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Comparison of the Prognostic Value of Cardiac Iodine-123 Metaiodobenzylguanidine Imaging and Heart Rate Variability in Patients With Chronic Heart Failure

A Prospective Study

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OBJECTIVES We sought to prospectively compare the prognostic value of cardiac iodine-123 (I-123) metaiodobenzylguanidine (MIBG) imaging with that of heart rate variability (HRV) in patients with mild-to-moderate chronic heart failure (HF).

BACKGROUND Cardiac I-123 MIBG imaging, which reflects cardiac adrenergic nerve activity, provides prognostic information on chronic HF patients. Reduced HRV, indicating derangement in cardiac autonomic control, was also reported to be associated with a poor prognosis in chronic HF patients.

METHODS At study entry, I-123 MIBG imaging and 24-h Holter monitoring were performed in 65 chronic HF outpatients with a radionuclide left ventricular ejection fraction <40%. The cardiac MIBG heart to mediastinum ratio (H/M) and washout rate (WR) were obtained from MIBG imaging. The time and frequency domain parameters of HRV were calculated from 24-h Holter recordings.

RESULTS At a mean follow-up of 34 ± 19 months, WR ($p < 0.0001$), H/M on the delayed image ($p = 0.01$), and normalized very-low-frequency power (n-VLFP) ($p = 0.047$) showed a significant association with the cardiac events (sudden death in 3 and hospitalization for worsening chronic HF in 10 patients) on univariate analysis. Multivariate analysis revealed that WR was the only independent predictor of cardiac events, although the predictive accuracy for the combination of abnormal WR and n-VLFP significantly increased, compared with that for abnormal WR (82% vs. 66%, $p < 0.05$).

CONCLUSIONS Cardiac MIBG WR has a higher prognostic value than HRV parameters in patients with chronic HF. The combination of abnormal WR and n-VLFP would be useful to identify chronic HF patients at a higher risk of cardiac events. (J Am Coll Cardiol 2003;41:231–8)
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In chronic heart failure (HF), abnormalities in cardiac autonomic control, characterized by sympathetic overactivity and parasympathetic withdrawal (1), contribute to the progression of the disease and are associated with an unfavorable prognosis (2,3). Therefore, assessing cardiac autonomic status is clinically important in the management of patients with chronic HF. Heart rate variability (HRV) analysis is proposed as a noninvasive tool for the assessment of cardiac autonomic regulation (4) and has been shown to predict the clinical outcome in patients with chronic HF (5–9). On the other hand, cardiac adrenergic nerve activity has been estimated using iodine-123 (I-123) metaiodobenzylguanidine (MIBG) as a noradrenaline analogue (10,11). It has been reported that cardiac MIBG imaging provides prognostic information on patients with chronic HF (12–15). Although some investigators have examined the relationship between the parameters in cardiac MIBG imaging and HRV analysis in patients with chronic HF (16–18), no information is available on the comparison of the prognostic value of cardiac MIBG imaging and HRV analysis in chronic HF. The aim of this study was to prospectively compare the prognostic value of cardiac MIBG imaging with that of HRV in patients with chronic HF.

METHODS

Study patients. We studied 71 consecutive chronic HF outpatients in sinus rhythm, whose radionuclide left ventricular ejection fraction (R-LVEF) was <40%. Patients were required to be stable for at least three months by use of conventional therapy with angiotensin-converting enzyme inhibitors, diuretics, and digoxin. Patients were excluded from the study if they had atrial fibrillation, sinus node dysfunction, atrioventricular block, a permanent pacemaker, significant renal dysfunction, insulin-dependent diabetes mellitus, or autonomic neuropathy. None of the patients were receiving beta-blockers, calcium antagonists, or anti-

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Abbreviations and Acronyms

HF	= heart failure
H/M	= heart to mediastinum ratio
HRV	= heart rate variability
I-123	= iodine-123
LAD	= left atrial dimension
LV	= left ventricle, left ventricular
MIBG	= metaiodobenzylguanidine
(n-)VLFP	= (normalized) very-low-frequency power
R-LVEF	= radionuclide left ventricular ejection fraction
ROI	= region of interest
WR	= washout rate

arrhythmic drugs, except for mexiletine (n = 10) and amiodarone (n = 3) at study enrollment. At study entry, all patients had cardiac MIBG imaging, 24-h ambulatory ECG monitoring, echocardiography, and a plasma noradrenaline assay. All patients gave written, informed consent for their participation in this study, which was approved by the Osaka Prefectural General Hospital's Review Committee.

Radionuclide angiography for entry criteria. Before entering this study, patients underwent electrocardiography (ECG)-gated blood-pool scintigraphy at rest in the supine position, using a conventional rotating gamma camera (Prism 2000, Picker, Bedford, Ohio) equipped with a low-energy, high-resolution, parallel-hole collimator. Patients were given 740 MBq of technetium-99m–labeled human serum albumin (Nihon Medi-Physics, Nishinomia, Japan). The camera was positioned in the modified left anterior oblique projection to isolate the left ventricle (LV) from other cardiac structures, and data acquisition was then completed. The LVEF was calculated using a standard program (19).

Cardiac MIBG imaging. No patients were taking tricyclic antidepressant drugs, sympathomimetic agents, or other drugs known to interfere with MIBG uptake in the month preceding cardiac MIBG imaging.

CARDIAC MIBG ACQUISITION. All patients underwent myocardial imaging with I-123 MIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan), using the same gamma camera as for the radionuclide angiography. Patients were placed in the supine position. A 111-MBq dose of I-123 MIBG was injected intravenously at rest after an overnight fast. Initial and delayed image acquisitions were performed in the anterior chest view 20 and 200 min after the isotope injection.

IMAGE ANALYSIS. Two independent observers who were unaware of the clinical status of patients assessed cardiac MIBG uptake (Fig. 1). Left ventricular activity was recorded using a manually drawn region of interest (ROI) over the whole LV myocardium, and the mean heart counts per pixel were calculated. Another 7 × 7 pixel ROI was recorded over the upper mediastinal area, and the mean counts per pixel were calculated. Background subtraction was performed using the upper mediastinal ROI. The heart-to-mediastinum ratio (H/M) was then determined by dividing the mean counts per pixel in the LV by the mean counts per pixel in the mediastinum. After taking radioactive decay of I-123 into consideration, the cardiac MIBG washout rate (WR) was calculated from the initial and delayed images, as previously reported (15). Based on our previous study, abnormal WR was defined as more than 27% (15).

24-h ambulatory ECG monitoring. Patients underwent 24-h dual-channel ambulatory ECG recording with a Marquette Electronics (Milwaukee, Wisconsin) 8000 Holter monitoring system. Recordings were analyzed by two independent observers who were blinded to the clinical status of the patients. Recordings with more than 15% noise or ectopic beats during 24 h and those with <20 h of analyzable data were excluded from this analysis. Ventricular arrhythmias were classified according to Lown's grade, and nonsustained ventricular tachycardia was defined as five or more consecutive premature ventricular beats, each lasting <30 s.

Traditional measurements of HRV were analyzed using the HRV system, DSC-3100;MemCalc/Chiram (Nihon Koden Co. Ltd., Tokyo, Japan), according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (4). Time domain analysis of HRV included the mean RR (mean duration of all normal to normal [NN] intervals), SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the averages of NN intervals in all 5-min segments), SDNN index (mean of the standard deviations of all NN intervals for all 5-min segments), rMSSD (square root of the mean of the sum of the squares of differences between adjacent NN intervals), pNN50 (number of NN intervals differing by more than 50 ms from the adjacent interval divided by the total number of NN intervals), and HRV triangular index. Spectral analysis was performed using the maximum entropy method (20). Power spectra were quantified by the area within the following frequency band: total power (0.0001 to 0.5 Hz), ultra-low-frequency power (ULFP: 0.0001 to 0.003 Hz), very-low-frequency power (VLFP: 0.003 to 0.04 Hz), low-frequency power (LFP: 0.04 to 0.15 Hz), and high-frequency power (HFP: 0.15 to 0.4 Hz). The LFP/HFP ratio was also calculated. The power within each band was also expressed as the percentage of the total power (normalized ULFP, VLFP, LFP, and HFP). We determined a control value for the HRV parameter in 20 persons (12 men and 8 women; mean age 55 ± 12 years) who had no history of heart disease, a normal physical examination, and normal ECG and chest X-ray findings. The mean value of normalized VLFP (n-VLFP) was 32.3 ± 5.1%. Therefore, we defined abnormal n-VLFP as <22%, which is the mean control value −2 SD.

Echocardiography. Two-dimensional echocardiography was performed with a Toshiba SSH-380A recorder equipped with a 2.5- or 3.75-MHz transducer. The standard technique was employed for sizing the LV and atrium

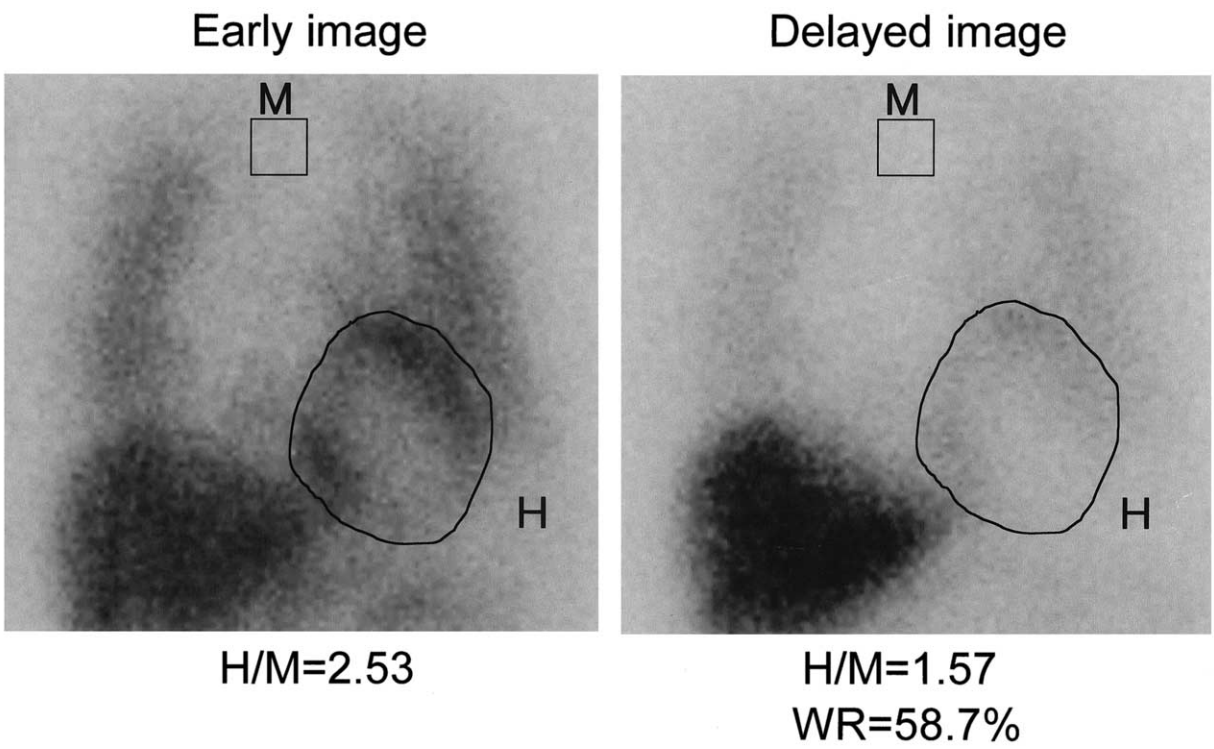

Figure 1. Iodine-123 metaiodobenzylguanidine (MIBG) imaging in a patient with chronic heart failure (HF). Heart (H) and mediastinum (M) were selected, as shown, to measure the H/M ratio. The cardiac MIBG washout rate (WR) was calculated from the initial **(left)** and delayed images **(right)**.

(21). The LV dimension was measured at end-diastole on the R-wave of the ECG-derived QRS complex, just below the level of the mitral leaflets through the standard left parasternal window. The left atrial dimension (LAD) was measured as the distance from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at end-systole.

Plasma noradrenaline concentration. Blood sampling for determination of the plasma noradrenaline concentration was done from an intravenous cannula after resting for at least 30 min in the supine position. The plasma noradrenaline concentration was determined in EDTA plasma by high-performance liquid chromatography (22) at Shionogi Biomedical Laboratories (Osaka, Japan). A duplicate determination in the laboratory showed a coefficient of variation of 0.4% to 5.5%.

Follow-up. All of the study patients were then followed up in our hospital at least once a month by clinicians who did not know the results of the cardiac MIBG imaging and HRV analysis. The end point of this study was when a patient died either suddenly or from other cardiac diseases, or hospital admission for worsening HF failure.

Statistical analysis. Data are presented as the mean value ± SD. The Student *t* test and a Fisher exact test were used to compare differences for continuous and discrete variables, respectively, in patients with and without cardiac events. The cardiac event–free rates in the two groups were calculated using the Kaplan-Meier method, and the difference between them was detected using the log-rank test. The Cox proportional hazards regression model was used to determine the significance of variables predictive of outcome by univariate analysis ($p < 0.05$) as independent predictors of cardiac events on multivariate analysis. The Fisher exact test was used to compare sensitivity, specificity, predictive accuracy, and positive and negative predictive values among the different criteria for prediction of cardiac events. All statistical analyses were carried out using the Stat-View statistical package, version 4.5. A p value <0.05 was considered statistically significant.

RESULTS

Characteristics of patients. Of 71 enrolled patients, six were excluded: five because of the presence of >15% ectopic beats or noise during 24-h ambulatory ECG monitoring and one because of the recording of <20 h of analyzable data. Thus, analysis of both HRV and cardiac MIBG imaging was possible in 65 patients. The mean age of the 65 patients was 63 ± 12 years (range 28 to 85). Fifty-one patients (79%) were men and 14 (21%) were women. Radionuclide LVEF was 28 ± 8%; 13 patients (20%) were in functional class I, 38 patients (58%) were in class II, and 14 patients (22%) were in functional class III. Heart failure was due to ischemic heart disease in 41 patients (63%) and due to idiopathic dilated cardiomyopathy in 24 patients (37%).

Follow-up outcome. All patients were followed up completely. The mean period of follow-up was 34 months

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Table 1. Clinical and Study Characteristics in Patients With Chronic Heart Failure in Relation to Cardiac Events

	With Events (n = 13)	Without Events (n = 52)	p Value
Age (yrs)	61 ± 16	64 ± 10	NS
Gender (male)	77%	79%	NS
Ischemic heart disease	46%	67%	NS
NYHA functional class	2.1 ± 0.8	2.0 ± 0.6	NS
6-min walk distance (m)	355 ± 86	368 ± 94	NS
Heart rate (beats/min)	74 ± 15	76 ± 10	NS
Systolic blood pressure (mm Hg)	122 ± 15	130 ± 18	NS
Diastolic blood pressure (mm Hg)	76 ± 13	73 ± 8	NS
LVEF (%)	26 ± 8	29 ± 8	NS
Ventricular tachycardia (%)	15%	21%	NS
Lown's grade	3.8 ± 0.7	3.3 ± 1.5	NS
LVEDD (mm)	65 ± 8	62 ± 7	NS
LAD (mm)	46 ± 9	40 ± 7	0.01
Noradrenaline (pg/ml)	570 ± 290	409 ± 227	0.035
Drugs			
ACE inhibitors	85%	83%	NS
Digitalis	85%	90%	NS
Diuretics	100%	70%	NS
Beta-blocker*	31%	56%	NS
Anti-arrhythmic drug (Ib/III)†	30% (2/2)	17% (8/1)	NS

*Use of beta-blocker (carvedilol), as scored at the last follow-up visit. †Class Ib anti-arrhythmic drug = mexiletine; class III = amiodarone. Data are presented as the mean value ± SD or percentage of patients.

ACE = angiotensin-converting enzyme; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association.

(maximum 57 months). All patients were examined at least once a month in our hospital during a study period. During that period, 13 (20%) of 65 patients had cardiac events. Three patients died suddenly, 10 patients were admitted for worsening chronic HF, and one of these patients subsequently died of progressive pump failure.

Comparison of baseline characteristics between patients with and without cardiac events. The baseline characteristics of patients with and without cardiac events are listed in Table 1. There were no differences in age, gender, or functional class between the two groups. Although there were no significant differences in the 6-min walk distance, heart rate, blood pressure, R-LVEF, LV end-diastolic dimension, Lown's grade, or presence of nonsustained ventricular tachycardia between the two groups, the LAD was significantly greater and the plasma noradrenaline concentration was significantly higher in patients with than in those without the cardiac events.

There was also no significant difference in drug use between patients with and without cardiac events. As for beta-blockers, 22 of 65 study patients received carvedilol just after study entry. There were no significant differences in the number of patients receiving beta-blockade just after study entry (23% [3/13] vs. 37% [19/52], p = 0.51) or at the last follow-up (31% [4/13] vs. 56% [29/52], p = 0.13) between the two groups. The mean dose of carvedilol in patients with events was similar to that in patients without events (15.0 ± 5.8 vs. 15.7 ± 5.9 mg/day).

Figure 2 shows the results of cardiac MIBG imaging. Patients with cardiac events had a significantly lower H/M ratio on the delayed image (1.56 ± 0.29 vs. 1.77 ± 0.28, p = 0.02) and a higher WR (44.0 ± 14.7% vs. 25.6 ± 12.8%, p < 0.0001) than those without cardiac events, although there was no significant difference in H/M on the early image between the two groups (1.80 ± 0.30 vs. 1.85 ± 0.26). The results of HRV parameters in patients with and without cardiac events are listed in Table 2. Patients with cardiac events had significantly lower n-VLFP than did

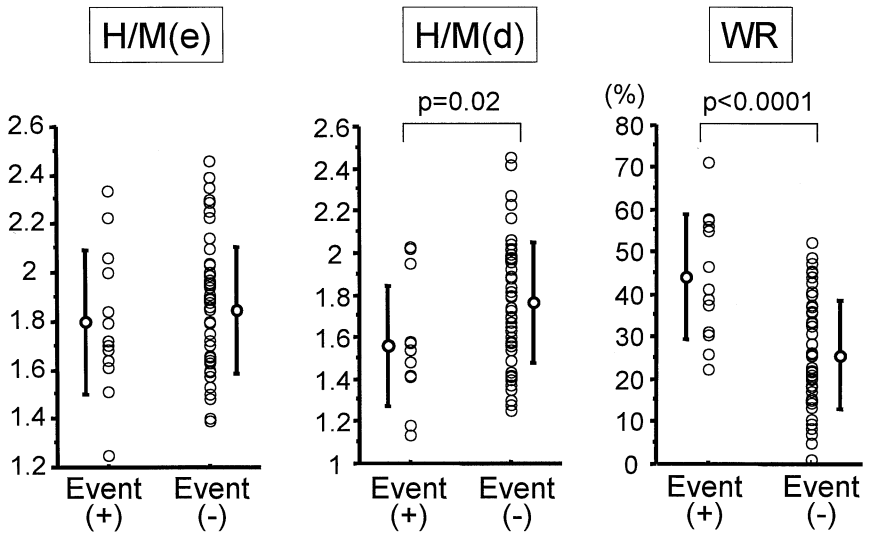

Figure 2. Plots of data of cardiac metaiodobenzylguanidine (MIBG) imaging in patients with chronic heart failure with and without cardiac events. H/M(e) and H/M(d) denote the cardiac MIBG heart to mediastinum ratio (H/M) on the early and delayed images, respectively. Patients with cardiac events had a significantly lower H/M(d) and higher washout rate (WR) than did those without cardiac events, although there was no significant difference in H/M(e) between the two groups.

Table 2. Heart Rate Variability Measurements in Patients With Chronic Heart Failure in Relation to Cardiac Events

	With Events (n = 13)	Without Events (n = 52)	p Value
Mean RR (ms)	810 ± 44	822 ± 201	NS
SDNN (ms)	120 ± 43	120 ± 32	NS
SDANN (ms)	112 ± 44	110 ± 32	NS
SDNN index (ms)	39 ± 12	44 ± 14	NS
rMSSD (ms)	28 ± 7	27 ± 14	NS
pNN50 (%)	6.1 ± 4.5	7.5 ± 8.4	NS
HRV index	17.8 ± 4.9	20.8 ± 9.2	NS
TP (ms^2)	3,964 ± 2,311	4,568 ± 2,487	NS
ULFP (ms^2)	2,639 ± 1,611	2,777 ± 1,509	NS
n-ULFP (%)	66.1 ± 9.8	61.3 ± 10.2	NS
VLFP (ms^2)	969 ± 665	1311 ± 823	NS
n-VLFP (%)	23.2 ± 6.4	29.1 ± 9.0	0.03
LFP (ms^2)	235 ± 196	261 ± 171	NS
n-LFP (%)	6.1 ± 4.1	5.8 ± 2.5	NS
HFP (ms^2)	101 ± 71	139 ± 152	NS
n-HFP (%)	3.4 ± 2.7	2.8 ± 1.9	NS
LFP/HFP	2.5 ± 1.9	2.9 ± 1.9	NS

Data are presented as the mean value ± SD.

HFP = high-frequency power; HRV = heart rate variability; LFP = low-frequency power; Mean RR = mean duration of all normal to normal (NN) intervals; n = normalized; pNN50 = number of NN intervals differing by >50 ms from an adjacent interval divided by the total number of NN intervals; rMSSD = square root of the mean of the sum of squares of differences between adjacent NN intervals; SDANN = standard deviation of averages of NN intervals in all 5-min segments; SDNN = standard deviation of all NN intervals; SDNN index = mean of standard deviations of all NN intervals for all 5-min segments; TP = total power; ULFP = ultra-low frequency power; VLFP = very-low-frequency power.

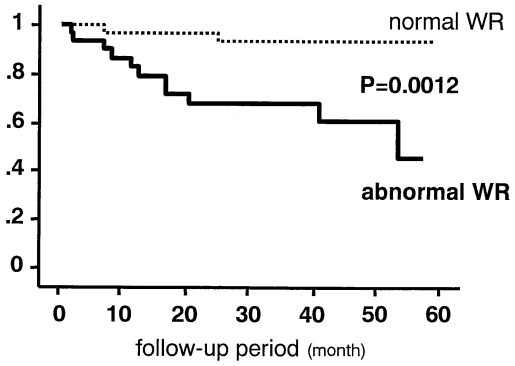

Figure 3. The cardiac event-free rate curves by Kaplan-Meier analysis in patients with chronic heart failure with and without an abnormal washout rate (WR) (>27%). The cardiac event-free rate was significantly lower in patients with an abnormal WR than in those without it.

those without cardiac events, although other time and frequency domain parameters did not differ significantly between the groups.

Prognostic analysis. On univariate analysis, WR, H/M on the delayed image, LAD, plasma noradrenaline concentration, and n-VLFP were significantly associated with cardiac events (Table 3). The risk ratio of cardiac events in patients with an abnormal WR was 6.0 (95% confidence interval [CI] 1.5 to 25.1), which was greater than the risk ratio (3.9 [95% CI 1.5 to 10.3]) in patients with abnormal n-VLFP. Multivariate Cox analysis revealed that WR was the only independent predictor of cardiac events.

Cardiac event–free rate curves, according to abnormal WR and n-VLFP, are shown in Figures 3 and 4, respectively. Cardiac events were significantly more frequently observed in patients with than without abnormal WR (35% vs. 6%, $p = 0.0012$). Abnormal WR gave a sensitivity of 85%, a specificity of 62%, a positive predictive value of 35%, and a negative predictive value of 94% for the prediction of cardiac events in the chronic HF patients. On the other hand, patients with abnormal n-VLFP had cardiac events significantly more frequently than did those without abnormal n-VLFP (42% vs. 11%, $p = 0.0028$). Abnormal n-VLFP gave a sensitivity of 61%, a specificity of 79%, a positive predictive value of 42%, and a negative predictive value of 89% for the prediction of cardiac events in the chronic HF patients.

The combination of abnormal WR and n-VLFP gave a sensitivity of 54%, a specificity of 88%, a positive predictive value of 54%, and a negative predictive value of 82% for the identification of chronic HF patients at risk of cardiac events. Predictive accuracy (82%) for the combination significantly increased ($p < 0.05$), compared with that for abnormal WR (66%) (Table 4). Cardiac events were significantly more frequently observed in patients with both abnormal WR and n-VLFP than in those with both normal WR and n-VLFP (54% [7/13] vs. 4% [1/28], $p < 0.0001$) (Fig. 5).

DISCUSSION

In patients with chronic HF, cardiac adrenergic function is characterized by a reduction in noradrenaline uptake and

Table 3. Univariate and Multivariate Cox Proportional Hazard Analyses for the Identification of Patients With Chronic Heart Failure at Risk for Cardiac Events

	Univariate Analysis		Multivariate Analysis	
	p Value	HR (95% CI)	p Value	HR (95% CI)
WR	<0.0001	1.078 (1.041–1.116)	0.029	1.072 (1.007–1.14)
LAD	0.006	1.13 (1.036–1.236)	0.15	1.071 (0.975–1.175)
H/M(d)	0.01	0.067 (0.008–0.577)	0.42	3.994 (0.136–116.8)
NE	0.01	1.002 (1.000–1.004)	0.7	1.0 (0.998–1.003)
n-VLFP	0.047	0.924 (0.835–0.997)	0.53	0.972 (0.891–1.061)

CI = confidence interval; H/M(d) = heart to mediastinum metaiodobenzylguanidine uptake ratio on the delayed images; HR = hazard ratio; LAD = left atrial dimension; NE = plasma noradrenaline concentration; n-VLFP = normalized very-low-frequency power; WR = washout rate of cardiac metaiodobenzylguanidine.

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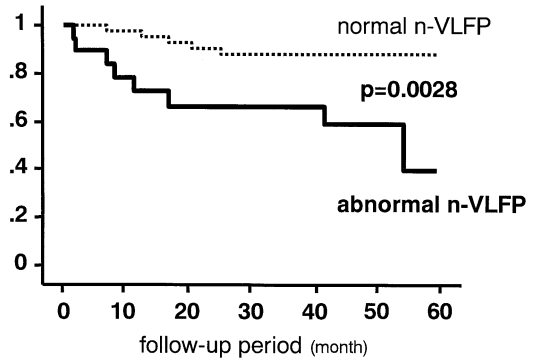

Figure 4. The cardiac event-free rate curves by Kaplan-Meier analysis in patients with chronic heart failure with and without abnormal normalized very-low-frequency power (n-VLFP) (<22). The cardiac event-free rate was significantly lower in patients with abnormal n-VLFP than in those without it.

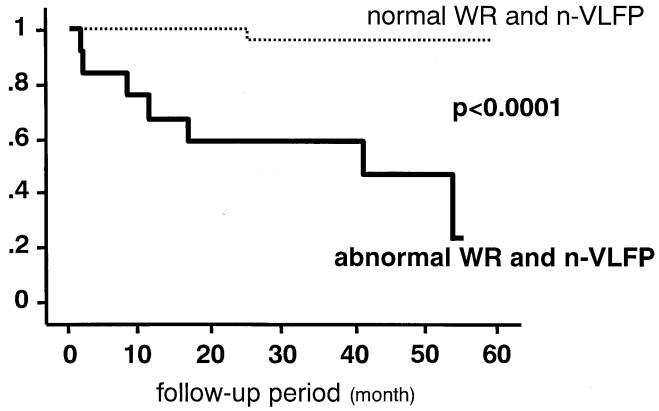

Figure 5. The cardiac event-free rate curves by Kaplan-Meier analysis in patients with chronic heart failure, according to a combination of abnormal washout rate (WR) and normalized very-low-frequency power (n-VLFP). The cardiac event-free rate was significantly lower in patients with both an abnormal WR and n-VLFP than in those with both a normal WR and n-VLFP.

acceleration of spillover in the myocardial adrenergic terminals (23,24). Imaging with MIBG, an analogue of noradrenaline that shares the same uptake pathway within the myocardial adrenergic synapse, reflects cardiac adrenergic nerve activity (10,11,24,25). It has been shown that cardiac MIBG imaging has prognostic value in patients with chronic HF (12-15), but a comparison with reduced HRV, which indicates derangement in cardiac autonomic control (5-9), has not yet been performed. Therefore, we attempted to prospectively compare the prognostic value of cardiac MIBG imaging with that of HRV analysis in patients with chronic HF. This study demonstrated that cardiac MIBG WR has higher prognostic value than HRV parameters, and that the combination of abnormal WR and n-VLFP would identify a higher-risk subset for cardiac events in chronic HF.

Prognostic value of MIBG and HRV in chronic HF. An accurate noninvasive assessment of cardiac sympathetic nerve activity would be particularly important in the setting of chronic HF because of the association between high sympathetic activity in this condition and an adverse prognosis (2). Cardiac MIBG imaging provides direct information on the function and integrity of the presynaptic sympathetic nerve endings (10,24,25). On the other hand, HRV, which depends on postsynaptic signal transduction, reflects the end-organ response of the sinus node. In conditions characterized by marked, persistent sympathetic activation, which is often observed in chronic HF, the sinus node may drastically diminish its responsiveness to neural inputs. The HRV parameters, tending toward very low levels in chronic HF, might have a reduced dispersion, thus limiting their possible statistical power in the regression model. Furthermore, cardiac MIBG imaging may be useful in the assessment of cardiac sympathetic alteration in patients with a high incidence of ectopic activity, in whom HRV analysis cannot always be performed reliably. Therefore, in the present study, cardiac MIBG imaging had a higher prognostic value than HRV analysis in patients with chronic HF.

Table 4. Prediction of Cardiac Events in Patients With Chronic Heart Failure by a Combination of Abnormal Washout Rate and Normalized Very-Low-Frequency Power

	Abnormal WR	Abnormal n-VLFP	Abnormal WR and n-VLFP
Sensitivity (%)	85 (11/13)	61 (8/13)	54 (7/13)
Specificity (%)	62 (32/52)	79 (41/52)	88* (46/52)
Positive predictive value (%)	35 (11/31)	42 (8/19)	54 (7/13)
Negative predictive value (%)	94 (32/34)	89 (41/46)	82 (46/52)
Predictive accuracy (%)	66 (43/65)	75 (49/65)	82* (53/65)

*$p < 0.05$ vs. abnormal WR. The numbers in parentheses are patient numbers.
n-VLFP = normalized very-low-frequency power; WR = washout rate of cardiac metaiodobenzylguanidine.

Cardiac MIBG WR. Uptake of MIBG in the myocardium decreases with time, and there is evidence that MIBG WR could be an index of noradrenaline spillover. There are conflicting data on the relative prognostic values of MIBG WR versus H/M on the delayed images (12-15). In the present study, multivariate analysis showed that only MIBG WR contributes to the estimation of clinical outcome, although H/M on the delayed image was significantly lower in patients with than in those without cardiac events. This result is inconsistent with previous studies showing that H/M has a powerful predictive value, whereas MIBG WR does not (12,13). Different results concerning the predictive value of WR may be due to differences in the method used to calculate WR (application of background subtraction) and the etiology of chronic HF. Metaiodobenzylguanidine WR could reflect adrenergic activity more accurately in patients with chronic HF, in whom denervation is suspected, because WR is independent of the amount of adrenergic neurons, whereas H/M is not. Therefore, in the present study, MIBG WR was superior to H/M with regard to the estimation of prognosis in patients with chronic HF.

Effect of beta-blockade by carvedilol on cardiac MIBG imaging. We assessed the effect of beta-blockade by carvedilol on the MIBG parameters in 21 study patients. The WR significantly decreased (30.8 ± 16.0% to 27.2 ± 17.1%, $p = 0.008$) and H/M on the delayed images increased (1.68 ± 0.28 to 1.74 ± 0.28, $p = 0.02$) one year after the administration of carvedilol, although there was no change in H/M on the early images (1.78 ± 0.20 to 1.79 ± 0.29). Furthermore, R-LVEF significantly increased one year after carvedilol therapy (30.1 ± 7.9% to 37.8 ± 11.8%, $p < 0.0001$). The degree of decrease in MIBG WR roughly correlated with the degree of increase in R-LVEF ($r = -0.46$, $p < 0.05$). These findings were similar to those reported in previous studies (26,27). These results suggest that carvedilol would improve cardiac adrenergic function by an increase in noradrenaline uptake and a reduction of the spillover in cardiac adrenergic terminals and that the improvement in LV function with carvedilol therapy might be accompanied by an attenuation of activation of cardiac adrenergic nerve function.

Heart rate variability in chronic HF. Previous studies showed that time domain measurements of HRV, especially SDNN, were independently associated with mortality (6-8). However, in the present study, none of the time domain measures of HRV were related to cardiac events. The discrepancy may derive from differences in the severity of chronic HF and the study end point, which we defined as not only cardiac death but also hospitalization for worsening chronic HF.

In the present study, on univariate analysis, n-VLFP showed a significant association with cardiac events. Bigger et al. (28) reported that VLFP after myocardial infarction was strongly associated with a poor prognosis, although the physiologic mechanism for this component has not been fully identified. Very-low-frequency power may be influenced by a number of factors other than autonomic balance, such as thermoregulation, the renin-angiotensin system, or peripheral chemoreceptors (29-31). Recently, it has been shown that breathing disorders increase the spectral power to the VLFP range in patients with chronic HF and confound the use of HRV analysis (32). In the present study, n-VLFP in patients with chronic HF was significantly lower than that in normal control subjects with normal breathing (27.9 ± 8.8% vs. 32.3 ± 5.1%, $p < 0.05$). Therefore, it appears that our study was not affected by this confounding effect.

Study limitations. There are several limitations of this study. First, medications used during follow-up may affect MIBG uptake, HRV measurements, and clinical outcome. There was a trend toward a decrease in the use of carvedilol in patients with cardiac events, although the difference was not statistically significant, which may be due to the small sample size in the present study. However, even if the Cox analysis were performed in the subgroups with and without carvedilol therapy separately, the same result—that MIBG WR was significantly associated with the cardiac events–was obtained ($p = 0.035$, hazard ratio 1.076 [95% CI 1.024 to 1.130] in subgroup with carvedilol therapy vs. $p = 0.02$, hazard ratio 1.074 [95% CI 1.010 to 1.142] in subgroup without therapy). Second, there may be a problem in quantifying the cardiac MIBG images. In the present study, 55 (85%) of 65 study patients had an exceedingly low H/M on the early images (<2.11, mean −2 SD of normal value: 2.43 ± 0.16). This may introduce errors when drawing the ROI manually on cardiac MIBG images of patients with chronic HF. In the present study, two independent observers drew the ROI. The interobserver variation in counts per pixel was within 1.2%. Thus, errors introduced by drawing the ROI manually on the cardiac MIBG images are likely to be subtle. Third, we excluded patients with atrial fibrillation, a pacemaker implant, frequent ectopic beats, or insulin-dependent diabetes mellitus. Some of these conditions could be associated with a worse prognosis and therefore could introduce a bias—namely, selecting a subgroup of patients with chronic HF with a lower event rate. Fourth, in this study, we studied only stable outpatients who had mild-to-moderate chronic HF. The results of our study should not be generalized to inpatients with severe chronic HF. Further study is needed to address this issue.

Conclusions. To the best of our knowledge, this is the first study to show that the prognostic value of cardiac MIBG imaging is more powerful than that of HRV analysis and that the combination of abnormal WR and n-VLFP would identify a higher-risk subset for cardiac events in patients with mild-to-moderate chronic HF.

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