Usefulness of Cardiac Sympathetic Nerve Imaging Using Iodine-Metaiodobenzylguanidine Scintigraphy for Predicting Sudden Cardiac Death in Patients With Heart Failure

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SUMMARY

The autonomic nervous system plays an important role in the human heart. Activation of the cardiac sympathetic nervous system is a cardinal pathophysiological abnormality associated with the failing human heart. Myocardial imaging using \(^{123}\)I-metaiodobenzylguanidine (MIBG), an analog of norepinephrine, can be used to investigate the activity of norepinephrine, the predominant neurotransmitter of the sympathetic nervous system. Many clinical trials have demonstrated that \(^{123}\)I-MIBG scintigraphic parameters predict cardiac adverse events, especially sudden cardiac death, in patients with heart failure. In this review, we summarize results from published studies that have focused on the use of cardiac sympathetic nerve imaging using \(^{123}\)I-MIBG scintigraphy for risk stratification of sudden cardiac death in patients with heart failure. (Int Heart J 2016; 57: 140-144)

Key words: Sympathetic nervous system, Nuclear imaging, Prognostic value

Heart failure has a > 20% mortality rate during the first year after diagnosis and a 5-year mortality rate of approximately 50%. The cardiac sympathetic nervous system, with the renin-angiotensin-aldosterone system, is a crucial compensatory mechanism during heart failure. Subsequently, activation of the sympathetic nervous system is one of the cardinal pathophysiological abnormalities associated with human heart failure. Initially, an increased sympathetic response is favored as it compensates for decreased cardiac output. However, as heart failure progresses, this response leads to deleterious neurohormonal and myocardial structural changes that worsen the condition and increase the likelihood of arrhythmias and cardiac death.

Despite dramatic advances in the diagnosis and management of patients with heart failure, the incidence of sudden cardiac death remains extraordinarily high. In most cases (about 70%), and in a variety of clinical scenarios, the mechanism of sudden cardiac death is a lethal ventricular tachyarrhythmia. If a patient at risk can be identified, an implantable cardioverter defibrillator (ICD) can be implanted that can shock and/or pace the patient out of a lethal arrhythmia. A reduced left ventricular ejection fraction (LVEF) is the criterion currently used to identify patients at risk, and thus largely determines who receives an ICD as primary prevention. However, in a considerable number of patients who receive an ICD on this basis, the device never has to deliver therapy. At the same time, most patients who die from sudden cardiac death have a preserved LVEF and thus by current guidelines, do not qualify for ICD placement. Therefore, a parameter other than LVEF is needed to better select patients at risk for lethal ventricular arrhythmias who need an ICD. This may include more effective identification of patients with low LVEF who will not benefit from an ICD and patients at risk for SCD who are not being considered for the device because of apparent (by LVEF) preserved cardiac functioning.

Cardiac radionuclide imaging offers a variety of methods for identifying patients at risk for sudden cardiac death from ventricular arrhythmias, therefore potentially offering a way to select patients for an ICD that is better than current methods. In this review, the potential utility of nuclear imaging to identify increased risk of sudden cardiac death will be described.

Cardiac Sympathetic Nerve Imaging With \(^{123}\)I-MIBG

Myocardial imaging with \(^{123}\)I-MIBG, an analog of norepinephrine (NE), is a useful tool for detecting abnormalities in the myocardial adrenergic nervous system in heart failure patients. There is an association between myocardial NE and \(^{123}\)I-MIBG myocardial uptake in heart failure patients; therefore, cardiac sympathetic nerve activity (CSNA), evaluated by \(^{123}\)I-MIBG scintigraphy, is a useful tool for evaluating heart failure severity.

The cellular mechanism of MIBG uptake and storage in presynaptic vesicles is identical to NE. MIBG and NE share two uptake systems: specific (type-1 or uptake-1) and non-specific (type-2), using passive diffusion. Type-1 uptake is an active process catalyzed by a temperature and sodium-dependent membrane carrier protein with high affinity and low capacity, which is oxygen-dependent and desipramine and cocaine-sensitive. Type-2 uptake is temperature-dependent, but...
patterns. At low concentrations, MIBG is primarily taken up via the type-1 mechanism. However, at high concentrations, for example in $^{123}$I-MIBG treatment, the type-2 mechanism is predominant. After diffusing through the cell membrane, the tracer is taken up by neurosecretory vesicles via an active transport mechanism.

During the scintigraphic cardiac sympathetic nerve imaging, views are obtained after the intravenous administration of $^{123}$I-MIBG at rest, after 10-30 minutes (early), and again after 3-4 hours (delayed). Planar images with an anterior view are adequate for the evaluation of cardiac sympathetic function. Single photon emission computed tomography (SPECT) images are often acquired to evaluate regional myocardial uptake patterns. The common semi-quantitative indices used for the interpretation of cardiac sympathetic nerve images are the heart to mediastinum ratio (H/M) and washout rate (WR). The H/M ratio is determined from anterior planar delayed $^{123}$I-MIBG images (Figure 1). The WR is calculated using the following formula:

$$WR = \frac{\text{early H/M} - \text{delayed H/M}}{\text{early H/M}} \times 100\%$$

where [H] = mean count/pixel in the left ventricle and [M] = mean count/pixel in the upper mediastinum. The delayed H/M ratio and WR represent myocardial NE content (ie, intravesicular NE concentration) and presynaptic NE kinetics at the myocardial sympathetic nerve endings, respectively.

**Prognostic Value of $^{123}$I-MIBG Scintigraphy for Cardiac Death in Heart Failure Patients**

Many studies have shown that the evaluation of CSNA using $^{123}$I-MIBG scintigraphy can assist in estimating cardiac mortality in patients with heart failure. The first demonstration of the prognostic value of $^{123}$I-MIBG scintigraphy was by Merlet, et al in 1992, in a study of 90 heart failure patients with LVEF < 45% and in New York Heart Association (NYHA) functional classes II-IV. They concluded that a delayed H/M ratio correlated with life expectancy for patients with dilated or ischemic cardiomyopathy, and a delayed H/M ratio < 1.20 indicated a poor prognosis and lesser chance of survival. These observations suggested that the prognostic value of cardiac $^{123}$I-MIBG scintigraphy was greater than that of LVEF.

In 2001, Imamura, et al evaluated 171 heart failure patients (96 patients with idiopathic and 75 patients with ischemic cardiomyopathy) from 6 institutions and reported that the WR calculated by early and delayed $^{123}$I-MIBG planar images was 66 ± 10% in patients who had cardiac death events, and 44 ± 11% in patients without cardiac death (P < 0.01). High WR was also an independent predictor of cardiac death (relative risk [RR] = 1.158, P < 0.0001). Furthermore, using Kaplan-Meier survival analysis, the survival rate of the high WR group was significantly lower than that of the low WR group (P < 0.0001). More recently, the J-MTEA study investigators represented by Nakata, et al evaluated 7 independent cohort studies in Japan between 1990 and 2009. These studies included 1,322 patients with heart failure who were followed for 78 months. Multivariate Cox proportional hazard model analysis for all-cause mortality identified age (P < 0.0001), NYHA functional class (P < 0.0001), LVEF (P = 0.0029), and delayed H/M ratio of cardiac $^{123}$I-MIBG images (P < 0.0001) as significant independent predictors. They concluded that pooled analyses of independent cohort studies confirmed the long-term prognostic value of cardiac $^{123}$I-MIBG uptake in patients with heart failure independently of other markers.

Furthermore, the ADMIRE-HF study also confirmed previous data. The investigators prospectively evaluated $^{123}$I-MIBG scintigraphy for identifying heart failure patients (NYHA class II/III and LVEF ≤ 35%) most likely to experience cardiac events. During the follow-up period of 17 months (median), about 25% of the 961 patients experienced adverse events. For patients with a delayed H/M ratio < 1.60, 2-year probabilities of cardiac death and all-cause mortality were 11.2% and 16.1% versus 1.8% and 3.0% for the group with H/M ≥ 1.60. The ADMIRE-HF study provided prospective validation of the independent prognostic value of $^{123}$I-MIBG scintigraphy in the assessment of patients with heart failure.

**Table. Multivariate Predictors of a Sudden Cardiac Death**

<table>
<thead>
<tr>
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<th>Multivariate Analysis 1</th>
<th>Multivariate Analysis 2</th>
<th>Multivariate Analysis 3</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>1.001</td>
<td>0.951-1.055</td>
<td>0.963</td>
</tr>
<tr>
<td>Bata-blocker</td>
<td>0.373</td>
<td>0.081-1.714</td>
<td>0.205</td>
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<tr>
<td>(yes = 1)</td>
<td></td>
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<tr>
<td>LVEF</td>
<td>0.946</td>
<td>0.897-0.998</td>
<td>0.044</td>
</tr>
<tr>
<td>Delta-WR quartile</td>
<td>3.774</td>
<td>1.703-8.361</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>3.433</td>
<td>1.538-7.665</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>3.533</td>
<td>1.615-7.727</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; and WR, washout rate. (Kasama, et al. Int J Cardiol 2015; 179: 82-3.)
Prognostic Value for Sudden Cardiac Death or Lethal Ventricular Arrhythmias Using $^{123}$I-MIBG Scintigraphy

In previous studies, sudden cardiac death has been found to account for 20% to 70% of total mortality in patients with heart failure. Approximately 60% of patients with congestive cardiomyopathy develop complex ventricular ectopy and nonsustained ventricular tachycardia. It is well known that abnormal CSNA is associated with recurrent ventricular arrhythmic events during long-term follow-up in heart failure patients. Therefore, many clinical trials have demonstrated that $^{123}$I-MIBG scintigraphic parameters are predictive of sudden cardiac death and/or lethal ventricular arrhythmias in patients with heart failure.

Kasama, et al showed that delta WR (ie, follow-up WR minus baseline WR) obtained from serial $^{123}$I-MIBG scintigraphic studies was a useful parameter for predicting cardiac death and sudden death in stabilized patients with heart failure. They evaluated 208 patients with heart failure (LVEF < 45%) but no cardiac events for at least 5 months after hospital discharge, and all patients were identified according to their history of decompensated acute heart failure requiring hospitalization. These findings were confirmed in a subsequent study by the same investigators. They evaluated the same heart failure patients who were followed up for a median period of 4.83 years (0.78 to 7.48 years), and also evaluated sudden death events. In three models of multivariate analysis, delta-WR quartile was the incremental predictor of sudden death, among which this parameter had the strongest predictive factor in each model (Table). Using Kaplan-Meier analysis, the sudden death ratio was 0%, 2.0%, 5.8%, and 16.7% per increasing delta-WR quartile, respectively (Figure 2).

Moreover, Tamaki, et al found that WR was a powerful predictor of sudden death in patients with mild to moderate heart failure, independent of LVEF; however, signal-averaged electrocardiograms (SAECG), heart rate variability (HRV), and QT dispersion were not. Akutsu, et al also evaluated 86 patients with a history of ventricular tachycardia or fibrillation who were followed for approximately 11 years. They concluded that a low H/M ratio was associated with sudden cardiac death or recurrent ventricular tachyarrhythmic events ($P = 0.004$) in these patients. Bax, et al examined the relationship between abnormalities of CSNA obtained from $^{123}$I-MIBG SPECT images and inducible ventricular tachyarrhythmias in heart failure patients with left ventricular dysfunction. They demonstrated that defect sizes of $^{123}$I-MIBG SPECT images are associated with lethal arrhythmias, and may guide appropriate ICD implantation in these patients.

Summary of the Clinical Usefulness of $^{123}$I-MIBG Scintigraphy for Heart Failure

Because heart failure is associated with high mortality, appropriate clinical management is necessary to prevent cardiac death, including sudden death. It is well known that the

Figure 2. Kaplan-Meier curves for sudden cardiac death events among delta-WR quartiles. WR indicates washout rate. (Kasama, et al. Int J Cardiol 2015; 179: 82-3.)

Figure 3. Delayed anterior planar $^{123}$I-metaiodobenzylguanidine images at baseline and 6 months after hospital discharge in the highest quartile group (Q4). The delayed H/M ratios at baseline and after 6 months were 1.64 and 1.34, respectively, and WRs were 58% and 76%, respectively.
presence of LV dysfunction and LV dilatation are the prognostic indicators for patients with heart failure. On the other hand, 123I-MIBG scintigraphy has been reported to be a more useful predictor than the LV parameters. The plasma BNP concentration is also a useful prognostic value in these patients, and combination of the 123I-MIBG scintigraphy and BNP concentration provides a more incremental prognostic value than BNP alone. Furthermore, the prediction formula and nomograms using 123I-MIBG scintigraphy can be used for risk stratifying in heart failure patients. Accordingly, we propose to use this imaging modality to evaluate the severity of heart failure, medical management, and prognosis.

**Study Limitations:** Quantitative 123I-MIBG parameters differ between institutions and instruments because the choice of collimator influences the H/M ratio and WR value; therefore, cardiac 123I-MIBG has yet to achieve broad clinical acceptance. However, a correction method that can standardize the 123I-MIBG imaging among various gamma cameras and collimators has been reported. The clinical usefulness of 123I-MIBG scintigraphy in evaluating the prognosis of patients with heart failure should be examined using a prospective, multi-center trial with larger numbers of patients in the future.

**Conclusions:** This review underlines the clinical usefulness of myocardial 123I-MIBG scintigraphy in patients with heart failure. This cardiac sympathetic nerve imaging method can be successfully used to assess the prognosis, especially sudden cardiac death, in patients with heart failure.

**DISCLOSURES**

No conflicts of interest are declared by the authors.

**REFERENCES**


