



## Prognostic Significance of Neuroadrenergic Dysfunction for Cardiovascular Events in Patients With Acute Myocardial Infarction

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**Background:** The dysregulation of systemic blood pressure (BP) variation or cardiac neuroadrenergic dysfunction is associated with adverse cardiovascular events. We aimed to clarify the prognostic significance of neuroadrenergic dysfunction for cardiovascular events in patients with acute myocardial infarction (AMI).

**Methods and Results:** We enrolled 63 AMI patients (mean age, 67±12 years) underwent ambulatory BP monitoring (ABPM) and cardiac iodine-<sup>123</sup> metaiodobenzylguanidine (MIBG) imaging within 4 weeks after AMI onset. We analyzed the circadian BP pattern and heart-to-mediastinum (H/M) MIBG uptake ratio. All the patients were followed for 2 years. The study endpoint was a composite of major adverse cardiovascular events, including all-cause death, MI, coronary revascularization except for the MI culprit lesion, and stroke. Patients with a non-dipper pattern (n=29) or an H/M ratio <1.96 (n=28) had a worse prognosis than those with either a dipper pattern (n=34) or an H/M ratio ≥1.96 (n=35; log-rank, P=0.013 and 0.010, respectively). Patients with both a non-dipper pattern and an H/M ratio <1.96 (n=12) had a significantly worse prognosis than did the other patients (P=0.0020).

**Conclusions:** Dysregulation of BP variation and cardiac MIBG uptake were associated with cardiovascular events following AMI. Examining ABPM with MIBG imaging may potentially improve risk stratification in these patients. (*Circ J* 2015; **79**: 2238–2245)

**Key Words:** Acute myocardial infarction; Autonomic nervous system; Blood pressure; Cardiovascular events

**P**ronounced disturbances in autonomic function are observed in patients with acute myocardial infarction (AMI), at the time of the event and during the subsequent convalescent period. A delayed heart-to-mediastinum (H/M) uptake ratio on iodine-<sup>123</sup> metaiodobenzylguanidine (MIBG) imaging, which represents myocardial sympathetic activity, has been used to assess the prognosis of patients with chronic heart failure.<sup>1–3</sup> A previous report demonstrated that the washout ratio of cardiac MIBG is a significant predictor of cardiovascular (CV) events following AMI;<sup>4</sup> however, the prognostic value of the H/M MIBG uptake ratio in patients with AMI has not been elucidated.

The autonomic nervous system influences circadian blood pressure (BP) variability.<sup>5</sup> Although the mechanisms responsible for a nocturnal decrease in BP are not yet fully understood, the withdrawal of sympathetic activity seems to play a pivotal role in the dipper pattern, because the circadian fluctuation of intrinsic catecholamine levels is similar to that of

systemic BP.<sup>6</sup> Therefore, dysregulation of the autonomic nervous system is associated with the non-dipper phenomenon,<sup>7</sup> which has been related to early atherosclerosis<sup>8</sup> and a high incidence of CV events in patients with essential hypertension and obstructive sleep apnea syndrome.<sup>7,9</sup> Nevertheless, the prognostic significance of BP variability in patients with AMI is still poorly understood.

Dual examination using ambulatory BP monitoring (ABPM) and MIBG imaging may help identify patients with advanced autonomic dysfunction. In fact, abnormalities in ABPM and MIBG uptake have been associated with an elevated risk for syncope/presyncope in patients with Parkinson's disease.<sup>10</sup> We hypothesized that dual examination of ABPM and MIBG imaging would contribute to identifying high-risk patients and determining secondary prevention measures after AMI. Therefore, the aim of this study was to clarify the prognostic significance of dysregulation of systemic BP variability on ABPM and cardiac sympathetic nervous dysfunction on MIBG

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imaging in patients with AMI.

## Methods

### Study Population

We screened 72 consecutive patients with AMI who were admitted to Shinshu University Hospital between June 2008 and December 2010. All patients were enrolled into the prospective multicenter study entitled "Assessment of lipophilic vs. hydrophilic statin therapy in AMI (ALPS-AMI)," which was registered in the University Hospital Medical Information Network (UMIN000001521). Details of the ALPS-AMI study have been published.<sup>11,12</sup> In summary, the inclusion criteria were age >20 years, a serum low-density lipoprotein-cholesterol level (LDL-C) >70 mg/dl, and percutaneous coronary intervention to treat AMI performed up to 96 h prior to enrollment. Exclusion criteria were planned surgery for coronary artery bypass grafting; pregnancy; active liver or renal disease; malignancy; withdrawal of informed consent; serious arrhythmic events; or the presence of hemodynamic instabilities (hypotension, congestive heart failure, or mechanical complications following AMI). Of 72 patients, 64 patients underwent ABPM and cardiac MIBG imaging, and were followed prospectively for 2 years in Shinshu University Hospital.

The Ethics Committee of Shinshu University School of Medicine approved the protocol. Written informed consent was given by all patients, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

### ABPM

Ambulatory BP was monitored using a non-invasive automatic ABPM system (RAC-3502, Nihon Kohden Co Ltd, Tokyo, Japan) 2–4 weeks after AMI onset during the index hospitalization. Measurements were performed every 30 min during the daytime and every 60 min during the nighttime by default setting, although it should be noted that the Japanese guideline for the clinical use of ABPM recommends every 30 min during the nighttime.<sup>13</sup> The daytime and nighttime periods were determined by interviewing each patient. The average systolic BP values during the daytime and nighttime were calculated, and the nighttime BP decline (%) was defined as follows: (daytime BP–nighttime BP)/daytime BP×100. Circadian BP variation was classified as a dipper pattern (nighttime decline ≥10%) or a non-dipper pattern (nighttime decline <10%).<sup>5,13</sup>

### MIBG Imaging

Cardiac MIBG imaging was performed 2–4 weeks after AMI onset using the following standard procedure. Early images were acquired 15 min after the administration of 111 MBq of high specific activity MIBG (FUJIFILM RI Pharma Co Ltd, Tokyo, Japan),<sup>14</sup> and delayed images were acquired at 4 h. The H/M ratio was determined as previously described from the anterior planar images,<sup>15</sup> which were acquired using a gamma camera (PRISM IRIX; Shimadzu, Kyoto, Japan) that was equipped with a low-energy collimator. Next, the cardiac MIBG uptake was quantified as delayed H/M by an experienced nuclear medicine technician who was unaware of the patients' clinical characteristics. The delayed myocardial single-photon emission computed tomography images of each patient were divided into 17 segments in post-MI patients, as shown in a previous report.<sup>4</sup> Regional tracer uptake was analyzed using a 5-point scoring system (0=normal uptake; 1=mildly reduced uptake; 2=moderately reduced uptake; 3=significantly reduced

uptake; 4=no uptake). Total defect score was calculated as the sum of all defect scores. We analyzed regional abnormalities on MIBG imaging by calculating a regional defect score (RDS) for each of the 17 segments. Then the infarcted RDS index (RDSI) was calculated as the average RDS of the culprit segment. The non-infarcted RDSI was calculated as the average RDS of the non-culprit segments.<sup>4</sup>

### Study Definition and Endpoints

AMI was diagnosed according to the AHA/ACC guidelines.<sup>16</sup> Patients with systolic BP >140 mmHg and/or diastolic pressure >90 mmHg and those taking antihypertensive agents were considered to have hypertension. Dyslipidemia was defined as serum LDL-C >140 mg/dl, high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl, or the requirement for treatment with lipid-lowering agents. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl or clinical history of oral hypoglycemic agent and/or insulin use. Patients were considered smokers if they were current smokers. Estimated glomerular filtration rate was calculated using the Modification of Diet and Renal Disease equation coefficients modified for Japanese patients.<sup>17</sup> Left ventricular ejection fraction was calculated using the biplane Simpson's method from the apical 4- and 2-chamber views. The study endpoints were major adverse cardiac events (MACE), including all-cause death, MI, coronary revascularization except for the MI culprit lesion, and stroke. Event-free survival for all patients was tracked for 2 years.

### Statistical Analysis

Continuous variables are summarized as mean±standard deviation if normally distributed, or as median and interquartile ranges if non-normally distributed. Normality was evaluated using the Shapiro-Wilk test. Patients were divided into an event-free group and a MACE group. The baseline categorical data between groups were compared using a 2-sided chi-square test, and differences between the continuous variables were analyzed using an unpaired t-test or Mann-Whitney U test. We assessed the diagnostic accuracy of the H/M ratio by using a receiver-operating characteristic (ROC) curve. The optimal ROC curve cutoff value for MACE prediction was chosen as the value maximizing sensitivity and specificity. Kaplan-Meier event-free curves were calculated from AMI onset to the time of MACE and were compared using the log-rank test. To identify variables associated with MACE, univariate and age-adjusted Cox proportional hazards regression analyses were performed using the clinical characteristics, risk factors, MIBG imaging findings, and circadian BP patterns. Cox proportional hazards assumptions were checked by Martingale residuals plots. All analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL, USA) and R 3.1.2. A value of P<0.05 was considered to indicate statistical significance.

## Results

A total of 64 patients were recruited and 63 patients were followed prospectively for 2 years because 1 patient had a riser pattern. Baseline characteristics of the present patients and those in the ALPS-AMI study (n=508) showed no difference with regard to age (66.8±11.5 vs. 66.0±11.6, P=0.61), sex (male, 78% vs. 81%, P=0.56), values of total cholesterol (207.8±39.9 vs. 203.6±39.7 mg/dl, P=0.45), LDL-C (129.6±11.5 vs. 130.6±33.5 mg/dl, P=0.82), HDL-C (50.0±12.6 vs. 47.8±11.9 mg/dl, P=0.18), hemoglobin A1c (6.3±1.0% vs.

**Table 1. Baseline Characteristics of AMI Patients With and Without MACE**

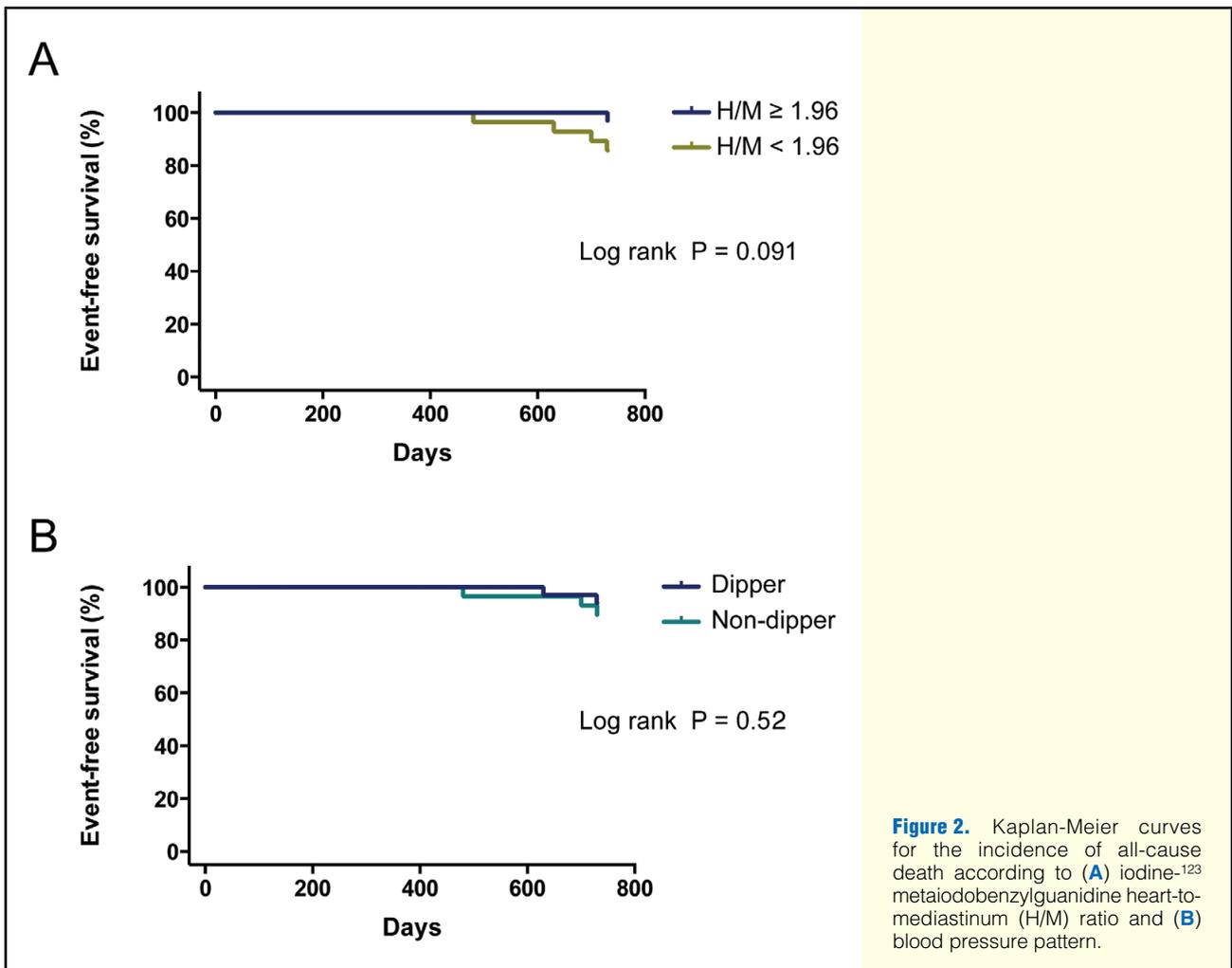
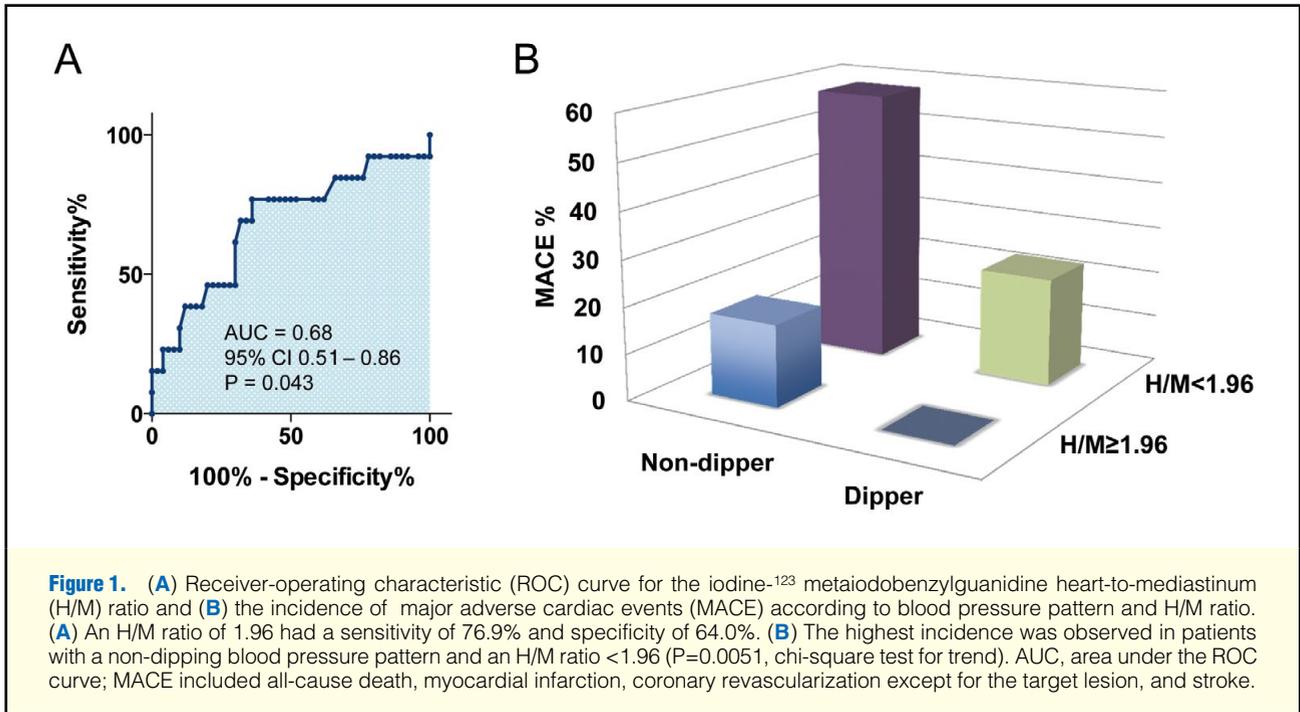
Characteristic	Overall (n=63)	MACE (+) (n=13)	MACE (-) (n=50)	P value
Age	66.8±11.5	65.7±11.0	67.1±11.7	0.69
Sex, M/F	49/14	10/3	39/11	0.51
BP, all day (mmHg)				
Systolic	114.5±14.9	113.7±17.8	114.7±14.2	0.83
Diastolic	71.1±7.3	71.5±9.8	71.0±6.6	0.83
BP, daytime (mmHg)				
Systolic	120.1±13.2	118.2±14.4	120.6±12.9	0.56
Diastolic	73.8±8.0	73.7±16.6	73.9±7.3	0.52
BP, nighttime (mmHg)				
Systolic	108.9±12.8	110.9±14.0	108.3±12.6	0.52
Diastolic	68.0±7.5	71.6±10.3	67.1±6.5	0.056
Hypertension	34 (54)	6 (46)	28 (56)	0.53
Dyslipidemia	26 (41)	9 (69)	17 (34)	0.022
Diabetes mellitus	15 (24)	4 (31)	11 (22)	0.37
Smoking	38 (60)	10 (77)	28 (56)	0.17
Atrial fibrillation	6 (10)	3 (23)	3 (6)	0.096
CKD, eGFR ≤45 ml/min/1.73 m <sup>2</sup>	4 (6)	2 (15)	2 (4)	0.19
Multivessel disease	29 (46)	9 (69)	20 (40)	0.060
LVEF (%)	55.1±12.3	51.3±11.4	55.9±12.5	0.29
Log BNP	4.28±1.06	4.56±1.18	4.21±1.04	0.28
Peak CK (IU/L)	3,179±2,668	2,852±2,607	3,265±2,704	0.62
H/M ratio	1.98±0.36	1.82±0.44	2.02±0.33	0.068
Total defect score	23.0±8.5	24.5±8.6	22.6±8.5	0.49
Infarcted RDSI	2.00±0.73	1.96±0.96	2.00±0.66	0.85
Non-infarcted RDSI	1.05±0.55	1.24±0.62	1.00±0.53	0.17
Non-dipper	29 (46)	10 (77)	19 (38)	0.012
Medication				
ACEI/ARB	63 (100)	13 (100)	50 (100)	1.0
β-blocker	49 (78)	9 (69)	40 (80)	0.31
Calcium-channel blocker	19 (30)	4 (31)	15 (30)	0.60
Aldosterone antagonist	11 (17)	2 (15)	9 (18)	0.60
Loop diuretics	12 (19)	5 (38)	7 (14)	0.060
Statin	63 (100)	10 (100)	50 (100)	1.0

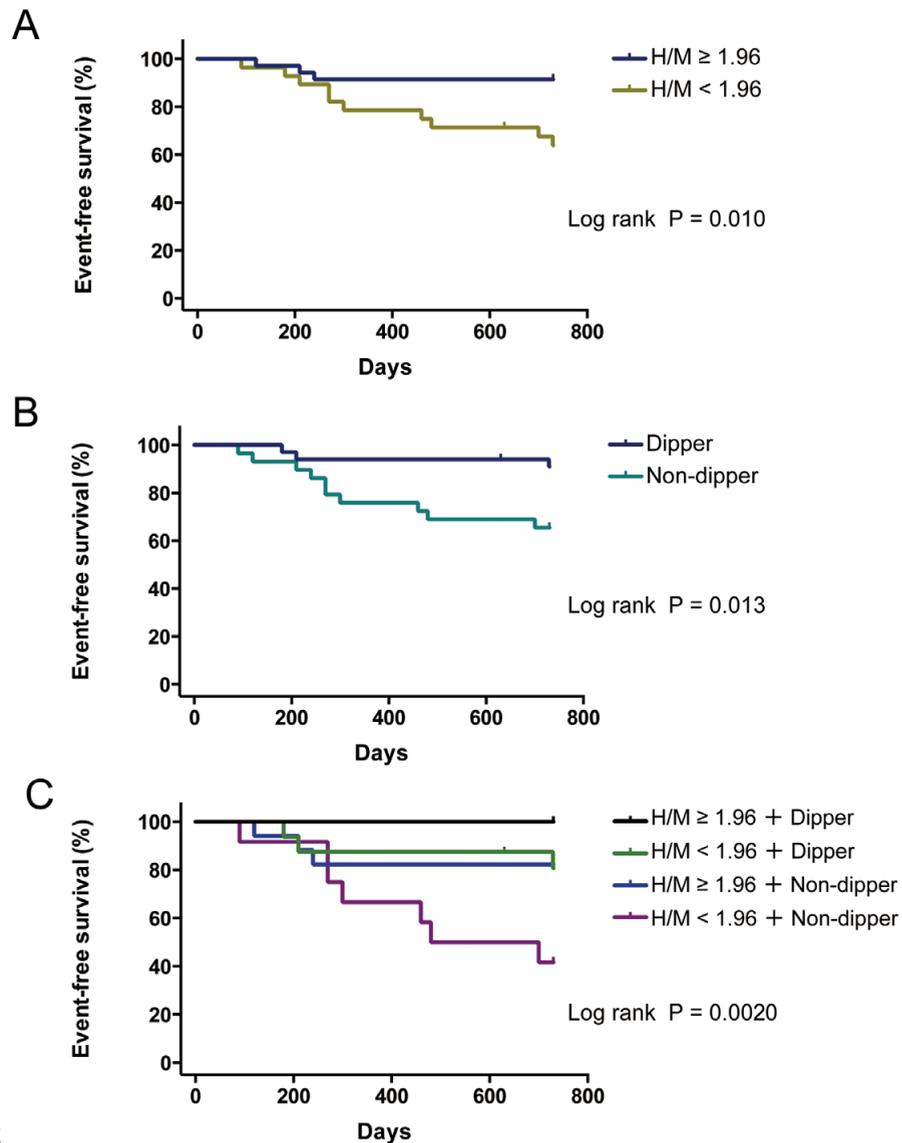
Data are shown as mean±standard deviation, or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; CK, creatine kinase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; H/M, delayed heart-to-mediastinum iodine-<sup>123</sup> metaiodobenzylguanidine uptake ratio; LV, left ventricular; LVEF, LV ejection fraction; MACE, major adverse cardiac events (all-cause death, myocardial infarction, coronary revascularization except for target lesion, or stroke); RDSI, regional defect score index.

6.3±1.3%, P=0.81), creatinine (0.92±1.2 vs. 0.89±0.56 mg/dl, P=0.18), plasma B-type natriuretic peptide (BNP: 106.5±113.4 vs. 134.6±33.6 pg/ml, P=0.32), and left ventricular ejection fraction (LVEF: 55.1±12.3 vs. 54.9±11.8%, P=0.90), as well as ST-segment elevation MI (76.2% vs. 81.6%, P=0.29) and Killip classification (P=0.28). During the follow-up period, MACE occurred in 13 patients (20.6%), including 5 (8%) all-cause deaths and 10 (16%) coronary revascularizations; no other events were observed. The revascularizations were for progressive coronary stenosis up to 90% in 8 patients and 2 symptomatic patients with up to 75% stenosis. The baseline characteristics of patients with and without MACE showed no differences with regard to age, sex, clinic BP, mean 24-h ambulatory BP, history of hypertension, diabetes mellitus, smoking, atrial fibrillation, and chronic kidney disease. However, dyslipidemia was significantly more common in patients with MACE (Table 1). All the patients underwent ABPM, revealing a dipper pattern in 34 (54%) and a non-dipper pat-

tern in 29 (46%). The non-dipper pattern was predominant in patients with MACE compared with those without MACE (77% vs. 38%, P=0.012). The levels of plasma BNP and peak serum creatine kinase, and LVEF were similar between patients with and without MACE. Treatment for secondary prevention following AMI was started, and no difference in medications was observed between the 2 groups.

The mean delayed H/M ratio of 1.82 in patients with MACE was modestly lower compared with patients without MACE (P=0.068). Single-photon emission computed tomography data with regard to total defect score, infarcted RDSI, and non-infarcted RDSI showed no differences between the 2 groups (Table 1). The area under the ROC curve of the H/M ratio for predicting the incidence of MACE was 0.68 (95% confidence interval: 0.51–0.86, P=0.043) (Figure 1A). The optimal cutoff value for the H/M ratio was 1.96, which had a sensitivity and specificity of 76.9% and 64.0%, respectively. Next, we compared the percent population of patients with MACE among 4





**Figure 3.** Kaplan-Meier curves for major adverse cardiac events (MACE)-free survival according to (A) iodine-123 metaiodobenzylguanidine heart-to-mediastinum (H/M) ratio, (B) blood pressure pattern, and (C) blood pressure pattern in combination with the H/M ratio. MACE included all-cause death, myocardial infarction, coronary revascularization except for the target lesion, and stroke.

subgroups classified according to the cutoff level of the delayed H/M ratio and BP pattern (Figure 1B). There was a significant difference in MACE (%) among the 4 subgroups (P=0.0051), and the highest incidence (58.3%) was observed in the subgroup of patients with both abnormalities: non-dip-

per pattern and low H/M ratio (<1.96). Kaplan-Meier analysis of the incidence of all-cause death demonstrated that there was no difference according to the cutoff level of the delayed H/M ratio and BP pattern (Figure 2). Kaplan-Meier analyses for MACE-free curves demonstrated that patients with H/M

**Table 2. Cox Proportional Hazards Analysis of Patients With AMI**

	Unadjusted		Adjusted for age	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.99 (0.94–1.04)	0.62		
Sex (M)	0.64 (0.14–2.90)	0.57	0.68 (0.15–3.11)	0.68
Systolic BP				
All day	0.99 (0.76–1.03)	0.87	0.99 (0.96–1.04)	0.93
Daytime	0.99 (0.94–1.03)	0.58	0.99 (0.95–1.04)	0.64
Nighttime	1.02 (0.97–1.06)	0.49	1.02 (0.98–1.06)	0.43
Hypertension	0.67 (0.22–1.99)	0.47	0.70 (0.23–2.15)	0.53
Dyslipidemia	3.77 (1.16–12.25)	0.030	3.83 (1.14–12.9)	0.030
Diabetes mellitus	1.59 (0.49–5.15)	0.44	1.88 (0.53–6.65)	0.33
Atrial fibrillation	2.67 (0.73–9.70)	0.14	3.38 (0.83–13.78)	0.089
CKD	3.18 (0.70–14.36)	0.13	5.51 (0.88–34.40)	0.068
Multivessel disease	3.04 (0.93–9.87)	0.070	3.29 (0.99–10.91)	0.052
$\beta$ -blocker	0.60 (0.19–1.96)	0.40	0.58 (0.18–1.89)	0.36
Aldosterone antagonist	0.89 (0.20–3.99)	0.88	0.93 (0.20–4.26)	0.93
Loop diuretic	2.86 (0.94–8.76)	0.070	3.78 (1.11–12.86)	0.033
LVEF	0.98 (0.93–1.03)	0.34	0.97 (0.93–1.03)	0.32
BNP	1.00 (0.99–1.00)	0.15	1.00 (0.99–1.00)	0.12
Log BNP	1.30 (0.76–2.24)	0.34	1.36 (0.78–2.36)	0.28
H/M ratio	0.22 (0.060–0.79)	0.020	0.21 (0.059–0.78)	0.019
Total defect score	1.02 (0.96–1.09)	0.46	1.02 (0.96–1.09)	0.53
Infarcted RDSI	0.91 (0.43–1.94)	0.81	0.96 (0.86–1.09)	0.58
Non-dipper	4.46 (1.23–16.22)	0.023	4.40 (1.20–16.08)	0.025

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

<1.96 had a worse prognosis than those with H/M ratio  $\geq$ 1.96 (Figure 3A). Similarly, patients with a non-dipper pattern had a significantly worse prognosis than those with a dipper pattern (Figure 3B). Unadjusted Cox proportional hazards analyses demonstrated that MACE were associated with a low H/M ratio, non-dipper pattern, and history of dyslipidemia, which were also significant after age adjustment (Table 2). Martingale residual analysis showed goodness-of-fit of the Cox proportional hazards assumption. Furthermore, when patients were divided into 4 groups according to the H/M ratio and BP pattern (Figure 3C), the subgroup of patients with both abnormalities (ie, low H/M ratio [ $<$ 1.96] and non-dipper pattern) showed a significantly worse prognosis than did the other groups (high H/M ratio and a dipper pattern, high H/M ratio and a non-dipper pattern, and low H/M ratio and a dipper pattern; log-rank:  $P<$ 0.0001,  $P=$ 0.037, and  $P=$ 0.043, respectively).

## Discussion

To the best of our knowledge, this study is the first to demonstrate the importance of dual abnormalities in circadian BP variation and MIBG imaging, which were associated with future CV events following AMI. The main finding can be summarized as follows. First, either a non-dipper pattern or low H/M ratio was associated with an increased incidence of MACE in patients with AMI. Second, the subgroup of patients with both abnormalities (ie, a non-dipper pattern and low H/M ratio) had the highest incidence of MACE compared with patients in the other subgroups.

Recent reports support the association of CV risk with a non-dipper pattern, which has been associated with increased platelet activation and inflammatory response,<sup>18</sup> cardiac remodel-

ing<sup>19</sup> and dysfunction,<sup>20–23</sup> and organ damage<sup>24–26</sup> (including renal insufficiency).<sup>27</sup> In patients with coronary artery disease, a high incidence of silent and nighttime ischemia was observed in patients with a non-dipper pattern.<sup>28</sup> Importantly, a non-dipper pattern has been associated with clinical evidence of CV disease<sup>27</sup> and a high incidence of future CV events.<sup>7,9,29</sup> Therefore, a non-dipper pattern may play a key role in the development of atherosclerosis, and it has been related to more advanced CV disease.<sup>27</sup> Furthermore, patients with a non-dipper pattern have predominant activity in the sympathetic nerve system, not the parasympathetic nerve system,<sup>5,30</sup> which suggests that there is a connection between BP variability and imbalance of the autonomic nerve system. The risk of the non-dipper pattern identified in this study suggests that systemic imbalance of the autonomic nervous system may play a key role in the development of secondary CV events after AMI.

Novel prognostic biomarkers have been identified for secondary prevention after the onset of AMI;<sup>31–33</sup> however, the prognostic significance of the index of autonomic nervous dysfunction for risk stratification in patients with AMI is poorly understood. The high incidence of MACE in the subgroup showing simultaneous abnormalities of low H/M ratio with a non-dipper pattern may suggest that dual neuroadrenergic dysregulation is synergistically associated with CV events. Although both the circadian BP pattern and cardiac MIBG reflect autonomic nervous activity, the benefit of dual evaluation is that each examination is independent and there is no significant interaction between the modalities. In addition, dual evaluation may complement and supplement diagnostic accuracy by overcoming the limitations of each modality. In fact, the reproducibility of ABPM has been reported as up to 60–65%,<sup>34</sup> whereas MIBG images can be changeable during

the acute phase of AMI.<sup>35</sup> Although a causal relationship between neuroadrenergic dysregulation and the occurrence of CV events has not been fully elucidated, our findings highlight the importance and prognostic potential of dual examination of AMI patients using ABPM and MIBG imaging. This combination may contribute to the identification of high-risk patients who require intensive secondary prevention.

The assessment of sympathetic activity in this study raises several points for discussion. First, cardiac MIBG activity can be changeable during the first few weeks to months post-AMI.<sup>35</sup> Although we demonstrated significant utility of MIBG and ABPM 2–4 weeks after AMI onset, the best timing for each of these modalities to predict patient outcome has not been fully established. Second, the cutoff value of the H/M ratio in the present study was relatively higher than the ratio of <1.6–1.7 that has been associated with increased risk in patients with heart failure.<sup>2,3,36</sup> Third, we compared regional defects on MIBG images using single-photon emission computed tomography, but we unexpectedly observed no significant regional difference between patients with and without MACE. In general, cardiac MIBG uptake can be heterogeneous and the regional uptake tends to be lower in the inferior than in the lateral wall in healthy individuals.<sup>37,38</sup> Based on these characteristics of MIBG distribution, it might be difficult to perform regional analysis of MIBG uptake in our study. Further large-scale studies are required to confirm (1) the best timing for the assessment of sympathetic activity, (2) the cut off value of the H/M ratio, and (3) the effect of regional defect on MIBG in patients following AMI.

Recovery of normal circadian BP variation following anti-hypertensive treatment or renal artery stenting has been reported.<sup>39–42</sup> However, the benefits of these interventions for BP variation as secondary CV prevention have not been addressed in patients following AMI. In the present study, insufficient serial data were available for changes in the H/M ratio and circadian BP variation.

### Study Limitations

Our findings represented a single center's experience of dual evaluation using ABPM and MIBG after AMI onset. Therefore, the first limitation was the small number of subjects. Because of this, no prognostic variable was associated with hard endpoints, and multivariate analysis could not be performed to predict patient prognosis. Second, each examination of ABPM and MIBG at a single time point after the onset of AMI was insufficient to validate reproducibility or to define when these findings were present, either before or after the onset of AMI. Third, our study did not provide the mechanisms of action of cardiac and/or systemic neuroadrenergic dysregulation in the development of each adverse CV event. Further large-scale multicenter studies are needed to confirm the synergistic prognostic effect of ABPM and MIBG evaluations and to also perform multivariate analysis to identify factors that predict patient prognosis. In addition, clinicians should understand the most cost-efficient way for implementing the dual evaluation by ABPM and MIBG in their clinical practice.

### Conclusions

The present study demonstrated that neuroadrenergic dysregulation of systemic BP variation and the MIBG H/M ratio were associated with the incidence of CV events in patients following AMI. Dual examination with ABPM and cardiac MIBG imaging can be used to identify high-risk patients, and this

may improve risk stratification for secondary CV prevention in patients with AMI.

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