Prognostic Value of Cardiac Sympathetic Nerve Imaging Using Long-Term Follow-up Data
– Ischemic vs. Non-Ischemic Heart Failure Etiology –
Shinro Matsuo, MD, PhD; Kenichi Nakajima, MD, PhD; Tomoaki Nakata, MD, PhD

Background: Although there are several known prognostic determinants in heart failure (HF), individual risk profiles can vary, in particular between ischemic and non-ischemic HF background. This study investigated the difference in prognostic efficacy of cardiac 123I-meta-iodobenzylguanidine (MIBG) imaging between the 2 etiologies.

Methods and Results: All 1,322 patients with HF were enrolled and followed up at most after 10 years. The HF patients were divided into 2 groups: an ischemic group (n=362) and non-ischemic group (n=960), and Cox proportional hazards model was used for data analysis. During 10 years of follow-up, 296 (22.4%) of 1,322 patients died; the mortality rates were 21.8% and 22.6% for the ischemic and non-ischemic groups, respectively. The ischemic group had greater prevalence of sudden death and lethal acute myocardial infarction, and the non-ischemic group had a higher rate of pump failure death. On multivariate Cox proportional hazards analysis using categorized variables, in the ischemic group, delayed heart-to-mediastinum ratio (HMR; P<0.0001), age (P=0.0002) and LVEF (P=0.03) were the independent significant predictors of lethal events. In the non-ischemic group, delayed HMR (P<0.0001), NYHA class (P<0.0001) and age (P<0.0001) were significant determinants of lethal outcome.

Conclusions: Cardiac MIBG imaging has nearly identical prognostic value in both ischemic and non-ischemic HF, independent of cause of cardiac death. (Circ J 2016; 80: 435–441)

Key Words: 123I-meta-iodobenzylguanidine; Heart failure; Heart-to-mediastinum ratio; Ischemic origin; Prognosis

Among the various cardiac imaging modalities, 123I-meta-iodobenzylguanidine (MIBG) imaging has the unique feature of visualizing sympathetic nervous function. MIBG has a similar mechanism to norepinephrine uptake, storage and release in the nerve endings. Increased tone of cardiac sympathetic nerve activity impairs MIBG uptake, corresponding to increased spill-over and deficiency of norepinephrine. This cardiac sympathetic nerve dysfunction is associated with increased occurrence of unfavorable cardiac events, including pump failure and lethal cardiac arrhythmia. Recent prospective and meta-analytic studies using MIBG scintigraphy in North America, Europe, and Japan have shown that it can predict cardiac death and fatal arrhythmia. In ischemic heart failure (HF), the prognostic value of myocardial perfusion imaging has been well established. Although there are several known prognostic determinants of HF, individual risk profiles can vary, in particular between ischemic and non-ischemic HF background. These differences between ischemic profiles have not been investigated as yet in long-term prognostic studies.

This study focused on cardiac death and, in particular, the prediction of fatal cardiac events in both ischemic and in non-ischemic subjects using a long-term pooled database of MIBG imaging. The purpose of the present study was to examine the prognostic value of MIBG imaging and to examine the contributing factors in each ischemic and non-ischemic subject with HF.

Methods
Subjects
Individual datasets from 6 prospective MIBG cohort studies performed in Japan between 1990 and 2009 were combined to make a pooled database of 1,322 chronic HF patients, as previously reported. Patients with HF from 6 Japanese medical institutions provided data for this study. All patients were enrolled in prospective observational studies, in which MIBG was approved for clinical use in Japan. All the original cohort studies were approved by the ethics committee or institutional review board in each hospital, and informed consent

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was obtained from the patients.

To create a single pooled database, cardiology specialists and/or nuclear medicine specialists in 6 hospitals created databases of common clinical parameters and updated the outcome in some institutions. This study includes the patients who were regularly followed up at the outpatient clinic of each facility for 10 years at most. The demographics of this population are summarized in Table 1. The subjects were divided into 2 groups: an ischemic group (n=362) and a non-ischemic group (n=960). The underlying diseases in the non-ischemic group were dilated cardiomyopathy (58%), valvular disease (13%), hypertensive heart disease (8%) and miscellaneous causes of HF (21%) including arrhythmia, secondary cardiomyopathies (diabetes, collagen diseases, etc), myocarditis and cardiac sarcoidosis. Eleven patients had implantable cardioverter-defibrillators (ICD) and 7 had cardiac resynchronization therapy (CRT).

Table 1. Clinical HF Subject Characteristics vs. Ischemia Status

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Ischemic group</th>
<th>Non-ischemic group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>40.1</td>
<td>36.6</td>
<td>0.25</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>66.3</td>
<td>64.7</td>
<td>0.60</td>
</tr>
<tr>
<td>β-blocker</td>
<td>51.8</td>
<td>54.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>69.3</td>
<td>69.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>45.9</td>
<td>48.0</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Data given as mean ± SD, n (%) or %. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; DM, diabetes mellitus; HF, heart failure; HMR, heart-to-mediastinum ratio; ICD, implantable cardioverter-defibrillators; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

123I-MIBG Imaging

The subjects with HF underwent MIBG imaging when they had become stabilized after HF treatment. Anterior planar images using scinticameras equipped with low-energy-type collimators were obtained at 15–30 min (early phase) and 3–4 h (late phase) after injection of 111 MBq 123I-MIBG (FUJIFILM RI Pharma, Tokyo, Japan) in all institutions. To calculate heart-to-mediastinum ratio (HMR), a whole heart region and a mediastinal rectangular region in the upper mediastinum were drawn manually. Both early and delayed HMR, as well as washout rate (WR) of MIBG, were calculated in each institution.

Left Ventricular (LV) Function

LV ejection fraction (LVEF) was determined using gated blood-pool study (n=317, 34%), 2-D echocardiography (n=498, 54%), gated single-photon emission computed tomography (SPECT; n=98, 11%) and either gated blood-pool study or echocardiography (n=18, 2%).

Outcome

All causes of death including HF death, sudden cardiac death (witnessed cardiac arrest and death within 1 h after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 h), acute myocardial infarction (AMI) and non-cardiac death were determined by the original study investigators. Patient medical records or telephone interviews in each institution confirmed clinical outcome. All patients were regularly followed up for the mean follow-up interval of 77.6 months. The final outcome and cause of death were evaluated after 10 years.

Statistical Analysis

All the clinical information and MIBG results were sent to a central institution (Kanazawa University), and were independently analyzed. Data are expressed as mean ± SD. Contingency table analysis was examined using likelihood ratio and Pearson statistics. Univariate and multivariate Cox proportional hazard analysis were performed with the categorized variables, for example age (<65 years, >65 years), New York Heart Association (NYHA) functional class (I/I vs. III/IV), hypertension, DM, male, LVEF (<35%, ≥35%), HMR (<1.7, ≥1.7), NYHA (I/I vs. III/IV), LVEF (<35%, ≥35%), HMR (<2.0, ≥2.0), and HMR (<1.4, ≥1.4). P<0.05 was considered significant. Survival curves for patient subgroups were created using the Kaplan-Meier method and compared using log-rank test. B-type natriuretic peptide (BNP) was not used in the multivariate Cox analysis because of the limited number of subjects (n=512) available for analysis. Statistical analysis was performed using JMP 10.0.2 (SAS Institute, Cary, NC, USA).

Results

Table 1 lists clinical background according to presence of ischemic background. LVEF was 36.4 ± 13.4% in the ischemic group and 36.9 ± 13.9% in the non-ischemic group (Table 1). The ischemic HF subjects were older and more frequently diabetic and had a prevalence of male sex compared with the non-ischemic group. Representative planar MIBG imaging in patients with and without cardiac events is shown in Figure 1.

Predictors of Mortality

Nineteen variables, including clinical factors and LVEF, were analyzed using univariate Cox hazard analysis in the ischemic group (n=362) and in the non-ischemic group (n=960;
Kaplan-Meier Event-Free Analysis and Cause of Death

Kaplan-Meier event-free curves according to HMR and LVEF in the ischemic group and in the non-ischemic group are shown in Figure 2. The optimal cut-off threshold for HMR, which represents maximum log-rank chi-squared on the Kaplan-Meier event-free curve, was 1.7 for both the ischemic and the non-ischemic groups.

In the ischemic group, 85 patients had died during the follow-up period: 29 (34%) due to sudden cardiac death, 34 (40%) due to HF, 9 (11%) due to AMI and 13 (15%) due to non-cardiac causes. Among 217 subjects who died in the non-ischemic group, death was due to sudden cardiac death in 46 (21%), HF in 123 (57%), AMI in 4 (2%), and non-cardiac causes in 44 (20%). Table 5 lists the causes of death in patients with delayed HMR <2.0, given that HMR ≥2.0 has a low risk of mortality. In the ischemic group, sudden cardiac death was the predominant cause of death, followed by HF. In contrast, in the non-ischemic group, HF and AMI were the most common causes of death.

Table 2. Univariate Indicators of All-Cause Mortality

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Ischemic group</th>
<th>Non-ischemic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$X^2$</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>3.74</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Male</td>
<td>0.27</td>
<td>1.14 (0.71–1.92)</td>
</tr>
<tr>
<td>LVEF</td>
<td>21.7</td>
<td>0.96 (0.94–0.98)</td>
</tr>
<tr>
<td>WR</td>
<td>23.5</td>
<td>1.04 (1.02–1.06)</td>
</tr>
<tr>
<td>Early HMR</td>
<td>10.6</td>
<td>0.32 (0.15–0.65)</td>
</tr>
<tr>
<td>Delayed HMR</td>
<td>22.9</td>
<td>0.20 (0.10–0.40)</td>
</tr>
<tr>
<td>DM</td>
<td>2.26</td>
<td>1.38 (0.90–2.10)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.76</td>
<td>1.23 (0.96–1.53)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3.98</td>
<td>0.63 (0.38–1.00)</td>
</tr>
<tr>
<td>VT</td>
<td>1.34</td>
<td>1.38 (0.85–2.17)</td>
</tr>
<tr>
<td>NYHA (I/II vs. III/VI)</td>
<td>10.8</td>
<td>2.06 (1.34–3.12)</td>
</tr>
<tr>
<td>Log$_{10}$BNP†</td>
<td>10.7</td>
<td>4.18 (1.74–10.6)</td>
</tr>
</tbody>
</table>

†n=512. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; VT, ventricular tachycardia; WR, washout rate. Other abbreviations as in Table 1.
death and death due to AMI were significantly more common (P=0.018, P=0.0005, respectively). Death due to pump failure occurred much more frequently in the non-ischemic group compared with the ischemic group (P=0.0023).

**Discussion**

The present study of HF patients using large-scale multicenter data showed that delayed HMR on ¹²³I-MIBG imaging was a strong predictor of cardiac mortality, either for ischemic or non-ischemic status. Cardiac sympathetic nerve study plays an important role in predicting death in HF patients. The present study clearly demonstrated the MIBG delayed HMR can determine both high-risk and low-risk probability for patient survival, with only minor differences in the cardiac death contributing factors. Thus the measurement of cardiac sympathetic nerve function on ¹²³I-MIBG imaging might be a better approach for assessing the severity of the disease and for better risk stratification in patients with HF in accordance with previous studies.¹³,¹⁴ The present long term follow-up study showed that this usefulness of ¹²³I-MIBG imaging could apply to both ischemic and non-ischemic patients with HF. This study also demonstrated that there were more deaths due to AMI or sudden cardiac death in ischemic HF patients, and that there was a higher possibility of death due to pump failure in the non-ischemic HF group.

**Recent Multicenter MIBG Studies**

Recent multicenter and meta-analytical studies have demonstrated the clinical value of ¹²³I-MIBG imaging in patients with HF.²-⁴ Use of cardiac ¹²³I-MIBG activity thresholds such as for HMR can identify patients at increased risk of fatal

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**Table 3. Multivariate Indicators of All-Cause Death in Ischemic HF**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Late HMR</td>
<td>0.58 (0.46–0.73)</td>
</tr>
<tr>
<td>Age (&lt;65 years, ≥65 years)</td>
<td>2.36 (1.49–3.85)</td>
</tr>
<tr>
<td>LVEF (≤35%, &gt;35%)</td>
<td>0.62 (0.40–0.95)</td>
</tr>
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</table>

HMR <1.4, 1.4≤HMR<1.7, 1.7≤HMR<2.0, HMR ≥2.0. Abbreviations as in Tables 1,2.

**Table 4. Multivariate Indicators of All-Cause Death in Non-Ischemic HF**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Late HMR</td>
<td>0.61 (0.53–0.70)</td>
</tr>
<tr>
<td>NYHA (I/II,III/IV)</td>
<td>2.43 (1.87–3.18)</td>
</tr>
<tr>
<td>Age (&lt;65 years, ≥65 years)</td>
<td>1.76 (1.36–2.28)</td>
</tr>
</tbody>
</table>

HMR <1.4, 1.4≤HMR<1.7, 1.7≤HMR<2.0, HMR ≥2.0. Abbreviations as in Tables 1,2.
Clinical Value of MIBG in HF Irrespective of Ischemia Status

Regardless of HF etiology, myocardial ischemia may be involved in the HF process because of coronary microcirculation abnormalities due to elevated LV end-diastolic pressure and mitochondrial dysfunction.31 Evaluation of the sympathetic nerve provides prognostic information and contributes to better risk stratification in these patients. In the present study, the powerful prognostic value of HMR was irrelevant to ischemic status in patients with HF. Therefore, MIBG imaging can give cardiologists much better information than LV functional test with regard to risk stratification, selection of therapeutic strategy, and prediction of long-term survival in HF patients. MIBG HMR could be used to predict therapeutic outcome before pharmacologic intervention. Drugs such as β-blocker or renin-angiotensin-aldosterone system inhibitors can prolong survival and improve quality of life. MIBG study can provide critical information on drug efficacy and non-pharmacological therapy. In a recent study, the efficacy of device treatment, including ICD and CRT therapy, seemed to be better related to MIBG HMR.39 Arrhythmic death or appropriate ICD discharge for fatal ventricular arrhythmias are associated with denervated myocardium.17,18 Further investigation is needed to establish the cost-effectiveness and decision-making for these clinical treatments.

MIBG and Collimator Choice

All MIBG examinations in each institution were performed using low-energy-type collimators. The choice of collimator substantially influences estimation of HMR, given that the presence of high-energy photons leads to a significant amount of septal penetration, and multiple complex scattering due to background activity. The low-medium energy collimator has characteristics to cover the higher energy scatter portion of the 123I energy spectrum, in accordance with the widely used 123I-labeled radiopharmaceutical in Japan. Quantitative MIBG imaging might be best performed using ME collimators. Stan-

<table>
<thead>
<tr>
<th>Table 5. Cause of Death in HF Patients With HMR &lt;2.0</th>
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<tr>
<td></td>
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<tr>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Pump failure</td>
</tr>
<tr>
<td>AMI</td>
</tr>
<tr>
<td>Non-cardiac death</td>
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</table>

Abbreviations as in Table 1.
ardized methods are required to be used with various gamma camera systems. Furthermore, the cross-calibration method could be used to apply previous data to one’s own institution using a cardiac phantom. The present study successfully demonstrated the prognostic value of MBG HMR derived from a similar low-energy-type collimator.

**Study Limitations**

First, BNP measurement was not available for all patients in the 1990's and it could not be included in the hazard model. In the prognosis evaluation, the utility of BNP is limited because BNP increases depending on blood sampling time points. Relatively high BNP was observed after starting β-blocker treatment. MBG HMR is more appropriate as a baseline assessment for long-term risk. Second, SPECT could be used to assess regional innervation, which indicates denervated but viable myocardium. Patients with severe HF tend to have markedly reduced sympathetic nerve function, such that SPECT images may be unable to be reconstructed, thereby making it difficult to achieve regional assessment. Therefore, further study of regional myocardial sympathetic nerve is needed using novel collimators, to facilitate treatment of localized denervation. Third, perfusion data were not available in the present study. Although the combined use of MBG and perfusion agents had prognostic value in previous studies, the added value of MBG for perfusion agent was not demonstrated in this study. Finally, recent reports showed that use of β-blocker has increased, in association with improved HF prognosis. Therefore, the treatment strategy for HF is very different between the early 1990's and 2000's. Therapeutic outcome should be evaluated with regard to recent optimal medical therapy.

**Conclusions**

MBG imaging, as determined in the present large-cohort multicenter study, has prognostic value in both ischemic and non-ischemic heart disease, irrespective of ischemia status.

**Acknowledgments**

The present multicenter pooled dataset was created through the collaboration of the following 6 Japanese medical centers: Sapporo Medical University, Tohoku University School of Medicine (Akiyoshi Hashimoto), Tokyo Women’s Medical University (Mitsuru Momose); Toho University Medical Center Ohmori Hospital (Junichi Yamazaki, Shohei Yamashina); Shiga University of Medical Science (Shintaro Yoshida, Toshiki Matsu); Cardiovascular Hospital of Central Japan (Shu Kasama); and Osaka Prefectural General Medical Center (Takahisa Yamada).

**Disclosures**

The authors declare no conflicts of interest.

**References**


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