF progression, potentially life-threatening arrhythmia, or cardiac death) than those with HMR within the normal range. Event status was monitored for 24 months, with final determinations made by an independent clinical adjudication committee of cardiologists. Secondary efficacy analyses employed a multiparameter Cox proportional hazards model fitted to multiple imaging and clinical variables, including early and late HMR, total and segmental $^{123}$I- $m$IBG SPECT defect scores, total and segmental cardiac $^{99m}$Tc-tetrofosmin SPECT MPI defect scores, LVEF, NYHA functional class, BNP, and NE levels, $^{123}$I- $m$IBG/$^{99m}$Tc-tetrofosmin SPECT mismatch score, and echocardiography left ventricular end-diastolic volume and left ventricular mass. All primary and secondary analyses were performed on the composite end point (first occurrence of any specified adverse cardiac event) and on each individual event category (Table 1). Results of the trials were recently presented at the American College of Cardiology scientific sessions, in March 2009, and the publication of the manuscript is expected to follow soon.

**Prediction of inducibility of ventricular tachycardia: MBG203.** MBG203 was a prospective pilot study to determine whether alterations in cardiac sympathetic innervation as measured by $^{123}$I- $m$IBG were related to inducibility of ventricular tachyarrhythmias during electrophysiology (EP) testing in patients with previous myocardial infarction. The primary objective was to evaluate results on planar
123I-1-mIBG imaging and the combination of SPECT 
123I-1-mIBG innervation and 99mTc-tetrofosmin MPI 
in comparison with results on EP testing (positive or 
negative for inducible sustained ventricular tachycardia 
as determined by a clinical adjudication committee of 
3 EP specialists). Primary inclusion criteria were 
history of myocardial infarction, left ventricular dys-
function, and referral for a clinically indicated cardiac 
study because of syncope or nonsustained ven-
tricular tachycardia (Table 2).

In a multivariable analysis, the only variable that 
showed a significant difference between EP-positive 
and EP-negative patients was the 4-h 123I-1-mIBG 
SPECT defect score. The 4-h 123I-1-mIBG SPECT 
defect score of 137 yielded a sensitivity of 77% and 
specificity of 75% for predicting EP results (53). The 
results of this pilot study suggest that the simple index 
of 123I-1-mIBG cardiac uptake represented by the 
HMR ratio will not be sufficiently sensitive to catego-
rize levels of arrhythmic risk in ischemic heart 
disease patients. However, the extent of denervated 
myocardium, as assessed by 123I-1-mIBG SPECT im-
ing, does appear to correlate with inducibility of 
ventricular tachyarrhythmias during EP testing.

<p>| Table 1. Demographics of Patients in ADMIRE-HF (MBG311/312 Trials) |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean Age (yrs)</th>
<th>% Male</th>
<th>Mean LVEF (%)</th>
<th>% NYHA Functional Class II</th>
<th>% Ischemic</th>
<th>% With ICDs at Any Time During Trial*</th>
</tr>
</thead>
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<tr>
<td>MBG311</td>
<td>63.1</td>
<td>82</td>
<td>27.1</td>
<td>82</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>MBG312</td>
<td>61.5</td>
<td>78</td>
<td>26.0</td>
<td>83</td>
<td>65</td>
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<td>80</td>
<td>26.6</td>
<td>82</td>
<td>66</td>
<td>36</td>
</tr>
</tbody>
</table>

*Estimated.
ADMIRE-HF = AdreView Myocardial Imaging for Risk Evaluation in Heart Failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Cardiac 123I-1-mIBG imaging in 2009. Despite the extensive research on cardiac 123I-1-mIBG imaging performed over the past 20 years, the exact role of this procedure in diagnosis and management of patients with heart disease remains uncertain. Although the importance of the sympathetic innervation of the heart is unquestioned, and the benefits of therapies that ameliorate the effects of neurohormonal imbalance are well established, doubt lingers about the manner in which quantitative assessment of adrenergic neuronal status should be used. Particularly for HF medical therapies, the conventional reasoning is that all appropriate medications will be used as tolerated and as dictated by symptom improvement, so a monitoring tool such as 123I-1-mIBG imaging offers no additional benefit. From a medical and economic point of view, it is easier to treat all patients with moderately priced drugs that have been shown to benefit the large majority than to attempt to individualize treatment based upon a physiological assessment that might produce equivocal results in a subset of the patients. 123I-1-mIBG imaging can provide an estimate of prognosis and can demonstrate whether therapies are producing the desired effect on cardiac pre- and post-synaptic function, but other readily available methods already inform the clinician regarding the success of his/her treatment approach. It is thus unlikely that 123I-1-mIBG imaging will become a routine clinical procedure for monitoring heart disease status or treatment response. It is in the realm of device therapy that 123I-1-mIBG imaging is likely to have its greatest impact in the next few years.

Most of the patients who have a Class I indication for receiving an implantable cardioverter-defibrillator will never experience an appropriate discharge, and about one-third of patients who receive cardiac resynchronization therapy do not improve. For both these patient groups, 123I-1-mIBG imaging holds promise as a technique capable of identifying both high and low risk for the adverse outcomes the devices are intended to prevent or at least forestall. The results from the ADMIRE-HF study should provide additional impetus for the development of

| Table 2. Clinical and Imaging Findings of Patients in MBG203 Trial |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable                      | EP+ Patients (n = 30) | EP− Patients (n = 20) | p Value |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age (yrs)                     | 65.0 ± 9.0      | 65.2 ± 9.9      | >0.50           |
| LVEF (%)                      | 32.1 ± 7.6      | 32.7 ± 7.3      | >0.50           |
| NYHA functional class (I/II/III)* | 3/14/7        | 2/10/3          | >0.50           |
| Plasma norepinephrine (nmol/l)† | 1.30 ± 1.24    | 1.90 ± 2.14     | 0.25            |
| Plasma BNP (pmol/l)†          | 60.2 ± 62.4     | 82.4 ± 78.3     | 0.31            |
| Late planar 123I-1-mIBG HMR ratio | 1.44 ± 0.21    | 1.47 ± 0.13     | >0.50           |
| Washout (%)                   | 47.1 ± 15.6     | 43.5 ± 12.3     | 0.39            |
| Late 123I-1-mIBG SPECT summed score | 42.7 ± 8.8     | 34.9 ± 9.8      | 0.005           |
| 99mTc-tetrofosmin SPECT summed score | 17.6 ± 9.0   | 12.7 ± 10.4     | 0.086           |
| Late 123I-1-mIBG/99mTc-tetrofosmin mismatch score | 21.4 ± 13.1 | 17.3 ± 11.1 | 0.26 |

Values are mean ± 1 SD, unless otherwise indicated. *Thirty-nine subjects with history of HF; †based upon 28 EP+ and 17 EP− subjects with adequate blood samples. EP+ = positive for inducible sustained ventricular tachycardia by electrophysiology testing; EP− = negative for inducible sustained ventricular tachycardia by electrophysiology testing; HF = heart failure; mIBG = metaiodobenzylguanidine; SPECT = single-photon emission computed tomography; other abbreviations as in Table 1.
criteria for use of $^{123}$I-$m$IBG imaging (alone or more likely in combination with other procedures) to identify those HF patients at highest and lowest risk for potentially fatal arrhythmic events.

Conclusions

$^{123}$I-$m$IBG imaging provides a noninvasive tool for the investigation of cardiac sympathetic innervation. Although defining the exact criteria to be used for clinical decision-making will depend on the results of currently ongoing trials, it appears that $^{123}$I-$m$IBG imaging will soon be added to the resources available to the clinical cardiologist. In the future, imaging of the cardiac sympathetic system will aid in quantifying the functional severity of myocardial injury and remodeling associated with ischemic and nonischemic cardiomyopathy, judging the likely response to medical and device therapy for HF, and identifying the substrate that places the patient at the highest risk for arrhythmic sudden cardiac death.

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