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Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A cohort study

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Article Summary

Article Focus

Despite clinical efficacies in left ventricular (LV) systolic dysfunction, the prognostic value of cardiac sympathetic activity was in heart failure (HF) without reduced LV ejection fraction has not been determined. Thus the aim of this study was to determined whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with LV hypertrophy and increased left atrial (LA) size in HF patients without reduced LV ejection fraction.

Key Messages

LA dimension and cardiac MIBG activity quantified as heart-to-mediastinum ratio (HMR) were shown by multivariate Cox analysis to be significant predictors of 34 cardiac events observed in 178 consecutive HF patients during a period of 80 months and identified high-risk patients with a lower event-free rate. HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LA dimension or LV hypertrophy identified patients at most increased risk.

Strengths and Limitations

Independently and synergistically, LA size and cardiac MIBG activity were associated with cardiac events in HF patients without reduced LV ejection fraction. Despite various etiologies in HF with normal LV ejection fraction, cardiac sympathetic innervation assessment can contribute to better risk-stratification by combining with evaluation of LA size and LV hypertrophy. Further study is needed to establish etiology-based risk assessment and therapeutic strategy in HF patients without reduced LVEF who are at increased risk.
ABSTRACT

OBJECTIVES: The aim of this study was to determine whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with left ventricular hypertrophy (LVH) and left atrial size in heart failure (HF) patients without reduced left ventricular ejection fraction (LVEF).


Setting/Participants: With primary endpoints of cardiac death and re-hospitalization due to HF progression, 178 consecutive symptomatic HF patients including 74% males with a mean age of 56 years and mean LVEF of 64.5% were followed up for 80 months. The entry criteria consisted of LVEF more than 50%, completion of pre-discharge clinical evaluations including cardiac MIBG and echocardiographic studies, and at least more than one-year follow-up when survived.

RESULTS: Thirty-four patients with cardiac events had larger left atrial dimension (LAD), higher LV mass index, and lower MIBG activity quantified as heart-to-mediastinum ratio (HMR) than did patients without cardiac events. Multivariate Cox analysis showed that LAD and HMR were significant predictors [hazard ratios of 1.080 (95% CI, 1.00 to 1.16, p=0.044) and 0.107 (95% CI, 0.01 to 0.61, p=0.012, respectively]. Thresholds of HMR (1.65) and LAD (37 mm) were closely related to identification of high-risk patients. HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LAD or LV hypertrophy identified patients at most increased risk: overall log-rank value, 11.5, p = 0.0032 for LAD and 17.5, p=0.0002, respectively.
CONCLUSIONS: In HF patients without reduced LV ejection fraction, impairment of cardiac sympathetic innervation is related to cardiac outcomes independently and synergistically with LA size and LV hypertrophy. Cardiac sympathetic innervation assessment can contribute to better risk-stratification in combination with evaluation of LA size and LV mass but must be evaluated in more detail for establishing etiology-based risk assessment in HF patients at increased risk.
INTRODUCTION

Clinical risks and therapeutic strategy in chronic heart failure (HF) with reduced left ventricular systolic function have been established, though 30-40% of patients presenting with symptomatic HF have preserved left ventricular ejection fraction (LVEF) and a high mortality rate in such patients has been reported (1-7). Compared to HF patients with depressed LVEF, HF patients with preserved LVEF are less symptomatic, the pathophysiology is not fully understood, and risk-stratification is still limited because of a lack of reproducible and reliable markers for determining disease severity. Recent guidelines for the management of HF (1, 2), therefore, have highlighted the importance of recognition and the differential diagnosis of HF with/without diastolic dysfunction or alternatively preserved systolic function. Left ventricular hypertrophy is one of major causes of diastolic dysfunction or HF with preserved LVEF. There are several quantitative Doppler indices for identifying diastolic failure and high-risk patients with preserved LVEF, but most of them are limited to patients without atrial fibrillation, significant valvular disease or non-cardiac diseases responsible for left atrial enlargement (3).

Alterations of autonomic function have pathophysiological and prognostic implications in systolic heart failure. Excess systemic augmentation of autonomic nervous function is harmful to the heart by triggering and/or exacerbating HF due to myocyte injury and/or myocardial remodeling, leading to sudden cardiac death or lethal pump failure. On the other hand, cardiac neuroimaging with iodine-123 metaiodobenzylguanidine (MIBG) has demonstrated that impairment of cardiac sympathetic innervation is closely related to unfavorable clinical outcomes in HF.
patients with reduced systolic function not only independently of but also together with LVEF, New York Heart Association (NYHA) functional class, plasma brain natriuretic peptide (BNP) level and coexisting non-cardiac diseases (8-13). In HF patients with preserved LVEF, however, the prognostic value of cardiac sympathetic innervation has not been fully investigated (14, 15).

We hypothesized that a quantitatively assessed cardiac echo index and sympathetic innervation marker can contribute to better assessment of prognosis in HF patients with preserved LVEF. In this study, we analyzed data from 178 consecutive symptomatic HF patients with LVEF of more than 50% who had been followed up for a period of 79.6 months.

METHODS

Patient population

Data for 178 consecutive patients with symptomatic HF and LVEF of more than 50% who were enrolled in our prospective HF cohort study were analyzed. Patients who survived had been followed up regularly at the outpatient clinic of our university hospital following echocardiographic and MIBG examinations for at least one year. Congestive HF was diagnosed by the following clinical symptoms and signs according to the Framingham criteria: typical symptoms (palpitation, dyspnea or orthopnea), neck vein distension, peripheral edema, lung rales, S3 gallop and tachycardia together with chest X-ray findings, such as cardiomegaly, bilateral lung congestion and/or pleural effusion. The diagnosis of HF without reduced LVEF (more than 50%) was confirmed at admission using conventional two-dimensional/Doppler echocardiography and, when necessary, in combination with chest computed tomography to exclude non-cardiac
diseases showing similar symptoms or signs. Patients with end-stage renal failure, insulin-dependent diabetes mellitus or neurogenic disorders involving the autonomic nervous system, patients who had been treated with tricyclic antidepressant drugs, sympathomimetic agents or other drugs known to interfere with cardiac MIBG uptake, and patients who were scheduled to undergo any cardiac surgery were excluded from this study. When clinical conditions were stabilized after admission, patients were enrolled in this study and underwent cardiac MIBG imaging and blood tests. Informed consent for participation in this study was obtained in accordance with the guidelines of the ethics committee of our hospital. Table 1 shows clinical backgrounds and results of baseline examinations. Underlying heart diseases of HF were as follows: 15 patients (8.4%) had ischemic heart disease and the remaining 163 patients (91.6%) had non-ischemic heart diseases, including idiopathic dilated cardiomyopathy (n=23, 12.9%), hypertrophic cardiomyopathy (n=73, 41.0%), arrhythmogenic right ventricular cardiomyopathy (n=13, 7.3%), hypertensive heart disease (n=8, 4.5%), valvular heart disease (n=41, 23.0%) and other diseases (n=5, 2.8%). None of the patients underwent non-pharmacological treatment such as implantable cardioverter defibrillator or resynchronization therapy.

Cardiac MIBG imaging

Cardiac MIBG imaging was performed in a stable condition during hospitalization within two weeks from echocardiographic examination using $^{123}$I-MIBG of 111 MBq with a high specific activity (9-11) before discharge. Cardiac planar and tomographic MIBG images were obtained in the fasting and in resting conditions 15–30 minutes (early) and 4 hours (late) after an intravenous tracer injection using a gamma camera equipped with low-energy, general-purpose collimator. Cardiac $^{123}$I-MIBG
activity was quantified as a heart-to-mediastinum ratio (HMR) by manually setting a region of interest on the upper mediastinum and the whole cardiac region on a planar image from an anterior projection by an experienced nuclear medicine technician who did not know any clinical data. $^{123}$I-MIBG washout kinetics from the heart was also calculated as washout rate (WR) using a polar-map technique with tomographic data because of the elimination of background activity. Our previous studies (9-11) showed high reproducibilities of this quantitative method.

**Conventional echocardiographic examination**

Standard two-dimensional echocardiographic examination was performed by experienced cardiologists in our echocardiography laboratory using commercially available ultrasound machines (SSH-160A, Toshiba, Tokyo, Japan; SSD760, Aloka, Tokyo, Japan; SONOS 2500, Hewlett-Packard, Andover, Massachusetts, USA; Vivid 7, General Electric Medical Systems, Milwaukee, WI, USA) that were each equipped with a 2.5-MHz variable frequency transducer. Two-dimensional and pulsed Doppler imaging modes were used from apical four-, three- and two-chamber views in a left lateral decubitus position. Left atrial (LA) dimension (LAD, mm) was measured by M-mode echocardiography. Standard two-dimensional measurements (LV end-diastolic and end-systolic dimensions and septal and posterior wall thicknesses at end-diastole) were performed and then LV mass index was calculated using the American Society of Echocardiography recommended formula (16) and was normalized for body surface area (LVMI, g/m$^2$). Left ventricular hypertrophy was defined as LVMI of more than 115 g/m$^2$ for men and more than 95 g/m$^2$ for women. LVEF was measured using the biplane modified Simpson’s method. Transmitral flow velocities were obtained by pulsed-wave Doppler echocardiography, positioning a sample volume at the level of a
mitral tip in an apical four-chamber view. Mitral flow parameters, including peak velocities at early diastole (E) and at late diastole (A) and deceleration time of E (Dct), were measured and then E/A was calculated. Pulsed-wave Doppler signals were obtained at a sweep speed of 100 mm/s.

**Laboratory data assessment**

Blood sampling for measurements of plasma BNP level, hemoglobin and serum concentrations of sodium and creatinine was done from an intravenous cannula in a spine position when cardiac MIBG imaging was performed. Samples used for measurements of BNP were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator units/ml) and immediately placed on ice and centrifuged at 4°C. The concentration was measured by a specific immunoradiometric assay using a commercial kit (Shionogi, Osaka, Japan) (11).

**Follow-up protocol**

After discharge, all patients were prospectively followed at least every 3 months for a mean period of 79.6 months at the outpatient clinic of our university hospital by cardiologists who determined the necessity of blood tests, electrocardiography, chest X-ray, echocardiography or other examinations. The primary endpoints were fatal or near-fatal cardiac events consisting of pump failure death, sudden cardiac death and re-hospitalization due to progression of congestive HF for necessity of intense medical treatment, including intravenous drug infusion, oxygenation and respiratory control and/or use of an assist device. All cardiac events were confirmed using medical records after final diagnosis had been made. The first cardiac event was used for prognosis analysis when one of the above-mentioned primary endpoints was observed during follow-up. Sudden cardiac death was defined as witnessed cardiac arrest and death.
within 1 hour after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 hours. Patients who had undergone implantable cardioverter defibrillator therapy were not included in this study.

Statistics

Statistical values are shown as means ± 1 SD. Mean values were compared between the two groups using the unpaired t-test, and the prevalence was compared using the chi-square test. A p-value less than 0.05 was considered significant. Following univariate analysis, multivariate analysis with a Cox hazard proportional model was carried out using the statistically appropriate number of significant variables identified by univariable analysis, which depended on incidence of cardiac events. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of an independent significant parameter. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. These analyses were performed using a computer software program, SPSS statistical program package (SPSS version 11.0, SPSS Inc., Chicago, IL).

RESULTS

During an 80-month follow-up period, primary cardiac events were documented in 34 patients (19%), 7 of whom died of refractory pump failure, 2 of whom had sudden death and 25 of whom had re-admissions due to progression of congestive HF, but non-cardiac death was not documented in this study. There was no significant difference in background disease among cardiac events (Table 2). Although patients with cardiac events were more frequently treated with diuretics and calcium
channel-blockers than were those without cardiac events, there was no significant
difference in any clinical or laboratory data between groups with and without cardiac
events (Table 1).

There was no significant difference in two-dimensional or Doppler
echocardiographic functional parameters between the two groups with and without
cardiac events (Table 3). LVMI and LAD in the cardiac event group were, however,
significantly greater than those in the non-cardiac event group: 172.3 ± 10.9 vs. 130.2 ±
5.5 g/m², p = 0.0008 and 43.8 ± 7.4 vs. 36.1 ± 7.4 mm, p<0.0001, respectively. On the
other hand, the cardiac event group had significantly reduced cardiac MIBG activities
(early HMR: 1.86 ± 0.38 vs. 2.00 ± 0.31, p = 0.041; late HMR: 1.64 ± 0.35 vs. 1.89 ±
0.33 p = 0.0003) and a significantly greater washout rate (40.3 ± 9.1% versus 32.3 ±
12.9%, p = 0.0027) than those in the non-cardiac event group (Figure 1). Table 4
summarizes overall results of univariate and multivariate analyses using six parameters
that were found to be significantly different between the two groups. Based on the
significant results of univariate analysis and because of the number (34) of cardiac
events in the present study, multivariate Cox analysis was performed using the top three
variables in the univariate analysis results: use of diuretics, LAD and late HMR. LAD
and late HMR were identified to be independent significant determinants of cardiac
events with hazard ratios of 1.080 (95% CI, 1.00-1.16) for LAD (p=0.044) and 0.107
(95% CI, 0.01-0.61) for late HMR (p = 0.012) (Table 4). Late HMR was a significant
determinant of cardiac events for both patient groups with and without left ventricular
hypertrophy: hazard ratios of 0.167 (95% CI, 0.05-0.052, p=0.047) (Table 5) and 0.010
(95% CI, 0.01-0.37, p=0.0155) (Table 6), respectively. When re-hospitalization (i.e.,
exclusion of cardiac death) was considered as a single endpoint for analysis, LAD and
late HMR were independent significant determinants in patients with left ventricular hypertrophy (Table 7), but only late HMR was a significant determinant in patients without left ventricular hypertrophy (Table 8).

ROC analysis revealed optimal thresholds of late HMR and LAD for identifying cardiac events to be 1.65 (chi-square value, 65.95; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively (Figure 2). When adjusted by age, sex, and use of diuretics and calcium channel-blockers, patients with late HMR of less than 1.65 or LAD of 37 mm or more had significantly lower event-free rates than did those without (Figure 3 A and B). When patients were divided into three subgroups using the cutoff values of late HMR and LAD, there were significant differences in event-free rate among the three subgroups, and patients with late HMR less than of 1.65 and LAD of 37 mm or more had the lowest event-free rate (Figure 3C). When, instead of LAD, left ventricular hypertrophy was used for prognosis analysis, patients with both reduced HMR and LVH had the lowest event-free rate among the subgroups (Figure 4). Figure 5 shows echocardiograms and cardiac planar MIBG images of two cases: one is from a 43-year-old man with a markedly reduced HMR (1.32) and an increased LAD (46 mm) who was admitted for intense medical therapy due to pump failure and the other is from a 38-year-old male with relatively preserved HMR (1.92) and a nearly normal LAD (36 mm) in whom no cardiac event was documented.

DISCUSSION

The present study clearly demonstrated that echocardiographic LA enlargement and impaired cardiac sympathetic innervation assessed by MIBG activity are independently and additively related to unfavorable clinical outcomes in HF patients.
without reduced LVEF. Assessment of LA size and cardiac sympathetic innervation can contribute to better risk-stratification of HF patients without reduced LVEF who are at increased risk and probably can benefit most from aggressive medical treatment.

HF syndrome is heterogeneous regardless of systolic or diastolic dysfunction and the concept of HF has been changing depending on alterations of population demographics, background diseases and risk factors for HF. The concept of heart failure with preserved LV ejection fraction (HFpEF) has recently been established as a specific entity of HF in patients without reduced LVEF and organic cardiac diseases such valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. This study, however, was simply designed to test whether cardiac MIBG activity has a long-term prognostic value in consecutive HF patients without systolic dysfunction as already shown in HF patients with reduced LVEF. In this study, it was found that patients with cardiac events had a higher LVMI than did those without cardiac events, that left ventricular hypertrophy was additively related to unfavorable outcomes when cardiac sympathetic innervation was impaired (HMR of less than 1.65) and that LA enlargement was significantly prognostic in patients with left ventricular hypertrophy. These findings are identical to pathophysiological roles of left ventricular hypertrophy often observed in patients with HFpEF (4-7). However, LVMI was not an independent predictor of cardiac events in multivariate Cox analysis, and LA dimension was also not a predictor in patients without left ventricular hypertrophy. Independent of left ventricular hypertrophy (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because left ventricular hypertrophy is common in hypertensive or elderly patients and can be one of caused of diastolic impairment and also because left ventricular hypertrophy is not necessarily a
critical determinant of prognosis in patients without reduced LVEF but with impaired cardiac sympathetic activity who do not meet the concept of HFpEF.

Many studies have demonstrated the prognostic values of Doppler diastolic measurements such as E/A ratio, deceleration time, S/D ratio and E/e’ in HF patients with depressed LVEF, but few data are available for HF patients with preserved LVEF (3). Diastolic dysfunction in HF patients with normal LVEF and the diagnostic standard of this syndrome are still controversial (17, 18). This is because assessment of diastolic function is complex and less reproducible, involving Doppler and tissue Doppler techniques of an array of real-time hemodynamic data, and also because multiple factors such as age, filling pressure, pre- or after-loading condition, heart rate and sympathetic tone affect these Doppler indices and left ventricular diastolic performance. On the other hand, measurement of LA size is simple, highly feasible and reliable in most routine echo studies and reflects overall LA function and left ventricular diastolic performance. In particular, LA volume has been shown to have prognostic values (19, 20) and is highly recommended by major guidelines (3). Unfortunately, patient enrollment for this study started before LA volume assessment was routinely performed in our laboratory, and LA dimension was used instead and was shown to have additive prognostic value to cardiac sympathetic activity, independent of clinical and other echocardiographic functional variable, in HF patients with normal LVEF and LV hypertrophy. LA size is affected by several conditions such as anemia, bradycardia, atrial tachyarrhythmias and mitral valve disease irrespective of the presence of diastolic dysfunction. Nevertheless, LA enlargement may be an overall and cumulative result of increases in left ventricular filling pressure and mass and of abnormal relaxation and
stiffness (21-23), leading to unfavorable clinical outcomes in HF patients without reduced LVEF.

The present study also revealed the powerful prognostic values of cardiac sympathetic innervation assessed by MIBG neuroimaging in HF patients with preserved LVEF as well as in HF patients with left ventricular systolic dysfunction (8-13). Impaired cardiac sympathetic innervation quantified using cardiac MIBG activity was not only a significant independent predictor of cardiac events but was also additively related to adverse outcomes together with LA size. These findings indicate critical roles of combined use of these quantitative markers in better identification of HF patients with preserved LVEF at increased risk. Cardiac MIBG activity is determined by microvasculature and anatomical integrity and functions of pre-synaptic nerve terminals, such as capability of ATP production, uptake-1 and storage systems of norepinephrine (NE), central regulation of sympathetic tone and washout/spill-over as a balance between release and re-uptake of NE (MIBG) molecules (24). The mechanisms behind impairment of cardiac sympathetic innervation leading to unfavorable outcomes in HF patients with preserved LVEF, however, remain to be investigated. Impairment of microcirculation due to increases in filling pressure, myocardial stress, stiffness and mass reduces ATP production in failing hearts, possibly resulting in neuron damage. This is because sympathetic nerve endings are more susceptible to ischemia than are myocytes (25-27). Blunted response of systolic function to exercise stress observed in denervated hearts (28) may elucidate the development of HF with preserved LVEF. Excess stimulation of beta-adrenoeceptors, down-regulated beta-function and post-synaptic denervation supersensitivity (29) are other possible mechanisms responsible for cardiac events in HF patients with preserved LVEF. Thus, alterations of
LA size (remodeling) and cardiac MIBG activity may be associated with prognosis through different mechanisms and probably can occur before ischemia-induced contractile dysfunction becomes manifest.

Limitations

Despite the consecutive enrollment of HF patients without reduced LVEF, the possibility of a selection bias could not be completely ruled out due to the fact that this study was a single-center study using limited number of patients. The relatively good long-term prognosis in Japanese HF patients with preserved LVEF suggests the requirement of a larger population for establishing the presented method. Although non-pharmacological treatment was not indicated in HF patients with preserved LVEF in this study, alterations of drug treatment may have affected clinical outcomes during the long follow-up period. A future study is needed to establish a specific therapeutic strategy in HF patients with preserved systolic function at increased risk who are identified by the presented methods and also to reveal how cardiac MIBG activity and LA size alter interactively in response to therapeutic intervention during the clinical course. The presented quantitative techniques of cardiac MIBG imaging (9, 10) and two-dimensional echocardiography are simple, reproducible and easily available in daily practice. For comparison of the quantitative MIBG index (HMR), however, it is important to understand the type of collimator, study protocol and specific activity of $^{123}$I-MIBG used for the high-quality neuroimaging (30, 31).

CONCLUSIONS

Impairment of cardiac sympathetic innervation is related to unfavorable clinical outcomes independently and synergistically with left atrial enlargement and left
ventricular hypertrophy in HF patients without reduced LVEF. The combined quantitative assessment of echocardiographic left atrial size and cardiac MIBG activity can contribute to better identification of HF patients without reduced LVEF who are at increased risk. Further study is needed to establish etiology-based risk assessment in HF patients at increased risk who have been identified by the presented method.

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Figure Legends

Figure 1  Comparison of quantitative cardiac MIBG parameters between patient groups with and without cardiac events. HMR, heart-to mediastinum ratio of metaiodobenzylguanidine activity.

Figure 2  Receiver operating characteristic (ROC) analysis of late HMR (heart-to mediastinum ratio) of cardiac MIBG activity (left panel) and left atrial dimension (LAD) (right panel), indicating that optimal cutoff values for identifying cardiac events are 1.65 (chi-square value, 65.95; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively.

Figure 3  Kaplan-Meier event-free curves adjusted for age, sex, and use of diuretics and calcium channel-blockers of subgroups classified by a late HMR (heart-to mediastinum ratio) of 1.65 (A), left atrial dimension (LAD) of 37 mm (B) and both (C). Patients with late HMR of less than 1.65 and LAD of 37 mm or more and patients with late HMR of 1.65 or more or LAD of less than 37 mm had a significantly lower event-free rate than did those with late HMR of 1.65 or more and LAD of less than 37 mm; 5-year survival rates were 67.9%, 85.5% and 97.3%, respectively.

Figure 4  Kaplan-Meier event-free curves adjusted for age, and sex, use of diuretics and calcium channel-blockers of subgroups classified by late HMR and left ventricular hypertrophy (LVH).

Figure 5  Echocardiograms of the left atrium and anterior planar MIBG images. (A) A 43-year-old man who had a markedly decreased MIBG activity with a late heart-to mediastinum ratio (HMR) of 1.32 and an increased left atrial dimension (LAD) of 46 mm and who was re-hospitalized due to progression...
of congestive heart failure during a follow-up.

(B) A 38-year-old man who had both maintained HMR (1.92) and a nearly normal LAD (36 mm) and who had no cardiac event during follow-up.
Comparison of quantitative cardiac MIBG parameters between patient groups with and without cardiac events. HMR, heart-to-mediastinum ratio of metaiodobenzyl-guanidine activity.

Figure 1
Receiver operating characteristic (ROC) analysis of late HMR (heart-to-mediastinum ratio) of cardiac MIBG activity (left panel) and left atrial dimension (LAD) (right panel), indicating that optimal cutoff values for identifying cardiac events are 1.65 (chi-square value, 65.95; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively.
Kaplan-Meier event-free curves adjusted for age, sex, and use of diuretics and calcium channel-blockers of subgroups classified by a late HMR (heart-to-mediastinum ratio) of 1.65 (A), left atrial dimension (LAD) of 37 mm (B) and both (C). Patients with late HMR of less than 1.65 and LAD of 37 mm or more and patients with late HMR of 1.65 or more or LAD of less than 37 mm had a significantly lower event-free rate than did those with late HMR of 1.65 or more and LAD of less than 37 mm; 5-year survival rates were 67.9%, 85.5% and 97.3%, respectively.

254x190mm (96 x 96 DPI)
Kaplan-Meier event-free curves adjusted for age, and sex, use of diuretics and calcium channel-blockers of subgroups classified by late HMR and left ventricular hypertrophy (LVH).

254x190mm (96 x 96 DPI)
Echocardiograms of the left atrium and anterior planar MIBG images.

(A) A 43-year-old man who had a markedly decreased MIBG activity with a late heart-to-mediastinum ratio (HMR) of 1.32 and an increased left atrial dimension (LAD) of 46 mm and who was re-hospitalized due to progression of congestive heart failure during a follow-up.

(B) A 38-year-old man who had both maintained HMR (1.92) and a nearly normal LAD (36 mm) and who had no cardiac event during follow-up.

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<td>Heart rate (beats/min)</td>
<td>68.4±12.8</td>
<td>68.5±12.8</td>
<td>0.929</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (14.7%)</td>
<td>20 (13.8%)</td>
<td>0.959</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (26.4%)</td>
<td>34 (23.6%)</td>
<td>0.919</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5 (14.7%)</td>
<td>21 (14.6%)</td>
<td>0.677</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (35.2%)</td>
<td>31 (21.5%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Ventricular tachycardia/Ventricular fibrillation</td>
<td>10 (29.4%)</td>
<td>37 (25.7%)</td>
<td>0.757</td>
</tr>
<tr>
<td>Underlying heart diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart diseases</td>
<td>1 (3.0%)</td>
<td>14 (9.7%)</td>
<td>0.542</td>
</tr>
<tr>
<td>Non-ischemic heart diseases</td>
<td>33 (97.0%)</td>
<td>131 (90.3%)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>18 (53.0%)</td>
<td>38 (26.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACE-I</td>
<td>6 (17.6%)</td>
<td>25 (17.4%)</td>
<td>0.963</td>
</tr>
<tr>
<td>ARB</td>
<td>5 (14.7%)</td>
<td>23 (15.9%)</td>
<td>0.620</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>15 (44.5%)</td>
<td>39 (27.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>14 (41.2%)</td>
<td>57 (39.6%)</td>
<td>0.983</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5 (14.7%)</td>
<td>12 (8.3%)</td>
<td>0.307</td>
</tr>
<tr>
<td>Digitalis</td>
<td>7 (16.2%)</td>
<td>25 (17.4%)</td>
<td>0.727</td>
</tr>
<tr>
<td>Statins</td>
<td>3 (8.8%)</td>
<td>14 (9.7%)</td>
<td>0.923</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs</td>
<td>8 (23.5%)</td>
<td>40 (27.8%)</td>
<td>0.758</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>18 (53.0%)</td>
<td>69 (47.9%)</td>
<td>0.753</td>
</tr>
<tr>
<td>Plasma BNP (pg/dl)</td>
<td>126.4±101.1</td>
<td>129.0±297.2</td>
<td>0.932</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>13.1±2.1</td>
<td>13.1±1.9</td>
<td>0.935</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1±0.9</td>
<td>1.0±1.4</td>
<td>0.891</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>139.6±13.0</td>
<td>138.8±14.2</td>
<td>0.760</td>
</tr>
</tbody>
</table>
Values are shown as means±one standard deviation. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BNP, brain natriuretic peptide.
Table 2. Background cardiac diseases of 34 cardiac events

<table>
<thead>
<tr>
<th></th>
<th>Pump failure (n=7)</th>
<th>Sudden death (n=2)</th>
<th>Re-hospitalization (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>HCM (n=73)</td>
<td>3 (4.1%)</td>
<td>1 (1.4%)</td>
<td>10 (13.7%)</td>
</tr>
<tr>
<td>Valvular (n=41)</td>
<td>3 (7.3%)</td>
<td>1 (2.4%)</td>
<td>3 (7.3%)</td>
</tr>
<tr>
<td>Ischemic (n=15)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (14.6%)</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy
Table 3. Comparison of two-dimensional echocardiographic and Doppler parameters between groups with and without cardiac events

<table>
<thead>
<tr>
<th></th>
<th>Cardiac events group</th>
<th>No cardiac events group</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=34)</td>
<td>(n=144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66.4±8.2</td>
<td>64.1±9.4</td>
<td>50.6~88.0</td>
<td>0.833</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>49.1±10.1</td>
<td>47.6±7.1</td>
<td>33.0~69.9</td>
<td>0.358</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>30.2±8.2</td>
<td>30.4±7.2</td>
<td>14.0~50.5</td>
<td>0.911</td>
</tr>
<tr>
<td>IVSTD (mm)</td>
<td>13.1±4.0</td>
<td>12.2±4.4</td>
<td>5.0~24.0</td>
<td>0.256</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>12.5±3.1</td>
<td>11.1±2.9</td>
<td>5.0~20.1</td>
<td>0.147</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>172.3±10.9</td>
<td>130.2±5.5</td>
<td>61.8~330</td>
<td>0.0008</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>43.8±7.4</td>
<td>36.1±7.4</td>
<td>29.0~62.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>E velocity (m/s)</td>
<td>0.64±0.32</td>
<td>0.65±0.25</td>
<td>0.28~1.7</td>
<td>0.858</td>
</tr>
<tr>
<td>A velocity (m/s)</td>
<td>0.72±0.45</td>
<td>0.63±0.23</td>
<td>0.19~2.17</td>
<td>0.224</td>
</tr>
<tr>
<td>E/A</td>
<td>0.98±0.54</td>
<td>1.02±0.10</td>
<td>0.23~2.43</td>
<td>0.675</td>
</tr>
<tr>
<td>E/A&lt;1.0 / E/A≥1.0</td>
<td>9 / 7 (47.1%)</td>
<td>29 / 42 (49.3%)</td>
<td></td>
<td>0.356</td>
</tr>
<tr>
<td>Dct (msec)</td>
<td>192±50</td>
<td>216±62</td>
<td>124~500</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Values are shown as means±one standard deviation. Dct, deceleration time; LAD, left atrial diameter; LV, left ventricular; LVEF, left ventricular ejection fraction; LVDD, end-diastolic left ventricular diameter; LVDs, end-systolic left ventricular diameter; IVSTD, end-diastolic interventricular septal wall thickness; PWTd, end-diastolic posterior wall thickness.
Table 4. Overall results of univariate and multivariate analyses for all cardiac events (n=178)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.762</td>
<td>8.194</td>
<td>1.38~5.52</td>
<td>0.004</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.658</td>
<td>1.987</td>
<td>0.82~3.30</td>
<td>0.160</td>
</tr>
<tr>
<td>LV mass index</td>
<td>1.007</td>
<td>6.457</td>
<td>1.00~1.01</td>
<td>0.011</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.080</td>
<td>12.45</td>
<td>1.03~1.12</td>
<td>0.0004</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.030</td>
<td>7.381</td>
<td>1.01~1.06</td>
<td>0.007</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.191</td>
<td>7.215</td>
<td>0.06~0.63</td>
<td>0.007</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.075</td>
<td>17.73</td>
<td>0.02~0.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.084</td>
<td>0.019</td>
<td>0.32~1.92</td>
<td>0.890</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.080</td>
<td>4.050</td>
<td>1.00~1.16</td>
<td>0.044</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.107</td>
<td>6.314</td>
<td>0.01~0.61</td>
<td>0.012</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 5. Univariate and multivariate analyses for all cardiac events in patients with left ventricular hypertrophy (n=104)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.165</td>
<td>4.052</td>
<td>1.02~4.59</td>
<td>0.041</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.658</td>
<td>1.661</td>
<td>0.77~3.45</td>
<td>0.197</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.066</td>
<td>5.881</td>
<td>1.01~1.12</td>
<td>0.015</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.030</td>
<td>4.622</td>
<td>1.01~1.06</td>
<td>0.032</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.287</td>
<td>3.598</td>
<td>0.08~1.04</td>
<td>0.058</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.103</td>
<td>11.19</td>
<td>0.02~0.40</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.887</td>
<td>0.037</td>
<td>0.24~2.91</td>
<td>0.8471</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.077</td>
<td>4.381</td>
<td>1.01~1.14</td>
<td>0.0363</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.216</td>
<td>4.549</td>
<td>0.05~0.88</td>
<td>0.0329</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 6. Univariate and multivariate analyses for all cardiac events in patients without left ventricular hypertrophy (n=74)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>4.426</td>
<td>6.877</td>
<td>1.46~9.28</td>
<td>0.0087</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.675</td>
<td>0.876</td>
<td>0.54~4.83</td>
<td>0.349</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.089</td>
<td>2.945</td>
<td>0.98~1.19</td>
<td>0.086</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.034</td>
<td>2.158</td>
<td>0.98~1.08</td>
<td>0.142</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.314</td>
<td>1.792</td>
<td>0.06~1.73</td>
<td>0.186</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.072</td>
<td>9.715</td>
<td>0.01~0.37</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.289</td>
<td>1.889</td>
<td>0.52~5.49</td>
<td>0.1692</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.018</td>
<td>1.607</td>
<td>0.82~1.23</td>
<td>0.2062</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.010</td>
<td>6.391</td>
<td>0.01~0.37</td>
<td>0.0155</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 7. Univariate and multivariate analyses for re-hospitalization due to heart failure progression in patients with left ventricular hypertrophy (n=98)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>( X^2 )</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.912</td>
<td>1.997</td>
<td>0.77~4.63</td>
<td>0.1572</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.938</td>
<td>2.144</td>
<td>0.79~4.73</td>
<td>0.1413</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.081</td>
<td>6.817</td>
<td>1.02~1.13</td>
<td>0.0090</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.039</td>
<td>4.911</td>
<td>1.00~1.07</td>
<td>0.0267</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.147</td>
<td>4.889</td>
<td>0.02~0.80</td>
<td>0.0270</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.049</td>
<td>11.11</td>
<td>0.01~0.31</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>( X^2 )</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.284</td>
<td>0.037</td>
<td>0.42~3.75</td>
<td>0.6433</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.137</td>
<td>4.420</td>
<td>1.01~1.30</td>
<td>0.0355</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.091</td>
<td>7.314</td>
<td>0.01~0.54</td>
<td>0.0068</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 8. Univariate and multivariate analyses for re-hospitalization due to heart failure progression in patients without left ventricular hypertrophy (n=71)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.749</td>
<td>1.452</td>
<td>0.50~14.9</td>
<td>0.228</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.896</td>
<td>0.876</td>
<td>0.03~3.28</td>
<td>0.532</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.132</td>
<td>5.251</td>
<td>0.03~0.22</td>
<td>0.0224</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.021</td>
<td>0.365</td>
<td>0.95~1.09</td>
<td>0.545</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.039</td>
<td>4.288</td>
<td>0.01~0.83</td>
<td>0.0384</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.039</td>
<td>5.876</td>
<td>0.01~0.53</td>
<td>0.0153</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.124</td>
<td>0.016</td>
<td>0.52~5.49</td>
<td>0.1692</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.125</td>
<td>3.465</td>
<td>0.99~1.29</td>
<td>0.0627</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.059</td>
<td>4.221</td>
<td>0.01~0.37</td>
<td>0.0399</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
June 30, 2012/06/30
Adam Timmis, Editor, Heart/BMJ Open

Dear Dr Timmis, Chief Editor:

Thank you for reviewing our manuscript and for the comments and questions. According to your advice and requests, our manuscript was greatly revised by responding the reviewers’ comments and questions point by point, although it took a longer time than we expected. The format was also revised for the *BMJ open*, including structured abstract and article summary. Please look at our answers and revisions shown in red as follows and new tables.

Yours sincerely,

Takahiro Doi, MD
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Sapporo Medical University School of Medicine
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Phone: +81-11-611-2111 Fax: +81-11-644-7958
E-mail: doitaka518@yahoo.co.jp

Number888
To Reviewer#1

1. Patient population and title

REPLY: Authors really understand the reviewer’s points and accept that the diversity of patient backgrounds is a major limitation of this study to investigate heart failure with preserved ejection fraction (HFpEF). Basically, however, the aim of our study was different from so-called HFpEF study, which has been established specifically as one of the heart failure entities. In the past 15 years, a number of studies have demonstrated prognostic efficacies of cardiac sympathetic neuroimaging in heart failure (HF) patients with impaired systolic function. In HF patients with maintained systolic function, however, the prognostic value of cardiac sympathetic innervation has not been fully investigated. As pointed out, this study includes HF patients with LV ejection fraction more than of 50% who had various HF etiologies. This is simply because this study aimed to clarify the prognostic values of cardiac sympathetic function assessed by MIBG activity in HF without systolic LV dysfunction and, therefore, because consecutive HF patients without systolic LV dysfunction who underwent cardiac MIBG imaging independently of background diseases were enrolled in this study. As is well known, irrespective of systolic or diastolic dysfunction, HF syndrome is heterogeneous and the HF concept has been changing depending on alterations of population demographics, background diseases and risk factors for HF. As pointed out, the concept of “heart failure with preserved LV ejection fraction (HFpEF) or with normal ejection fraction (HFNEF)”, has recently been established and has been noted in patients with HFPEF/HFNEF without organic cardiac diseases such valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy (Bursi F, et al. *JAMA*, 2006; 296:2209-16; Paulus WJ, et al. *Eur Heart J* 2007; 28:2539-50; Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM, et al. *N Engl J Med.* 2006; 20;355:251-9). In this study, the specific concept of HFpEF/HFNEF is not necessarily identical to the general meaning of HF with normal LVEF or without reduced LVEF. Hence, since the term of HFpEF/HFNEF would mislead readers, “HFpEF” was deleted from the text and was changed to “chronic heart failure without reduced left ventricular ejection fraction”. The title was also changed and this issue was discussed in the DISCUSSION section as follows.

Title, Page 1

Synergistic prognostic values of cardiac sympathetic innervation with left
ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A cohort study

DISCUSSION, Page 9, the second paragraph

HF syndrome is heterogeneous regardless of systolic or diastolic dysfunction and the concept of HF has been changing depending on alterations of population demographics, background diseases and risk factors for HF. The concept of heart failure with preserved LV ejection fraction (HFpEF) has recently been established as a specific entity of HF in patients without reduced LVEF and organic cardiac diseases such valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. This study, however, was simply designed to test whether cardiac MIBG activity has a long-term prognostic value in consecutive HF patients without systolic dysfunction as already shown in HF patients with reduced LVEF. In this study, it was found that patients with cardiac events had a higher LVMI than did those without cardiac events, that left ventricular hypertrophy was additively related to unfavorable outcomes when cardiac sympathetic innervation was impaired (HMR of less than 1.65) and that LA enlargement was significantly prognostic in patients with left ventricular hypertrophy. These findings are identical to pathophysiological roles of left ventricular hypertrophy often observed in patients with HFpEF (4-7). However, LVMI was not an independent predictor of cardiac events in multivariate Cox analysis, and LA dimension was also not a predictor in patients without left ventricular hypertrophy. Independent of left ventricular hypertrophy (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because left ventricular hypertrophy is common in hypertensive or elderly patients and can be one of caused of diastolic impairment and also because left ventricular hypertrophy is not necessarily a critical determinant of prognosis in patients without reduced LVEF but with impaired cardiac sympathetic activity who do not meet the concept of HFpEF.

2. HF hospitalization and a past history of HF hospitalization

REPLY: As pointed out and as is already known, a past history of HF hospitalization is important for predicting HF progression. Unfortunately, however, because the information was insufficient for analysis in this study, data on a past history of HF hospitalization were not included. Concerning background diseases of cardiac events, new data were added as Table 2, showing that there was no significant difference in background disease among cardiac events; i.e., HCM was not specifically related to HF hospitalization. The following revision was made by adding a new table.
RESULTS, Page 7
During an 80-month follow-up period, primary cardiac events were documented in 34 patients (19%), 7 of whom died of refractory pump failure, 2 of whom had sudden death and 25 of whom had re-admissions due to progression of congestive HF, but non-cardiac death was not documented in this study. There was no significant difference in background disease among cardiac events (Table 2).

3. LA size measurement

REPLY: The authors absolutely agree with the importance of LA volume measurement by two-dimensional echocardiography in HF patients. Unfortunately, patient enrollment for this study started before LA volume assessment rather than LA dimension was widely accepted and routinely performed at our laboratory. This limitation in this study was added to the Discussion section as follows.

Discussion, Page 9 (the third paragraph)- Page 10

………………… and also because multiple factors such as age, filling pressure, pre- or after-loading condition, heart rate and sympathetic tone affect these Doppler indices and left ventricular diastolic performance. On the other hand, measurement of LA size is simple, highly feasible and reliable in most routine echo studies and reflects overall LA function and left ventricular diastolic performance. In particular, LA volume has been shown to have prognostic values (19, 20) and is highly recommended by major guidelines (3). Unfortunately, patient enrollment for this study started before LA volume assessment was routinely performed in our laboratory, and LA dimension was used instead and was shown to have additive prognostic value to cardiac sympathetic activity, independent of clinical and other echocardiographic functional variable, in HF patients with normal LVEF and LV hypertrophy. LA size is affected by several…………

4. ICD and prediction of any aborted sudden death episodes
REPLY: In this study using patients with maintained LVEF, there was no patient treated with ICD. Generally speaking, ICD is indicated for patients with reduced LVEF less than 35%. Therefore, an appropriate ICD shock against lethal arrhythmic events was not one of end points in this study. As shown below, however, our previous studies have already demonstrated the possibility of cardiac MIBG activity for predicting patients at increased risk for ICD shock (lethal arrhythmic events) who can benefit most from the device therapy. This statement was added to the METHODS, Patients population section, Page 5 as follows.

METHODS, Patients population section, Page 5, the first paragraph

None of the patients underwent non-pharmacological treatment such as implantable cardioverter defibrillator or resynchronization therapy.

References

1. Diversity of patient populations and the definition of heart failure with preserved ejection fraction.

**REPLY:** We appreciate the major limitation of this study in terms of a study on heart failure with preserved ejection fraction (HFpEF). Basically, however, the aim of our study was different from so-called HFpEF study, which had been specifically established as one of the heart failure entities. In the past 15 years, a number of studies have demonstrated prognostic efficacies of cardiac MIBG imaging in patients with systolic heart failure (HF). In this study, consecutive HF patients without reduced LVEF were enrolled because this study aimed to clarify the prognostic values of cardiac sympathetic function assessed by MIBG activity in such HF patients. Irrespective of systolic or diastolic function, HF syndrome is clinically heterogeneous.

The concept of “heart failure with preserved LV ejection fraction (HFpEF) or with normal ejection fraction (HFNEF)”, has been noted and defined more specifically as HFPEF/HFNEF without organic cardiac diseases such valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy (Bursi F, et al. *JAMA*. 2006; 296:2209-16; Paulus WJ, et al. *Eur Heart J* 2007; 28:2539-50; Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM, et al. *N Engl J Med*. 2006; 20;355:251-9). In this context, the specific concept of HFPEF/HFNEF is not necessarily identical to the general meaning of HF with normal LVEF used in this study. Hence, since the term of HFPEF/HFNEF may mislead readers, “HFPEF” was deleted from the text and was changed to “chronic heart failure without reduced left ventricular ejection fraction”.

The title was also changed and this issue was discussed in the DISCUSSION section as follows.

**Title, Page 1**

*Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A cohort study*

**DISCUSSION, Page 9, the second paragraph**

Irrespective of systolic or diastolic dysfunction, HF syndrome is heterogeneous.
and HF concept has been changing dependent on alterations of population demographics, background diseases and risk factors for HF. The concept of heart failure with preserved LV ejection fraction (HFpEF) has recently been established as a specific entity of HF in patients without reduced LVEF and organic cardiac diseases such valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. This study, however, was simply designed to test whether cardiac MIBG activity has a long-term prognostic value in consecutive HF patients without systolic dysfunction as already shown in HF patients with reduced LVEF. In this study, patients with cardiac events had more increased LVMI than did those without, left ventricular hypertrophy was additively related to unfavorable outcomes when cardiac sympathetic innervation was impaired (HMR less than 1.65) and LA size enlargement was significantly prognostic in patients with left ventricular hypertrophy. These findings are identical with pathophysiological roles of left ventricular hypertrophy often observed in patients with HFpEF (4-7). However, LVMI was not an independent predictor of cardiac events in multivariate Cox analysis and LA dimension was also not in patients without left ventricular hypertrophy. Independent of left ventricular hypertrophy (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because left ventricular hypertrophy is common in hypertensive or elderly patients and can be one of reasons for diastolic impairment and also because left ventricular hypertrophy is not necessarily a critical determinant of prognosis in patients without reduced LVEF but impaired cardiac sympathetic activity who do not meet the concept of HFpEF.

2. LA size and prognostic values

REPLY: Authors absolutely agree with the importance of LA volume measurement by two-dimensional echocardiography in HF patients. Unfortunately, patient enrollment for this study had started before LA volume assessment rather than LA dimension was widely accepted and routinely performed at our laboratory. This limitation in this study was added to the Discussion section as follows. Although the role of left atrial size in predicting outcome in heart failure has been extensively documented, the prognostic values are limited to patients without atrial fibrillation, significant valvular disease or non-cardiac diseases responsible for left atrial enlargement (Ref 3). The present results clearly showed the synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction.
Discussion, Page 9 (the third paragraph)- Page 10

Doppler indices and left ventricular diastolic performance. On the other hand, measurement of LA size is simple, highly feasible and reliable in most routine echo studies and reflects overall LA function and left ventricular diastolic performance. In particular, LA volume has been shown to have prognostic values (19, 20) and is highly recommended by major guidelines (3). Unfortunately, patient enrollment for this study started before LA volume assessment was routinely performed in our laboratory, and LA dimension was used instead and was shown to have additive prognostic value to cardiac sympathetic activity, independent of clinical and other echocardiographic functional variable, in HF patients with normal LVEF and LV hypertrophy.

3. Re-hospitalization as a single end point for analysis.

REPLY: According to the advice and because of the limited number of other events, re-hospitalization due to HF progression (exclusion of cardiac death) was used as an end-pint. The results of univariate and multivariate analyses were separately presented in new tables (Tables 7 and 8). The results were substantially identical independent of inclusion of cardiac death in patients with and without LV hypertrophy (Table 7 and 8, respectively). The correspond part in the Results section was revised using these data as follows.

Results, Page 8, the first paragraph

and 0.010 (95%CI, 0.01-0.37, p=0.0155) (Table 6), respectively. When re-hospitalization (i.e., exclusion of cardiac death) was considered as a single endpoint for analysis, LAD and late HMR were independent significant determinants in patients with left ventricular hypertrophy (Table 7), but only late HMR was a significant determinant in patients without left ventricular hypertrophy (Table 8).

4. ROC analysis

REPLY: As stated in Statistics (Page 7), we and our statisticians believe that Kaplan-Meier analysis with a log-rank test for survival rate comparisons and univariate and multivariate analyses with a Cox hazard proportional model are the most
appropriate and sufficient for this study. If Reviewer#2 could explain the rationale for
the suggestions and details, the authors will be happy to answer more appropriately and
sincerely.
Review from Heart

1. Kaye David

- The authors report that they examined the prognostic value of cardiac MIBG scanning and echocardiography in patients with heart failure symptoms and a LVEF>50%. Whilst this is potentially a very interesting question, I do not believe the study provides the necessary information to address the question.

Comments:
1. The major issue is that most of the patients described are not consistent with the diagnosis of HFPEF. In particular many patients have other major confounding diagnoses such as HOCM, idiopathic dilated cardiomyopathy, ARVD, congenital HD and sarcoidosis. Each of these conditions have a very varied prognosis.
2. Most of the end-points were HF hospitalisation. Was a past history of HF hospitalisation predictive of readmission? Did the HF admissions occur mainly in the HOCM group? Patients with marked atrial enlargement and HOCM are already at high risk of HF events.
3. LA size should be measured with LA volume as per most guidelines.
4. How many patients had ICDs? Did MIBG predict any aborted sudden death episodes?

2. Marwick, Thomas H
Cleveland Clinic

- In this outcome study, investigators from Sapporo followed 178 consecutive patients presenting with heart failure and preserved ejection fraction who underwent echocardiography and cardiac MIBG imaging. Over a mean period of nearly 80 months, 19% of the patients had cardiac events, and these events were predicted by left atrial dimension(or left ventricular hypertrophy) and heart to mediastinal ratio of MIBG. The authors conclude that these investigations can be used to provide better risk stratification of patients with heart failure and preserved ejection fraction.

The authors have certainly chosen an important and difficult topic which has remained unsolved. They comprise expert echocardiographers and nuclear imagers, and the methodology of the study is appropriate (with exception of the use of left atrial dimension, see below).

Unfortunately there are some major flaws with the study:
1) Patients with heart failure and preserved ejection fraction include 31% of individuals with hypertrophic cardiomyopathy and 23% with valvular heart disease. These, particularly the valvular heart disease, represent a different group to what is normally included in the term heart failure with preserved ejection fraction. Almost certainly, this experience would not be transferable to other centers who use a more restrictive definition of heart failure with preserved ejection fraction to exclude other diagnoses.
2) The authors have used left atrial dimension as their marker of left atrial size. There are two problems here. First, left atrial dimension has been replaced in the guidelines by left atrial volume, because the atrium enlarges in a non-uniform fashion. Additionally, the role of left atrial size in predicting outcome in heart failure has been extensively documented.
3) The investigators used a composite end point of pump failure death, sudden death, and rehospitalization with heart failure. Not only are these outcomes of mixed significance clinically, but the numbers were heavily weighted towards rehospitalization. It is possible that each of these end points may have separate associations with the testing performed.
4) The investigators have used a time dependent analysis for predicting events (which is appropriate), but then use a receiver operating characteristic curve, which usually evaluates events that are binary, rather than time dependent. This should be explained further.
Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A cohort study

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Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A Cohort Study

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Subject headings: LV hypertrophy, LA size and cardiac MIBG activity in heart failure

There is no potential conflict of interest in this study.
Article Summary

Article Focus

Despite clinical efficacies in left ventricular (LV) systolic dysfunction, prognostic value of cardiac sympathetic activity was undetermined in heart failure (HF) without reduced LV ejection fraction. This study tested whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with LV hypertrophy and left atrial (LA) size in HF patients without reduced LV ejection fraction.

Key Messages

LA dimension and cardiac MIBG activity quantified as heart-to-mediastinum ratio (HMR) were significant predictors of 34 cardiac events observed in 178 consecutive HF patients during 80 months in multivariate Cox analysis and identified high-risk patients with a lower event-free rate. In particular, HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LA dimension or LV hypertrophy identified patients at most increased risk.

Strengths and Limitations

Independently and synergistically, LA size and cardiac MIBG activity were associated with cardiac events in HF patients without reduced LV ejection fraction. Despite various etiologies in HF with normal LV ejection fraction, cardiac sympathetic innervation assessment can contribute to better risk-stratification by combining with evaluation of LA size and LV hypertrophy. Future study is needed to establish etiology-based risk assessment and therapeutic strategy in HF patients without reduced LVEF at increased risk.
ABSTRACT

Objectives: This study tested whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with left ventricular hypertrophy (LVH) and left atrial size in heart failure (HF) patients without reduced left ventricular ejection fraction (LVEF).


Setting/Participants: With primary endpoints of cardiac death and re-hospitalization due to HF progression, 178 consecutive symptomatic HF patients with 74% males, mean age of 56 years and mean LVEF of 64.5% were followed up for 80 months. The entry criteria consisted of LVEF more than 50%, completion of pre-discharge clinical evaluations including cardiac MIBG and echocardiographic studies and at least more than one-year follow-up when survived.

Results: Thirty-four patients with cardiac evens had larger left atrial dimension (LAD), increased LV mass index, reduced MIBG activity quantified as heart-to-mediastinum ratio (HMR) than did the others. Multivariable Cox analysis showed that LAD and HMR were significant predictors [hazard ratios of 1.080 (95% CI, 1.00 to 1.16, p=0.044) and 0.107 (95% CI, 0.01 to 0.61, p=0.012, respectively]. Thresholds of HMR (1.65) and LAD (37 mm) were closely related to identification of high-risk patients. In particular, HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LAD or LV hypertrophy identified patients at most increased risk; overall log-rank value, 11.5, p = 0.0032 for LAD and 17.5, p=0.0002, respectively.

Conclusions: In HF patients without reduced LV ejection fraction, impairment of
cardiac sympathetic innervation is related to cardiac outcomes independently and synergistically with LA size and LV hypertrophy. Cardiac sympathetic innervation assessment can contribute to better risk-stratification in combination with evaluation of LA size and LV mass but is needed to be evaluated for establishing etiology-based risk assessment in HF patients at increased risk.
INTRODUCTION

Clinical risks and therapeutic strategy in chronic heart failure (HF) with reduced left ventricular systolic function have been established, whereas 30-40% of patients presenting with symptomatic HF have preserved left ventricular ejection fraction (LVEF) and the high mortality rate has been noted (1-7). Compared to HF patients with depressed LVEF, HF patients with preserved LVEF are less symptomatic, the pathophysiology is not fully understood, and risk-stratification is still limited because of a lack of reproducible and reliable markers for identifying the disease severity. Recent guidelines for the management of HF (1, 2), therefore, have highlighted the importance of recognition ad the differential diagnosis of HF with/without diastolic dysfunction or alternatively preserved systolic function. Left ventricular hypertrophy is one of major reasons for diastolic dysfunction or HF with preserved LVEF. There are several quantitative Doppler indices for identifying diastolic failure and high-risk patients with preserved LVEF but most of them are limited to patients without atrial fibrillation, significant valvular disease or non-cardiac diseases responsible for left atrial enlargement (3).

Alterations of autonomic function have pathophysiological and prognostic implications in systolic heart failure. Excess systemic augmentation of autonomic nervous function is harmful to the heart by triggering and/or exacerbating HF due to myocyte injury and/or myocardial remodeling, leading to sudden cardiac death or lethal pump failure. On the other hand, cardiac neuroimaging with idoin-123 metaiodobenzylguanidine (MIBG) has demonstrated that impairment of cardiac sympathetic innervation is closely relate to unfavorable clinical outcomes in HF patients.
with reduced systolic function not only independently of but also together with LVEF, New York Heart Association (NYHA) functional class, plasma brain natriuretic peptide (BNP) level and coexisting non-cardiac diseases (8-13). In HF patients with preserved LVEF, however, a prognostic value of cardiac sympathetic innervation has not been fully investigated (14, 15).

In this study, we hypothesized that quantitatively assessed cardiac echo index and sympathetic innervation marker can contribute to better prognosis assessment of HF patients with preserved LVEF. We analyzed data from 178 consecutive symptomatic HF patients with LVEF more than 50% who had been followed up for 79.6 months.

METHODS

Patient population

Data on 178 consecutive patients with symptomatic HF and LVEF more than 50% enrolled in our prospective HF cohort study since 1998 were analyzed. Entry criteria for this study as follows: patients who had been followed up regularly at outpatient clinic of our university hospital following conventional echocardiographic and MIBG examinations; patients had congestive HF established by the following clinical symptoms and signs according to the Framingham criteria, typical symptoms (dyspnea or orthopnea), neck vein distension, peripheral edema, lung palpitation, dy) ray findings, such as rales, S3 gallop and tachycardia together with chest X cardiomegaly, bilateral lung congestion and/or pleural effusion; and patients had LVEF dimensional/Doppler -using conventional two more than 50% at admission echocardiography. The following patients were excluded from this study; patients cardiac diseases showing similar symptoms or signs, p had non patients had end-stage renal failure, insulin-dependent diabetes mellitus or neurogenic disorders involving the
autonomic nervous system, patients who had been treated with tricyclic antidepressant
drugs, sympathomimetic agents or other drugs known to interfere with cardiac MIBG
uptake, and patients who were scheduled to undergo any cardiac surgery were excluded
from this study. When clinical conditions were stabilized after admission, patients were
enrolled in this study and underwent cardiac MIBG imaging and blood tests. Informed
consent for participation in this study was obtained in accordance with the guidelines of
the ethics committee of our hospital. Table 1 shows clinical backgrounds and results of
baseline examinations. Underlying heart diseases of HF were as follows: 15 patients
(8.4%) had ischemic heart disease and the remaining 163 patients (91.6%) had
non-ischemic heart diseases, including idiopathic dilated cardiomyopathy (n=23,
12.9%), hypertrophic cardiomyopathy (n=73, 41.0%), arrhythmogenic right ventricular
cardiomyopathy (n=13, 7.3%), hypertensive heart disease (n=8, 4.5%), valvular heart
disease (n=41, 23.0%) and others (n=5, 2.8%). No patients underwent
non-pharmacological treatment such as implantable cardioverter defibrillator or
resynchronization therapy.
Cardiac MIBG imaging

Cardiac MIBG imaging was performed at a stable condition during
hospitalization within two weeks from echocardiographic examination using \(^{123}\text{I-MIBG}\)
of 111 MBq with a high specific activity (9-11) before discharge. Cardiac planar and
tomographic MIBG images were obtained at the fasting and at resting condition 15–30
minutes (early) and 4 hours (late) after an intravenous tracer injection using a gamma
camera equipped with a low-energy, general-purpose collimator. Cardiac \(^{123}\text{I-MIBG}\)
activity was quantified as a heart-to-mediastinum ratio (HMR) by manually setting a
region of interest on the upper mediastinum and the whole cardiac region on a planar
image from an anterior projection by an experienced nuclear medicine technician who
did not know any clinical data. $^{123}$I-MIBG washout kinetics from the heart was also
calculated as washout rate (WR) using a polar-map technique with tomographic data
because of the elimination of background activity. Our previous studies (9-11) showed
high reproducibilities of this quantitative method.

Conventional echocardiographic examination

Standard two-dimensional echocardiographic examination was performed by
experienced cardiologists in our echocardiography laboratory using commercially
available ultrasound machines (SSH-160A, Toshiba, Tokyo, Japan; SSD760, Aloka,
Tokyo, Japan; SONOS 2500, Hewlett-Packard, Andover, Massachusetts, USA; Vivid 7,
General Electric Medical Systems, Milwaukee, WI, USA) that were each equipped with
a 2.5-MHz variable frequency transducer. Two-dimensional and pulsed Doppler
imaging modes were used from apical four-, three- and two-chamber views at a left
lateral decubitus position. Left atrial (LA) dimension (LAD, mm) was measured by
M-mode echocardiography. Standard two-dimensional measurements (LV end-diastolic
and end-systolic dimensions and septal and posterior wall thicknesses at end-diastole)
were determined and then LV mass index was calculated using the American Society of
Echocardiography recommended formula (16) and was normalized for body surface
area (LVMI, g/m$^2$). Left ventricular hypertrophy was defined as the LVMI more than
115 g/m$^2$ for men and more than 95 g/m$^2$ for female. LVEF was measured using the
biplane modified Simpson’s method. Trans-mitral flow velocities were obtained by
pulsed-wave Doppler echocardiography, positioning a sample volume at the level of a
mitral tip in an apical four-chamber view. Mitral flow parameters, including peak
velocities at early diastole (E) and at late diastole (A) and deceleration time of E (Dct),
were measured and then E/A was calculated. Pulsed-wave Doppler signals were obtained at a sweep speed of 100 mm/s.

Laboratory data assessment

Blood sampling for measurements of plasma BNP level, hemoglobin and serum concentrations of sodium and creatinine was done from an intravenous cannula in a spine position when cardiac MIBG imaging was performed. Samples used for measurements of BNP were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator units/ml) and immediately placed on ice and centrifuged at 4°C. The concentration was measured by a specific immunoradiometric assay using a commercial kit (Shionogi, Osaka, Japan) (11).

Follow-up protocol

After discharge, all patients were prospectively followed for at least every 3 months for a mean period of 79.6 months at the outpatient clinic of our university hospital by cardiologists who determined necessity of blood tests, electrocardiography, chest X-ray, echocardiography or other examinations. The primary endpoints were fatal or near-fatal cardiac events consisting of pump failure death, sudden cardiac death and re-hospitalization due to progression of congestive HF for necessity of intense medical treatment, including intravenous drug infusion, oxygenation and respiratory control and/or use of assist device. All cardiac events were confirmed using medical records after final diagnosis was made. The first cardiac event was used for the prognosis analysis when one of the above-mentioned primary end-points was observed during follow-up. Sudden cardiac death was defined as witnessed cardiac arrest and death within 1 hour after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 hours. Patient who had undergone implantable
cardioverter defibrillator therapy were not included in this study.

Statistics

Statistical values are shown as means ± 1 SD. Mean values were compared between the two groups using the unpaired \( t \)-test, and the prevalence was compared using the chi-square test. A p-value less than 0.05 was considered significant. Following univariate analysis, multivariate analysis with a Cox hazard proportional model was carried out using the statistically appropriate number of significant variables identified by univariable analysis, which depended on incidence of cardiac events. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of an independent significant parameter. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. These analyses were performed using a computer software program, SPSS statistical program package (SPSS version 11.0, SPSS Inc., Chicago, IL).

Depending on the distribution, continuous variables are presented as means ± standard deviation (mean ± SD) with one decimal point. Mean values were compared between the two groups using the unpaired \( t \)-test, and the prevalence was compared using Fisher’s exact test where appropriate. Univariate and multivariate Cox proportional hazards regression models was used to examine the association between the incidence of cardiac events and potential confounding factors. Variables that were significantly associated with the cardiac events at univariate analysis were included in the multivariate models if \( p \) was <0.05. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. Receiver operating characteristic (ROC)
analysis was performed to determine the optimal cutoff value of an independent
significant parameter. In this prospective cohort study, all clinical data obtained at entry
were used for this study as far as patients met entry criteria. If a patient was lost to
follow-up during the study period more than one year, follow-up data were dealt with as
discontinued data at the time when patient outcome was confirmed. These analyses
were performed using a computer software program, SPSS statistical program package
(SPSS version 11.0, SPSS Inc., Chicago, IL).

RESULTS

Table 1 shows clinical backgrounds and results of baseline examinations. Underlying heart diseases of HF were as follows: 15 patients (8.4%) had ischemic heart disease and the remaining 163 patients (91.6%) had non-ischemic heart diseases, including idiopathic dilated cardiomyopathy (n=23, 12.9%), hypertrophic cardiomyopathy (n=73, 41.0%), arrhythmogenic right ventricular cardiomyopathy (n=13, 7.3%), hypertensive heart disease (n=8, 4.5%), valvular heart disease (n=41, 23.0%) and others (n=5, 2.8%). No patients underwent non-pharmacological treatment such as implantable cardioverter defibrillator or resynchronization therapy. During a 80-month follow-up period, primary cardiac events were documented in 34 patients (19%), 7 of whom died of refractory pump failure, 2 of whom had sudden death and 25 of whom had re-admissions due to progression of congestive HF but non-cardiac death was not documented in this study. Thereafter, 4 of the 25 patients with re-hospitalization due to progression of congestive HF had cardiac death as the second events (one sudden cardiac death and 3 due to pump failure). There was no significant difference in background disease among cardiac events (Table 2). Although patients
with cardiac events were more frequently treated with diuretics and calcium channel blockers than those without cardiac events, there was no significant difference in any clinical or laboratory data between groups with and without cardiac events (Table 1).

There was no significant difference in two-dimensional or Doppler echocardiographic functional parameters between the two groups with and without cardiac events (Table 3). LVMI and LAD in the cardiac event group were, however, significantly greater than those in the non-cardiac event group; 172.3 ± 10.9 vs. 130.2 ± 5.5 g/m², p = 0.0008 and 43.8 ± 7.4 vs. 36.1 ± 7.4 mm, p<0.0001, respectively. On the other hand, the cardiac event group had significantly reduced cardiac MIBG activities (early HMR; 1.86 ± 0.38 vs. 2.00 ± 0.31, p = 0.041; late HMR; 1.64 ± 0.35 vs. 1.89 ± 0.33 p = 0.0003, respectively) and a significantly greater washout rate (40.3 ± 9.1% versus 32.3 ± 12.9%, p = 0.0027) than those in the non-cardiac event group (Figure 1).

Table 4 summarizes overall results of univariate and multivariate analyses using six parameters that were found to be significantly different between the two groups. Based on the significant results of univariate analysis and because of the number (34) of cardiac events in the present study, multivariate Cox analysis was performed using the top three variables in the univariate results; diuretics use, LAD and late HMR. LAD and late HMR were identified to be independent significant determinants of cardiac events with hazard ratios of 1.080 (95%CI, 1.00-1.16) for LAD (p=0.044) and 0.107 (95%CI, 0.01-0.61) for late HMR (p = 0.012) (Table 4). Late HMR was a significant determinant of cardiac events for both patient groups with and without left ventricular hypertrophy; hazard ratios of 0.167 (95%CI, 0.05-0.52, p=0.047) (Table 5) and 0.010 (95%CI, 0.01-0.37, p=0.0155) (Table 6), respectively. When re-hospitalization (i.e., exclusion of
cardiac death) was considered as a single end-point for analysis, LAD and late HMR were independent significant determinants in patients with left ventricular hypertrophy (Table 7) but only late HMR was a significant determinant in patients without left ventricular hypertrophy (Table 8).

ROC analysis determined optimal thresholds of late HMR and LAD for identifying cardiac events to be 1.65 (chi-square value, 65.95; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively (Figure 2). When adjusted by age, sex, diuretics and calcium channel-blockers, patients with late HMR less than 1.65 or LAD of 37 mm or more had significantly lower event-free rates than did those without (Figure 3 A and B). When patients were divided into three subgroups using the cutoff values of late HMR and LAD, there were significant differences in event-free rate among the three subgroups and particularly patients with late HMR less than 1.65 and LAD of 37 mm or more had the lowest event-free rate (Figure 3C). When, instead of LAD, left ventricular hypertrophy was used for prognosis analysis, patients with both reduced HMR and LVH had the lowest event-free rate among the subgroups (Figure 4). Figure 5 demonstrates echocardiograms and cardiac planar MIBG images of two cases; one is from a 43-year-old man with a markedly reduced HMR (1.32) and an increased LAD (46 mm) who was admitted for intense medical therapy due to pump failure and the other is from a 38 year-old male with relatively preserved HMR (1.92) and a nearly normal LAD (36 mm) in whom any cardiac event was documented.

DISCUSSION

The present study clearly demonstrated that echocardiographic enlargement of LA size and impaired cardiac sympathetic innervation assessed by MIBG activity are
independently and additively related to unfavorable clinical outcomes in HF patients without reduced LVEF. Assessment of LA size and cardiac sympathetic innervation can contribute to better risk-stratification of HF patients without reduced LVEF who are at increased risk and probably can benefit most from aggressive medical treatment.

Irrespective of systolic or diastolic dysfunction, HF syndrome is heterogeneous and HF concept has been changing dependent on alterations of population demographics, background diseases and risk factors for HF. The concept of heart failure with preserved LV ejection fraction (HFpEF) has recently been established as a specific entity of HF in patients without reduced LVEF and organic cardiac diseases such as valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. This study, however, was simply designed to test whether cardiac MIBG activity has a long-term prognostic value in consecutive HF patients without systolic dysfunction as already shown in HF patients with reduced LVEF. In this study, patients with cardiac events had more increased LVMI than did those without, left ventricular hypertrophy was additively related to unfavorable outcomes when cardiac sympathetic innervation was impaired (HMR less than 1.65) and LA size enlargement was significantly prognostic in patients with left ventricular hypertrophy. These findings are identical with pathophysiological roles of left ventricular hypertrophy often observed in patients with HFpEF (4-7). However, LVMI was not an independent predictor of cardiac events in multivariate Cox analysis and LA dimension was also not in patients without left ventricular hypertrophy. Independent of left ventricular hypertrophy (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because left ventricular hypertrophy is common in hypertensive or elderly patients and can be one of reasons for diastolic impairment and also because left
ventricular hypertrophy is not necessarily a critical determinant of prognosis in patients without reduced LVEF but impaired cardiac sympathetic activity who do not meet the concept of HFpEF.

Many studies have demonstrated the prognostic values of Doppler diastolic measurements such as E/A ratio, deceleration time, S/D ratio or E/e’ in HF patients with depressed LVEF but there were a few data available in HF patients with preserved LVEF (3). Diastolic dysfunction in HF patients with normal LVEF and diagnostic standard of this syndrome is still controversial (17, 18). This is because assessment of diastolic function is complex and less reproducible, involving Doppler and tissue Doppler techniques of an array of real-time hemodynamic data, and also because multiple factors such as age, filling pressure, pre- or after-loading condition, heart rate and sympathetic tone affect these Doppler indices and left ventricular diastolic performance. On the other hand, LA size is simple, highly feasible and reliable in most routine echo studies and reflects overall LA function and left ventricular diastolic performance. In particular, LA volume has been shown to have prognostic values (19, 20) and is highly recommended by the major guidelines (3). Although unfortunately patient enrollment for this study had started before LA volume assessment was routinely performed at our laboratory, LA dimension was used instead and shown to have additive prognostic values to cardiac sympathetic activity, independent of clinical and other echocardiographic functional variables in HF patients with normal LVEF and LV hypertrophy. LA size is affected by several conditions such as anemia, bradycardia, atrial tachyarrhythmias and mitral valve disease irrespective of the presence of diastolic dysfunction. Nevertheless, LA enlargement may function as overall and cumulative results of increases in left ventricular filling pressure and mass and of abnormal
relaxation and stiffness (21-23), leading to unfavorable clinical outcomes in HF patients without reduced LVEF.

The presented study also revealed the powerful prognostic values of cardiac sympathetic innervation assessed by MIBG neuroimaging in HF patients with preserved LVEF as well as in HF patients with left ventricular systolic dysfunction (8-13). Impaired cardiac sympathetic innervation quantified using cardiac MIBG activity was not only a significant independent predictor of cardiac events but also was additively related to adverse outcomes together with LA size. These findings indicate critical roles of combined use of these quantitative markers on better identification of HF patients with preserved LVEF at increased risk. Cardiac MIBG activity is determined by microvasculature and anatomical integrity and functions of pre-synaptic nerve terminals, such as capability of ATP production, the uptake-1 and storage systems of norepinephrine (NE), central regulation of sympathetic tone and washout/spill-over as a balance between release and re-uptake of NE (MIBG) molecules (24). The mechanisms behind impairment of cardiac sympathetic innervation leading to unfavorable outcomes in HF patients with preserved LVEF, however, remain to be investigated. Impairment of microcirculation due to increases in filling pressure, myocardial stress, stiffness and mass reduces ATP production in failing hearts, possibly resulting in neuron damage. This is because sympathetic nerve endings are more susceptible to ischemia than myocytes (25-27). Blunted response of systolic function to exercise stress observed in denervated hearts (28) may elucidate the development of HF with preserved LVEF. Excess stimulation of beta-adrenoceptor, down-regulated beta-function and post-synaptic denervation supersensitivity (29) are other possible mechanisms responsible for cardiac events in HF patients with preserved LVEF. Thus, alterations of
LA size (remodeling) and cardiac MIBG activity may be associated with prognosis through different mechanisms and probably can occur before ischemia-induced contractile dysfunction becomes manifest.

Limitations

Despite the consecutive enrollment of HF patients without reduced LVEF, selection bias could not be completely ruled out due to a single-center study using the limited number of patients. The relatively better long-term prognosis in Japanese HF patients with preserved LVEF suggest requirement of a larger population for establishing the presented method. In this long-term follow-up study, four patients with re-hospitalization due to progression of congestive HF as the first events had cardiac death as the second events (one sudden cardiac death and 3 due to pump failure). Because this study used the first cardiac events for prognosis analysis, the results may have been biased or significant variables identified here such as MIBG and LAD might have a greater impact on cardiac death than shown in this analysis. Although non-pharmacological treatment was not indicated in HF patients with preserved LVEF in this study, alterations of drug treatment may have affected clinical outcomes during a long-term follow-up interval. A future study is needed to establish specific therapeutic strategy in HF patients with preserved systolic function at increased risk who are identified by the presented methods and also to reveal how cardiac MIBG activity and LA size alter interactively in response to therapeutic intervention during a clinical course. The presented quantitative techniques of cardiac MIBG imaging (9, 10) are reproducible and two-dimensional echocardiography is simple and easily applicable in daily practice. It is, however, essential to standardize quantitative techniques of high-quality cardiac MIBG imaging, including a type of collimator, imaging protocol
and specific activity of $^{123}$I-MIBG, for multicenter study (30, 31).

CONCLUSIONS

Impairment of cardiac sympathetic innervation are related to unfavorable clinical outcomes independently and synergistically with left atrial enlargement and left ventricular hypertrophy in HF patients without reduced LVEF. The combined quantitative assessment of echocardiographic left atrial size and cardiac MIBG activity can contribute to better identification of HF patients without reduced LVEF at increased risk. Future study is needed to establish etiology-based risk assessment in HF patients at increased risk identified the presented method.

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Figure Legends

Figure 1 Comparison of quantitative cardiac MIBG parameters between patient groups with and without cardiac events. HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity.

Figure 2 Receiver operating characteristic (ROC) analysis of late HMR (heart-to-mediastinum ratio) of cardiac MIBG activity (left panel) and left atrial dimension (LAD) (right panel), indicating that optimal cutoff values for identifying cardiac events are 1.65 (chi-square value, 659.59; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively.

Figure 3 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by a late HMR (heart-to-mediastinum ratio) of 1.65 (A), left atrial dimension (LAD) of 37 mm (B) and the both (C). Patients with late HMR less than 1.65 and LAD of 37 mm or more and patients with late HMR of 1.65 or more or LAD less than 37 mm had a significantly lower event-free rate than did those with late HMR of 1.65 or more and LAD less than 37 mm; 5-year survival rates were 67.9%, 85.5% and 97.3%, respectively.

Figure 4 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by late HMR and left ventricular hypertrophy (LVH).

Figure 5 Echocardiograms of left atrium and anterior planar MIBG images. (A) A 43-year-old man had a markedly decreased MIBG activity with a late heart-to-mediastinum ratio (HMR) of 1.32 and an increased left atrial dimension (LAD) of 46 mm who was re-hospitalized due to progression of
congestive heart failure during a follow-up.

(B) A 38-year-old man had both maintained HMR (1.92) and a nearly normal LAD (36 mm) who had no cardiac event during a follow-up.

Table 1. Comparison of clinical data between groups with and without cardiac events

<table>
<thead>
<tr>
<th></th>
<th>Cardiac events group (n=34)</th>
<th>No cardiac events group (n=144)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>58.2±14.6</td>
<td>55.1±14.6</td>
<td>0.312</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>17/17</td>
<td>90/54</td>
<td>0.147</td>
</tr>
<tr>
<td>NYHA (I/II/III/IV)</td>
<td>19/9/4/2</td>
<td>113/22/4/5</td>
<td>0.326</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>22.7±7.0</td>
<td>22.8±6.1</td>
<td>0.855</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.8±25.9</td>
<td>129.3±21.0</td>
<td>0.519</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73.3±19.2</td>
<td>75.7±13.3</td>
<td>0.572</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.4±12.8</td>
<td>68.5±12.8</td>
<td>0.929</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (14.7%)</td>
<td>20 (13.8%)</td>
<td>0.590</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (26.4%)</td>
<td>34 (23.6%)</td>
<td>0.466</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5 (14.7%)</td>
<td>21 (14.6%)</td>
<td>0.583</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (35.2%)</td>
<td>31 (21.5%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Ventricular tachycardia/Ventricular fibrillation</td>
<td>10 (29.4%)</td>
<td>37 (25.7%)</td>
<td>0.439</td>
</tr>
<tr>
<td>Underlying heart diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart diseases</td>
<td>1 (3.0%)</td>
<td>14 (9.7%)</td>
<td>0.203</td>
</tr>
<tr>
<td>Non-ischemic heart diseases</td>
<td>33 (97.0%)</td>
<td>131 (90.3%)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>18 (53.0%)</td>
<td>38 (26.4%)</td>
<td>0.025</td>
</tr>
<tr>
<td>ACE-I</td>
<td>6 (17.6%)</td>
<td>25 (17.4%)</td>
<td>0.571</td>
</tr>
<tr>
<td>ARB</td>
<td>5 (14.7%)</td>
<td>23 (15.9%)</td>
<td>0.557</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>15 (44.5%)</td>
<td>39 (27.1%)</td>
<td>0.126</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>14 (41.2%)</td>
<td>57 (39.6%)</td>
<td>0.520</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5 (14.7%)</td>
<td>12 (8.3%)</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>Pump failure (n=7)</td>
<td>Sudden death (n=2)</td>
<td>Re-hospitalization (n=25)</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Hypertensive (n=7)</strong></td>
<td>1 (14.3%)</td>
<td>0 (0%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>HCM (n=73)</td>
<td>3 (4.1%)</td>
<td>1 (1.4%)</td>
<td>10 (13.7%)</td>
</tr>
<tr>
<td>Valvular (n=41)</td>
<td>3 (7.3%)</td>
<td>1 (2.4%)</td>
<td>3 (7.3%)</td>
</tr>
<tr>
<td>Ischemic (n=15)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Miscellaneous (41)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (14.6%)</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy

Values are shown as mean±one standard deviation or for categorical is number of observation and (percentages). The p-values are from t-test or Fisher’s exact test. ACE-I, angiotensin-converting enzyme-inhibitors; ARB, angiotensin-receptor blockers; BNP, brain natriuretic peptide.

Table 2. Background cardiac diseases of 34 cardiac events
Table 3. Comparison of two-dimensional echocardiographic and Doppler parameters between groups with and without cardiac events

<table>
<thead>
<tr>
<th></th>
<th>Cardiac events group</th>
<th>No cardiac events group</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=34)</td>
<td>(n=144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66.4±8.2</td>
<td>64.1±9.4</td>
<td>50.6~88.0</td>
<td>0.833</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>49.1±10.1</td>
<td>47.6±7.1</td>
<td>33.0~69.9</td>
<td>0.358</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>30.2±8.2</td>
<td>30.4±7.2</td>
<td>14.0~50.5</td>
<td>0.911</td>
</tr>
<tr>
<td>IVSTd (mm)</td>
<td>13.1±4.0</td>
<td>12.2±4.4</td>
<td>5.0~24.0</td>
<td>0.256</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>12.5±3.1</td>
<td>11.1±2.9</td>
<td>5.0~20.1</td>
<td>0.147</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>172.3±10.9</td>
<td>130.2±5.5</td>
<td>61.8~330</td>
<td>0.0008</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>43.8±7.4</td>
<td>36.1±7.4</td>
<td>29.0~62.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>E velocity (m/s)</td>
<td>0.64±0.32</td>
<td>0.65±0.25</td>
<td>0.28~1.7</td>
<td>0.858</td>
</tr>
<tr>
<td>A velocity (m/s)</td>
<td>0.72±0.45</td>
<td>0.63±0.23</td>
<td>0.19~2.17</td>
<td>0.224</td>
</tr>
<tr>
<td>E/A</td>
<td>0.98±0.54</td>
<td>1.02±0.10</td>
<td>0.23~2.43</td>
<td>0.675</td>
</tr>
<tr>
<td>E/A&lt;1.0 / E/A≥1.0</td>
<td>9 / 7</td>
<td>29 / 42</td>
<td></td>
<td>0.325</td>
</tr>
<tr>
<td></td>
<td>(47.1%)</td>
<td>(49.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dct (msec)</td>
<td>192±50</td>
<td>216±62</td>
<td>124~500</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Values are shown as means±one standard deviation. Dct, deceleration time; LAD, left atrial diameter; LV, left ventricular; LVEF, left ventricular ejection fraction; LVDd, end-diastolic left ventricular diameter; LVDs, end-systolic left ventricular diameter; IVSTd, end-diastolic interventricular septal wall thickness; PWTd, end-diastolic posterior wall thickness.
Table 4. Overall results of univariate and multivariate analyses for all cardiac events (n=178)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.762</td>
<td>8.194</td>
<td>1.38~5.52</td>
<td>0.004</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.658</td>
<td>1.987</td>
<td>0.82~3.30</td>
<td>0.160</td>
</tr>
<tr>
<td>LV mass index</td>
<td>1.007</td>
<td>6.457</td>
<td>1.00~1.01</td>
<td>0.011</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.080</td>
<td>12.45</td>
<td>1.03~1.12</td>
<td>0.0004</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.030</td>
<td>7.381</td>
<td>1.01~1.06</td>
<td>0.007</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.191</td>
<td>7.215</td>
<td>0.06~0.63</td>
<td>0.007</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.075</td>
<td>17.73</td>
<td>0.02~0.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.084</td>
<td>0.019</td>
<td>0.32~1.92</td>
<td>0.890</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.080</td>
<td>4.050</td>
<td>1.00~1.16</td>
<td>0.044</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.107</td>
<td>6.314</td>
<td>0.01~0.61</td>
<td>0.012</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 5. Univariate and multivariate analyses for all cardiac events in patients with left ventricular hypertrophy (n=104)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.165</td>
<td>4.052</td>
<td>1.02~4.59</td>
<td>0.041</td>
</tr>
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<td>Use of CCB</td>
<td>1.658</td>
<td>1.661</td>
<td>0.77~3.45</td>
<td>0.197</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.066</td>
<td>5.881</td>
<td>1.01~1.12</td>
<td>0.015</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.030</td>
<td>4.622</td>
<td>1.01~1.06</td>
<td>0.032</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.287</td>
<td>3.598</td>
<td>0.08~1.04</td>
<td>0.058</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.103</td>
<td>11.19</td>
<td>0.02~0.40</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.887</td>
<td>0.037</td>
<td>0.24~2.91</td>
<td>0.8471</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.077</td>
<td>4.381</td>
<td>1.01~1.14</td>
<td>0.0363</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.216</td>
<td>4.549</td>
<td>0.05~0.88</td>
<td>0.0329</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 6. Univariate and multivariate analyses for all cardiac events in patients without left ventricular hypertrophy (n=74)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>4.426</td>
<td>6.877</td>
<td>1.46~9.28</td>
<td>0.0087</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.675</td>
<td>0.876</td>
<td>0.54~4.83</td>
<td>0.349</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.089</td>
<td>2.945</td>
<td>0.98~1.19</td>
<td>0.086</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.034</td>
<td>2.158</td>
<td>0.98~1.08</td>
<td>0.142</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.314</td>
<td>1.792</td>
<td>0.06~1.73</td>
<td>0.186</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.072</td>
<td>9.715</td>
<td>0.01~0.37</td>
<td>0.0018</td>
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</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>χ²</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.289</td>
<td>1.889</td>
<td>0.52~5.49</td>
<td>0.1692</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.018</td>
<td>1.607</td>
<td>0.82~1.23</td>
<td>0.2062</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.010</td>
<td>6.391</td>
<td>0.01~0.37</td>
<td>0.0155</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 7. Univariate and multivariate analyses for re-hospitalization due to heart failure progression in patients with left ventricular hypertrophy (n=98)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.912</td>
<td>1.997</td>
<td>0.77~4.63</td>
<td>0.1572</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.938</td>
<td>2.144</td>
<td>0.79~4.73</td>
<td>0.1413</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.081</td>
<td>6.817</td>
<td>1.02~1.13</td>
<td>0.0090</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.039</td>
<td>4.911</td>
<td>1.00~1.07</td>
<td>0.0267</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.147</td>
<td>4.889</td>
<td>0.02~0.80</td>
<td>0.0270</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.049</td>
<td>11.11</td>
<td>0.01~0.31</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.284</td>
<td>0.037</td>
<td>0.42~3.75</td>
<td>0.6433</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.137</td>
<td>4.420</td>
<td>1.01~1.30</td>
<td>0.0355</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.091</td>
<td>7.314</td>
<td>0.01~0.54</td>
<td>0.0068</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Table 8. Univariate and multivariate analyses for re-hospitalization due to heart failure progression in patients without left ventricular hypertrophy (n=71)

(A) Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>2.749</td>
<td>1.452</td>
<td>0.50~14.9</td>
<td>0.228</td>
</tr>
<tr>
<td>Use of CCB</td>
<td>1.896</td>
<td>0.876</td>
<td>0.03~3.28</td>
<td>0.532</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.132</td>
<td>5.251</td>
<td>0.03~0.22</td>
<td>0.0224</td>
</tr>
<tr>
<td>Washout rate</td>
<td>1.021</td>
<td>0.365</td>
<td>0.95~1.09</td>
<td>0.545</td>
</tr>
<tr>
<td>Early HMR</td>
<td>0.039</td>
<td>4.288</td>
<td>0.01~0.83</td>
<td>0.0384</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.039</td>
<td>5.876</td>
<td>0.01~0.53</td>
<td>0.0153</td>
</tr>
</tbody>
</table>

(B) Multivariate analysis following the univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>$\chi^2$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of diuretics</td>
<td>1.124</td>
<td>0.016</td>
<td>0.52~5.49</td>
<td>0.1692</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.125</td>
<td>3.465</td>
<td>0.99~1.29</td>
<td>0.0627</td>
</tr>
<tr>
<td>Late HMR</td>
<td>0.059</td>
<td>4.221</td>
<td>0.01~0.37</td>
<td>0.0399</td>
</tr>
</tbody>
</table>

CCB, calcium channel blockers; CI, confidence interval; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.
Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: A Cohort Study

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Subject headings: LV hypertrophy, LA size and cardiac MIBG activity in heart failure

There is no potential conflict of interest in this study.
Article Summary

Article Focus

Despite clinical efficacies in left ventricular (LV) systolic dysfunction, prognostic value of cardiac sympathetic activity was undetermined in heart failure (HF) without reduced LV ejection fraction. This study tested whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with LV hypertrophy and left atrial (LA) size in HF patients without reduced LV ejection fraction.

Key Messages

LA dimension and cardiac MIBG activity quantified as heart-to-mediastinum ratio (HMR) were significant predictors of 34 cardiac events observed in 178 consecutive HF patients during 80 months in multivariate Cox analysis and identified high-risk patients with a lower event-free rate. In particular, HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LA dimension or LV hypertrophy identified patients at most increased risk.

Strengths and Limitations

Independently and synergistically, LA size and cardiac MIBG activity were associated with cardiac events in HF patients without reduced LV ejection fraction. Despite various etiologies in HF with normal LV ejection fraction, cardiac sympathetic innervation assessment can contribute to better risk-stratification by combining with evaluation of LA size and LV hypertrophy. Future study is needed to establish etiology-based risk assessment and therapeutic strategy in HF patients without reduced LVEF at increased risk.
ABSTRACT

Objectives: This study tested whether cardiac sympathetic innervation assessed by metaiodobenzylguanidine (MIBG) activity has long-term prognostic value in combination with left ventricular hypertrophy (LVH) and left atrial size in heart failure (HF) patients without reduced left ventricular ejection fraction (LVEF).


Setting/Participants: With primary endpoints of cardiac death and re-hospitalization due to HF progression, 178 consecutive symptomatic HF patients with 74% males, mean age of 56 years and mean LVEF of 64.5% were followed up for 80 months. The entry criteria consisted of LVEF more than 50%, completion of pre-discharge clinical evaluations including cardiac MIBG and echocardiographic studies and at least more than one-year follow-up when survived.

Results: Thirty-four patients with cardiac events had larger left atrial dimension (LAD), increased LV mass index, reduced MIBG activity quantified as heart-to-mediastinum ratio (HMR) than did the others. Multivariable Cox analysis showed that LAD and HMR were significant predictors [hazard ratios of 1.080 (95% CI, 1.00 to 1.16, p=0.044) and 0.107 (95% CI, 0.01 to 0.61, p=0.012, respectively]. Thresholds of HMR (1.65) and LAD (37 mm) were closely related to identification of high-risk patients. In particular, HMR was a significant determinant of cardiac events in both patients with and without LV hypertrophy. Reduced HMR with enlarged LAD or LV hypertrophy identified patients at most increased risk; overall log-rank value, 11.5, p = 0.0032 for LAD and 17.5, p=0.0002, respectively.

Conclusions: In HF patients without reduced LV ejection fraction, impairment of
cardiac sympathetic innervation is related to cardiac outcomes independently and synergistically with LA size and LV hypertrophy. Cardiac sympathetic innervation assessment can contribute to better risk-stratification in combination with evaluation of LA size and LV mass but is needed to be evaluated for establishing etiology-based risk assessment in HF patients at increased risk.
INTRODUCTION

Clinical risks and therapeutic strategy in chronic heart failure (HF) with reduced left ventricular systolic function have been established, whereas 30-40% of patients presenting with symptomatic HF have preserved left ventricular ejection fraction (LVEF) and the high mortality rate has been noted (1-7). Compared to HF patients with depressed LVEF, HF patients with preserved LVEF are less symptomatic, the pathophysiology is not fully understood, and risk-stratification is still limited because of a lack of reproducible and reliable markers for identifying the disease severity. Recent guidelines for the management of HF (1, 2), therefore, have highlighted the importance of recognition and the differential diagnosis of HF with/without diastolic dysfunction or alternatively preserved systolic function. Left ventricular hypertrophy is one of major reasons for diastolic dysfunction or HF with preserved LVEF. There are several quantitative Doppler indices for identifying diastolic failure and high-risk patients with preserved LVEF but most of them are limited to patients without atrial fibrillation, significant valvular disease or non-cardiac diseases responsible for left atrial enlargement (3).

Alterations of autonomic function have pathophysiological and prognostic implications in systolic heart failure. Excess systemic augmentation of autonomic nervous function is harmful to the heart by triggering and/or exacerbating HF due to myocyte injury and/or myocardial remodeling, leading to sudden cardiac death or lethal pump failure. On the other hand, cardiac neuroimaging with idoin-123 metaiodobenzylguanidine (MIBG) has demonstrated that impairment of cardiac sympathetic innervation is closely relate to unfavorable clinical outcomes in HF patients.
with reduced systolic function not only independently of but also together with LVEF, New York Heart Association (NYHA) functional class, plasma brain natriuretic peptide (BNP) level and coexisting non-cardiac diseases (8-13). In HF patients with preserved LVEF, however, a prognostic value of cardiac sympathetic innervation has not been fully investigated (14, 15).

In this study, we hypothesized that quantitatively assessed cardiac echo index and sympathetic innervation marker can contribute to better prognosis assessment of HF patients with preserved LVEF. We analyzed data from 178 consecutive symptomatic HF patients with LVEF more than 50% who had been followed up for 79.6 months.

METHODS

Patient population

Data on 178 consecutive patients with symptomatic HF and LVEF more than 50% enrolled in our prospective HF cohort study since 1998 were analyzed. Entry criteria for this study as follows: patients who had been followed up regularly at outpatient clinic of our university hospital following conventional echocardiographic and MIBG examinations; patients had congestive HF established by the following clinical symptoms and signs according to the Framingham criteria, typical symptoms (palpitation, dyspnea or orthopnea), neck vein distension, peripheral edema, lung )ray findings, such as -rales, S3 gallop and tachycardia together with chest X and/or pleural effusion; and patients had cardiomegaly, bilateral lung congestion LVEF dimensional/Doppler -more than 50% at admission using conventional two echocardiography. The following patients were excluded from this study; patients p,cardiac diseases showing similar symptoms or signs had non,patients had end-stage renal failure, insulin-dependent diabetes mellitus or neurogenic disorders involving the
autonomic nervous system, patients who had been treated with tricyclic antidepressant
drugs, sympathomimetic agents or other drugs known to interfere with cardiac MIBG
uptake, and patients who were scheduled to undergo any cardiac surgery were excluded
from this study. When clinical conditions were stabilized after admission, patients were
enrolled in this study and underwent cardiac MIBG imaging and blood tests. Informed
consent for participation in this study was obtained in accordance with the guidelines of
the ethics committee of our hospital. Table 1 shows clinical backgrounds and results of
baseline examinations. Underlying heart diseases of HF were as follows: 15 patients
(8.4%) had ischemic heart disease and the remaining 163 patients (91.6%) had
non-ischemic heart diseases, including idiopathic dilated cardiomyopathy (n = 23,
12.0%), hypertrophic cardiomyopathy (n = 73, 41.0%), arrhythmogenic right ventricular
cardiomyopathy (n = 13, 7.3%), hypertensive heart disease (n = 8, 4.5%), valvular heart
disease (n = 41, 23.0%) and others (n = 5, 2.8%). No patients underwent
non-pharmacological treatment such as implantable cardioverter defibrillator or
resynchronization therapy.

Cardiac MIBG imaging

Cardiac MIBG imaging was performed at a stable condition during
hospitalization within two weeks from echocardiographic examination using $^{123}$I-MIBG
of 111 MBq with a high specific activity (9-11) before discharge. Cardiac planar and
tomographic MIBG images were obtained at the fasting and at resting condition 15–30
minutes (early) and 4 hours (late) after an intravenous tracer injection using a gamma
camera equipped with a low-energy, general-purpose collimator. Cardiac $^{123}$I-MIBG
activity was quantified as a heart-to-mediastinum ratio (HMR) by manually setting a
region of interest on the upper mediastinum and the whole cardiac region on a planar
image from an anterior projection by an experienced nuclear medicine technician who did not know any clinical data. I-MIBG washout kinetics from the heart was also calculated as washout rate (WR) using a polar-map technique with tomographic data because of the elimination of background activity. Our previous studies (9-11) showed high reproducibilities of this quantitative method.

**Conventional echocardiographic examination**

Standard two-dimensional echocardiographic examination was performed by experienced cardiologists in our echocardiography laboratory using commercially available ultrasound machines (SSH-160A, Toshiba, Tokyo, Japan; SSD760, Aloka, Tokyo, Japan; SONOS 2500, Hewlett-Packard, Andover, Massachusetts, USA; Vivid 7, General Electric Medical Systems, Milwaukee, WI, USA) that were each equipped with a 2.5-MHz variable frequency transducer. Two-dimensional and pulsed Doppler imaging modes were used from apical four-, three- and two-chamber views at a left lateral decubitus position. Left atrial (LA) dimension (LAD, mm) was measured by M-mode echocardiography. Standard two-dimensional measurements (LV end-diastolic and end-systolic dimensions and septal and posterior wall thicknesses at end-diastole) were determined and then LV mass index was calculated using the American Society of Echocardiography recommended formula (16) and was normalized for body surface area (LVMI, g/m$^2$). Left ventricular hypertrophy was defined as the LVMI more than 115 g/m$^2$ for men and more than 95 g/m$^2$ for female. LVEF was measured using the biplane modified Simpson’s method. Trans-mitral flow velocities were obtained by pulsed-wave Doppler echocardiography, positioning a sample volume at the level of a mitral tip in an apical four-chamber view. Mitral flow parameters, including peak velocities at early diastole (E) and at late diastole (A) and deceleration time of E (Dct),
were measured and then E/A was calculated. Pulsed-wave Doppler signals were obtained at a sweep speed of 100 mm/s.

**Laboratory data assessment**

Blood sampling for measurements of plasma BNP level, hemoglobin and serum concentrations of sodium and creatinine was done from an intravenous cannula in a spine position when cardiac MIBG imaging was performed. Samples used for measurements of BNP were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator units/ml) and immediately placed on ice and centrifuged at 4°C. The concentration was measured by a specific immunoradiometric assay using a commercial kit (Shionogi, Osaka, Japan) (11).

**Follow-up protocol**

After discharge, all patients were prospectively followed for at least every 3 months for a mean period of 79.6 months at the outpatient clinic of our university hospital by cardiologists who determined necessity of blood tests, electrocardiography, chest X-ray, echocardiography or other examinations. The primary endpoints were fatal or near-fatal cardiac events consisting of pump failure death, sudden cardiac death and re-hospitalization due to progression of congestive HF for necessity of intense medical treatment, including intravenous drug infusion, oxygenation and respiratory control and/or use of assist device. All cardiac events were confirmed using medical records after final diagnosis was made. The first cardiac event was used for the prognosis analysis when one of the above-mentioned primary end-points was observed during follow-up. Sudden cardiac death was defined as witnessed cardiac arrest and death within 1 hour after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 hours. Patient who had undergone implantable
cardioverter defibrillator therapy were not included in this study.

Statistics

Statistical values are shown as means ± 1 SD. Mean values were compared between the two groups using the unpaired *t*-test, and the prevalence was compared using the chi-square test. A *p*-value less than 0.05 was considered significant. Following univariate analysis, multivariate analysis with a Cox hazard proportional model was carried out using the statistically appropriate number of significant variables identified by univariable analysis, which depended on incidence of cardiac events. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of an independent significant parameter. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. These analyses were performed using a computer software program, SPSS statistical program package (SPSS version 11.0, SPSS Inc., Chicago, IL).

Depending on the distribution, continuous variables are presented as means ± standard deviation (mean ± SD) with one decimal point. Mean values were compared between the two groups using the unpaired *t*-test, and the prevalence was compared using Fisher’s exact test where appropriate. Univariate and multivariate Cox proportional hazards regression models was used to examine the association between the incidence of cardiac events and potential confounding factors. Variables that were significantly associated with the cardiac events at univariate analysis were included in the multivariate models if *p* was <0.05. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. Receiver operating characteristic (ROC)
analysis was performed to determine the optimal cutoff value of an independent significant parameter. In this prospective cohort study, all clinical data obtained at entry were used for this study as far as patients met entry criteria. If a patient was lost to follow-up during the study period more than one year, follow-up data were dealt with as discontinued data at the time when patient outcome was confirmed. These analyses were performed using a computer software program, SPSS statistical program package (SPSS version 11.0, SPSS Inc., Chicago, IL).

RESULTS

Table 1 shows clinical backgrounds and results of baseline examinations. Underlying heart diseases of HF were as follows: 15 patients (8.4%) had ischemic heart disease and the remaining 163 patients (91.6%) had non-ischemic heart diseases, including idiopathic dilated cardiomyopathy (n=23, 12.9%), hypertrophic cardiomyopathy (n=73, 41.0%), arrhythmogenic right ventricular cardiomyopathy (n=13, 7.3%), hypertensive heart disease (n=8, 4.5%), valvular heart disease (n=41, 23.0%) and others (n=5, 2.8%). No patients underwent non-pharmacological treatment such as implantable cardioverter defibrillator or resynchronization therapy. During a 80-month follow-up period, primary cardiac events were documented in 34 patients (19%), 7 of whom died of refractory pump failure, 2 of whom had sudden death and 25 of whom had re-admissions due to progression of congestive HF but non-cardiac death was not documented in this study. Thereafter, 4 of the 25 patients with re-hospitalization due to progression of congestive HF had cardiac death as the second events (one sudden cardiac death and 3 due to pump failure). There was no significant difference in background disease among cardiac events (Table 2). Although patients
with cardiac events were more frequently treated with diuretics and calcium channel blockers than those without cardiac events, there was no significant difference in any clinical or laboratory data between groups with and without cardiac events (Table 1).

There was no significant difference in two-dimensional or Doppler echocardiographic functional parameters between the two groups with and without cardiac events (Table 3). LVMI and LAD in the cardiac event group were, however, significantly greater than those in the non-cardiac event group; 172.3 ± 10.9 vs. 130.2 ± 5.5 g/m², p = 0.0008 and 43.8 ± 7.4 vs. 36.1 ± 7.4 mm, p<0.0001, respectively. On the other hand, the cardiac event group had significantly reduced cardiac MIBG activities (early HMR; 1.86 ± 0.38 vs. 2.00 ± 0.31, p = 0.041: late HMR; 1.64 ± 0.35 vs. 1.89 ± 0.33 p = 0.0003, respectively) and a significantly greater washout rate (40.3 ± 9.1% versus 32.3 ± 12.9%, p = 0.0027) than those in the non-cardiac event group (Figure 1).

Table 4 summarizes overall results of univariate and multivariate analyses using six parameters that were found to be significantly different between the two groups. Based on the significant results of univariate analysis and because of the number (34) of cardiac events in the present study, multivariate Cox analysis was performed using the top three variables in the univariate results; diuretics use, LAD and late HMR. LAD and late HMR were identified to be independent significant determinants of cardiac events with hazard ratios of 1.080 (95%CI, 1.00-1.16) for LAD (p=0.044) and 0.107 (95%CI, 0.01-0.61) for late HMR (p = 0.012) (Table 4). Late HMR was a significant determinant of cardiac events for both patient groups with and without left ventricular hypertrophy; hazard ratios of 0.167 (95%CI, 0.05-0.52, p=0.047) (Table 5) and 0.010 (95%CI, 0.01-0.37, p=0.0155) (Table 6), respectively. When re-hospitalization (i.e., exclusion of...
cardiac death) was considered as a single end-point for analysis, LAD and late HMR were independent significant determinants in patients with left ventricular hypertrophy (Table 7) but only late HMR was a significant determinant in patients without left ventricular hypertrophy (Table 8).

ROC analysis determined optimal thresholds of late HMR and LAD for identifying cardiac events to be 1.65 (chi-square value, 65.95; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively (Figure 2). When adjusted by age, sex, diuretics and calcium channel-blockers, patients with late HMR less than 1.65 or LAD of 37 mm or more had significantly lower event-free rates than did those without (Figure 3 A and B). When patients were divided into three subgroups using the cutoff values of late HMR and LAD, there were significant differences in event-free rate among the three subgroups and particularly patients with late HMR less than 1.65 and LAD of 37 mm or more had the lowest event-free rate (Figure 3C). When, instead of LAD, left ventricular hypertrophy was used for prognosis analysis, patients with both reduced HMR and LVH had the lowest event-free rate among the subgroups (Figure 4). Figure 5 demonstrates echocardiograms and cardiac planar MIBG images of two cases; one is from a 43-year-old man with a markedly reduced HMR (1.32) and an increased LAD (46 mm) who was admitted for intense medical therapy due to pump failure and the other is from a 38 year-old male with relatively preserved HMR (1.92) and a nearly normal LAD (36 mm) in whom any cardiac event was documented.

DISCUSSION

The present study clearly demonstrated that echocardiographic enlargement of LA size and impaired cardiac sympathetic innervation assessed by MIBG activity are
independently and additively related to unfavorable clinical outcomes in HF patients without reduced LVEF. Assessment of LA size and cardiac sympathetic innervation can contribute to better risk-stratification of HF patients without reduced LVEF who are at increased risk and probably can benefit most from aggressive medical treatment.

Irrespective of systolic or diastolic dysfunction, HF syndrome is heterogeneous and HF concept has been changing dependent on alterations of population demographics, background diseases and risk factors for HF. The concept of heart failure with preserved LV ejection fraction (HFpEF) has recently been established as a specific entity of HF in patients without reduced LVEF and organic cardiac diseases such as valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. This study, however, was simply designed to test whether cardiac MIBG activity has a long-term prognostic value in consecutive HF patients without systolic dysfunction as already shown in HF patients with reduced LVEF. In this study, patients with cardiac events had more increased LVMI than did those without, left ventricular hypertrophy was additively related to unfavorable outcomes when cardiac sympathetic innervation was impaired (HMR less than 1.65) and LA size enlargement was significantly prognostic in patients with left ventricular hypertrophy. These findings are identical with pathophysiological roles of left ventricular hypertrophy often observed in patients with HFpEF (4-7). However, LVMI was not an independent predictor of cardiac events in multivariate Cox analysis and LA dimension was also not in patients without left ventricular hypertrophy. Independent of left ventricular hypertrophy (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because left ventricular hypertrophy is common in hypertensive or elderly patients and can be one of reasons for diastolic impairment and also because left
ventricular hypertrophy is not necessarily a critical determinant of prognosis in patients without reduced LVEF but impaired cardiac sympathetic activity who do not meet the concept of HFpEF.

Many studies have demonstrated the prognostic values of Doppler diastolic measurements such as E/A ratio, deceleration time, S/D ratio or E/e’ in HF patients with depressed LVEF but there were a few data available in HF patients with preserved LVEF (3). Diastolic dysfunction in HF patients with normal LVEF and diagnostic standard of this syndrome is still controversial (17, 18). This is because assessment of diastolic function is complex and less reproducible, involving Doppler and tissue Doppler techniques of an array of real-time hemodynamic data, and also because multiple factors such as age, filling pressure, pre- or after-loading condition, heart rate and sympathetic tone affect these Doppler indices and left ventricular diastolic performance. On the other hand, LA size is simple, highly feasible and reliable in most routine echo studies and reflects overall LA function and left ventricular diastolic performance. In particular, LA volume has been shown to have prognostic values (19, 20) and is highly recommended by the major guidelines (3). Although unfortunately patient enrollment for this study had started before LA volume assessment was routinely performed at our laboratory, LA dimension was used instead and shown to have additive prognostic values to cardiac sympathetic activity, independent of clinical and other echocardiographic functional variables in HF patients with normal LVEF and LV hypertrophy. LA size is affected by several conditions such as anemia, bradycardia, atrial tachyarrhythmias and mitral valve disease irrespective of the presence of diastolic dysfunction. Nevertheless, LA enlargement may function as overall and cumulative results of increases in left ventricular filling pressure and mass and of abnormal
relaxation and stiffness (21-23), leading to unfavorable clinical outcomes in HF patients without reduced LVEF.

The presented study also revealed the powerful prognostic values of cardiac sympathetic innervation assessed by MIBG neuroimaging in HF patients with preserved LVEF as well as in HF patients with left ventricular systolic dysfunction (8-13). Impaired cardiac sympathetic innervation quantified using cardiac MIBG activity was not only a significant independent predictor of cardiac events but also was additively related to adverse outcomes together with LA size. These findings indicate critical roles of combined use of these quantitative markers on better identification of HF patients with preserved LVEF at increased risk. Cardiac MIBG activity is determined by microvasculature and anatomical integrity and functions of pre-synaptic nerve terminals, such as capability of ATP production, the uptake-1 and storage systems of norepinephrine (NE), central regulation of sympathetic tone and washout/spill-over as a balance between release and re-uptake of NE (MIBG) molecules (24). The mechanisms behind impairment of cardiac sympathetic innervation leading to unfavorable outcomes in HF patients with preserved LVEF, however, remain to be investigated. Impairment of microcirculation due to increases in filling pressure, myocardial stress, stiffness and mass reduces ATP production in failing hearts, possibly resulting in neuron damage. This is because sympathetic nerve endings are more susceptible to ischemia than myocytes (25-27). Blunted response of systolic function to exercise stress observed in denervated hearts (28) may elucidate the development of HF with preserved LVEF. Excess stimulation of beta-adrenoceptor, down-regulated beta-function and post-synaptic denervation supersensitivity (29) are other possible mechanisms responsible for cardiac events in HF patients with preserved LVEF. Thus, alterations of
LA size (remodeling) and cardiac MIBG activity may be associated with prognosis through different mechanisms and probably can occur before ischemia-induced contractile dysfunction becomes manifest.

Limitations

Despite the consecutive enrollment of HF patients without reduced LVEF, selection bias could not be completely ruled out due to a single-center study using the limited number of patients. The relatively better long-term prognosis in Japanese HF patients with preserved LVEF suggest requirement of a larger population for establishing the presented method. In this long-term follow-up study, four patients with re-hospitalization due to progression of congestive HF as the first events had cardiac death as the second events (one sudden cardiac death and 3 due to pump failure). Because this study used the first cardiac events for prognosis analysis, the results may have been biased or significant variables identified here such as MIBG and LAD might have a greater impact on cardiac death than shown in this analysis. Although non-pharmacological treatment was not indicated in HF patients with preserved LVEF in this study, alterations of drug treatment may have affected clinical outcomes during a long-term follow-up interval. A future study is needed to establish specific therapeutic strategy in HF patients with preserved systolic function at increased risk who are identified by the presented methods and also to reveal how cardiac MIBG activity and LA size alter interactively in response to therapeutic intervention during a clinical course. The presented quantitative techniques of cardiac MIBG imaging (9, 10) are reproducible and two-dimensional echocardiography is simple and easily applicable in daily practice. It is, however, essential to standardize quantitative techniques of high-quality cardiac MIBG imaging, including a type of collimator, imaging protocol
and specific activity of $^{123}$I-MIBG, for multicenter study (30, 31).

CONCLUSIONS

Impairment of cardiac sympathetic innervation are related to unfavorable clinical outcomes independently and synergistically with left atrial enlargement and left ventricular hypertrophy in HF patients without reduced LVEF. The combined quantitative assessment of echocardiographic left atrial size and cardiac MIBG activity can contribute to better identification of HF patients without reduced LVEF at increased risk. Future study is needed to establish etiology-based risk assessment in HF patients at increased risk identified the presented method.

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Figure Legends

Figure 1 Comparison of quantitative cardiac MIBG parameters between patient groups with and without cardiac events. HMR, heart-to-mediastinum ratio of metaiodobenzyl-guanidine activity.

Figure 2 Receiver operating characteristic (ROC) analysis of late HMR (heart-to-mediastinum ratio) of cardiac MIBG activity (left panel) and left atrial dimension (LAD) (right panel), indicating that optimal cutoff values for identifying cardiac events are 1.65 (chi-square value, 659.59; p<0.0001) and 37 mm (chi-square value, 17.88; p<0.0001), respectively.

Figure 3 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by a late HMR (heart-to-mediastinum ratio) of 1.65 (A), left atrial dimension (LAD) of 37 mm (B) and the both (C). Patients with late HMR less than 1.65 and LAD of 37 mm or more and patients with late HMR of 1.65 or more or LAD less than 37 mm had a significantly lower event-free rate than did those with late HMR of 1.65 or more and LAD less than 37 mm; 5-year survival rates were 67.9%, 85.5% and 97.3%, respectively.

Figure 4 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by late HMR and left ventricular hypertrophy (LVH).

Figure 5 Echocardiograms of left atrium and anterior planar MIBG images. (A) A 43-year-old man had a markedly decreased MIBG activity with a late heart-to-mediastinum ratio (HMR) of 1.32 and an increased left atrial dimension (LAD) of 46 mm who was re-hospitalized due to progression of
congestive heart failure during a follow-up.

(B) A 38-year-old man had both maintained HMR (1.92) and a nearly normal LAD (36 mm) who had no cardiac event during a follow-up.
Figure 1

Early HMR

Late HMR

Washout rate (%)

119x90mm (300 x 300 DPI)
Figure 2

![Graph showing sensitivity and 1-specificity for HMR and LAD cutoff values.]

Area: 0.701
χ² = 65.95
P < 0.0001

Area: 0.767
χ² = 17.88
P < 0.0001

119x90mm (300 x 300 DPI)
Figure 4

119x90mm (300 x 300 DPI)
Figure 5

(A) Late HMR = 1.32

(B) Late HMR = 1.92

119x90mm (300 x 300 DPI)