J waves are associated with the increased occurrence of life-threatening ventricular tachyarrhythmia in patients with non-ischemic cardiomyopathy

Short title: J Wave and VT/VF of Non-Ischemic Cardiomyopathy

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Abstract

***Introduction*:** Recent studies showed that J waves were associated with higher incidence of ventricular tachyarrhythmia (VT/VF) in patients with idiopathic ventricular fibrillation (VF) and myocardial infarction. We sought to assess the association between J waves and VT/VF in patients with non-ischemic cardiomyopathy (NICM).

***Methods and Results*:** We retrospectively enrolled 109 patients (79 men; mean age, 60±15 years) with NICM who underwent implantable cardioverter defibrillator (ICD) implantation. The primary endpoint of this study was the occurrence of appropriate device therapy due to sustained VT/VF. The J wave was electrocardiographically defined as an elevation of the terminal portion of the QRS complex of >0.1 mV in at least 2 contiguous inferior or lateral leads. Among the 109 patients, 37 (34%) experienced an episode of appropriate device therapy during a median follow-up period of 25.9 (IQR 11.5–54.3) months. Kaplan-Meier curves showed that the presence of J waves on the 12-lead ECG obtained before device implantation was associated with an increased occurrence of appropriate device therapy (P<0.001). Multivariate Cox proportional regression analysis revealed that the presence of J waves (HR 2.95; 95% CI 1.31–6.64; P=0.009) was an independent predictor for the occurrence of appropriate device therapy. In the sub-group analysis of the patients with dilated or hypertrophic cardiomyopathy, J wave tended to increase the occurrence of appropriate device therapy (P=0.056 and P=0.092, respectively).

Conclusions: The presence of J waves was an independent predictor for the occurrence of appropriate device therapy in patients with NICM who underwent ICD implantation.

Key Words: Non-ischemic cardiomyopathy; J wave; ventricular tachyarrhythmia; implantable cardioverter defibrillator

Introduction

The J wave has historically been regarded as an innocuous finding in healthy young people.[1,2] While considered benign, the potential role of the J wave in arrhythmogenicity has been suggested in experimental studies.[3] Recent evidence has linked J waves to idiopathic ventricular fibrillation (VF) in patients with no structural heart disease.[4-6]

Besides idiopathic VF, recent studies showed that the presence of a J wave was associated with higher incidence of ventricular tachyarrhythmia (VT/VF) in patients with Brugada syndrome,[7-9] short QT syndrome,[10] noncompaction cardiomyopathy,[11] Takotsubo cardiomyopathy,[12] and ischemic heart disease.[13-18] However, it is still unknown whether there is an association between J waves and VT/VF occurrences in patients with non-ischemic cardiomyopathy (NICM). We hypothesized that concomitant J waves would carry an increased risk of a VT/VF occurrence in patients with NICM. Accordingly, the purpose of this study was to clarify this point.

Methods

Study Population

Between October 2006 and April 2013, 162 consecutive patients with NICM who underwent implantable cardioverter defibrillator (ICD) implantation at the University of Tsukuba Hospital and Yokohama Rosai Hospital were retrospectively included in the present study. Among the 162 patients, 45 patients had a QRS duration of more than 120 ms and 8 were lost to follow-up. After excluding these patients, the remaining 109 patients (79 men and 30 women; mean age, 60±15 years) were finally included in this study (Figure 1).

The primary endpoint of this study was the occurrence of appropriate device therapy

including shock and anti-tachycardia pacing (ATP) due to sustained VT/VF. Patients were classified on the basis of the occurrence of appropriate device therapy, and the clinical data were analyzed in both the event occurrence and no event occurrence study groups. Data collection covered the variables of age, sex, body mass index, comorbid disease, ejection fraction measured by echocardiography, medications before device implantation, and ECG findings. Hypertension, hypercholesterolemia, and diabetes mellitus were scored on the basis of the previous diagnosis and initiation of therapy. Ethical approval was obtained from the institutional review board of each participating hospital. Owing to the retrospective and observational nature of the present study, written informed consents were not necessary under Japanese law.

ECG Analysis

To blind the ECG interpreters from the patient clinical characteristics and groupings, all tracings were scanned and coded. We evaluated the last 12-lead ECG recorded before device implantation with sweep speed of 25 mm/sec, low cut filter of 0.05 Hz, and high cut filter of 150 Hz. The median duration from ECG recording to device implantation was 2 days (interquartile range [IQR] 1–6 days). The J wave was electrocardiographically defined as the presence of an end-QRS notch or slur on the downslope of a prominent R-wave and J peak (Jp) of $\geq$0.1 mV in at least 2 contiguous inferior (II, III, and aVF) or lateral (I, aVL, and V4 to V6) leads (Figure 2).[19] An end-QRS notch denoted a notch that occurs on the final 50% of the downslope of an R-wave occurring as the final segment of the QRS complex and an end-QRS slur was defined as an apparent slowing of the inscription of the waveform at the end of the QRS complex that merges with the ST-segment of the complex. Jp denoted the peak of a notch or onset of a slur and the amplitude of Jp was measured. The anterior precordial leads (V1 to V3) were excluded from the

analysis of the J wave. We used two predefined cutoff points ($\geq$0.1 mV and $\geq$0.2 mV) to assess the significance of the amplitude of Jp. Further, we analyzed ST-segment characteristics independently according to the criteria proposed by a consensus paper.[19] J termination (Jt) denoted the end of a notch or slur. We classified ST-segment characteristics into 2 groups. J wave with an ascending ST-segment was defined as follows; the amplitude of the ST-segment 100ms after Jt was greater than the amplitude at Jt. On the other hand, the definition of J wave with a horizontal or descending ST-segment was that the amplitude of the ST-segment 100ms after Jt was less than or equal to the amplitude at Jt.[19] We assessed the prevalence, localization, amplitude, morphology, and ST-segment of the J wave in both patient groups. Two trained investigators independently evaluated the baseline 12-lead ECGs for the presence of J waves with no knowledge of the other observer's judgment or the clinical information.

ICD Programming and Assessment of ICD Therapy

The border between the ventricular tachycardia (VT) zone and the VF zone of an ICD was set around 280–320 ms according to the nominal settings of each maker. Typical cut off rate of VT zone was set around 360–400 ms with detection interval of 16 beats that depended on the cycle length of clinically documented VT. In VT zone, shock therapy followed some attempts of ATP. On the other hand, shock therapy is immediately performed in VF zone and ATP during charge period was applied if available.

A well trained electrophysiologist reviewed all records of ICD therapy and adjudicated them as appropriate or inappropriate at an outpatient clinic or a ward. Inappropriate ICD therapies were not included in analyses of this study.

Statistical Analysis

Continuous variables were expressed as means ± standard deviation or medians (interquartile range [IQR]). Comparisons between two groups were tested by an unpaired *t*-test or Mann-Whitney U-test according to the data distribution with or without normality. All categorical variables were presented as the number and percent in each group and were compared by a Fisher's exact test. A comparison of the probability of the freedom from appropriate device therapy between the two groups was performed with Kaplan-Meier survival analysis. "Time 0" for the survival analyses was the date of device implantation. A univariate analysis of the patient characteristics was compared between the event occurrence group and no event occurrence group, and a multivariable Cox proportional regression analysis was performed to detect any independent significant predictors by adjusting for multiple variables (reported as the hazard ratio [HR] with a 95% confidence interval [CI]). Variables, including multivariable Cox proportional hazard models, were those that achieved statistical significance ($P<0.05$) or were close to significance ($P<0.1$) in the univariable analysis. A P value <0.05 was considered statistically significant. All analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.1.1).

Results

Demographic and Clinical Characteristics of the Patients with and without J Waves

Underlying heart diseases included hypertrophic cardiomyopathy (HCM) in 43, dilated cardiomyopathy (DCM) in 35, arrhythmogenic right ventricular cardiomyopathy (ARVC) in 15, valvular heart disease in 5, cardiac sarcoidosis in 5, congenital heart disease in 2, myocarditis in 2, and others in the remaining 2 patients. J waves were observed in 12 (11%) patients. There was

no significant difference in age, sex, comorbid disease, ejection fraction, medication, ECG findings, and the prevalence of primary prevention, syncope, and family history between the patients with and without J waves (Table 1).

Out of 60 patients who received amiodarone, sustained VT/VF were documented in 35 patients, non-sustained VT in 9, atrial fibrillation in 7, and both VT/VF and atrial fibrillation in the remaining 9. The ECG before taking amiodarone was available in 25 patients (J wave–3, no J wave–22). The presence and absence of J wave did not differ before and after taking amiodarone in all but 1 patient who acquired J wave after receiving amiodarone.

Univariable and Multivariable Analyses for the Occurrence of Appropriate Device Therapy

Among the 109 patients, 37 (34%) experienced an episode of appropriate device therapy during a median follow-up period of 25.9 (IQR 11.5–54.3) months. Kaplan-Meier curves showed that the presence of J waves on the 12-lead ECG obtained before device implantation was associated with an increased occurrence of appropriate device therapy ($P<0.001$ by log rank test, Figure 3). A multivariate Cox proportional regression analysis revealed that the presence of J waves (HR 2.95; 95% CI 1.31–6.64; $P=0.009$) was an independent predictor for the occurrence of appropriate device therapy during the follow-up period (Table 2). ATP was attempted before cardioversion in 29 patients. The success rate of anti-tachycardia therapy did not differ significantly in the patients with and without J wave (86% vs. 92%; $P=0.536$).

In the sub-group analysis of the patients with DCM or HCM, concomitant J wave tended to be associated with an increased risk of the occurrence of appropriate device therapy ($P=0.056$ and $P=0.092$, respectively; Figure 4A, B).

Detailed Analyses of J Waves for Prediction of Event Occurrence

J waves were present in 12 patients and were more prevalent in patients with appropriate device therapy (24% vs. 4%; *P*=0.003, Table 3). Among these 12 patients, the J-point elevation was in the inferior leads in 8 (67%) patients, in the lateral leads in the remaining 4 (33%) (Table 3). A J wave in the inferior leads was associated with increased event occurrence (16% vs. 3%; *P*=0.018, Table 3), whereas a J wave in the lateral leads or both leads was not (Table 3).

A J wave amplitude of $\geq$0.2 mV was found in the inferior or lateral leads in 3 (25%) patients, and it did not differ significantly between the patients with and without event occurrence (Table 3).

The prevalence of a slurred J wave (11% vs. 0%; *P*=0.012) differed significantly between the patients with and without event occurrence, however that of a notched J wave did not (Table 3).

The prevalence of a J wave with horizontal/descending ST-segment was higher in the patients with event occurrence than in those without (19% vs. 4%; *P*=0.030). Conversely, the incidence of a J wave with upsloping ST-segment did not differ significantly between the two groups (Table 3).

Discussion

Main Findings

To the best of our knowledge, this is the first time that the following findings have been reported: 1) approximately 10% of the NICM patients had J waves on the ECG recorded before device

implantation; 2) only the presence of J waves was an independent predictor for the occurrence of appropriate device therapy in patients with NICM who underwent ICD implantation; 3) as features of a J wave pattern, J waves in the inferior leads, a slurred morphology, and J waves with horizontal/descending ST-segment were significantly associated with the occurrence of appropriate device therapy; and 4) in the sub-group analysis of the patients with DCM or HCM, concomitant J wave tended to be associated with an increased risk of the occurrence of appropriate device therapy.

Proposed Mechanism of VT/VF in Patients with J Waves

Transmural differences in the early phases (phases 1 and 2) of the cardiac action potential, which are created by a disproportionate amplification of the repolarizing current in the epicardial myocardium due to an increase in the outward potassium currents mediated by the I_{to}, $I_{K\text{-}ATP}$, and $I_{K\text{-}Ach}$ channels, are considered to be responsible for the inscription of the ECG J wave.[20] The trigger and substrate for the development of phase 2 reentry and VT/VF may eventually emerge from the transmural dispersion of the duration of the cardiac action potentials.[20]

Although repolarization abnormalities were mainly recognized as a cause of J wave, we cannot exclude that J waves, at least some of them, are related to depolarization abnormalities. Patients with NICM have scar tissue in the myocardium that gives rise to activation delay due to lengthened conduction pathways and consequently could become a substrate for VT. We speculated that phase 2 reentry and scar tissue play an important role in the development of sustained VT/VF as the trigger and substrate, respectively, resulting in the higher prevalence of an occurrence of appropriate device therapy in the patients with J waves than in those without.

Previous Studies

Although the link between J waves and VT/VF is well known in patients with idiopathic VF and ischemic cardiomyopathy, the association between J waves and VT/VF in patients with NICM remains unclear. Chan et al. investigated 59 patients with ARVC who underwent catheter ablation for VT and showed that the prevalence of induced VF was higher and the cycle length of VT was shorter during the procedure in the patients with J waves than in those without J waves.[21]

Li et al. showed that the J wave was associated with an increased risk of sudden cardiac arrest in patients with HCM.[22] The present study showed that a concomitant J wave predicted the increased occurrence of VT/VF not only in the patients with HCM but also in those with DCM.

Previous studies have identified the characteristics of J waves in those who have suffered from VT/VF associated with idiopathic VF and myocardial infarction.[14-17,23,24] In the present study, J waves in the inferior leads, a slurred morphology, and J waves with horizontal/descending ST-segment were associated with an increased risk of the occurrence of appropriate device therapy in the patients with NICM, which was similar to the findings of the previous studies. We consider that these J wave patterns could indicate a malignant form.

Clinical Implications

Our study showed that the presence of J waves increased the risk for the occurrence of appropriate device therapy in patients with NICM. In particular, increased attention should be paid to the patients with J waves in the inferior leads and J waves with horizontal/descending ST-segment.

Study Limitations

First, our study is a hypothesis-generating trial, not a conclusive trial, based on a retrospective design and with a relatively small sample size. The small sample size limited the power of the study and was reflected in the broad confidence intervals, most notably in the adjusted statistical analyses. Second, we included various etiologies of NICM such as DCM, HCM, and ARVC. Third, the findings in this study were obtained during drug treatment in the large majority of the patients, including amiodarone with major impact on depolarization and repolarization criteria, and also the occurrence of fast VT. Fourth, our study population seemed to be high risk of appropriate device therapy during the median follow-up period of 26 months even though approximately half of the patients received ICD as a primary prevention. We speculated that high prevalence of sustained or non-sustained VT/VF in spite of taking amiodarone and relatively short detection interval of ICD therapy resulted in this findings. Fifth, we set high cut-off rate of VF zone (280–320ms) according to the nominal settings of each maker. This settings could be inappropriate because at cycle length above 250 ms the rhythm is usually not VF but VT and could be terminated by ATP. Therefore, further prospective studies with a larger sample size, long-term follow-up, and the participation of many hospitals and many countries may be needed to resolve these limitations and to confirm and enhance our results.

Conclusion

The presence of J waves was an independent predictor for the occurrence of appropriate device therapy in patients with NICM who underwent ICD implantation.

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Author Contributions

Dr. Naruse contributed to the conception and design of this work and to the drafting of the article. Drs. Shinoda, Hanaki, Shirai, Machino, Kuroki, Yamasaki, and Igarashi contributed to the acquisition of the data. Drs. Kowase, Kurosaki, and Sekiguchi contributed to the analysis and interpretation of the data. Drs. Nogami, Kato, and Aonuma contributed to critical revision of the manuscript for important intellectual content. Dr Aonuma contributed to final approval of the manuscript submitted.

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Figure Legends

Figure 1. Study design. Patients excluded from the analysis are indicated by arrows directed to the right. ICD indicates implantable cardioverter defibrillator; and IQR, interquartile range.

Figure 2. Representative cases of J waves. (A) Notched J waves (arrows) with horizontal/descending ST-segment in the inferior leads were recognized in a 73-year-old man with dilated cardiomyopathy. (B) Notched J waves (arrows) with horizontal/descending ST-segment in the lateral leads were observed in a 54-year-old man with hypertrophic cardiomyopathy. (C) A 62-year-old man with hypertrophic cardiomyopathy had slurred J waves (arrows) with horizontal/descending ST-segment in the inferior leads.

Figure 3. Kaplan-Meier curves for the primary endpoint. There was a significant difference in the occurrence of appropriate device therapy between the patients with and without J waves.

Figure 4. Kaplan-Meier curves in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy. (**A**) Concomitant J waves tended to be associated with increased occurrence of appropriate device therapy in 35 patients with dilated cardiomyopathy. (**B**) Among 43 patients with hypertrophic cardiomyopathy, the occurrence of appropriate device therapy tended to be higher in the patients with J waves than in those without.

Table 1. Demographic and Clinical Characteristics of the Patients with and without J Waves

Characteristics	Total (n=109)	With J waves (n=12)	Without J waves (n=97)	*P* value
Age, years	60±15	63±14	60±15	0.529
Male sex, n (%)	79 (72%)	9 (75%)	70 (72%)	1.0
Comorbid disease				
Hypertension, n (%)	39 (36%)	4 (33%)	35 (36%)	1.0
Hyperlipidemia, n (%)	25 (23%)	0 (0%)	25 (26%)	0.064
Diabetes mellitus, n (%)	13 (12%)	3 (25%)	10 (10%)	0.154
Atrial fibrillation, n (%)	25 (23%)	3 (25%)	22 (23%)	1.0
Chronic kidney disease, n (%)	38 (35%)	3 (25%)	35 (36%)	0.536
Primary prevention, n (%)	45 (41%)	5 (42%)	40 (41%)	1.0
Non sustained VT, n (%)	30 (28%)	5 (42%)	25 (26%)	0.305
Syncope, n (%)	32 (29%)	2 (17%)	30 (31%)	0.503
Family history, n (%)	24 (22%)	3 (25%)	21 (22%)	0.724
NYHA class	1 [1–2]	1 [1–2]	1 [1–2]	0.901
Left ventricular ejection fraction, %	57±19	52±20	58±19	0.306
Left ventricular ejection fraction <35%, n (%)	16 (15%)	3 (25%)	13 (13%)	0.379
Medication				
β-blocker, n (%)	80 (73%)	8 (67%)	72 (74%)	0.730
ACE-I/ARB, n (%)	69 (63%)	10 (83%)	59 (61%)	0.204
Calcium channel blocker, n (%)	25 (23%)	4 (33%)	21 (22%)	0.465
Amiodarone, n (%)	60 (55%)	8 (67%)	52 (54%)	0.542
Digitalis, n (%)	2 (2%)	1 (8%)	1 (1%)	0.209
ECG findings				
Heart rate, beats/minute	63±13	65±11	62±13	0.529

QRS duration, ms	100±12	107±8	99±12	0.031
QTc interval, ms	439±31	434±19	440±32	0.576
LVH, n (%)	37 (34%)	3 (25%)	34 (35%)	0.748

Values are reported as the mean ± standard deviation, median (interquartile range), or n (%). ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVH, left ventricular hypertrophy; VT, ventricular tachycardia; and NYHA, New York Heart Association.

Table 2. Univariable and Multivariable Cox Proportional Regression Analyses for the Occurrence of Ventricular Tachyarrhythmias or Sudden Death

Variables	Univariable		Multivariable	
	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Age	1.011 (0.988–1.034)	0.336		
Male sex	1.414 (0.719–2.780)	0.315		
Digitalis	4.437 (1.054–18.67)	0.042	1.528 (0.323–7.243)	0.593
Ejection fraction	0.982 (0.965–0.999)	0.033	0.985 (0.968–1.003)	0.098
Primary prevention	1.704 (0.886–3.279)	0.110		
NYHA class	1.188 (0.775–1.821)	0.429		
J wave	3.559 (1.675–7.560)	0.001	2.946 (1.307–6.642)	0.009

NYHA indicates New York Heart Association.

Table 3. Details of J waves in the Patients with and without Appropriate Device Therapy

	Total (n=109)	Event occurrence (n=37)	No event occurrence (n=72)	*P* value
J wave	12 (11%)	9 (24%)	3 (4%)	0.003
Distribution				
Inferior leads, n (%)	8 (7%)	6 (16%)	2 (3%)	0.018
Lateral leads, n (%)	4 (4%)	3 (8%)	1 (1%)	0.112
Both leads, n (%)	0 (0%)	0 (0%)	0 (0%)	1.0
Amplitude of J point				
≥0.2 mV, n (%)	3 (3%)	2 (5%)	1 (1%)	0.265
Morphology				
Notching, n (%)	8 (7%)	5 (14%)	3 (4%)	0.118
Slurring, n (%)	4 (3%)	4 (11%)	0 (0%)	0.012
ST segment				
Upsloping ST segment, n (%)	2 (2%)	2 (5%)	0 (0%)	0.113
Horizontal or descending ST segment, n (%)	10 (9%)	7 (19%)	3 (4%)	0.030

Figure and Figure captions

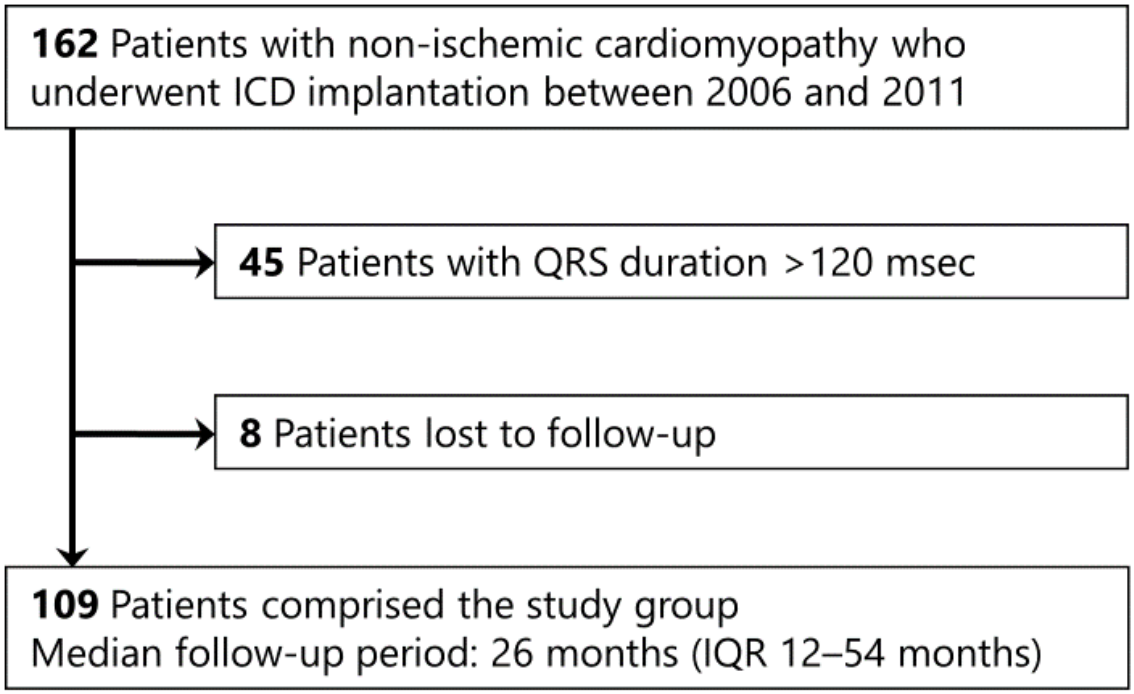

Figure 1. Study design. Patients excluded from the analysis are indicated by arrows directed to the right. ICD indicates implantable cardioverter defibrillator; and IQR, interquartile range.

5

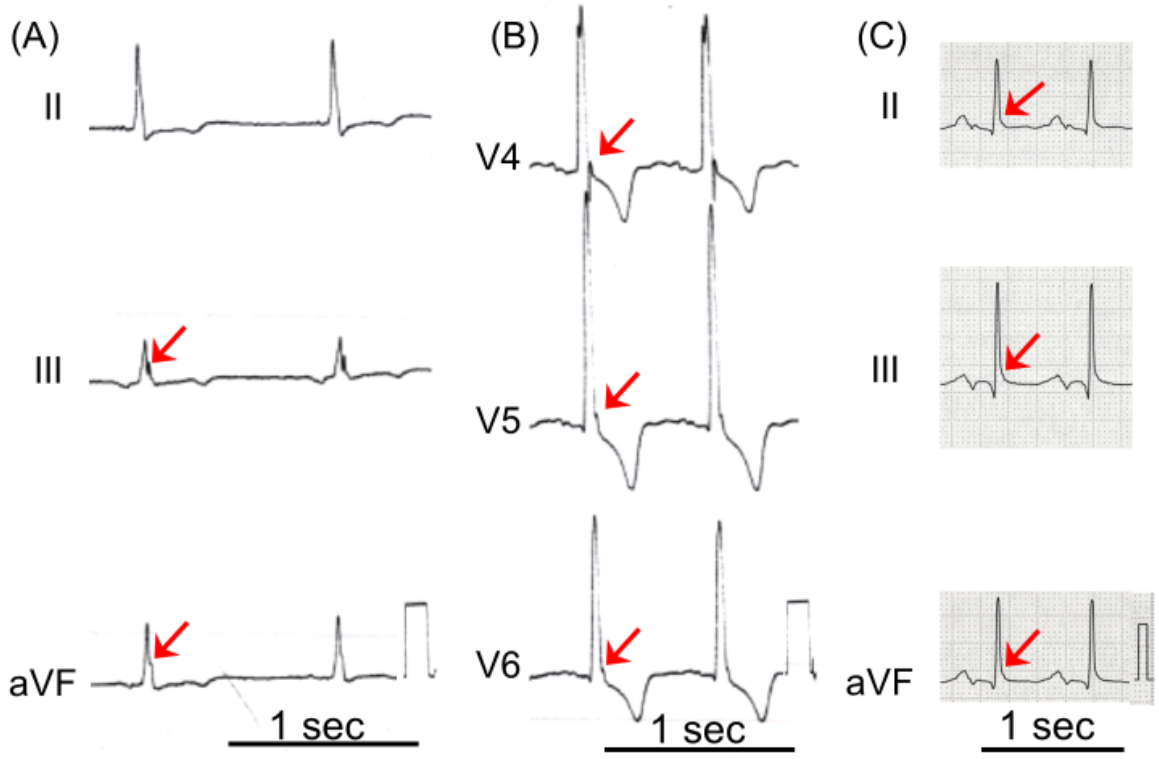

Figure 2. Representative cases of J waves. (A) Notched J waves (arrows) with horizontal/descending ST-segment in the inferior leads were recognized in a 73-year-old man with dilated cardiomyopathy. (B) Notched J waves (arrows) with horizontal/descending ST-segment in the lateral leads were observed in a 54-year-old man with hypertrophic cardiomyopathy. (C) A 62-year-old man with hypertrophic cardiomyopathy had slurred J waves (arrows) with horizontal/descending ST-segment in the inferior leads.

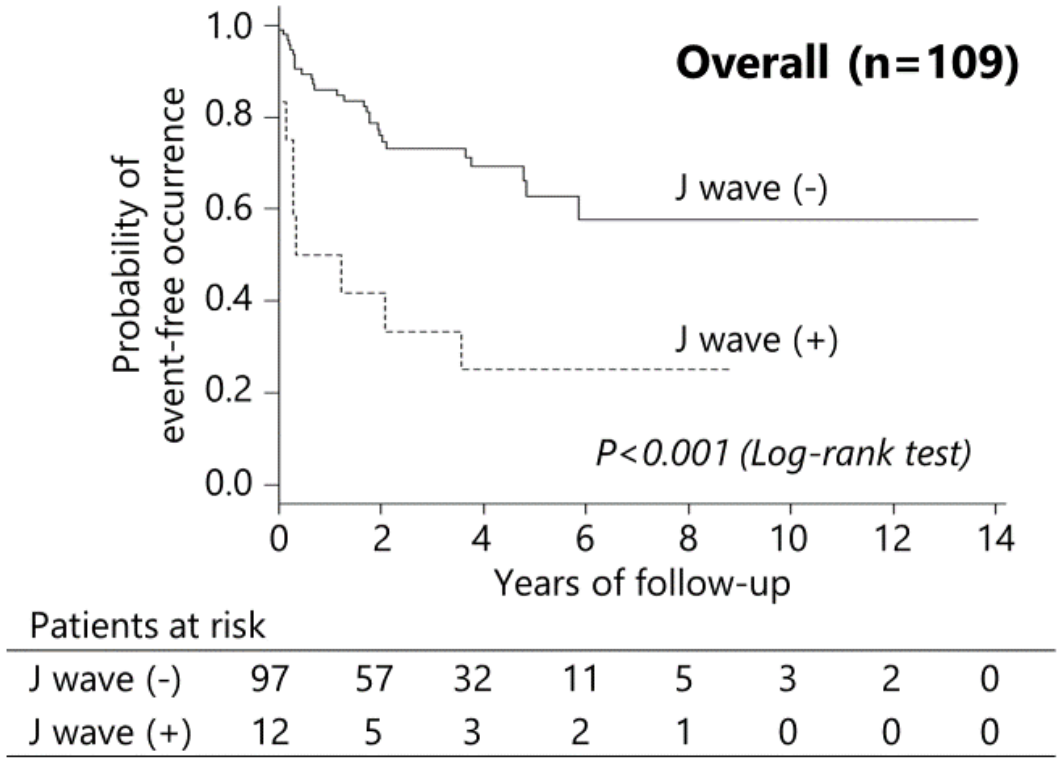

Figure 3. Kaplan-Meier curves for the primary endpoint. There was a significant difference in the occurrence of appropriate device therapy between the patients with and without J waves.

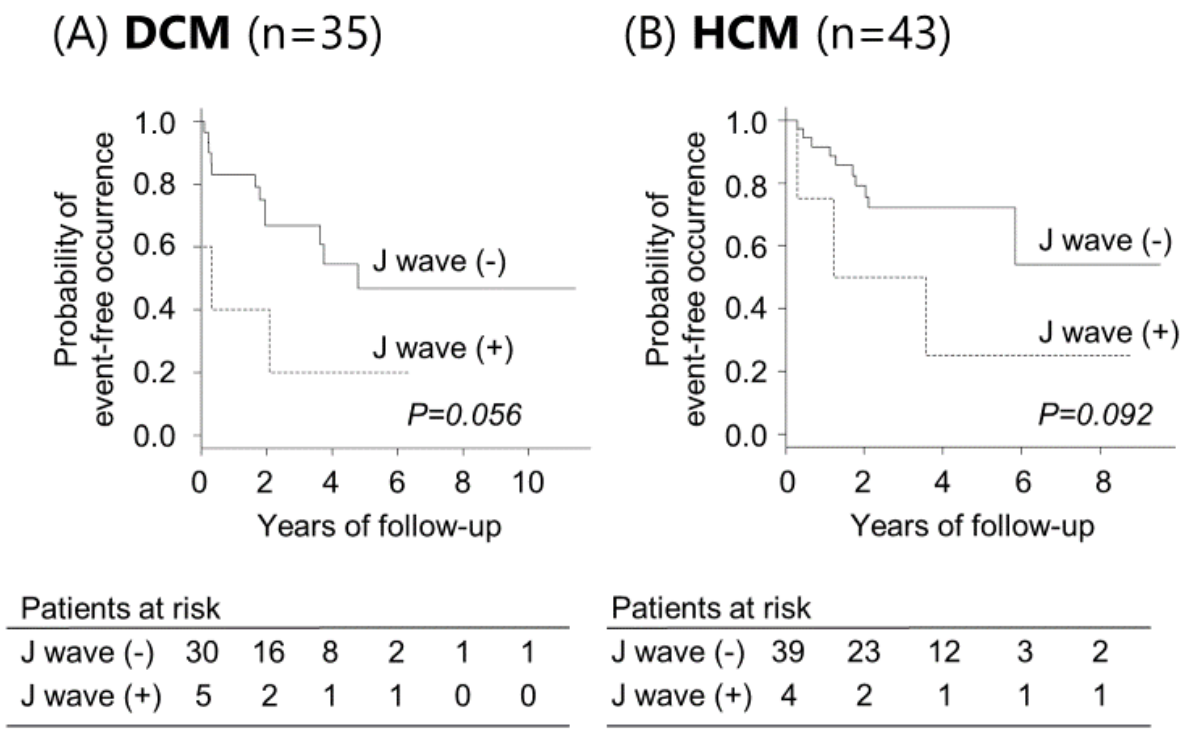

Figure 4. Kaplan-Meier curves in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy. (**A**) Concomitant J waves tended to be associated with increased occurrence of appropriate device therapy in 35 patients with dilated cardiomyopathy. (**B**) Among 43 patients with hypertrophic cardiomyopathy, the occurrence of appropriate device therapy tended to be higher in the patients with J waves than in those without.