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Usefulness of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in the prediction of cardiac events in patients with cardiomyopathy showing stabilization of symptoms or preserved cardiac function

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Objective: It is not rare for patients with cardiomyopathy to be asymptomatic for long periods or to show improved cardiac function following various medical interventions. Conversely, cardiac events sometimes occur in those patients, requiring close observation. We assessed the usefulness of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (MIBG) to predict the occurrence of cardiac events in patients with stable cardiomyopathy. ***Methods:*** The subjects comprised 74 outpatients with stable cardiomyopathy. MIBG was performed calculate the extent score, severity score, washout rate (WR), and heart-to-mediastinum ratio. At about the same time, the left ventricular ejection fraction (LVEF) by echocardiography and the plasma brain natriuretic peptide were measured. The mean observation period extended for 741 ± 437 days with an end point of cardiac events (cardiac death, heart failure requiring hospitalization, and arrhythmias requiring hospitalization). ***Results:*** During the mean follow-up period, 15 cardiac events occurred. Results of multivariate analysis revealed that LVEF was the most powerful predictor of cardiac events (0.006, $p < 0.01$). However, WR was the only significant predictor of hard events such as cardiac death (1.171, $p < 0.001$) and cardiac events in the group of patients who preserved cardiac function with LVEF 0.4 or higher (1.079, $p < 0.05$). ***Conclusion:*** Combined use of LVEF and WR is useful to predict the occurrence of cardiac events in patients with stable cardiomyopathy.

Key words: ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, stable cardiomyopathy, prognosis, left ventricular ejection fraction

INTRODUCTION

CARDIOMYOPATHIES are disorders with poor prognoses, and the only curative treatment currently available is heart transplantation. In recent years, large-scale clinical studies have demonstrated that drugs such as β-blockers and angiotensin-converting enzyme (ACE) inhibitors improve the long-term prognosis,[1–6] to the extent that some patients progress without symptoms or exhibit amelioration in cardiac function. However, a study reported that the long-term prognosis of asymptomatic patients did not differ greatly from that of patients with heart failure,[7] and another study reported that regardless of systolic-function type, hospitalized patients with heart failure have a high severity of illness.[8] Therefore, strict follow-up and treatment are necessary also for patients whose symptoms are stabilized or cardiac functions improved. Left ventricular ejection fraction (LVEF), maximum oxygen consumption in the exercise test, age, family history of sudden death, β-blockers, ACE inhibitors, whether spironolactone is used or not, whether any implantable cardioverter defibrillator is used or not, whether heart transplantation has been undertaken or not, sympathetic nerve activity, and serum brain natriuretic peptide (BNP) level have been implicated as factors determining the prognosis in cardiac

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failure.[9] Given the increase in cases of such mild disorders and cases with improvement of cardiac function, new factors for prediction of cardiac events have to be sought. Not only cardiac function but also sympathetic nerve function should be taken into consideration, given that cardiac sudden deaths reportedly account for approximately 40% of deaths from chronic heart failure,[10] that improvement of LVEF via treatment with cardiotonic and other agents does not necessarily lead to amelioration in the prognosis,[11] and that prophylactic efficacy for sudden death has been observed only with β-blockers but not with ACE inhibitors.[12] ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (MIBG) visualizes the state of sympathetic nerve activity at the myocardial cell level and has recently been documented to be useful in the prognostic evaluation of heart failure.[13–16] There has as yet been no report dealing with the use of this imaging technique in such mild cases or cases showing improved cardiac function. Meanwhile, cardiac function and MIBG imaging parameters do not necessarily correlate well; hence, the latter seems to reflect cardiac status from a viewpoint different to that of cardiac function. The potential usefulness of these parameters as factors predictive of cardiac events in such cases is anticipated. This study was undertaken to assess the usefulness of MIBG imaging in the prediction of cardiac events in patients with cardiomyopathy showing stabilization of symptoms or preserved cardiac function.

METHODS

Study populations

Included in the study were consecutive 74 non ischemic cardiomyopathy patients (57 males and 17 females; mean age: 57 ±12 years). The patients' medical treatment had been determined, and they were treated as outpatients after attaining stabilization of heart failure on drug treatment. The underlying condition was dilated cardiomyopathy in 69 cases and secondary cardiomyopathy in 5 cases (acromegalic cardiomyopathy in 2 cases, doxorubicin-induced cardiomyopathy in 3 cases). Cardiac catheterization revealed no significant (50% or greater) coronary artery stenosis in any patients and ischemic cardiomyopathy was excluded. The patients were followed through periodic checkups over an average period of 741 ± 437 days (30 to 1570 days), taking cardiac events (cardiac death, heart failure requiring hospitalization, and arrhythmias requiring hospitalization) as endpoints. MIBG myocardial imaging was performed with the patient at rest under fasting after at least 60 days of clinical improvement following the establishment of medical treatment. The day of the MIBG imaging was taken as Day 0 of observation, and echocardiography and serum BNP determination were carried out within 14 days before and after MIBG was performed.

Data acquisition by ^{123}I-MIBG myocardial scintigraphy

111 MBq (3 mCi) of ^{123}I-MIBG was intravenously administered, and static data images on a 128 × 128 matrix were obtained for 5 minutes at 20 minutes (early image) and 4 hours (delayed image) after administration of MIBG with the patient resting. After the static planar images were collected, SPECT was performed. The images were taken by IRIX (Picker Corp., Cleveland, Ohio/Shimadzu Corp., Kyoto), a triple headed gamma camera equipped with a low-energy, general all-purpose collimator. SPECT data were collected with a matrix size of 64 × 64 and a mode adjusted to step & shoot, 5 degree steps (37.5 sec)/view, for a total of 72 views. The MIBG myocardial SPECT images were reconstructed from 180 degree data extending from the right anterior oblique (RAO) at 40 degrees through to the left anterior oblique (LAO) at 40 degrees.

Analysis of MIBG myocardial planar and SPECT imagings

(1) Planar imaging

The region of interest (ROI) was placed over the left ventricular myocardium and upper mediastinal area, and the heart-mediastinum activity ratio (H/M) was calculated to quantify cardiac MIBG uptake.

Table 1 Baseline clinical characteristics of all study patients

Patients (n)	74
Age (yrs)	57 ± 12
Gender (female)	17
NYHA class (I/II/III/IV)	19/49/6/0
MIBG data	
eH/M	1.82 ± 0.28
dH/M	1.70 ± 0.31
WR (%)	42.1 ± 10.8
eEXT	36.6 ± 24.7
dEXT	45.2 ± 32.8
eSEV	53.8 ± 55.8
dSEV	69.6 ± 67.5
Echocardiogram data	
LVDd (mm)	59.5 ± 8.3
EF	0.44 ± 0.16
Neurohormonal data	
BNP	225.4 ± 325.0
Medical treatment (%)	
β-blocker	67.6
ACE-inhibitor	40.5
furosemide	71.6
nitrate	18.9
digoxin	33.8
spironolactone	20.3
Atrial fiblation (%)	17.6

Data are presented as the mean value ± SD.

NYHA, New York Heart Association; MIBG, ^{123}I-metaiodobenzylguanidine; e, early; d, delayed; H/M, heart to mediastinum ratio; WR, washout rate; EXT, extent score; SEV, severity score; LVDd, left ventricular end-diastolic dimension; EF, left ventricular ejection fraction; BNP, brain natriuretic peptide; ACE, angiotensin-converting enzyme.

Table 2 Comparison of clinical characteristics based on outcome

	Events (+)	Events (–)	P value
Patients (n)	15	59	
Age (yrs)	53 ± 15	58 ± 12	N.S.
Gender (male %)	73.3	78.0	N.S.
MIBG data			
eH/M	1.69 ± 0.27	1.85 ± 0.28	$p < 0.05$
dH/M	1.52 ± 0.27	1.74 ± 0.31	$p < 0.05$
eEXT	50.3 ± 25.1	33.1 ± 23.7	$p < 0.05$
dEXT	62.3 ± 38.2	40.9 ± 30.2	$p < 0.05$
eSEV	85.0 ± 79.1	45.8 ± 45.8	$p < 0.05$
dSEV	98.3 ± 71.0	62.2 ± 65.1	N.S.
WR (%)	47.6 ± 12.6	0.7 ± 10.0	$p < 0.05$
Echocardiogram data			
LVDd (mm)	62.1 ± 7.5	58.8 ± 8.5	N.S.
EF	0.33 ± 0.16	0.46 ± 0.15	$p < 0.01$
Neurohormonal data			
BNP	542.3 ± 473.5	137.4 ± 203.6	$p < 0.01$
Medical treatment (%)			
β-blocker	53.3	75.0	N.S.
ACE-inhibitor	46.6	41.1	N.S.
furosemide	80.0	73.2	N.S.
nitrate	33.3	16.1	N.S.
digoxin	46.7	32.1	N.S.
spironolactone	33.3	16.9	N.S.
Atrial fiblation (%)	26.7	15.3	N.S.

Data are presented as the mean value ± SD.
Abbreviation as in Table 1.

(2) SPECT imaging

The washout rate (WR) for the entire left ventricle was calculated from the early and delayed images based on the polar map. A polar map was prepared from the data acquired from 17 healthy volunteers to obtain a normal range (mean ± 2SD) of myocardial MIBG uptake. For further objective evaluation, a polar map was constructed from short axis images, from the apex to the base of the left ventricle in both the early and delayed images. The extent score (EXT), representing the area of reduced MIBG uptake and, the severity score (SEV) representing the severity of defect, were calculated in the patients.

Echocardiography

Echocardiography was performed at about the same time as MIBG. From the left ventricular long-axis image, the left ventricular end-diastolic diameters (LVDd) and the left ventricular end-systolic diameters (LVDs) were recorded and the ejection fraction (LVEF) was calculated by the following formula:

$$LVEF = (LVDd^3 - LVDs^3)/LVDd^3$$

Blood BNP

BNP determination was performed during essentially the same period as the MIBG imaging. Peripheral venous blood was withdrawn into a blood collection tube containing EDTA (1 m*l*/m*l*) and aprotinin (10^3 KIU/m*l*).

Table 3 Prognosis analysis of cardiac events on cardiomyopathy

Univariate prodictors of cardiac events on cardiomyopathy

Variables	Hazard ratio	95% CI	P value
Age	0.973	0.973–1.011	0.16
Gender (male)	0.839	0.267–2.637	0.76
NYHA class	2.110	0.869–5.120	0.10
MIBG data			
eH/M	0.156	0.022–1.137	0.07
dH/M	0.144	0.024–0.847	0.03
eEXT	1.022	1.001–1.044	0.04
dEXT	1.015	1.002–1.028	0.02
eSEV	1.006	1.000–1.012	0.05
dSEV	1.005	0.999–1.012	0.10
WR	1.054	1.008–1.101	0.02
Echocardiogram data			
LVDd	1.036	0.981–1.093	0.20
EF	0.005	$1.087E^{-4}$–0.244	0.007
Neurohormonal data			
BNP	1.002	1.001–1.003	0.001
Medical treatment			
β–blocker	2.218	0.804–6.120	0.12
ACE-inhibitor	0.826	0.299–2.279	0.83
furosemide	0.688	0.194–2.443	0.56
nitrate	0.462	0.158–1.717	0.16
digoxin	0.622	0.225–4.184	0.62
spironolactone	0.499	0.170–1.467	0.21
Atrial fiblation	0.508	0.162–1.597	0.51

Multivariate predictors of cardiac events on cardiomyopathy

Variables	P value
dH/M	0.04
eEXT	0.04
dEXT	0.02
WR	0.03
EF	0.005

Abbreviation as in Table 1.

Immunoradiometric assay (IRMA) with S-1215 (Shionogi & Co., Ltd.) sandwiching BNP was carried out, using two monoclonal antibodies specifically recognizing the C-terminal (principal active site) and the ring structure containing the 15-position amino acid of BNP, respectively.

Statistical analysis

Statistical analysis was performed using Statview for Windows. Group mean data were expressed as the mean ± standard deviation. An unpaired Student t test or chi-square test (for non parametrically distributed values) was employed for intergroup comparisons. Univariate and multivariate Cox proportional hazards regression analyses using stepwise analysis were used to identify predictors of cardiac events. For determining optimal thresholds of individual parameters for occurrence of any cardiac events, each group was divided into two subgroups using the mean and 0.25SD and subjected to stratified analysis

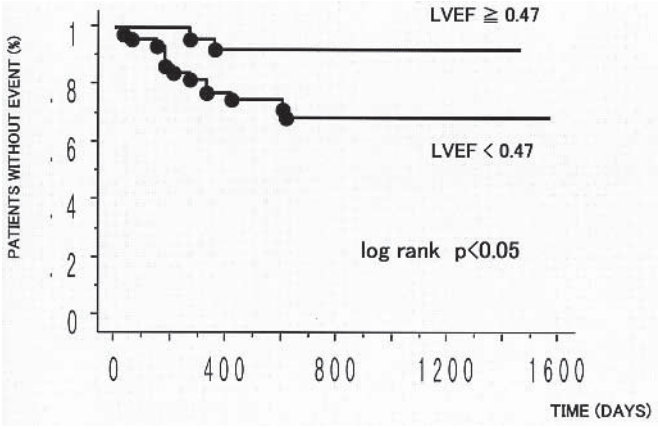

Fig. 1 Kaplan-Meier analysis of occurrence of cardiac events. The optimal threshold of the most powerful predictive factor, LVEF, being set at 0.47-fold of the mean + 0.25SD, the incidence of cardiac events was significantly lower for the EF > 0.47 group.

by sequential log-rank tests. Cumulative rates of event-free cases, above or below the threshold, over time were presented by the Kaplan-Meier estimation and analyzed using log-rank tests. Values at $p < 0.05$ were considered statistically significant in all instances.

RESULTS

Fifteen patients experienced cardiac events during the observation period (i.e., cardiac death, 4 cases; hospitalization due to heart failure, 7 cases; and hospitalization due to arrhythmias, 4 cases). For estimation of the prognostic values, 20 clinical characteristic factors were used: age, gender, NYHA class, MIBG data (the early (e) heart-mediastinum activity ratio (H/M), delayed (d) H/M, washout rate (WR), early extent score (EXT), delayed EXT, early severity score (SEV), and delayed SEV, echocardiogram data (left ventricular end-diastolic diameter (LDVd) and ejection fraction (LVEF)), BNP, medical treatment (β-blocker, ACE-inhibitor, furosemide, nitrates, digoxin, and spironolactone), and atrial fibrillation (Table 1).

Assessment of cardiac event prediction for the overall study population

When comparisons between the event (+) group and the event (−) group were made, eH/M (1.69 ± 0.27 vs. 1.85 ± 0.28, $p < 0.05$) and dH/M (1.52 ± 0.27 vs. 1.74 ± 0.31, $p < 0.05$) were significantly lower for the event (+) group. eEXT (50.3 ± 25.1 vs. 33.1 ± 23.7, $p < 0.05$), dEXT (62.3 ± 38.2 vs. 40.9 ± 30.2, $p < 0.05$), eSEV (85.0 ± 79.1 vs. 45.8 ± 45.8, $p < 0.05$) and WR (47.6 ± 12.6 vs. 40.7 ± 10.0, $p < 0.05$) were significantly higher for the event (+) group.

Significant intergroup differences were noted with respect to LVEF (0.33 ± 0.16 vs. 0.46 ± 0.15, $p < 0.01$) and BNP (542.3 ± 473.5 vs. 137.4 ± 203.6, $p < 0.01$) (Table 2).

Table 4 Comparison of clinical characteristics based on cardiac death

	Events (+)	Events (−)	P value
Patients (n)	4	70	
Age (yrs)	53 ± 11	57 ± 12	N.S.
Gender (male %)	75.0	77.1	N.S.
MIBG data			
eH/M	1.69 ± 0.20	1.82 ± 0.28	N.S.
dH/M	1.49 ± 0.20	1.70 ± 0.32	N.S.
eEXT	51.3 ± 34.9	35.8 ± 34.9	N.S.
dEXT	57.8 ± 39.5	44.5 ± 32.6	N.S.
eSEV	92.8 ± 63.2	51.5 ± 55.1	N.S.
dSEV	134.5 ± 93.0	65.8 ± 64.6	p < 0.05
WR (%)	60.8 ± 15.0	41.0 ± 9.6	p < 0.01
Echocardiogram data			
LVDd (mm)	64.2 ± 11.1	59.2 ± 8.2	N.S.
EF	0.33 ± 0.13	0.44 ± 0.16	N.S.
Neurohormonal data			
BNP	530.5 ± 597.6	196.4 ± 282.6	p < 0.05
Medical treatment (%)			
β-blocker	25.0	73.1	N.S.
ACE-inhibitor	25.0	43.3	N.S.
furosemide	75.0	74.6	N.S.
nitrate	50.0	17.9	N.S.
digoxin	25.0	35.8	N.S.
spironolactone	33.3	16.9	N.S.
Atrial fiblation (%)	0.00	21.4	

Data are presented as the mean value ± SD.
Abbreviation as in Table 1.

On univariate analysis of data, dH/M, eEXT, dEXT, WR, LVEF and BNP proved to constitute statistically significant cardiac event-predictive factors. Multivariate analysis by Cox proportional hazard model using variable stepwise selection demonstrated LVEF to be the most powerful factor for prediction of cardiac events ($p = 0.005$) (Table 3).

The optimal threshold of LVEF, the most powerful of all predictive factors, being set at 0.47-fold of the mean + 0.25SD, the incidence of cardiac events was found to be significantly lower for the EF > 0.47 group (Fig. 1).

Assessment of cardiac death prediction for the overall study population

Data from the 4 cases of cardiac death were analyzed. The deaths were due to arrhythmia and heart failure in 2 patients each. When compared between the event (+) group and the event (−) group, dSEV (134.5 ± 93.0 vs. 65.8 ± 64.6, $p < 0.05$), WR (60.8 ± 15.0 vs. 41.0 ± 9.6, $p < 0.01$) and BNP (530.5 ± 597.6 vs. 196.4 ± 282.6, $p < 0.05$) were significantly higher for the event (+) group (Table 4).

On univariate analysis of data, WR alone proved to constitute a statistically significant cardiac death-predictive factor. Multivariate analysis by a Cox proportional hazard model using variable stepwise selection demonstrated WR to be the most powerful factor for prediction

Table 5 Prognosis analysis of cardiac death on cardiomyopathy

Univariate predictors of cardiac death on cardiomyopathy

Variables	Hazard ratio	95% CI	P value
Age	0.975	0.908–1.047	0.49
Gender (male)	0.890	0.092–8.559	0.92
MIBG data			
eH/M	0.163	0.004–7.507	0.35
dH/M	0.096	0.003–3.429	0.20
eEXT	1.024	0.983–1.067	0.26
dEXT	1.010	0.986–1.035	0.41
eSEV	1.007	0.996–1.018	0.19
dSEV	1.011	0.999–1.024	0.07
WR	1.175	1.068–1.294	0.0001
Echocardiogram data			
LVDd	1.061	0.959–1.173	0.25
EF	0.012	$9.221E^{-6}$–616.67	0.23
Neurohormonal data			
BNP	1.001	1.000–1.003	0.12
Medical treatment			
β-blocker	6.781	0.705–65.213	0.10
ACE-inhibitor	2.227	0.232–21.414	0.49
furosemide	0.926	0.096–8.922	0.95
nitrate	0.262	0.037–1.864	0.18
digoxin	1.693	0.176–16.275	0.65
spironolactone			
Atrial fiblation	0.606	0.063–5.829	0.66

Multivariate predictors of cardiac events on cardiomyopathy

Variables	Hazard ratio	P value
WR	1.174	0.0011

Abbreviation as in Table 1.

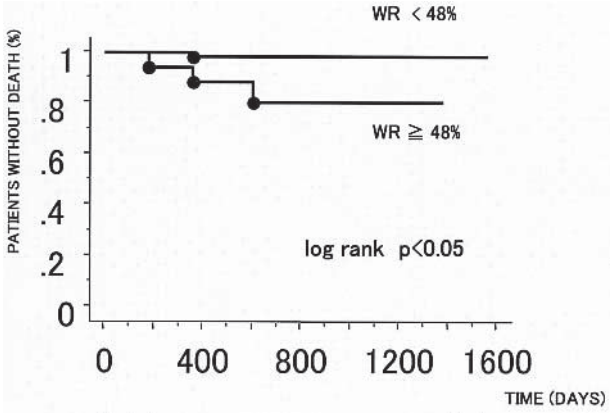

Fig. 2 Kaplan-Meier analysis of occurrence of cardiac death. When the optimal threshold of the statistically significant predictive factor, WR, was set at 48% of the mean + 0.5SD, the incidence of cardiac death was significantly lower for the WR < 48% group.

of cardiac death (p = 0.0011) (Table 5).

The optimal threshold of WR, the statistically significant predictive factor, being set at 48% of the mean + 0.5SD, the incidence of cardiac death was found to be significantly lower for the WR < 48% group (Fig. 2).

Table 6 Comparison of clinical characteristics based on outcome (EF > 0.4)

	Events (+)	Events (–)	P value
Patients (n)	4	38	
Age (yrs)	59 ± 8	57 ± 11	N.S.
Gender (male %)	50.0	81.6	N.S.
MIBG data			
eH/M	1.71 ± 0.33	1.90 ± 0.27	N.S.
dH/M	1.55 ± 0.26	1.80 ± 0.31	N.S.
eEXT	46.0 ± 22.1	29.5 ± 24.3	N.S.
dEXT	52.5 ± 8.9	34.9 ± 27.0	N.S.
eSEV	71.8 ± 50.1	41.9 ± 50.2	N.S.
dSEV	68.5 ± 52.4	52.6 ± 61.8	N.S.
WR (%)	49.5 ± 15.5	37.8 ± 10.1	p < 0.05
Echocardiogram data			
LVDd (mm)	54.5 ± 1.8	56.9 ± 7.7	N.S.
EF	0.54 ± 0.18	0.55 ± 0.10	N.S.
Neurohormonal data			
BNP	368.0 ± 250.3	73.8 ± 177.5	p < 0.05
Medical treatment (%)			
β-blocker	50.0	78.4	N.S.
ACE-inhibitor	50.0	43.2	N.S.
furosemide	75.0	70.3	N.S.
nitrate	25.0	16.2	N.S.
digoxin	25.0	37.8	N.S.
spironolactone	25.0	15.8	N.S.
Atrial fiblation (%)	0.00	13.2	

Data are presented as the mean value ± SD.
Abbreviation as in Table 1.

Assessment of cardiac event prediction for patients with preserved cardiac function (LVEF > 0.4)

There were 42 patients with preserved cardiac function (LVEF > 0.4), data from whom were analyzed to predict cardiac events. Four of these 42 cases experienced cardiac events (i.e., cardiac death, 1 case; hospitalization due to heart failure, 1 case; and hospitalization due to arrhythmias, 2 cases). When compared between the event (+) group and the event (–) group, WR (49.5 ± 15.5 vs. 37.8 ± 10.1, p < 0.05) and BNP (368.0 ± 250.3 vs. 73.1 ± 177.5, p < 0.05) were significantly higher for the event (+) group (Table 6).

On univariate analysis of data, WR alone proved to constitute a statistically significant cardiac event-predictive factor. Multivariate analysis by a Cox proportional hazard model using variable stepwise selection demonstrated WR to be the most powerful factor for prediction of cardiac events (p = 0.04) (Table 7).

The optimal threshold of WR, the statistically significant predictive factor, being set at 45% of the mean + 0.5SD, the incidence of cardiac events was found to be significantly lower for the WR < 45% group (Fig. 3).

Table 7 Prognosis analysis of cardiac events on cardiomyopathy (EF > 0.4)

Univariate predictors of cardiac death on cardiomyopathy (EF > 0.4)

Variables	Hazard ratio	95% CI	P value
Age	1.031	0.934–1.139	0.55
Gender (male)	0.240	0.034–1.702	0.15
NYHA class	2.489	0.350–17.705	0.36
MIBG data			
eH/M	0.044	$3.604E^{-4}$–5.494	0.21
dH/M	0.035	0.001–2.335	0.12
eEXT	1.027	0.983–1.073	0.23
dEXT	1.022	0.986–1.059	0.23
eSEV	1.008	0.993–1.024	0.30
dSEV	1.003	0.989–1.017	0.65
WR	1.081	1.007–1.162	0.03
Echocardiogram data			
LVDd	0.967	0.847–1.104	0.62
EF	0.238	$1.402E^{-5}$–4042.1	0.77
Neurohormonal data			
BNP	1.003	0.999–1.006	0.10
Medical treatment			
β-blocker	2.945	0.415–20.917	0.28
ACE-inhibitor	0.896	0.126–6.367	0.91
furosemide	0.701	0.073–6.744	0.76
nitrate	0.714	0.074–6.870	0.57
digoxin	2.040	0.212–19.622	0.54
spironolactone	0.569	0.059–5.478	0.63
Atrial fiblation			

Multivariate predictors of cardiac death on cardiomyopathy (EF > 0.4)

Variables	Hazard ratio	P value
WR	1.080	0.04

Abbreviation as in Table 1.

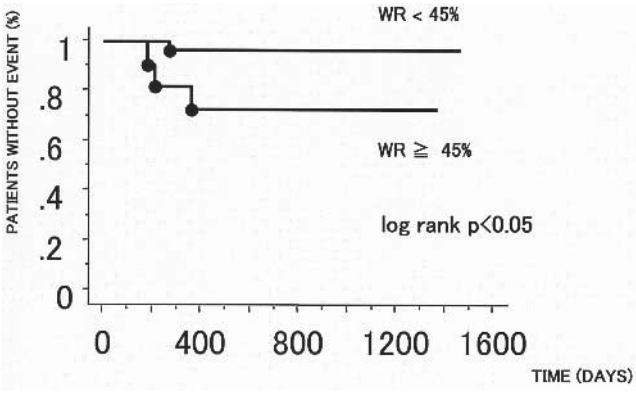

Fig. 3 Kaplan-Meier analysis of occurrence of cardiac events (EF > 0.4). The optimal threshold of the statistically significant predictive factor, WR, being set at 45% of the mean + 0.5SD, the incidence of cardiac events was significantly lower for the WR < 45% group.

DISCUSSION

In the present study conducted in patients with relatively mild, stable cardiomyopathy on settled medical treatment, the analyses disclosed LVEF to be the most powerful predictive factor of cardiac events. While the overall mean LVEF was as high as 44% because a considerable proportion consisted of milder cases, compared with the studies published previously, there did exist cases showing noticeably low LVEF values, indicating that the occurrence of cardiac events is not infrequent in such cases. Patients displaying such low LVEF values are considered (even if symptoms are stabilized on medical treatment) to have organic abnormalities of advanced myocardial degeneration such as necrosis, loss of myocardial cells and interstitial fibrosis; hence severe abnormalities exist at a non-compensatory phase. In the clinical field, sudden cardiac events occur in patients whose cardiac functions have been improved or symptoms stabilized, posing a greater than who problem. Examinations of individual cases in the present study show that not all of the cardiac events occurred solely in patients with low EF values. One study reported that there was no marked difference in long-term prognosis between asymptomatic patients and patients with heart failure[7] and another study reported that regardless of systolic-function type, hospitalized patients with heart failure have a high severity of illness.[17] The present study investigated whether or not LVEF was the most useful predictor of cardiac events or even hard events, that is, cardiac death, in patients whose cardiac functions were improved to some degree. Regarding cardiac death, it was found that LVEF was not a significant predictive factor; only WR in the MIBG imaging proved to be a predictive factor. A reason for this, as mentioned before, is that the present study population comprises patients with mild disease, mostly showing relatively high LVEF values. It was demonstrated, in fact, in V-HEFT I and II cooperative large-scale clinical studies that the annual mortality rate was not linearly related to LVEF but rose sharply at LVEF values below 25%.[18,19] The second reason is that cardiac sudden death reportedly accounts for about 40% of causes of death in patients with chronic heart failure.[10] There is a possibility that, particularly in patients whose symptoms and medical treatment are both stabilized, cardiac sudden death may comprise an even greater proportion of causes of death. The principal cause in these cases is fatal ventricular arrhythmia, which is considered to be related to a sympathicotonic state. WR has been described to mostly reflect hypertonia of the cardiac sympathetic innervation, and the present results are consistent with this. Progression of myocardial disorders in cardiomyopathy is not uniform, so that the heterogeneity of sympathetic nerve involvement may possibly constitute a focus for the development of arrhythmias. It has been shown in laboratory animals that local sympathetic denervation promoted arrhythmia development.[20]

Although dSEV did not prove to be a significant predictive factor for cardiac death in the present series, it is of interest to note the significant difference in this parameter, which is indicative of the severity of the defect, that was observed between the subgroups with and without cardiac death. The usefulness of MIBG in assessing the risk of cardiac death in patients with heart failure has been reported,[21,22] but there is no unanimity of opinion regarding a direct relation of fatal arrhythmia with MIBG; further study would be needed to resolve this issue. Of the 4 cases of cardiac death identified in this study, death was due to heart failure in two. This finding indicates that even those patients showing improved cardiac function and/or attaining stabilization of symptoms may not only evince an increased risk of fatal arrhythmia again but may also have aggravation of cardiac function and symptomatic exacerbation insofar as their cardiac sympathetic innervation remains in a hypertonic state. This would suggest a potential use for MIBG imaging in the evaluation of cardiac failure over time. In patients whose cardiac functions were preserved with LVEF 0.4 or higher, WR was the only significant predictor of cardiac events. It is generally considered that there is a correlation between functions of cardiac sympathetic nerve and cardiac functions in patients with heart failure. However, the dissociation of the above two functions is often observed in patients. Investigation of our patients revealed that while there was a significant and negative correlation between LVEF and WR, the correlation coefficient was 0.548. Sympathetic disorders in patients with this dissociation are those of sympathetic hypertonicity, in which, while the sympathetic nerve is present, the nervous spill-over is accelerated. The accelerated state is said to be best reflected in WR in MIBG. The results of the present study suggested that it was highly possible that cardiac events would occur in patients whose cardiac functions were improved, yet sympathetic functions were not improved with hypertonicity persisting. For these patients, close follow-up is necessary, and MIBG was more useful than LVEE for evaluation of therapeutic effects and prognosis. In recent years, the efficacy of drugs such as β-blockers and ACE inhibitors in improving the long-term prognosis of patients with cardiac failure has been verified, and their use now constitutes standard therapy, with an increasing number of patients attaining improvement of cardiac function and long-term stabilization of symptoms. Accordingly, the time has arrived for reviewing the conventional predictive parameters for cardiac events. The present data indicate the possible predictability of cardiac events in such cases through the use of combinations of LVEF with MIBG parameters.

LIMITATION

One limitation of the present results involves the serum BNP data. Not all patients in this study were followed by measurements of serum BNP levels while the observation period ranged up to as long as 1570 days. Therefore, this parameter was subjected to univariate analysis but could not be included in the multivariate analysis. Indeed, several reports have documented the usefulness of BNP in the determination of prognosis of heart failure,[23–25] and this parameter seems very likely to be a significant predictive factor of cardiac events in relatively stable cases like those in the present series. The analyses limited to cases of cardiac death and those showing improvement of cardiac function nevertheless indicated that WR appears more likely to be more useful as a predictive factor than BNP. Closer investigation would be needed while MIBG parameters are still considered useful in such cases.

The rarity of both cardiac death and cardiac events in patients with improved cardiac function (as few as 4 cases within the parameters of this study) may pose a problem in terms of statistical reliability. We feel empirically the need for new predictive factors for cardiac events in addition to the conventional ones. Treatment of heart failure has changed and yet more cases have come to light in which the condition is relatively mild with stable symptoms, or shows improvement of cardiac function. Further to this paper, data from large-scale clinical studies assessing the usefulness of MIBG are keenly anticipated.

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