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Prognostic value of cardiac metaiodobenzylguanidine imaging and QRS duration in implantable cardioverter defibrillator patients with and without heart failure

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ABSTRACT

Background: Cardiac metaiodobenzylguanidine (MIBG) imaging provides prognostic information in patients with heart failure (HF). Recent studies showed that the highest rate of ventricular tachyarrhythmias (VTs) is seen in HF patients with an intermediate decrease in MIBG uptake, rather than in those with the lowest values. However, prolonged QRS duration (QRSd) has been shown to be associated with VTs in HF patients. This study assessed the prognostic value of the combination of an intermediate decrease in MIBG uptake and prolonged QRSd for predicting VTs in patients with implantable cardioverter defibrillators (ICDs) in relation to the presence of heart failure (HF).

Methods and results: A total of 196 outpatients with ICDs (age: 64 ± 14 years, male: 81%, left ventricular ejection fraction [LVEF]: 49% ± 16%) were prospectively enrolled; 135 had HF (NYHA class: 2.0 ± 0.6). At entry, cardiac MIBG imaging was performed, and QRSd was measured on standard 12-lead electrocardiography. An intermediate decrease in the heart-to-mediastinum ratio on the delayed planar image (ID-H/M) was defined as 1.40–1.89. During the 3.3 ± 2.2-year follow-up, 59 patients had appropriate ICD discharges (ATx) for VTs. On multivariate Cox analysis, ID-H/M and prolonged QRSd (≥147 ms) were significantly and independently associated with ATx. In both patients with and without HF, ATx were significantly more frequent in patients with ID-H/M and/or prolonged QRSd than in those with neither (with HF: 40% vs. 14%, $p = 0.020$; without HF: 43% vs. 10%, $p = 0.0028$).

Conclusions: The combination of ID-H/M and prolonged QRSd provided more prognostic information for predicting VTs in ICD patients, with and without HF.

1. Introduction

Despite recent advances in the diagnosis and management of patients with cardiac disease, sudden cardiac death remains a leading cause of cardiovascular death [1]. According to the current guidelines, the use of implantable cardioverter defibrillators (ICDs) for the primary prevention of sudden cardiac death (SCD) is recommended only in patients with ischemic and non-ischemic cardiomyopathy (CM) whose left ventricular ejection fraction (LVEF) is <35% [2,3]. However, in a community-wide study, only approximately one-third of patients who died from SCD had an LVEF that met the LVEF-based criteria for prophylactic ICD implantation under the current guidelines, and the major burden of SCD occurs in patients with less severe LV impairment [4]. The need to identify the subgroup of patients with mild and moderate reductions in LVEF or patients without chronic heart failure (CHF) at high risk for SCD has also been highlighted by the guidelines and statements

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[1] All authors have made an important contribution to the study and are thoroughly familiar with the primary data. TM, YF, ST, YI, AK, TK, MS, HK, and YS contributed to the conception and design of this study. TY contributed to both the conception and design of this study, and the analysis and interpretation of the data. MF gave the final approval of the manuscript to be submitted.

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[1–3,5]. Furthermore, ICD discharges are linked to significant mortality and impairment of quality of life (QoL) of patients with ICD implants [6–9]. Therefore, it is clinically relevant to identify those patients with cardiac disease, with or without CHF, at greatest risk for ventricular tachyarrhythmias and who would benefit most from ICD therapy.

The autonomic nervous system plays a major role in the pathophysiology of arrhythmias leading to SCD [10]. Cardiac metaiodobenzylguanidine (MIBG) imaging, which is useful for evaluating cardiac adrenergic nervous system activity [11], provides prognostic information in CHF patients with a reduced LVEF [12–17]. Recent studies have shown that the highest rate of severe arrhythmic events is seen in CHF patients with an intermediate decrease (ID) in MIBG uptake, rather than in those with the lowest values; however, there is a progressive increase in the all-cause mortality rate as cardiac uptake decreases [18–20]. On the other hand, prolonged QRS duration (pQRSd) on the resting 12-lead electrocardiogram (ECG) has been shown to be associated with SCD not only in CHF patients, but also in the general population [21–24]. Therefore, the goal of this study was to investigate the prognostic value of the combination of ID in MIBG uptake and pQRSd for the prediction of ventricular tachyarrhythmias in patients with ICDs with and without CHF.

2. Methods

2.1. Study patients

A total of 217 consecutive outpatients with ICDs who were followed-up at our hospital between January 2012 and September 2018 were enrolled. Patients were excluded from this study if they withdrew informed consent (n = 2) or were judged as inappropriate for the study due to difficulty in follow-up by primary care physicians (n = 19). Therefore, 196 patients were analyzed. Heart failure was diagnosed by a history of worsening heart failure, symptoms due to heart failure according to the Framingham criteria, or LVEF < 50%. LVEF <50% as the cut-off value for heart failure was based on a recent guideline [25]. Patients with heart failure were required to be stable for at least one month on the guideline-based optimum pharmacotherapy including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists. At entry, all patients underwent cardiac MIBG imaging, standard 12-lead electrocardiography (ECG), and echocardiography, and a venous blood sample was drawn. The study protocol was approved by the Ethics Committee of Osaka General Medical Center. Written, informed consent was provided by all patients before enrollment in the study. The trial was registered at UMIN-CTR (000018225).

2.2. Cardiac MIBG imaging

Cardiac iodine-123(^{123}I)-MIBG scintigraphy was performed at entry. No patients were taking any tricyclic antidepressant drugs, sympathomimetic agents, or other drugs known to interfere with MIBG uptake within the month preceding cardiac MIBG imaging. All patients underwent myocardial imaging with ^{123}I-MIBG (Myo-MIBG-I 123 Injection; FUJIFILM RI Pharma, Tokyo, Japan) using a conventional rotating gamma camera (BrightView; Philips, Amsterdam, The Netherlands) equipped with a low-energy type, cardiac high-resolution collimator. Patients were placed in the supine position. A 111-MBq dose of ^{123}I-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 isotope injection. Two independent observers who were unaware of the clinical status of the patients assessed cardiac MIBG uptake. Left ventricular activity was recorded with a manually drawn region-of-interest (ROI) over the entire left ventricular myocardium, and the mean heart counts/pixel were calculated. Another 7 × 7 pixel ROI was recorded over the upper mediastinal area, and the mean counts/pixel were calculated. Background subtraction was performed with the upper mediastinal ROI. The heart-to-mediastinum ratio (H/M) was then determined by dividing the mean counts/pixel in the mediastinum on the early and delayed images. After taking radioactive decay of ^{123}I into consideration, the cardiac MIBG washout rate was calculated from the initial and delayed images, as previously reported [26]. An intermediate decrease in the H/M (ID-H/M) was defined as 1.40–1.89, based on the previous report [27].

2.3. ECG

The standard resting 12-lead ECG was recorded in all subjects at baseline. ECG recordings were performed at a paper speed of 25 mm/s and amplitude of 10 mm/mV. QRS duration was measured by a computer on digitized ECGs from the beginning of the earliest to the end of the last QRS deflection.

2.4. Follow-up

All study patients were followed-up prospectively in our hospital at least once every 6 months. The endpoint of this study was appropriate ICD discharge. The appropriate ICD discharge events were determined from source documents, including ICD interrogation reports. When patients became unable to visit the outpatient clinic, the follow-up data were obtained by contacting the physicians in charge or the patients. As far as possible, ICD interrogations were performed in patients who died suddenly.

2.5. Statistical analysis

Data are presented as values and percentages, mean values ± standard deviation (SD), or medians with first to third quartiles [Q1–Q3]. Categorical variables were compared with the χ^2 test or Fisher's exact test. Continuous variables were compared using Student's *t*-test or the Wilcoxon rank sum test based on their distribution. A Cox proportional hazards regression model was used to assess the prognostic value of a late H/M and pQRSd for appropriate ICD discharge, adjusting for the clinical variables (NYHA functional class, LVEF, and blood urea nitrogen [BUN]) that are known to be associated with ventricular tachyarrhythmias [28]. The event-free rate was estimated by the Kaplan-Meier method, and the differences were assessed by the log-rank test. Patients who died during follow-up, those who were lost to follow-up, and those who elected to have the ICD turned off were censored at the date of death, last contact, or turning off their ICD. All statistical analyses were performed using JMP 13.0.0 software (SAS Institute, Inc., Cary, NC, USA). p values < 0.05 were considered significant.

3. Results

3.1. Patient characteristics

The subjects were 158 men and 38 women (mean age, 64 ± 14 years); 135 were diagnosed with CHF. An ICD was implanted, according to the Japanese Circulation Society Guidelines, for primary prevention in 75 patients and secondary prevention in 121 patients at 0.2 [0–1.8] years before study enrollment. As for primary prevention, 50 patients had ischemic (n = 19) and non-ischemic CM (n = 31), 9 had hypertrophic cardiomyopathy (HCM), and 8 had Brugada syndrome, 8 had arrhythmogenic right ventricular cardiomyopathy (ARVC, n = 1), hypertensive heart disease (n = 2), cardiac sarcoidosis (n = 2), or other cardiac diseases (n = 3). As for secondary prevention, 46 patients had ischemic CM or old myocardial infarction (OMI), 21 had non-ischemic CM, 13 had idiopathic ventricular fibrillation (IVF), 12 had Brugada syndrome, 7 had HCM, 6 had ARVC, 4 had long QT syndrome, and 12 had other cardiac diseases, such as cardiac sarcoidosis (n = 2), amyloidosis (n = 1), hypertensive heart disease (n = 1), vasospastic angina (VSA, n = 7), or congenital heart disease (n = 1). Cardiac resynchronization therapy (CRT) defibrillators were implanted in 50 patients. Fifty-nine of 72 patients with ischemic heart disease (IHD) (ICM, OMI or VSA) had HF. Out of the 59 patients with ischemic HF, there were 25 patients who had ischemia detected by Tl myocardial scintigraphy before ICD implantation. Twenty-three of 25 patients with ischemia underwent revascularization therapy, but one patient had residual ischemia due to multi-vessel disease. The remaining 2 patients did not have revascularization therapy because of small extent of myocardial ischemia.

3.2. Follow-up outcome

During the mean follow-up of 3.3 ± 2.2 years, 59 of 196 patients had at least one appropriate ICD discharge. In this follow-up period, 31 patients died of cardiovascular disease (pump failure death: n = 19, sudden cardiac death: n = 9 and stroke: n = 3), 16 patients died of non-cardiovascular disease, such as pneumonia or cancer, and 2 patients were lost to follow-up. Out of 72 patients with IHD (ICM, OMI or VSA), 8 patients (11%) had cardiac death (4 patients had sudden cardiac death and 4 had pump failure death). Out of 52 patients with non-ischemic CM, 15 patients had cardiac death (3 patients had sudden cardiac death and 12 had pump failure death).

Out of 70 patients with other disease, 2 patients (HCM and amyloidosis) had sudden cardiac death and 3 patients (HCM, ARVC and IVF) had pump failure death. One of patients with IVF died of pump failure caused by myocardial infarction which occurred 4 years after the entry.

As for patients with ischemic HF, 3 patients with residual myocardial ischemia before ICD implantation had a higher risk of appropriate ICD therapy and cardiovascular death than those ischemic HF patients without residual ischemia (appropriate ICD therapy, 67[2/3]% vs 27[15/56]%, $p = 0.082$, cardiovascular death, 33 [1/3]% vs 14[8/56]%, $p = 0.20$, respectively).

3.3. Comparison of the baseline characteristics between the patients with and without appropriate ICD discharges

The clinical characteristics of all study patients are shown in Table 1. There were no significant differences in age, sex, ischemic origin, period after ICD implantation, CRT, indication for ICD implantation, 6-minute walk distance, systolic and diastolic blood pressures, heart rate, comorbidities, body mass index, medications, left atrial dimension, or blood chemistry findings between patients with and without appropriate ICD discharges (Table 1). Patients with appropriate ICD discharges had significantly higher NYHA functional class, larger left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension (LVDs), and lower LVEF.

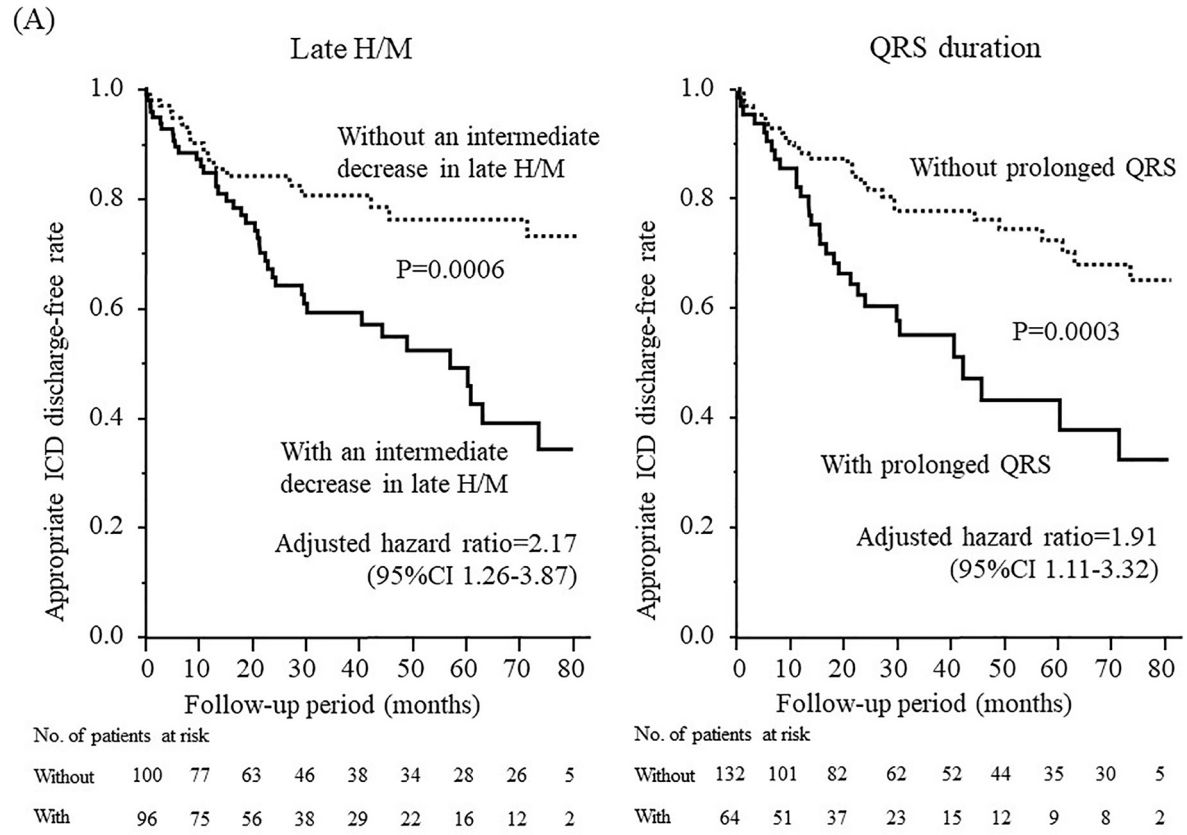
3.4. MIBG/ECG findings and appropriate ICD discharge rate

Although there were no significant differences in cardiac MIBG findings between patients with and without appropriate ICD discharges, the highest incidence of appropriate ICD discharge was seen in patients with ID-H/M (intermediate:1.40–1.89 vs. low: <1.40 vs. high: ≥1.90, 42%[40/96] vs. 20%[9/45] vs. 18%[10/55], $p = 0.0026$, respectively). Within the range of ID-H/M, the peak incidence of appropriate ICD discharges was in the late H/M range

Table 1
Clinical characteristics of study patients with and without appropriate ICD discharges.

	With an appropriate ICD discharge (n = 59)	Without an appropriate ICD discharge (n = 137)	*p* value
Age (y)	64 ± 13	65 ± 14	0.4186
Sex (male %)	85	79	0.3367
Ischemic origin (%)	36	39	0.6820
Period after the ICD implantation (years)	0 [0–2.5]	0 [0–1.6]	0.8270
Cardiac resynchronization therapy (%)	31	23	0.2921
Indication (secondary prevention %)	64	61	0.6135
6-min walk distance (m)	342 [218–436]	372 [280–436]	0.1229
Systolic blood pressure (mmHg)	111 ± 17	117 ± 22	0.0942
Diastolic blood pressure (mmHg)	71 ± 11	71 ± 13	0.7843
Heart rate (beat/min)	69 ± 12	69 ± 11	0.3487
Diabetes mellitus (%)	20	27	0.3227
Hypertension (%)	49	58	0.2323
Atrial fibrillation (%)	36	34	0.7848
Chronic heart failure (%)	78	65	0.0713
BMI (kg/m^2)	23.0 ± 3.9	22.7 ± 3.9	0.5306
NYHA functional class	1.9 ± 0.7	1.6 ± 0.7	0.0154
Medication			
Diuretics (%)	53	52	0.8739
Beta blockers (%)	81	69	0.0881
ACEIs/ARBs (%)	59	49	0.1979
Spironolactone	34	30	0.5515
Echocardiography			
LVDd (mm)	59 ± 12	54 ± 10	0.0040
LVDs (mm)	46 ± 14	41 ± 13	0.0066
LVEF (%)	45 ± 15	51 ± 17	0.0167
LVEF ≤35% (%)	29	20	0.1611
LAD (mm)	45 ± 13	41 ± 8	0.1189
Blood chemistry findings			
Hemoglobin (g/dL)	12.2 ± 2.2	12.4 ± 1.9	0.8078
Creatinine (mg/dL)	0.93 [0.84–1.41]	1.04 [0.82–1.28]	0.8577
Sodium (mEq/L)	139 ± 3	138 ± 4	0.0836
Potassium (mEq/L)	4.3 ± 0.5	4.2 ± 0.4	0.3596
BUN (mg/dL)	19 [15–28]	18 [14–26]	0.3299
BNP (pg/mL)	155 [43–388]	134 [32–328]	0.5156
NE (ng/mL)	0.37 [0.27–0.56]	0.37 [0.23–0.58]	0.8174
Cardiac MIBG imaging			
Early H/M	1.82 ± 0.29	1.86 ± 0.34	0.6057
Late H/M	1.67 ± 0.29	1.71 ± 0.40	0.6815
Washout rate (%)	33.8 ± 19.4	34.9 ± 20.6	0.5736
Electrocardiography			
QRS duration (ms)	142 ± 33	127 ± 26	0.0044
CRBBB (%)	10	7	0.5008
CLBBB (%)	5	0	0.0078
Ventricular pacing (%)	32	26	0.3387

Data are presented as mean values ± SD or as percentages of patients.
ICD, implantable cardioverter defibrillator; BMI, body mass index; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end systolic dimension; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NE, norepinephrine; MIBG, metaiodobenzylguanidine; H/M, heart to mediastinum ratio; CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block.



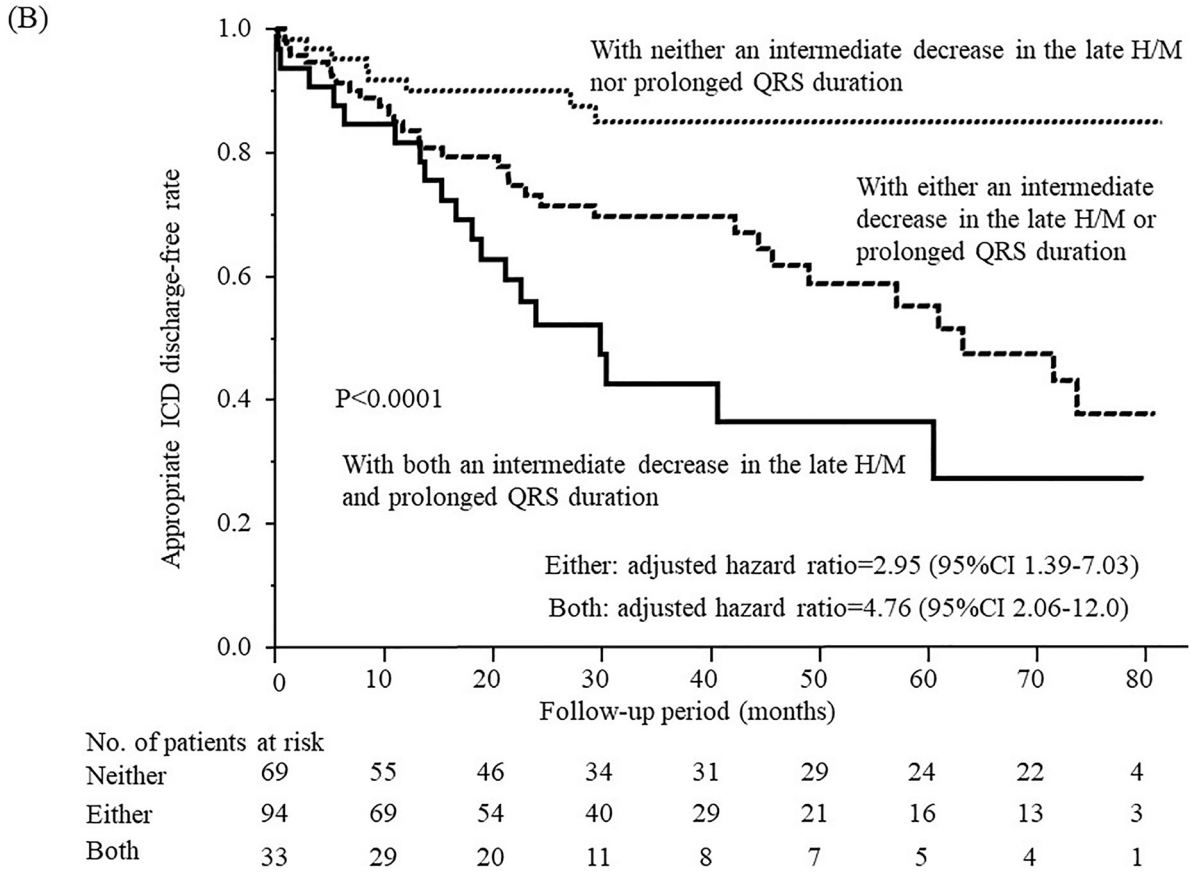


Fig. 1. Appropriate ICD discharge-free rate curves in patients with and without an intermediate decrease in the late H/M or prolonged QRS duration (A) and in patients with both an intermediate decrease in the late H/M and prolonged QRS duration, either, and neither an intermediate decrease in the late H/M nor prolonged QRS duration (B).

of 1.65–1.89 (47% [24/51]) rather than 1.40–1.65 (36% [16/45]). Appropriate ICD discharges were significantly more frequently observed in patients with ID-H/M than in those with a low ($p = 0.0081$) or high ($p = 0.0022$) late H/M, while there was no significant difference in the appropriate ICD discharge rate between patients with low and those with high late H/M ($p = 0.84$). Appropriate ICD discharges were significantly more frequently observed in patients with than without ID-H/M (Fig. 1A).

The QRSd was significantly longer in the patients with an appropriate ICD therapy. Appropriate ICD discharges were significantly more frequently observed in patients with than without pQRSd (≥147 ms: determined by the receiver operator characteristic [ROC] curve analysis, AUC 0.628) (Fig. 1A). Complete left bundle branch block (CLBBB) was rare, but significantly more frequently observed in patients with appropriate ICD therapy. There were no significant differences in the prevalence of complete right bundle branch block (CRBBB) or ventricular pacing between patients with and without appropriate ICD therapy. Appropriate ICD discharge was more frequent in patients with than without pQRSd (≥147 ms), regardless of ventricular pacing (with ventricular pacing 43% [19/44] vs 12% [2/17], $p = 0.066$; without ventricular pacing 55% [11/20] vs 23% [27/115], $p = 0.0013$).

Prognostic analysis for the identification of patients at risk for appropriate ICD discharges.

Univariate and multivariate analyses of all patients are shown in Table 2. On multivariate analysis, both ID-H/M (1.40–1.89) and pQRSd (≥147 ms) were independent predictors of appropriate ICD discharge after adjustment for the NYHA functional class, LVEF, and BUN. Kaplan-Meier analysis showed that the presence of ID-H/M and pQRSd increased the risk of appropriate ICD discharge by 2.2-fold and 1.9-fold, respectively (Fig. 1A). Patients with both ID-H/M and pQRSd had an increased risk of appropriate ICD discharge by 4.8-fold, and the presence of either of them increased the risk by 3.0-fold (Fig. 1B).

3.5. Combination of late H/M and QRS duration for predicting the risk of appropriate ICD discharge in patients with and without CHF

In patients with CHF, appropriate ICD discharge-free rate curves adjusted for the NYHA functional class, BUN, and LVEF showed that the presence of ID-H/M and/or pQRSd increased the risk of appropriate ICD discharge by 3.1-fold. In patients without CHF, the adjusted hazard ratio of appropriate ICD discharge was increased by 4.5-fold in cases with ID-H/M and/or pQRSd (Fig. 2).

3.6. Subgroup analysis of late H/M and QRS duration for predicting appropriate ICD discharge

As for the indication for ICD implantation in patients for whom the ICD was implanted for both primary and secondary prevention, the presence of ID-H/M and/or pQRSd increased the risk of appropriate ICD discharge (primary prevention 34% [18/53] vs. 14% [3/22], $p = 0.039$; secondary prevention 45% [33/74] vs. 11% [5/47], $p = 0.0002$). Furthermore, as for the presence of a reduced LVEF of ≤35%, in patients with both reduced and non-reduced LVEFs, appropriate ICD discharges were significantly more frequently observed in the group with ID-H/M and/or pQRSd than in the group with neither (reduced LVEF: 47% [17/36] vs. 0% [0/8], $p = 0.049$;

Table 2
Univariate and multivariate Cox proportional hazard analyses for the identification of ICD patients at risk for appropriate ICD discharges.

Variables	Univariate analysis		Multivariate analysis	
	p value	HR (95% CI)	*p* value	HR (95% CI)
Age (y)	0.6593	1.004 (0.986–1.024)		
Sex (male)	0.2190	1.563 (0.806–3.406)		
Ischemic origin	0.9970	0.999 (0.576–1.685)		
Period after the ICD implantation (years)	0.3594	1.000 (1.000–1.000)		
Cardiac resynchronization therapy	0.2341	1.406 (0.784–2.424)		
Indication (secondary prevention)	0.8613	1.049 (0.619–1.824)		
6-min walk distance (m)	0.0003	0.997 (0.995–0.999)		
Atrial fibrillation (%)	0.9985	1.001 (0.566–1.708)		
Chronic heart failure	0.0194	2.105 (1.162–4.092)		
Systolic blood pressure (mmHg)	0.0185	0.983 (0.968–0.997)		
Diastolic blood pressure (mmHg)	0.7537	1.003 (0.983–1.025)		
Heart rate (beat/min)	0.8277	1.003 (0.977–1.028)		
BMI (kg/m^2)	0.6277	1.018 (0.946–1.092)		
NYHA functional class	0.0026	1.746 (1.210–2.503)	0.3806	1.217 (0.779–1.876)
LVDd (mm)	0.0009	1.039 (1.015–1.062)		
LVDs (mm)	0.0006	1.033 (1.013–1.052)		
LVEF (%)	0.0017	0.974 (0.958–0.990)	0.1851	0.986 (0.967–1.006)
Creatinine (mg/dL)	0.1824	1.102 (0.933–1.250)		
Sodium (mEq/L)	0.3716	1.042 (0.958–1.147)		
Potassium (mEq/L)	0.0169	1.956 (1.112–3.329)		
BUN (mg/dL)	0.0095	1.014 (1.001–1.023)	0.6128	1.003 (0.988–1.015)
BNP (pg/mL)	0.6407	1.000 (0.999–1.001)		
NE (pg/mL)	0.3559	1.297 (0.661–2.051)		
Early H/M	0.5848	0.797 (0.349–1.782)		
Late H/M	0.3635	0.719 (0.350–1.453)		
Late H/M (1.40–1.89)	0.0009	2.531(1.482–4.478)	0.0059	2.191 (1.271–3.905)
Washout rate (%)	0.9048	1.001 (0.988–1.012)		
QRS duration (ms)	0.0017	1.013 (1.005–1.021)		
Prolonged QRS duration (≥147 ms)	0.0005	2.491 (1.485–4.184)	0.0181	1.916 (1.116–3.297)
CRBBB (%)	0.4000	1.465 (0.563–3.145)		
CLBBB (%)	0.0029	11.49 (2.718–33.21)		
Ventricular pacing (%)	0.2811	1.362 (0.768–2.334)		

HR, hazard ratio; CI, confidence interval; ICD, implantable cardioverter defibrillator; BMI, body mass index; NYHA, New York Heart Association; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end systolic dimension; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NE, norepinephrine; H/M, heart to mediastinum ratio.

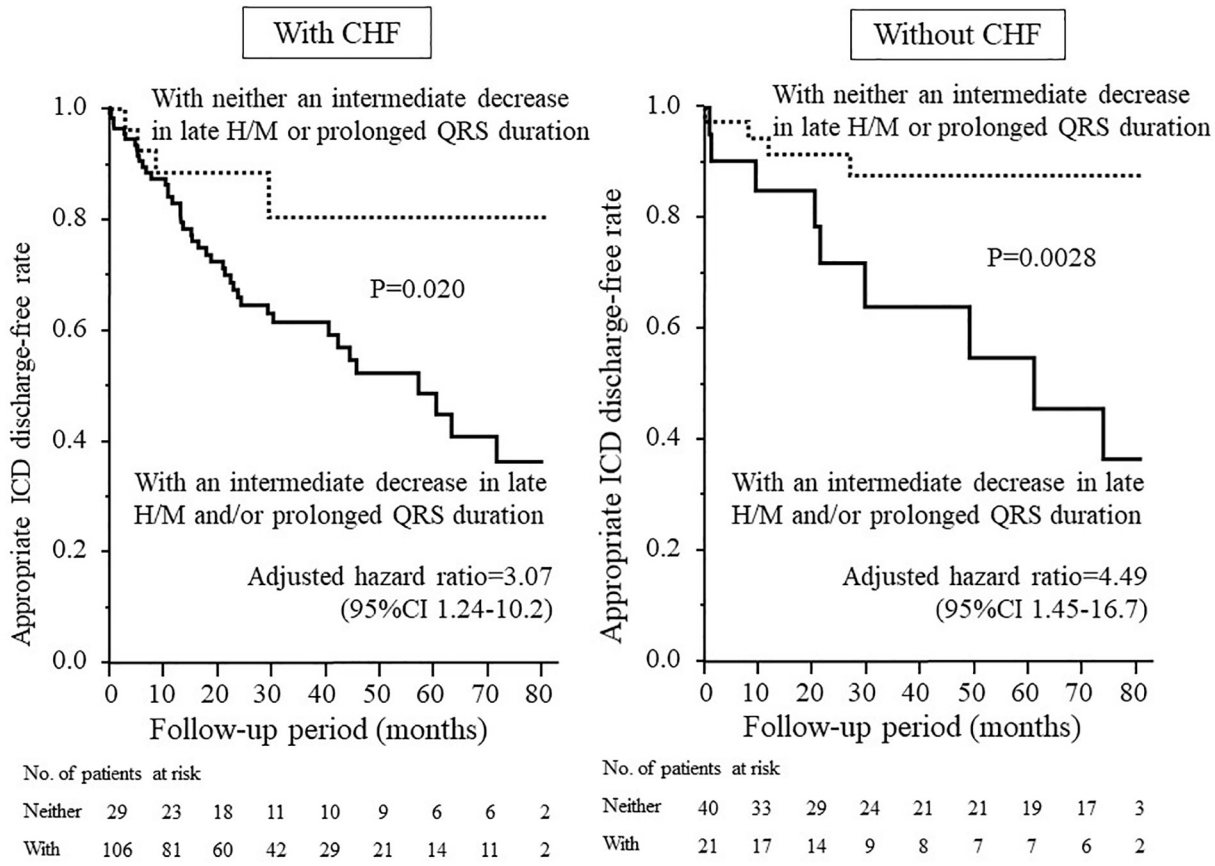


Fig. 2. Appropriate ICD discharge-free rate curves in patients with an intermediate decrease in the late H/M and/or prolonged QRS duration and none of them, with and without heart failure (HF).

non-reduced LVEF: 37% [34/91] vs. 13% [8/61], $p = 0.0009$). There were 20 patients with LVEF between 30 and 35%. Out of those patients, 7 patients had H/M > 1.6. There were 3 patients who had appropriate ICD therapy, and 3 patients who had cardiac death in patients with LVEF between 30 and 35% and H/M > 1.6. Patients with LVEF 30–35% and H/M > 1.76/1.91 had no appropriate ICD discharge/cardiovascular death. From the viewpoint of etiology, subgroup analyses in relation to CM such as ischemic or non-ischemic CM were performed, and similar results were obtained from these analyses (with CM 37% [25/67] vs. 6% [1/17], $p = 0.039$; without CM 43% [26/60] vs. 13% [7/52], $p = 0.0004$).

4. Discussion

This study demonstrated that ID-H/M and pQRSd were independently associated with appropriate ICD discharge, and the combination of the two indices provided more prognostic information to predict ventricular tachyarrhythmias in ICD patients, regardless of the presence of CHF.

4.1. Prognostic value of cardiac MIBG imaging

In the present study, cardiac MIBG imaging was shown to predict severe arrhythmic events (SAEs). The relationship between cardiac MIBG findings and SAEs would be explained by the previous findings that increased sympathetic activity can modulate the basic arrhythmia mechanisms of re-entry and automaticity and trigger activity to provoke lethal arrhythmias [29,30].

Previous studies showed that ID-H/M was associated with SAEs [18–20]. Narula et al. studied the occurrence of SAEs in relationship to the H/M in NYHA functional class II and III patients whose LVEF was <35%, in which patients with an intermediately reduced uptake (late H/M: 1.30–1.59) were shown to have an increased risk of SAEs [18]. Vincentis et al. reported that CHF patients with an intermediate late H/M ratio (1.2–1.6) were more likely to have SAEs compared to patients with low and high late H/M ratios [20]. Nakajima et al. showed that the normal value for late H/M is 1.9–3.1 for the low-energy collimator [27]. Major investigations that prospectively monitored patients with CHF adopted a range of 1.5–1.7 as the cutoff point for late H/M. Thus, in the present study, an intermediate decrease in the late H/M was defined as 1.40–1.89, and the peak rate of fatal arrhythmic events was seen with a late H/M of 1.65–1.89. This difference in the comparison with the previous studies might be due to the characteristics of the study patients, such as the presence or absence of CHF and LVEF.

4.2. Prognostic value of the QRS duration

QRS duration has been reported to be an independent predictor of the risk of SCD and may have utility in estimating the SCD risk in the general population and many cardiac diseases [21–24,31]. Previous trials have concluded that patients with LBBB or nonspecific intraventricular conduction delay, but not right bundle branch block, have a greater risk for arrhythmia and total mortality than patients with normal QRS duration [32,33]. Furthermore, prolonged paced QRS duration has been reported to have prognostic value in patients with complete atrioventricular block

receiving pacemaker treatment [34,35]. In the present study, CLBBB and pQRSd, with or without ventricular pacing, were associated with appropriate ICD discharge, consistent with previous reports.

It is known that intraventricular conduction delay is related to left ventricular dysfunction, and the relationship between depressed left ventricular systolic function and SCD has been well established. A prolonged QRS with perturbed depolarization may play a direct role in SCD via the facilitation of re-entrant tachyarrhythmias. Prolonged QRS duration may be due to a number of factors that predispose to such re-entry.

4.3. Combination of late H/M and QRS duration

Recent trials have focused on LVEF because of its demonstrated association with mortality risk in patients with coronary artery disease. However, LVEF lacks sensitivity for prediction of sudden death. Additionally, many factors besides LVEF might affect the prognosis of patients with cardiac disease. A combination of several factors associated with ventricular tachyarrhythmias is important to stratify patients who are candidates for an ICD. The present study showed that ID-H/M and pQRSd were independently associated with appropriate ICD discharges. This might be because a late H/M reflects the modifiers of arrhythmic risk and pQRSd reflects arrhythmic substrates such as myocardial fibrosis or impaired conduction system. Thus, they are complementary to each other, and the combination of a late H/M and QRSd improved the predictive value for appropriate ICD discharges.

4.4. Other variables associated with appropriate ICD discharges

In the present study, several variables were found to be significant on univariate analysis. Six-min walk distance, HF, systolic blood pressure, LVDd, LVDs, and serum potassium concentration level might also have clinical significance for detecting patients at high risk for ventricular tachyarrhythmias. However, from the perspective of the statistical analysis, these variables were excluded from the multivariate analysis. The other variables like brain natriuretic peptide or AF, which had been shown to be associated with SAEs in previous reports, were not associated with appropriate ICD discharges in the present study [28,36,37]. This difference might be due to the differences in the characteristics of the study patients, or the therapeutic approach for atrial fibrillation. In our institute, catheter ablation for atrial fibrillation was freely performed.

4.5. Clinical implications

Appropriate ICD discharges are well known to be associated with poor clinical outcomes [6–9], so it is significant to detect high-risk patients with ICDs for ventricular tachyarrhythmias. Furthermore, selecting eligible patients for prophylactic ICD therapy, who are assumed to be at high risk for ventricular tachyarrhythmias with or without an LVEF $\leq$ 35% or CHF, is suggested. The present study showed that the presence of ID-H/M and pQRSd increased the risk of appropriate ICD discharge in both primary and secondary prevention, which suggests that the combination of ID-H/M and pQRSd would be useful for stratifying the risk of appropriate ICD discharges in secondary prevention and selecting patients who will benefit from ICD therapy in primary prevention.

The recent guidelines recommend ICD implantation for the primary prevention of SCD in patients with ischemic and non-ischemic CM based on LVEF. However, numerous patients with implanted ICDs have never actually received ICD discharges [7,38]. In the present study, it was notable that, of the patients with LVEF $\leq$ 35%, none of those with ID-H/M or pQRSd had any appropriate ICD discharges. Therefore, the absence of both ID-H/M and pQRSd could identify patients with CHF and reduced LVEF who have no need for ICD implantation.

4.6. Limitations

The present study had several limitations. First, the number of patients was small, and the follow-up period was short, which are major limitations. Second, the study patient population was heterogeneous, but at the same time, this was the clinical reality. Although the mechanisms of ventricular tachyarrhythmia differ by the underlying cardiac disease, it is urgent to identify patients, whatever disease they have, at high risk for ventricular tachyarrhythmias in clinical practice. In the present study, in the group with various diseases such as HCM, ARVC, Brugada, and long QT syndrome, appropriate ICD discharges were also observed significantly frequently in patients with ID-H/M and/or pQRSd. Third, this study contained patients who already had an ICD at entry or had an indication for secondary prevention. In the primary prevention patients, therapy reduction programming according to the previous reports [39,40] was used. However, physician-tailored programing was preferred in those patients who had an indication for secondary prevention or had appropriate ICD therapy before study entry. Thus, the therapy programming of the ICD was not standardized. A further prospective study with large numbers of patients and longer follow-up periods is mandatory to confirm and enhance the present results.

5. Conclusion

To the best of our knowledge, this was the first study to show that a combination of an intermediate decrease in the late H/M and prolonged QRSd provided more prognostic information to help predict ventricular tachyarrhythmias in ICD patients, regardless of the presence of CHF.

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Declaration of Competing Interest

We have no financial conflict of interest to disclose concerning this study.

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