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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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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).

Design: A single-centre prospective cohort study.

Setting/participants: With primary endpoints of cardiac death and rehospitalisation due to HF progression, 178 consecutive symptomatic HF patients with 74% men, 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 predischarge clinical evaluations including cardiac MIBG and echocardiographic studies and at least more than 1-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 (HR 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

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 of this study

- Independently and synergistically, LA size and cardiac MIBG activity were associated with cardiac events in HF patients without reduced LV ejection fraction. Despite various aetiologies 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 aetiology-based risk assessment and therapeutic strategy in HF patients without reduced LVEF at increased risk.

in combination with evaluation of LA size and LV mass but is needed to be evaluated for establishing aetiology-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 death rate has been noted.[1–7] Compared with 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 (LVH) 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 HF. 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 remodelling, 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 unfavourable clinical outcomes in HF patients with reduced systolic function not only independently of but also together with LVEF, New York Heart Association 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 hypothesised that quantitatively assessed cardiac echo index and sympathetic innervation marker can contribute to better prognosis assessment of HF patients with preserved LVEF. We analysed 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 analysed. 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, dyspnoea or orthopnoea), neck vein distension, peripheral oedema, lung rales, S3 gallop and tachycardia together with chest x-ray findings, such as cardiomegaly, bilateral lung congestion and/or pleural effusion; and patients had LVEF more than 50% at admission using conventional two-dimensional/Doppler echocardiography. The following patients were excluded from this study; patients had non-cardiac diseases showing similar symptoms or signs, 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 stabilised 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 ischaemic heart disease and the remaining 163 patients (91.6%) had non-ischaemic 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 resynchronisation therapy.

Cardiac MIBG imaging

Cardiac MIBG imaging was performed at a stable condition during hospitalisation within 2 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 min (early) and 4 h (late) after an intravenous tracer injection using a γ-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.^{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, Wisconsin, 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-chamber, three-chamber and two-chamber views at a left lateral decubitus position. Left atrial (LA) dimension (left atrial 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 normalised for body surface area (LVMI, g/m^2). LVH 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, haemoglobin 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 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 rehospitalisation due to the progression of congestive HF for the 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 h after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 h. 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 χ^2 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 the incidence of cardiac events. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off 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 programme, SPSS statistical programme package (SPSS V.11.0, SPSS Inc, Chicago, Illinois, USA).

Depending on the distribution, continuous variables are presented as means±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 were 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 value 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. ROC analysis was performed to determine the optimal cut-off 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 1 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 programme, SPSS statistical programme package (SPSS V.11.0, SPSS Inc).

RESULTS

Table 1 shows clinical backgrounds and results of baseline examinations. Underlying heart diseases of HF were as follows: 15 patients (8.4%) had ischaemic heart disease and the remaining 163 patients (91.6%) had non-ischaemic 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 resynchronisation therapy. 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 the progression of congestive HF but non-cardiac death was not documented in this study. Thereafter, 4 of the 25 patients with re-hospitalisation due to the progression of congestive HF had cardiac death as the second events (one sudden cardiac death and three 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 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/m^2, 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 WR (40.3±9.1% vs 32.3±12.9%, p=0.0027) than

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

	Cardiac events group (n=34)	No cardiac events group (n=144)	p Value
Age (years)	58.2±14.6	55.1±14.6	0.312
Gender (male/female)	17/17	90/54	0.147
NYHA(I/II/III/IV)	19/9/4/2	113/22/4/5	0.326
Body mass index (kg/m^2)	22.7±7.0	22.8±6.1	0.855
Systolic blood pressure (mm Hg)	132.8±25.9	129.3±21.0	0.519
Diastolic blood pressure (mm Hg)	73.3±19.2	75.7±13.3	0.572
Heart rate (beats/min)	68.4±12.8	68.5±12.8	0.929
Diabetes mellitus	5 (14.7%)	20 (13.8%)	0.590
Hypertension	9 (26.4%)	34 (23.6%)	0.466
Dyslipidemia	5 (14.7%)	21 (14.6%)	0.583
Atrial fibrillation	12 (35.2%)	31 (21.5%)	0.213
Ventricular tachycardia/ventricular fibrillation	10 (29.4%)	37 (25.7%)	0.439
Underlying heart diseases			0.203
Ischaemic heart diseases	1 (3.0%)	14 (9.7%)	
Non-ischaemic heart diseases	33 (97.0%)	131 (90.3%)	
Diuretics	18 (53.0%)	38 (26.4%)	0.025
ACE-I	6 (17.6%)	25 (17.4%)	0.571
ARB	5 (14.7%)	23 (15.9%)	0.557
Calcium channel blockers	15 (44.5%)	39 (27.1%)	0.126
β-Blockers	14 (41.2%)	57 (39.6%)	0.520
Nitrates	5 (14.7%)	12 (8.3%)	0.234
Digitalis	7 (16.2%)	25 (17.4%)	0.438
Statins	3 (8.8%)	14 (9.7%)	0.592
Antiarrhythmic drugs	8 (23.5%)	40 (27.8%)	0.440
Antiplatelets	18 (53.0%)	69 (47.9%)	0.439
Plasma BNP (pg/dl)	126.4±101.1	129.0±197.2	0.932
Haemoglobin (mg/dl)	13.1±2.1	13.1±1.9	0.935
Creatinine (mg/dl)	1.1±0.9	1.0±1.4	0.891
Sodium (mmol/l)	139.6±3.0	138.8±14.2	0.760

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

Table 2 Background cardiac diseases of 34 cardiac events

	Pump failure (n=7)	Sudden death (n=2)	Rehospitalisation (n=25)
Hypertensive (n=7)	1 (14.3%)	0 (0%)	2 (28.6%)
HCM (n=73)	3 (4.1%)	1 (1.4%)	10 (13.7%)
Valvular (n=41)	3 (7.3%)	1 (2.4%)	3 (7.3%)
Ischaemic (n=15)	0 (0%)	0 (0%)	4 (26.7%)
Miscellaneous (n=41)	0 (0%)	0 (0%)	6 (14.6%)

HCM, hypertrophic cardiomyopathy.

those in the non-cardiac event group (figure 1). Table 4 summarises the 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 HR of 1.080 (95% CI, 1.00 to 1.16) for LAD (p=0.044) and 0.107 (95% CI, 0.01 to 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 LVH; HR of 0.167 (95% CI, 0.05 to 0.052, p=0.047; table 5) and 0.010 (95% CI, 0.01 to 0.37, p=0.0155; table 6), respectively. When re-hospitalisation (ie, exclusion of cardiac death) was considered as a single end-pint for analysis, LAD and late HMR were independent significant determinants in patients with LVH (table 7) but only late HMR was a significant determinant in patients without LVH (table 8).

ROC analysis determined optimal thresholds of late HMR and LAD for identifying cardiac events to be 1.65 (χ^2 value, 65.95; p<0.0001) and 37 mm (χ^2 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 3A,B). When patients were divided into three subgroups using the cut-off 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, LVH 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 man 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 unfavourable clinical outcomes in HF patients without reduced LVEF.

Table 3 Comparison of two-dimensional echocardiographic and Doppler parameters between groups with and without cardiac events

	Cardiac events group (n=34)	No cardiac events group (n=144)	Range	p Value
LVEF (%)	66.4±8.2	64.1±9.4	50.6–88.0	0.833
LVDd (mm)	49.1±10.1	47.6±7.1	33.0–69.9	0.358
LVDs (mm)	30.2±8.2	30.4±7.2	14.0–50.5	0.911
IVSTd (mm)	13.1±4.0	12.2±4.4	5.0–24.0	0.256
PWTd (mm)	12.5±3.1	11.1±2.9	5.0–20.1	0.147
LV mass index (g/m^2)	172.3±10.9	130.2±5.5	61.8–330	0.0008
LAD (mm)	43.8±7.4	36.1±7.4	29.0–62.1	<0.0001
E velocity (m/s)	0.64±0.32	0.65±0.25	0.28–1.7	0.858
A velocity (m/s)	0.72±0.45	0.63±0.23	0.19–2.17	0.224
E/A	0.98±0.54	1.02±0.10	0.23–2.43	0.675
E/A<1.0/E/A≥1.0	9/7 (47.1%)	29/42 (49.3%)		0.325
Dct (ms)	192±50	216±62	124–500	0.138

Values are shown as means±one SD.
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.

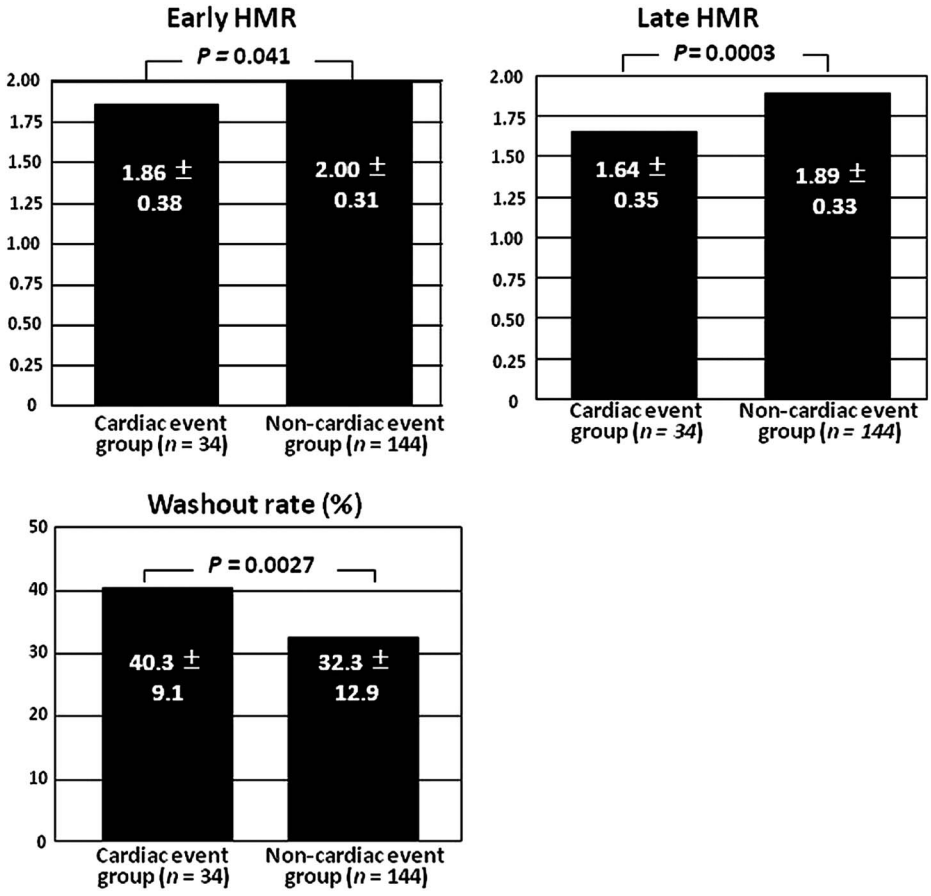

Figure 1 Comparison of quantitative cardiac metaiodobenzylguanidine parameters between patient groups with and without cardiac events. HMR, heart-to-mediastinum ratio of metaiodobenzyl-guanidine activity.

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 the HF concept has been changing dependent on alterations of population demographics, background diseases and risk factors for HF. The concept of HF 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

Table 4 Overall results of univariate and multivariate analyses for all cardiac events (n=178)

	HR	χ^2	95% CI	p Value
Univariate analysis				
Use of diuretics	2.762	8.194	1.38 to 5.52	0.004
Use of CCB	1.658	1.987	0.82 to 3.30	0.160
LV mass index	1.007	6.457	1.00 to 1.01	0.011
Left atrial diameter	1.080	12.45	1.03 to 1.12	0.0004
Washout rate	1.030	7.381	1.01 to 1.06	0.007
Early HMR	0.191	7.215	0.06 to 0.63	0.007
Late HMR	0.075	17.73	0.02 to 0.25	<0.0001
Multivariate analysis following the univariate analysis				
Use of diuretics	1.084	0.019	0.32 to 1.92	0.890
Left atrial diameter	1.080	4.050	1.00 to 1.16	0.044
Late HMR	0.107	6.314	0.01 to 0.61	0.012

CCB, calcium channel blockers; 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)

	HR	χ^2	95% CI	p Value
Univariate analysis				
Use of diuretics	2.165	4.052	1.02 to 4.59	0.041
Use of CCB	1.658	1.661	0.77 to 3.45	0.197
Left atrial diameter	1.066	5.881	1.01 to 1.12	0.015
Washout rate	1.030	4.622	1.01 to 1.06	0.032
Early HMR	0.287	3.598	0.08 to 1.04	0.058
Late HMR	0.103	11.19	0.02 to 0.40	0.0008
Multivariate analysis following the univariate analysis				
Use of diuretics	1.887	0.037	0.24 to 2.91	0.8471
Left atrial diameter	1.077	4.381	1.01 to 1.14	0.0363
Late HMR	0.216	4.549	0.05 to 0.88	0.0329

CCB, calcium channel blockers; 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)

	HR	χ^2	95% CI	p Value
Univariate analysis				
Use of diuretics	4.426	6.877	1.46 to 9.28	0.0087
Use of CCB	1.675	0.876	0.54 to 4.83	0.349
Left atrial diameter	1.089	2.945	0.98 to 1.19	0.086
Washout rate	1.034	2.158	0.98 to 1.08	0.142
Early HMR	0.314	1.792	0.06 to 1.73	0.186
Late HMR	0.072	9.715	0.01 to 0.37	0.0018
Multivariate analysis following the univariate analysis				
Use of diuretics	2.289	1.889	0.52 to 5.49	0.1692
Left atrial diameter	1.018	1.607	0.82 to 1.23	0.2062
Late HMR	0.010	6.391	0.01 to 0.37	0.0155

CCB, calcium channel blockers; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.

this study, patients with cardiac events had more increased LVMI than did those without, LVH was additively related to unfavourable outcomes when cardiac sympathetic innervation was impaired (HMR less than 1.65) and LA size enlargement was significantly prognostic in patients with LVH. These findings are identical with pathophysiological roles of LVH 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 LVH. Independent of LVH (defined by LVMI in this study), the prognostic value of cardiac MIBG activity was clearly identified. This is probably because LVH, which is often observed in hypertensive and elderly

Table 7 Univariate and multivariate analyses for rehospitalisation due to heart failure progression in patients with left ventricular hypertrophy (n=98)

	HR	χ^2	95% CI	p Value
Univariate analysis				
Use of diuretics	1.912	1.997	0.77 to 4.63	0.1572
Use of CCB	1.938	2.144	0.79 to 4.73	0.1413
Left atrial diameter	1.081	6.817	1.02 to 1.13	0.0090
Washout rate	1.039	4.911	1.00 to 1.07	0.0267
Early HMR	0.147	4.889	0.02 to 0.80	0.0270
Late HMR	0.049	11.11	0.01 to 0.31	0.0009
Multivariate analysis following the univariate analysis				
Use of diuretics	1.284	0.037	0.42 to 3.75	0.6433
Left atrial diameter	1.137	4.420	1.01 to 1.30	0.0355
Late HMR	0.091	7.314	0.01 to 0.54	0.0068

CCB, calcium channel blockers; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.

Table 8 Univariate and multivariate analyses for rehospitalisation due to heart failure progression in patients without left ventricular hypertrophy (n=71)

	HR	X^2	95% CI	p Value
Univariate analysis				
Use of diuretics	2.749	1.452	0.50 to 14.9	0.228
Use of CCB	1.896	0.876	0.03 to 3.28	0.532
Left atrial diameter	1.132	5.251	0.03 to 0.22	0.0224
Washout rate	1.021	0.365	0.95 to 1.09	0.545
Early HMR	0.039	4.288	0.01 to 0.83	0.0384
Late HMR	0.039	5.876	0.01 to 0.53	0.0153
Multivariate analysis following the univariate analysis				
Use of diuretics	1.124	0.016	0.52 to 5.49	0.1692
Left atrial diameter	1.125	3.465	0.99 to 1.29	0.0627
Late HMR	0.059	4.221	0.01 to 0.37	0.0399

CCB, calcium channel blockers; HMR, heart-to-mediastinum ratio of metaiodobenzylguanidine activity; LV, left ventricular.

patients, can be one of the reasons for diastolic impairment. Although LVH is not necessarily a critical determinant of prognosis in patients without reduced LVEF, cardiac sympathetic activity could be impaired in patients with LVH and 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, preloading 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 enrolment 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 anaemia, 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 unfavourable 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

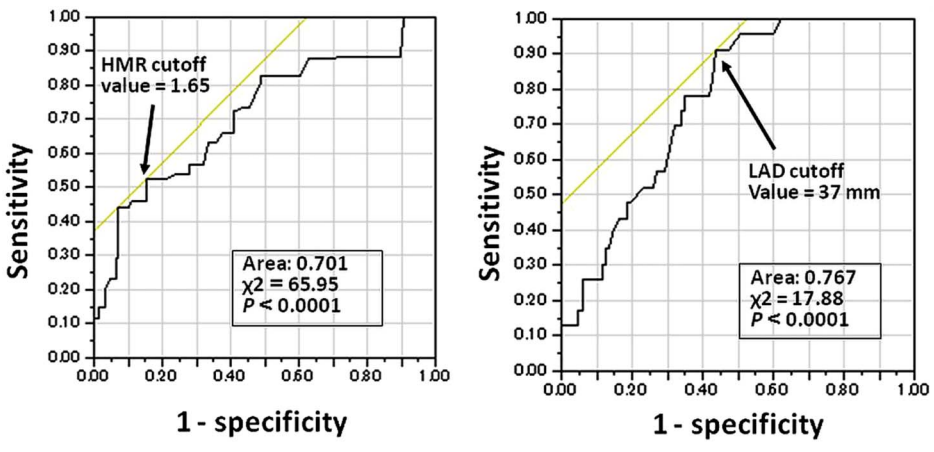

Figure 2 Receiver operating characteristic (ROC) analysis of late HMR (heart-to-mediastinum ratio) of cardiac metaiodobenzylguanidine (MIBG) activity (left panel) and left atrial dimension (LAD) (right panel), indicating that optimal cut-off values for identifying cardiac events are 1.65 (χ^2 value,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

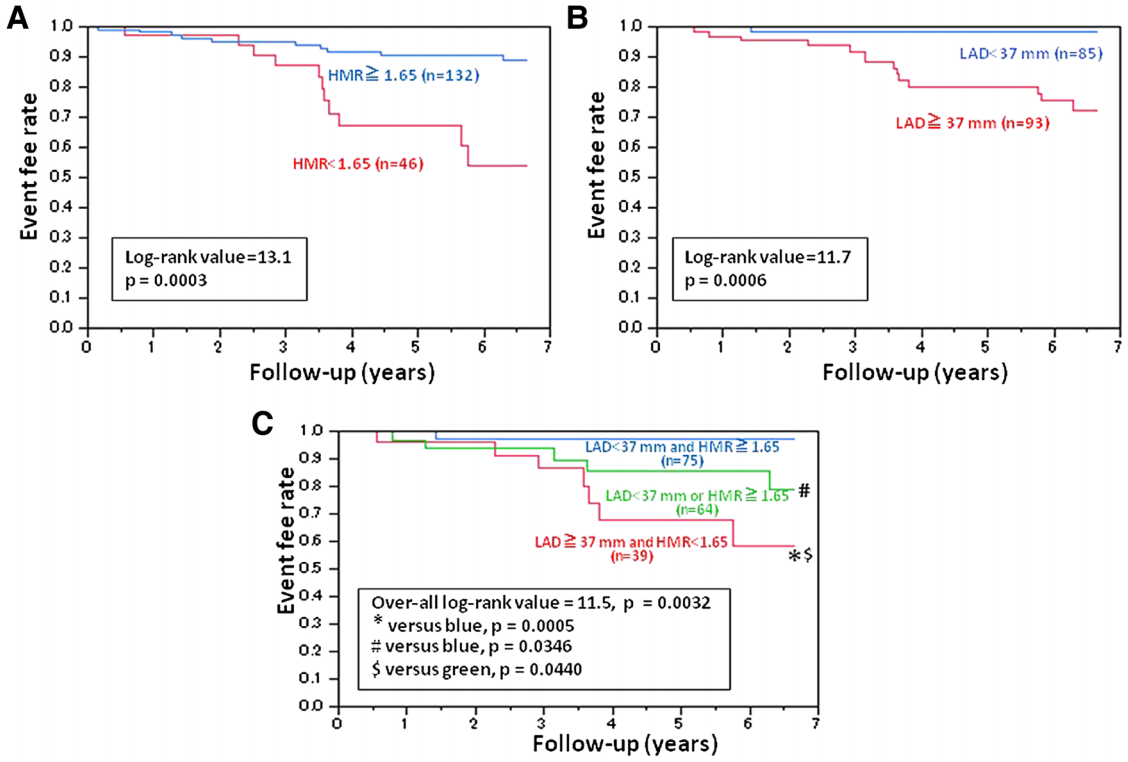

Figure 3 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by a late HMR (heart-to-mediastinum ratio) of 1.65 (A), left atrial dimension (LAD) of 37 mm (B) and the both (C). Patients with late HMR less than 1.65 and LAD of 37 mm 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.

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 presynaptic 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 the impairment of cardiac sympathetic innervation leading to unfavourable 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 ischaemia 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 β-adrenoceptor, down-regulated β-function and postsynaptic denervation supersensitivity[29] are other possible mechanisms responsible for cardiac events in HF patients with preserved LVEF. Thus, alterations of LA size (remodelling) and cardiac MIBG activity may be associated with prognosis through different mechanisms and probably can occur before ischaemia-induced contractile dysfunction becomes manifest.

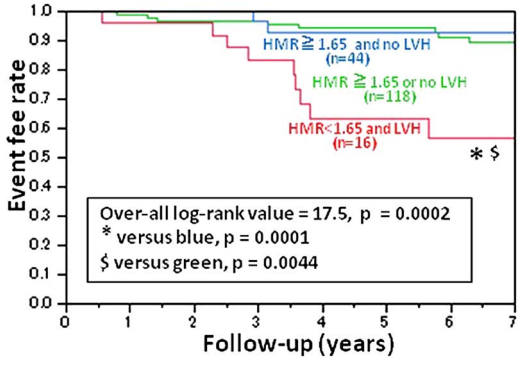

Figure 4 Kaplan-Meier event-free curves adjusted for age, sex, use of diuretics and calcium channel-blockers of subgroups classified by late heart-to-mediastinum ratio (HMR) and left ventricular hypertrophy (LVH).

Limitations

Despite the consecutive enrolment of HF patients without reduced LVEF, selection bias could not be completely ruled out due to a single-centre 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

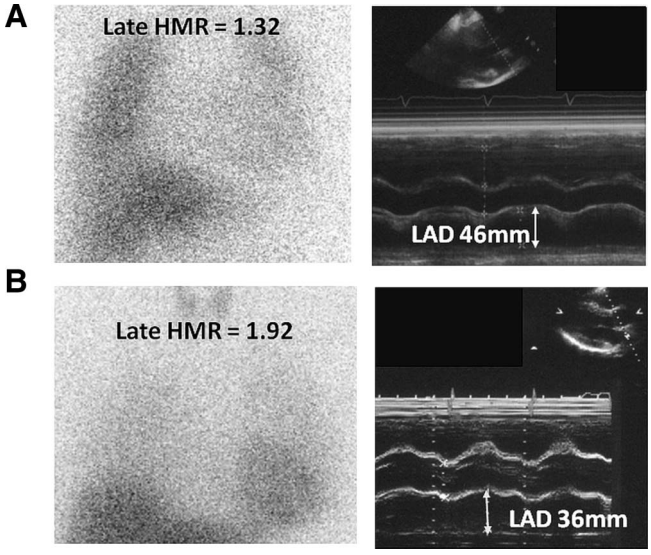

Figure 5 Echocardiograms of left atrium and anterior planar metaiodobenzylguanidine (MIBG) images. (A) A 43-year-old man had a markedly decreased MIBG activity with a late heart-to-mediastinum ratio (HMR) of 1.32 and an increased left atrial dimension (LAD) of 46 mm who was rehospitalised due to the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

follow-up study, four patients with rehospitalisation due to the progression of congestive HF as the first events had cardiac death as the second events (one sudden cardiac death and three 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 standardise quantitative techniques of high-quality cardiac MIBG imaging, including a type of collimator, imaging protocol and specific activity of ^{123}I-MIBG, for multicentre study.[30 31]

CONCLUSIONS

Impairment of cardiac sympathetic innervation is related to unfavourable clinical outcomes independently and synergistically with left atrial enlargement and LVH 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 aetiology-based risk assessment in HF patients at increased risk identified the presented method.

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Patient consent Obtained.

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