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ORIGINAL ARTICLE

Cardiac sympathetic activity and relationship to cardiac events and left ventricular reverse remodeling in patients with non-ischemic dilated cardiomyopathy

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Abstract

Background Delayed heart-to-mediastinum ratio (HMR) has been associated with catecholamine levels and contractile reserve in dilated cardiomyopathy (DCM); however, there is scant evidence regarding the association between cardiac sympathetic activity and left ventricular reverse remodeling (LV-RR). We calculated the ^{123}I-metaiodobenzylguanidine (^{123}I-mIBG) HMR and washout rate (WR) in patients with DCM and investigated their associations with LV-RR.

Methods From April 2003 to January 2020, in 120 patients with DCM who underwent ^{123}I-mIBG scintigraphy. 66 patients undergoing follow-up echo and taking a beta-blocker from baseline were examined the relationship between ^{123}I-mIBG and LV-RR. After that, this prognostic value for composite cardiac events was evaluated in the entire 120 patients.

Results In LV-RR analysis, patients were 50.4 ± 12.2 years, with a mean left ventricular ejection fraction of 28.6%. Of 66 patients, 28 (42.4%) achieved LV-RR. Multiple logistic regression analysis of LV-RR revealed that not delayed HMR but the WR (cutoff value: 13.5%) was an independent predictor of LV-RR (odds ratio 6.514, $p = 0.002$). In the analysis for composite cardiac events, even though WR itself does not have the prognostic capacity, Kaplan–Meier survival curves divided by the cutoff value (delayed HMR = 2.0, WR = 13.5) showed that delayed HMR and WR values enabled the stratification of high-risk patients (log-rank $p < 0.001$).

Conclusions The ^{123}I-mIBG WR was associated with the prevalence of LV-RR in patients taking 100% of beta-blockers and 98.5% of renin-angiotensin system inhibitors. Reflecting the contractile reserve, the combined assessment of the delayed HMR and WR could be used to further precisely stratify the patients with DCM.

Keywords ^{123}I-mIBG · Cardiomyopathy · Left ventricular reverse remodeling

Abbreviations

^{123}I-mIBG	^{123}I-metaiodobenzylguanidine
HMR	Heart-to-mediastinum ratio
DCM	Dilated cardiomyopathy
LV-RR	Left ventricular reverse remodeling
WR	Washout rate
LVEF	Left ventricular ejection fraction
HF	Heart failure
LVDd	Left ventricular end-diastolic diameter
LVDs	Left ventricular end-systolic diameter
LMEGP	Low-medium-energy general purpose
CCi	Conversion coefficient of the institutional camera/collimator system

Introduction

The sympathetic nervous system innervating the heart is an important neurohumoral compensation mechanism for patients with chronic heart failure, and increased sympathetic activity and norepinephrine levels are present in patients with myocardial dysfunction [1–5]. Alternatively, prolonged norepinephrine overload can adversely affect the myocardial structure, as shown in ventricular remodeling, eventually leading to increased mortality and morbidity.

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The accumulation and extraction of ^{123}I-metaiodobenzylguanidine (^{123}I-mIBG) in the heart showed kinetics similar to those of norepinephrine, reflecting cardiac sympathetic activity.

Various reports have shown that the myocardial delayed heart-to-mediastinum ratio (HMR) is decreased in patients with heart failure and is associated with prognosis in patients with heart failure (HF) [6, 7] and dilated cardiomyopathy (DCM) [8] Although myocardial ^{123}I-mIBG uptake has been associated with catecholamine levels and contractile reserve in DCM [9, 10], scant evidence regarding an association between cardiac sympathetic activity and left ventricular reverse remodeling (LV-RR) is available.

Because LV-RR has been regarded as a major prognostic phenomenon of DCM [11, 12], here, we calculated the ^{123}I-mIBG HMR and washout rate (WR) in patients with DCM by standardization using the cross-calibration phantom method and investigated their associations with LV-RR and cardiac events.

Methods

Ethics statements

The study protocol was approved by our institutional committee on human clinical investigations (approval number: 2017-0031), and written informed consent was obtained from all enrolled patients.

Study population

From April 2003 to January 2020, hemodynamic parameters of patients with cardiomyopathy, excluding those with New York Heart Association Functional Class IV, were collected. DCM was defined as < 50% left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVDd) > 55 mm, or indexed LVDd > 33 mm/m^2 (male) or 32 mm/m^2 (female) determined by echocardiography [13]. Coronary artery disease diagnosed by coronary angiography or coronary multidetector computed tomography, and primary valvular heart disease were excluded. With the exception of one case of a transient complete atrioventricular block at the time of the procedure, all patients underwent endomyocardial biopsy to exclude secondary cardiomyopathy. For 120 patients with DCM who underwent ^{123}I-mIBG scintigraphy, to estimate physical condition, we reviewed all patients' laboratory measurements, echocardiography and electrocardiography findings, and medication records. When analyzing LV-RR, patients who were prescribed a beta-blocker within 1 month before ^{123}I-mIBG imaging and/or those not taking a beta-blocker at ^{123}I-mIBG imaging and patients undergoing cardiac resynchronization therapy implantation during the follow-up period were excluded to minimize the influence of new beta-blockers and cardiac resynchronization therapy introduction for both ^{123}I-mIBG parameters and LV-RR. Finally, 66 patients with DCM who underwent ^{123}I-mIBG scintigraphy fulfilled the inclusion criteria.

Laboratory examinations

Blood samples were collected to measure patients' general biochemical data. Simultaneously, neurohormonal parameters (plasma adrenaline, noradrenaline, dopamine, and B-type natriuretic peptide levels) were measured.

Echocardiography

Standard M-mode and two-dimensional echocardiography, Doppler blood flow imaging, and tissue Doppler imaging were performed according to the guidelines of the American Society of Echocardiography [14] using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) within 1 week of the ^{123}I-mIBG study. LVDd, left ventricular end-systolic diameter (LVDs), and LVEF were calculated using the Teichholz method. The peak flow velocities at the mitral level during rapid filling, atrial contraction, rapid filling/atrial contraction, and deceleration time were calculated using pulsed Doppler imaging. We recorded the tissue Doppler imaging wave of the mitral annulus from the septal side of the apical four-chamber view and analyzed the early diastolic filling velocity.

^{123}I-mIBG protocol

Myocardial ^{123}I-mIBG scintigraphy was performed in patients with a stable status of heart failure, and patients with symptoms of heart failure at rest or on intravenous therapy, such as inotropic drugs or vasodilators, were excluded. 111 MBq ^{123}I-mIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan) was intravenously injected into the patients, and anterior planar images were obtained 15 min (initial image) and 3 h (delayed image) after the injection using various gamma cameras equipped with a low-energy or low-medium-energy collimator. Myocardial ^{123}I-mIBG uptake was quantified using a region of interest manually drawn to a suitable size for each patient. Before 2007, e.CAM and 9300A systems with a low-energy high-resolution collimator (Toshiba, Tochigi, Japan) were used (n = 40). After 2007, the Symbia S equipped with a low-medium-energy general-purpose (LMEGP) collimator (Siemens Japan Co., Ltd., Tokyo, Japan) (n = 72), Symbia T6 with an LMEGP collimator (Siemens Japan Co., Ltd.) (n = 10), Symbia T with an LMEGP collimator (Siemens Japan Co., Ltd.) (n = 2), and Symbia EVO with an LMEGP collimator (Siemens Japan Co., Ltd.)

($n=3$) were used. The HMR was calculated by dividing the mean count/pixel in the left ventricle by that in the upper mediastinum. After 2007, the HMRs were calculated using the semiautomatic region of interest setting software "smartMIBG" [15].

The average conversion coefficient (0.88) from the most common medium-energy group was used to calculate the standard HMR [16–19]. Standard HMR = 0.88/CCi (Conversion coefficient of the institutional camera/collimator system) × (institutional HMR − 1) + 1. Where CCi means the conversion coefficient of the institutional camera/collimator system (Supplemental Fig. 1). WR was calculated using the following formula [20]. Standard WR = (early HMR − delayed HMR)/early HMR × 100 (%).

Definition of LV-RR

LV-RR was defined as an absolute increase in the LVEF from ≥ 10% to a final value > 35% accompanied by a decrease in the LVDd ≥ 10% [21]. These values were obtained by echocardiography at baseline and within 12–18 months after registration.

Composite cardiac events

The composite cardiac events were evaluated in the entire 120 patients who underwent ^{123}I-mIBG scintigraphy in our institution from April 2003 to January 2020. The follow-up duration was calculated from the date of the ^{123}I-mIBG study to the date of the last clinical visit. Composite cardiac events were defined as sudden cardiac death, lethal arrhythmia, which is a potentially life-threatening arrhythmic event, including a documented episode of spontaneous sustained ventricular tachyarrhythmia, resuscitated cardiac arrest, appropriate implantable cardioverter defibrillator discharge (anti-tachycardia pacing or defibrillation), and hospitalization for worsening heart failure. Event data were collected from patient records at our hospital, telephone interviews, or correspondence by letter.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range and were compared using the Student t-test for parametric variables and Mann–Whitney U-test for non-parametric variables. Categorical variables are presented as number (%) and were compared using the chi-square test or Fisher exact test, as appropriate. Cox proportional hazard regression analysis was performed to compute the hazard ratios with 95% confidence intervals for the composite outcome. Univariate regression analyses were used to estimate LV-RR predictors, and odds ratios and 95% confidence intervals are presented with the logistic regression analysis. Receiver operating characteristic curve analysis was used to obtain the best prognostic predictor for composite outcomes and LV-RR. Kaplan–Meier curves were used to compare the composite outcomes according to sudden cardiac death, admission due to worsening heart failure, and ventricular tachycardia, and the differences were compared using the log-rank test.

All statistical analyses were performed using JMP Pro version 15.0 (SAS Institute, Cary, NC, USA). Figures were generated using Prism (GraphPad Software, San Diego, CA, USA).

Results

Baseline characteristics of patients with or without LV-RR

LV-RR analysis was performed for 66 patients who received a beta-blocker from the entry of the study (Table 1). After a mean 383 days of echocardiographic evaluation, 28 (42.4%) of 66 patients showed LV-RR. There were no significant differences between the groups with respect to age, sex, estimated glomerular filtration rate, LVEF, early and delayed HMR, and levels of B-type natriuretic peptide, noradrenaline, adrenaline, and dopamine. However, the QRS was significantly shorter and WR was significantly higher in patients with LV-RR than in those without it ($p<0.001$ and $p=0.022$, respectively) (Table 1, Fig. 1).

When receiver operating characteristic analysis was conducted using the WR, the receiver operating characteristic curve identified a WR cutoff value for LV-RR of 13.5% (area under the curve: 0.667; sensitivity, 64.3%; specificity, 73.7%) (Fig. 2).

Logistic regression analysis for predictors of LV-RR

In multiple logistic regression analysis for LV-RR ($n=66$) (Table 2), the QRS and WR, not the delayed HMR, were independent predictors of LV-RR (odds ratio 0.931; 95% confidence interval 0.884–0.980; $p<0.001$ and odds ratio, 6.514; 95% confidence interval 1.824–23.27; $p=0.002$, respectively).

Relationship between MIBG and cardiac events

In order to estimate the relationship between ^{123}I-mIBG and cardiac events, 120 patients with DCM who underwent ^{123}I-mIBG scintigraphy in our institution were enrolled in additional analysis. Because delayed HMR has been considered a strong predictor of cardiac events in patients with cardiomyopathy, receiver operating characteristic curve analysis was performed to assess the ability of the delayed HMR

Table 1 Baseline characteristics of the study patients ($n=66$)

	Total ($n=66$)	LV-RR (-) ($n=38$)	LV-RR (+) ($n=28$)	p value
Age (years)	50.4 ± 12.2	51.7 ± 13.4	48.7 ± 10.3	0.278
Female, *n*(%)	12 (18.2)	8 (21.1)	4 (14.3)	0.481
BMI (kg/m^2)	24.6 ± 4.7	24.4 ± 4.8	24.8 ± 4.6	0.492
Mean AP (mmHg)	88.6 ± 16.6	87.6 ± 18.7	90.0 ± 13.3	0.436
DM, *n*(%)	14 (21.2)	10 (26.3)	4 (14.3)	0.237
Af, *n*(%)	9 (13.6)	4 (10.5)	5 (17.9)	0.391
Laboratory measurements				
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.2	0.330
Estimated GFR (ml/min/1.73m^2)	67.5 ± 21.3	68.9 ± 24.1	65.7 ± 16.9	0.861
HbA1c (%)	6.2 ± 1.0	6.2 ± 1.2	6.2 ± 0.6	0.352
BNP (pg/mL)	254.7 (166.6–342.8)	220.2 (102.6–338.0)	301.4 (161.8–440.9)	0.154
Adrenaline (ng/mL)	0.042 (0.034–0.050)	0.043 (0.032–0.053)	0.041 (0.027–0.054)	0.835
Noradrenaline (ng/mL)	0.668 (0.5398–0.794)	0.597 (0.421–0.773)	0.763 (0.565–0.960)	0.096
Dopamine (ng/mL)	0.032 (0.021–0.042)	0.034 (0.018–0.050)	0.029 (0.015–0.043)	1.000
Echocardiography				
LVDd (mm)	65.6 ± 8.2	65.8 ± 9.5	65.3 ± 6.1	0.555
LVDs (mm)	56.3 ± 9.0	55.8 ± 10.8	57.0 ± 6.0	0.099
LAD (mm)	41.2 ± 6.5	40.1 ± 6.7	42.8 ± 6.0	0.103
LVEF (%)	28.6 ± 8.8	30.1 ± 10.2	26.6 ± 6.2	0.124
E/*A* ratio	1.2 ± 0.8	1.2 ± 0.6	1.2 ± 0.9	0.786
E/*e*′ ratio	16.0 ± 8.3	16.3 ± 10.2	15.5 ± 5.0	0.315
Dct (ms)	186.0 ± 68.2	203.1 ± 69.4	164.8 ± 61.5	0.088
Electrocardiogram				
QRS (ms)	119.2 ± 28.8	130.0 ± 33.6	104.6 ± 8.3	**0.001**
MIBG				
Early HMR	2.34 (2.22–2.46)	2.32 (2.14–2.51)	2.36 (2.21–2.51)	0.846
Delayed HMR	2.04 (1.93–2.15)	2.06 (1.90–2.15)	2.01 (1.87–2.15)	0.785
WR (%)	12.6 (10.8–14.4)	11.1 (8.8–13.4)	14.7 (11.8–17.6)	**0.022**
Medication at pre-examination				
RAS-Inhibitor, *n* (%)	61 (92.4)	37 (97.4)	24 (85.7)	0.077
Beta-blockers, *n* (%)	66 (100)	38 (100)	28 (100)	–
Carvedilol equivalents (mg/day)	6.8 (5.2–8.3)	7.9 (5.6–10.2)	5.3 (3.3–7.2)	0.119
Aldosterone antagonists, *n* (%)	45 (68.2)	25 (65.8)	20 (71.4)	0.627
Diuretics, *n* (%)	52 (78.8)	26 (68.4)	26 (92.9)	**0.016**
Amiodarone, *n* (%)	7 (10.6)	5 (13.2)	2 (7.1)	0.433
Medication at follow-up period				
RAS-Inhibitor, *n* (%)	65 (98.5)	38 (100)	27 (96.4)	0.240
Beta-blockers, *n* (%)	66 (100)	38 (100)	28 (100)	–
Carvedilol equivalents (mg/day)	11.2 (9.6–12.8)	10.8 (8.6–13.0)	11.8 (9.4–14.2)	0.394
Aldosterone antagonists, *n* (%)	45 (68.2)	26 (68.4)	19 (67.9)	0.961
Diuretics, *n* (%)	43 (65.2)	24 (63.2)	19 (67.9)	0.620
Amiodarone, *n* (%)	10 (15.2)	9 (23.7)	1 (3.6)	**0.024**

Data are mean ± SD or median (interquartile range)

BMI body mass index, *AP* atrial pressure, *DM* diabetes mellitus, *Af* atrial fibrillation, *GFR* glomerular filtration rate, *BNP* B-type natriuretic peptide, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *E/A ratio* ratio of early transmitral flow velocity to atrial flow velocity, *E/e′ ratio* ratio of early transmitral flow velocity to early diastolic mitral annular velocity, *Dct* deceleration time, *HMR* heart-to-mediastinum ratio, *WR* washout rate, *RAS* Renin–angiotensin system

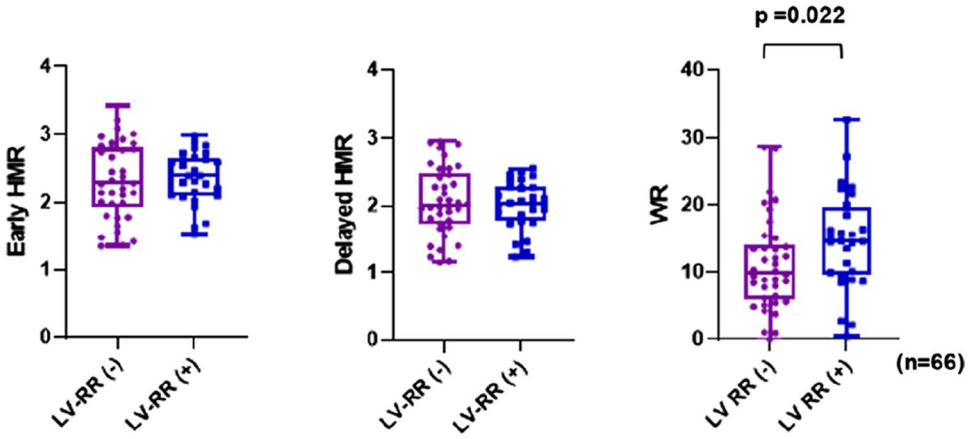

Fig. 1 Box plot of the early HMR, delayed HMR and WR in the patients with and without LV-RR. Distribution of early and delayed HMR shows no significant difference in the patients with and without LV-RR; however, the WR is significantly higher in the LV-RR group than in the non-LV-RR group ($p = 0.022$). *HMR* heart-to-mediastinum ratio, *WR* washout rate, *LV-RR* left ventricular reverse remodeling

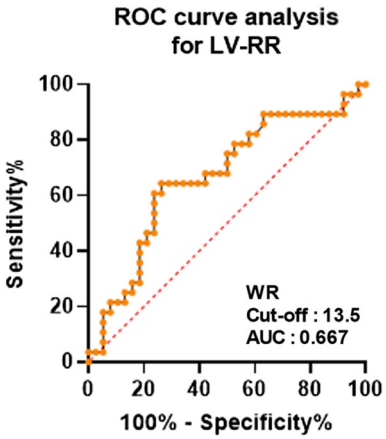

Fig. 2 ROC curve analysis of WR for LV-RR. The ROC curve identifies a WR cutoff value for LV-RR of 13.5% (area under the curve: 0.667, sensitivity: 64.3%, specificity: 73.7%). *ROC* receiver operating characteristic, *WR* washout rate, *LV-RR* left ventricular reverse remodeling

to distinguish between patients with and without composite cardiac events. A delayed HMR ≥ 2 was predictive of cardiac events, with a sensitivity of 69.3% and specificity of 66.7% (area under the curve: 0.646, $p = 0.014$) (Fig. 3). The baseline clinical characteristics of the patients are presented in Supplemental Table 1. The mean age was 50.7 years, LVEF was 30.1%.

There were no significant differences between delayed HMR < 2.0 and delayed HMR ≥ 2.0 groups ($n = 47$ and 73, respectively) in sex, the body mass index, rate of atrial fibrillation, estimated glomerular filtration rate, and adrenaline, dopamine, and hemoglobin levels. The rates of diabetes mellitus, B-type natriuretic peptide and noradrenaline levels, LVDd, LVDs, and left atrial diameter were significantly higher in the delayed HMR < 2 group than in the delayed HMR ≥ 2.0 group, whereas age, mean arterial pressure, LVEF, and deceleration time were significantly lower in the delayed HMR < 2 group than in the delayed HMR ≥ 2.0 group. Aldosterone antagonists, diuretics, and amiodarone tended to be more frequently prescribed in the delayed

Table 2 Multiple logistic regression analysis for the LV-RR ($n = 66$)

Variable	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Mean AP (mmHg)	1.009 (0.979–1.039)	0.559		
Creatinine (mg/dL)	1.816 (0.239–13.79)	0.563		
Plasma BNP** (pg/mL)	1.006 (0.992–1.021)	0.362		
LVEF (%)	0.955 (0.901–1.013)	0.114		
QRS (ms)	0.943 (0.904–0.983)	**< 0.001**	0.931 (0.884–0.980)	**< 0.001**
Delayed HMR ≥ 2.0	0.647 (0.240–1.741)	0.387		
WR ≥ 13.5%	4.418 (1.556–12.54)	**0.004**	6.514 (1.824–23.27)	**0.002**

Bold values indicate statistical significance

LV-RR left ventricular reverse remodeling, *CI* confidence interval, *OR* odds ratio. Other abbreviations as in Table 1

*The final model included all univariate predictors

**Per 10-pg/mL increments

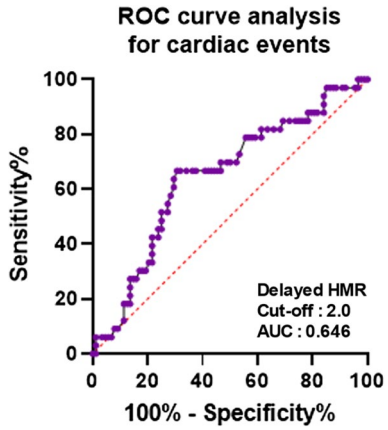

Fig. 3 ROC curve analysis of delayed HMR for cardiac events. The ROC curve identifies a HMR cutoff value for cardiac events of 2 (area under the curve: 0.646, sensitivity: 69.3%, specificity: 66.7%). *ROC* receiver operating characteristic, *HMR* heart-to-mediastinum ratio

HMR < 2 group than in the delayed HMR ≥ 2.0 group at both study entry and follow-up.

During the follow-up period (mean 6.0 years), sudden cardiac death, admission due to worsening heart failure, and lethal arrhythmia occurred in 3 (2.5%), 25 (20.8%), and 5 (4.2%) of patients, respectively.

The composite cardiac event-free survival rate was significantly lower in the delayed HMR < 2 group than in the delayed HMR ≥ 2 group ($p < 0.001$) (Fig. 4).

Cox proportional hazards model for predictors of cardiac events

We examined the associations between patient characteristics and hemodynamic variables for composite cardiac events using Cox proportional hazards analysis (Supplemental Table 2) ($n = 120$). The mean arterial pressure, LVEF, and delayed HMR were identified in univariate analysis as predictors of cardiac events. In multivariate analysis, delayed HMR was an independent predictor of cardiac events (hazard ratio 0.326; 95% confidence interval 0.145–0.733; $p = 0.007$).

Risk stratification of patients with a delayed HMR and WR cutoff values

Kaplan–Meier survival curves divided by the cutoff value (delayed HMR = 2.0, WR = 13.5) showed that delayed HMR and WR values enabled the stratification of high-risk patients (log-rank $p < 0.001$) and patients with a delayed HMR ≥ 2.0 and WR ≥ 13.5 experienced subsequently no cardiac events (Fig. 5). Furthermore, in the analysis of patients who were taking beta-blockers during ^{123}I-mIBG imaging and follow-up period ($n = 89$), WR was significantly lower in the patients with cardiac events in the delayed HMR ≥ 2 ($n = 54$) group, but this tendency was not detected in the group of patients with delayed HMR < 2 ($n = 35$) (Fig. 6). Representative cases of cardiac sympathetic nerve activity on ^{123}I-mIBG scintigraphy are shown in Fig. 7.

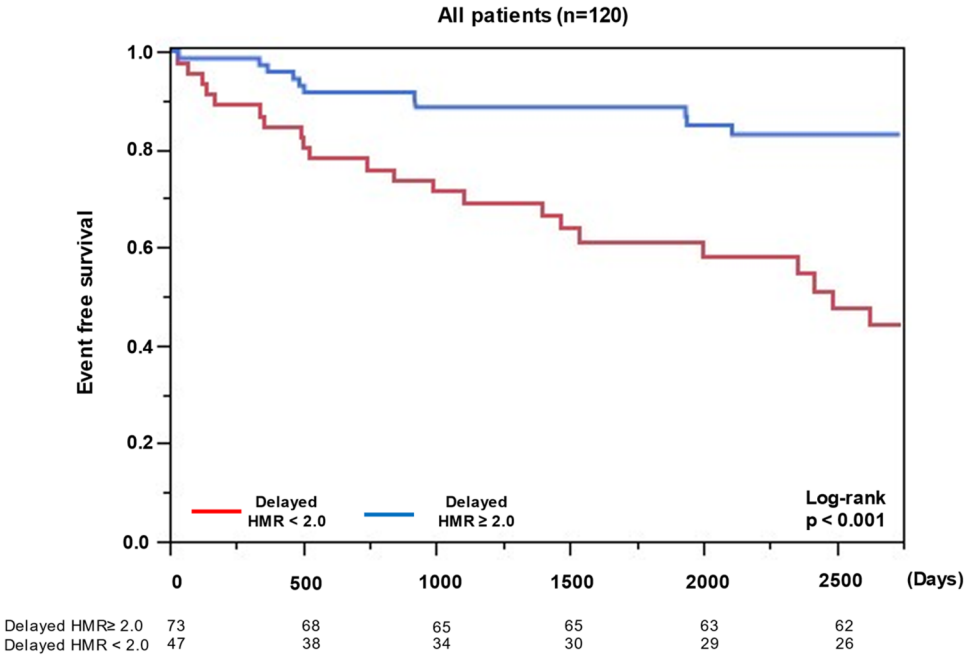

Fig. 4 Kaplan–Meier analysis of the probability of cardiac events for inpatients with DCM divided into 2 groups according to the delayed HMR cutoff value of 2.0. The delayed HMR < 2 group (red) shows a significantly higher probability of a cardiac event than the delayed HMR ≥ 2 group (blue) ($p < 0.001$; log-rank test). *DCM* dilated cardiomyopathy, *HMR* heart-to-mediastinum ratio

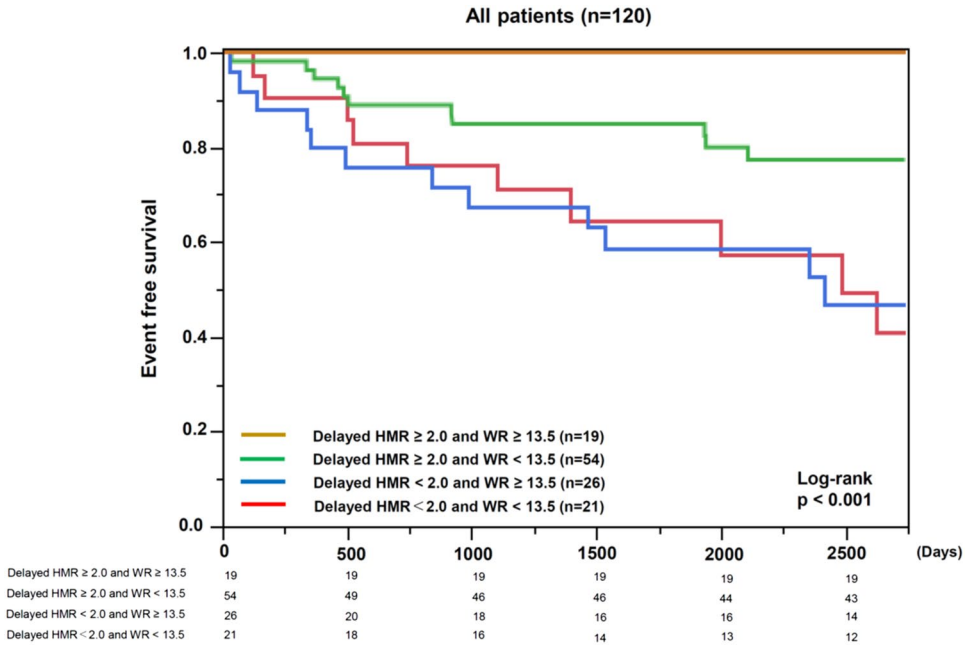

Fig. 5 Kaplan–Meier analysis of the probability of cardiac events for inpatients with DCM divided into 4 groups according to the HMR and WR. Kaplan–Meier survival curves for cardiac events reveals a significant difference divided into four groups according to the HMR and WR ($p < 0.001$). *DCM* dilated cardiomyopathy, *HMR* heart-to-mediastinum ratio, *WR* washout rate

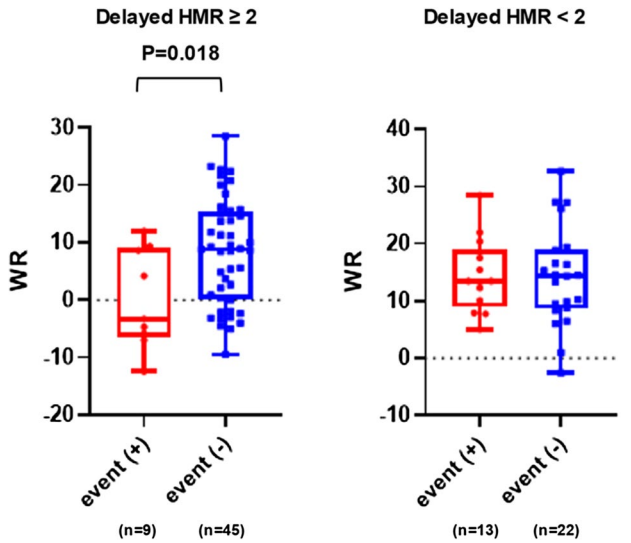

Fig. 6 Distribution of the WR in the HMR ≥ 2 and HMR < 2 patients with and without cardiac events. Distribution of WR was significantly lower in the patients with cardiac events in the delayed HMR ≥ 2 ($n = 54$) group; however, this difference was not detected in the group of patients with HMR < 2 ($n = 35$). *HMR* heart-to-mediastinum ratio, *WR* washout rate

Discussion

This study showed that the cutoff value for the delayed HMR to predict cardiac events was a delayed HMR < 2, as in the previous report [7]. Furthermore, the WR and QRS were associated with LV-RR under 100% of beta-blocker and 98.5% of renin–angiotensin system inhibitors prescriptions and patients with both a delayed HMR ≥ 2.0 and WR ≥ 13.5 experienced the most favorable clinical outcomes. From these results, evaluation of not only delayed HMR but also WR values in DCM may enable a more detailed stratification of patients with not severe but mildly progressed myocardial impairment.

Myocardial ^{123}I-mIBG scintigraphy is an analog of the adrenergic neuron blocking agent guanethidine, which is used to estimate myocardial presynaptic sympathetic innervation and activity, and reduced ^{123}I-mIBG uptake reflects the severity of myocardial damage. In the normal myocardium, the WR value ranges from 0 to 1% [22, 23]. An increased WR reflects impaired sympathetic presynaptic activity, dysregulation of adrenoceptor signal transduction, and myocardial degeneration, and contributes to worsening heart failure [24–27], poor response to cardiac resynchronization therapy [28] and lethal arrhythmogenicity, leading to sudden cardiac death [29]. Imamura et al. reported that a WR ≤ 39% was the only significant independent predictor of LV-RR at 6 months post-left ventricular assist device implant [30] and the ADMIRE-HF study also showed that when prospectively evaluating symptomatic heart failure, the WR in patients with heart failure who experienced cardiac events was significantly higher than that in others [6]. Yong-Mei Cha et al. reported that non-responders to cardiac resynchronization therapy had a higher WR than responders (62% versus 37%, $p = 0.003$) [28], and another group reported that the WR can be used to predict the response to a beta-blocker [31]. However, Nakata, et al. reported that their results of the WR cannot be used as a prognostic index [32] and the WR did not have a relationship with hemodynamic indexes including peak oxygen consumption, nor did it have

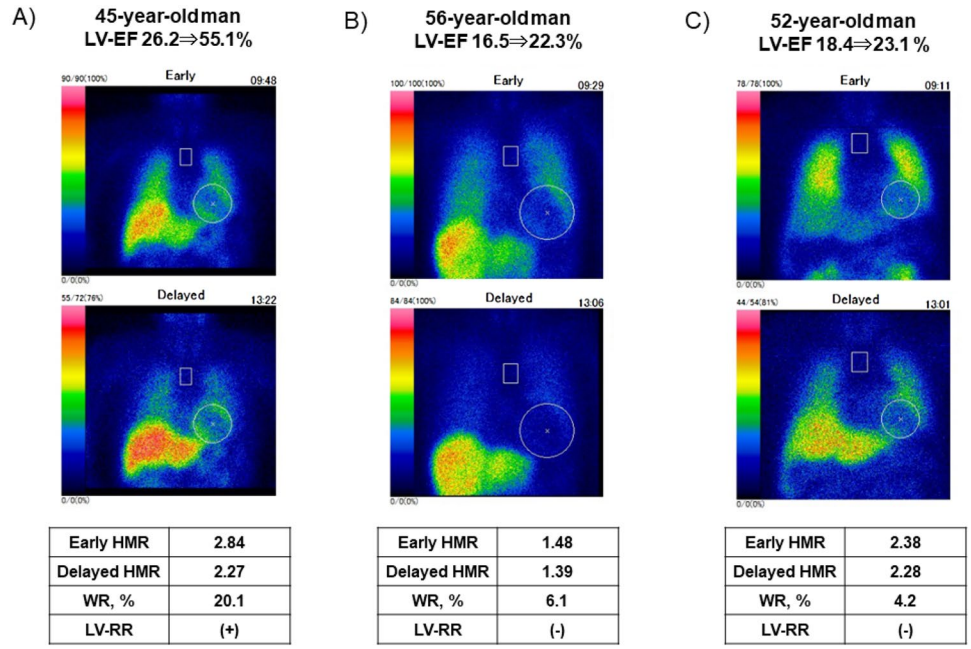

Fig. 7 Representative cases of ^{123}I-mIBG scintigraphy. **A** A 45-year-old man, and he was observed the delayed HMR was 2.27 and WR was 20.1. After 366 days later, LVEF was improved from 26.2% to 55.1%. **B** A 56-year-old man, and he was observed the delayed HMR was 1.39 and WR was 6.1. After 343 days later, LVEF was not significantly improved from 16.5 to 22.3%. **C** A 52-year-old man, and he was observed the delayed HMR was 2.28 and WR was decreased as 4.2. Even though delayed HMR ≥ 2, LVEF was not significantly improved from 18.4% to 23.1% after 354 days later. *HMR* heart-to-mediastinum ratio, *WR* washout rate, *LVEF* left ventricular ejection fraction

a prognostic value [33], Lee et al. and Hara et al. observed that the WR did not correlate with the percentage changes in LVEF after the initiation of beta-blocker therapy [20, 34]. Similar results were reported in a previous study in which beta-blockers were prescribed in all study participants [35].

The reason for the inconsistent usefulness of the WR as a predictor for cardiac events may be related to the biphasic change in the WR depending on the stage of heart failure and the course of treatment including beta-blockers [36].

Regarding the transition of WR value from early to late HF stage [37],

1. Early stage: WR was elevated due to sympathetic nervous system hyperactivity and is expected to be highly reactive to cardioprotective drugs.
2. Middle stage: WR was temporarily dropped due to sympathetic nervous system hypoactivity.
3. Late stage: WR was re-elevated, reflecting myocardial damage itself, and is not expected to be highly reactive to cardioprotective drugs in this phase.

Actually, Verschure et al. reported that the WR of cardiac resynchronization therapy responders tended to be higher than that of non-responders in the stable stage [38]. Tamaki et al. reported the predictive value of the WR for sudden cardiac death in patients with heart failure, that patients with LVEF > 35% had a low rate of sudden cardiac death regardless of the WR values, and that there was no event except in 1 patient after 3 years of enrollment [39] and reported that patients with DCM (≥ 90% belonging to New York Heart Association class I or II) showing a high WR have a favorable outcome after the initiation of beta-blocker therapy regardless of LVEF [36]. Our results demonstrating that DCM patients with a high WR had better outcomes are partially in accordance with the aforementioned studies' results.

The WR is thought to increase in the sympathetically hypersensitive state in the early heart failure phase and fluctuate with improvement in cardiac function. After myocardial degeneration progresses with the course of heart failure, the WR increases, reflecting myocardial degeneration, and when the damaged sympathetic nerve terminal relates to decreasing uptake-1, the WR function was finally decreased [36]. The patients with a high WR but subsequently declining WR had improved LVEF, suggesting that it varied not only with the degree of myocardial impairment but also with the therapeutic intervention and response [40–43]. Similar to our analysis, the QRS duration is a simple indicator that can be easily obtained from the ECG and has been reported to be related to the LV-RR [44]. Konishi et al. reported that QRS duration < 106 ms was associated with the rate of LV-RR in patients with non-ischemic cardiomyopathy [45]. WR alone is difficult to assess hemodynamics because it is expected to fluctuate depending on the stage of heart failure. We stratified patients using a combined assessment of the WR with the HMR. Just like us, Kasama et al. reported that the combined use of late ventricular potentials with the WR was useful to predict sudden cardiac death [46]. Recently, Chimura et al. reported that the combination of WR and late gadolinium enhancement on cardiac magnetic resonance is effective for risk stratification of DCM. The prognosis is good when WR is high but late gadolinium enhancement is negative, indicating that high WR is not a poor prognostic factor in itself in which myocardial damage is not advanced [47].

Deterioration of heart failure, arrhythmia, and sudden cardiac death results from multifactorial conditions and is related to various triggers. Although the biphasic nature of the WR makes it difficult to demonstrate its prognostic usefulness, it can be a powerful factor when combined with other factors. Further multicenter participation and prospective analyses of its prognostic value are needed to estimate the biphasic components of the WR.

Limitations

This study has some limitations. First, this was a single-center study with a small number of enrolled patients. Second, there were variations and deficiencies in the duration of the follow-up ultrasound sonographies in the retrospective study. Third, a detailed mechanistic analysis of the association between the WR and LV-RR was not performed in this retrospective analysis of clinical data. Finally, as a retrospective analysis, the effect of beta-blocker initiation time, titrated beta-blocker dose and length of HF on both delayed HMR and WR could not be examined and may have significant selection bias. In order to resolve these issues, further prospective validation is needed.

New knowledge gained

WR is difficult to predict cardiac events because it is variable depending on the stage of heart failure, influence of drug and device introduction. Combining the HMR and WR obtained by ^{123}I-mIBG imaging could stratify patients with DCM precisely.

Conclusions

The standardized delayed HMR is a useful prognostic predictor of cardiac events. Furthermore, the WR was significantly related to LV-RR frequency. A combined assessment of the delayed HMR and WR may be useful for a more precise stratification of patients with DCM.

Clinical implications

- The WR is an independent predictor of LV-RR in patients with DCM taking a beta-blocker.
- Using both an HMR and WR would lead to more accurate stratification of patients with a low risk of cardiac events than using individual parameters.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest T.O. received research grants from Ono Pharmaceutical Co. Ltd., Bayer Pharmaceutical Co. Ltd., Daiichi-Sankyo Pharma Inc., and Amgen Astellas BioPharma K.K. outside of the submitted work. T.O. received honoraria from Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., and Medtronic Japan Co. Ltd. T.M. received lecture fees from Bayer Pharmaceutical Co. Ltd., Daiichi-Sankyo Co. Ltd., Sumitomo Pharma Co. Ltd., Kowa Co. Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Sanofi-Aventis K. K., and Takeda Pharmaceutical Co. Ltd. T.M. received an unrestricted research grant from the Department of Cardiology, Nagoya University Graduate School of Medicine, from Astellas Pharma Inc., Daiichi-Sankyo Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Kowa Co. Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma K. K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-Aventis K. K., Takeda Pharmaceutical Co. Ltd., and Teijin Pharma Ltd. The authors declare that they have no conflicts of interest.

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