ORIGINAL ARTICLE

Impact of T wave amplitude in lead aVR on predicting cardiac events in ischemic and nonischemic cardiomyopathy patients with an implantable cardioverter defibrillator

Yoshihiro Tanaka MD¹ | Tetsuo Konno MD, PhD^{1,2} | Yudai Tamura MD¹ |
Toyonobu Tsuda MD¹ | Hiroshi Furusho MD, PhD¹ | Masayuki Takamura MD, PhD¹ |
Kenji Sakata MD, PhD¹ | Masakazu Yamagishi MD, PhD¹ | Kenshi Hayashi MD, PhD¹

¹Division of Cardiovascular Medicine,
Kanazawa University Graduate School of
Medicine, Kanazawa, Japan

²Research and Education Center for Innovative
and Preventive Medicine, Kanazawa
University, Kanazawa, Japan

Correspondence

Tetsuo Konno, MD, PhD, Division of
Cardiovascular Medicine, Kanazawa University
Graduate School of Medicine, Kanazawa,
Japan.
Email: konnokontetsu@staff.kanazawa-u.ac.jp

Funding information

This research did not receive any specific
grant from funding agencies in the public,
commercial, or not-for-profit sectors.

Background: T wave amplitudes during ventricular repolarization in the lead aVR (TAaVR) are shown to be associated with adverse cardiac events in patients with several cardiovascular diseases, such as postmyocardial infarction. However, the utility of TAaVR has not been previously evaluated in patients with cardiomyopathy who have received implantable cardioverter defibrillators (ICD). Patients with ischemic or nonischemic cardiomyopathy (ICM or NICM, respectively) and who received an ICD may experience worsening of their condition due to the introduction of electric shock during treatment. This study aimed to investigate the utility of TAaVR in the prediction of cardiac events in ICM or NICM patients with ICD.

Methods: Ninety-three consecutive ICM or NICM patients with ICD were retrospectively analyzed (median age: 64 years; male: 77.4%; ICD for secondary prevention: 76.3%; NICM: 64.5%). The median follow-up period was 31 months. The primary endpoint was defined as composite cardiac events, including cardiac death, major ventricular arrhythmic events (MVAE), or hospitalization due to heart failure (HHF).

Results: Multivariate Cox regression analysis demonstrated that less negative TAaVR ($-0.1 \text{ mV} \leq \text{TAaVR} < 0 \text{ mV}$ and $0 \text{ mV} \leq \text{TAaVR}$) was independently associated with the primary endpoint (HR: 3.75; 95% confidence interval [CI]: 1.09–23.7; $p = .04$). Kaplan–Meier curve also revealed that the event free survival rate in the less negative TAaVR group was significantly lower than that in the normal TAaVR group ($< -0.1 \text{ mV}$) ($p < .01$).

Conclusions: TAaVR is useful in risk stratification for cardiac events in ICM or NICM patients with ICD.

KEYWORDS

cardiomyopathy, heart failure, implantable cardioverter defibrillators, lead aVR, T wave amplitude

1 | INTRODUCTION

Cardiomyopathy can be classified into two major categories: ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM). Major ventricular arrhythmic events (MVAE) and hospitalization due to heart

failure (HHF) can be possible causes of death in patients with ICM and NICM. In recent years, the survival rate of patients with ICM and NICM has improved dramatically due to the emergence of implantable cardioverter defibrillators (ICD) that are used in combination with beneficial drug therapies as well as the advancement of catheter ablation

(Sapp et al., 2016). However, further attention should be given to patients with ICD since electrical shocks introduced during treatment, even if appropriate, might lead to a deterioration in cardiac function (Poole et al., 2008). Furthermore, a worsening of heart failure or the patient's condition can also cause arrhythmic episodes (Pedersen et al., 2014). Therefore, identifying high-risk patients experiencing MVAE and HHF is crucial for improving survival in ICM and NICM patients with ICD.

The utility of cardiac magnetic resonance with late gadolinium enhancement technique (LGE-CMR) was established while stratifying the risk of MVAE or HHF in patients with cardiomyopathy (Fujita et al., 2015; Konno et al., 2014; Scott, Rosengarten, Curzen, & Morgan, 2013). Currently, patients with magnetic resonance imaging – safe ICDs can undertake LGE-CMR if they satisfy certain requirements (Gold et al., 2015), but not all patients who require ICD implantation can appreciate the benefit of MRI-safe ICD because of facility criteria or the requirement of device experts. Furthermore, LGE-CMR may not be always available and involves significant cost. Therefore, simple and cost-effective modalities are still warranted in discriminating the risk of cardiac events in patients with ICM or NICM who have received an ICD. From this perspective, a simple and cost-effective 12-lead ECG may be used to assess high-risk patients for MVAE and HHF. Various parameters, such as QRS duration, bundle branch blocks, fragmented QRS, and T-wave alternans have been reported to be useful in the prediction of MVAE in patients with cardiomyopathy (Goldberger, Subačius, Patel, Cunnane, & Kadish, 2014).

Although the lead aVR is often neglected in daily clinical practice, ST elevation in lead aVR has been reported to be useful in the prediction of left main trunk involvement in ischemic heart disease and aortic dissection (Kireyev, Arkhipov, Zador, Paris, & Boden, 2010; Riera et al., 2011; Yan et al., 2007). Similarly, there is an increasing notion that T wave amplitude in the lead aVR (TAaVR) >0 mV (known as upright T wave) may be used as a prognostic tool in patients with postmyocardial infarction, in those with renal failure who undergo hemodialysis, and in male patients (Jaroszyński et al., 2015; Tan, Engel, Myers, Sandri, & Froelicher, 2008; Torigoe et al., 2012). However, few reports have demonstrated the ability of TAaVR to predict cardiac events, including MVAE and HHF in ICM and NICM patients with ICD. The purpose of this study was to investigate the ability of TAaVR to predict cardiac events in ICM and NICM patients with ICD.

2 | METHODS

2.1 | Study population

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Bioethical Committee on Medical Research, School of Medicine, Kanazawa University. We studied ICM and NICM patients who newly underwent ICD implantation, ICD exchange or ICD follow-up between January 2009 and December 2015 in Kanazawa University Hospital. ICM and NICM were diagnosed based on clinical and genetic data. Secondary cardiomyopathy, such as cardiac sarcoidosis and hypertensive heart

disease, were included in this study. Patients with Brugada syndrome, long QT syndrome, J wave syndrome, idiopathic ventricular fibrillation, idiopathic ventricular tachycardia, and coronary spastic angina were excluded from the study. Additionally, patients with complete left bundle branch block or right ventricular pacing were excluded since TAaVR was known to be upright in these settings (Verma, 2003). Patients follow-up occurred for up to 36 months.

2.2 | ICD interrogation, ICD therapy and patient follow-up

The primary endpoint was defined as composite cardiac events that included cardiac death, MVAE, or HHF. Cardiac death, MVAE, and HHF were evaluated, respectively, as secondary endpoints. Due to the relatively small number of subjects, we evaluated the primary endpoint and secondary endpoint separately. Cardiac events were retrospectively collected using the medical record system and/or device interrogation. Device interrogation was performed in the out-patient clinic routinely every 3–6 months, or whenever symptomatic events that were related to ventricular tachycardia or ICD shock delivery happened. All devices were programmed to monitor or deliver shocks during arrhythmic episodes. Information on MVAE, including sustained VT or VF requiring adequate ICD shock delivery or anti-tachycardia pacing, were obtained. Inadequate shock events were not included in MVAE.

2.3 | Evaluation of electrocardiogram findings

A standard 12-lead electrocardiogram (ECG; 0.5–150 Hz, 25 mm/s, 10 mm/mV) was recorded in the supine position during quiet respiration (NIHON KOHDEN, Cardiofax V; model ECG-1550K, or FUKUDA DENSHI, CardioMax; model FX-8222). Conventional ECG parameters included heart rate, bundle branch block, atrioventricular block, QRS axis deviation, abnormal Q waves, PR interval, QRS duration, QT duration, T wave inversion, left ventricular hypertrophy (Sokolow & Lyon, 1949), and fragmented QRS (fQRS). The T-wave axis was estimated in the same manner as the estimation of QRS axis deviation (Salles, Xavier, Sousa, Hasslocher-Moreno, & Cardoso, 2004). Abnormal Q wave was defined as a Q wave with more than 25% of the QRS complex depth in at least two contiguous leads except aVR (Konno et al., 2004). An isolated abnormal Q wave was not defined as an abnormal Q wave in this study. Likewise, T wave inversion was defined as a negative T wave (T amp <0 mV) in at least two contiguous leads except aVR, V₁, and V₂ (Konno et al., 2007). An isolated T wave inversion was not defined as a T wave inversion in this study. QTc was calculated using Bazett's formula. fQRS in patients with narrow QRS (<120 ms) and wide QRS (≥120 ms) were defined on the basis of previous studies (Das, Khan, Jacob, Kumar, & Mahenthiran, 2006; Das et al., 2008).

In addition to these conventional parameters, TAaVR was analyzed. T-wave amplitude was defined as the first deflection after the QRS complex and/or the maximum deviation from the PR isoelectric baseline (Yan et al., 2007). TAaVR was measured manually. The cut-off value in TAaVR was set at −0.1 mV for this study. Previously, Okuda

et al. (2011) reported that a cut-off value of -0.1 mV could predict all-causes of death in heart failure patients with narrow QRS complexes when the TAaVR < -0.1 mV was considered a reference. Thus, normal TAaVR was defined as TAaVR < -0.1 mV, while less negative TAaVR was defined as -0.1 mV $\leq$ TAaVR < 0 mV and 0 mV $\leq$ TAaVR. Figure 1 demonstrates representative ECGs of normal TAaVR (left, arrow) and less negative TAaVR (right, asterisk).

2.4 | Echocardiography

Echocardiographic studies were performed using IE33 Ultrasound System (Phillips Healthcare, DA Best, The Netherlands). End-diastolic left ventricular diastolic diameter (LVDd), end-systolic left ventricular systolic diameter (LVDs), and end-diastolic septal wall thickness (SWT) were evaluated using parasternal long-axis view images. Left ventricular ejection fraction (LVEF) was calculated using Teichholz's formula.

2.5 | Statistical analysis

Basic characteristics of the study population were compared between the positive composite endpoint group and that of the negative group. Categorical data are shown as frequency and percentage, whereas continuous variables are shown as median and interquartile range (IQR). Categorical variables were compared using the Chi-square test. Continuous variables were compared using Wilcoxon rank-sum test. A receiver-operating characteristics (ROC) curve was used to estimate the ability of TAaVR to predict primary endpoint. The cut-off point was determined using the Youden index (Youden, 1950).

Univariate and multivariate Cox regression analysis was performed to evaluate factors associated with the composite endpoint. Variables with $p < .1$ on univariate analysis were chosen in multivariate Cox regression analysis. According to the triangle of Einthoven, aVR is calculated by the following formula, $-1/2$ (I + II). Therefore, T wave

amplitudes in leads I and II were also measured manually, which were likewise included in the univariate Cox regression analysis.

A Kaplan–Meier Curve was used to estimate the event-free survival rate per the primary endpoint and each secondary endpoint (cardiac death, MVAE, and HHF), with comparison of groups by the log-rank test. A p value $< .05$ was assumed to indicate statistical significance. Statistical analysis was performed using statistical software JMP® Pro 11 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

A total of 208 patients who newly underwent ICD implantation, ICD exchange or ICD follow-up between January 2009 and December 2015 were enrolled in this study. Consecutive patients ($n = 93$) who were diagnosed with ICM or NICM were analyzed after excluding 115 patients due to: Brugada syndrome in 34 patients, J wave syndrome in six patients, long QT syndrome in 17 patients, idiopathic ventricular fibrillation in 17 patients, coronary spastic angina in nine patients, idiopathic ventricular tachycardia in two patients, complete left bundle branch block in four patients, or ventricular pacing in nine patients. A total of 18 patients were excluded as they did not have full clinical or follow-up data. The median follow-up duration was 31 (IQR: 13–36) months. During the study period, a primary endpoint was observed in 37 of 93 subjects (39.8%). Among these subjects, cardiac death was observed as a secondary endpoint in five subjects (5.4%), MVAE was observed as a secondary endpoint in 28 subjects (30.1%), and HHF was observed as a secondary endpoint in 16 subjects (17.2%).

Basic characteristics of the study population are described in Table 1. The median age of the study population was 64 years, and 77.4% of subjects were male. ICD implantation as a secondary prevention occurred in 76.3% and there was a notable trend ($p = .06$) of difference between

FIGURE 1 Representative ECGs of normal negative T wave amplitude and less negative T wave amplitude in lead aVR. Normal negative TAaVR (arrow) and less negative TAaVR (asterisk) are shown. TAaVR indicates T wave amplitude in lead aVR

TABLE 1 Basic characteristics of the study population

	Total, n = 93	Event (+), n = 37	Event (-), n = 56	p value
Age, year	64 (57–72)	64 (57–69)	65 (57–73)	.46
Male, n (%)	72 (77.4)	32 (86.5)	40 (71.4)	.09
Secondary prevention, n (%)	71 (76.3)	32 (86.5)	39 (69.6)	.06
NICM, n (%)	61 (65.6)	23 (62.2)	38 (67.9)	.57
DCM, n (%)	14 (15.1)	9 (24.3)	5 (8.9)	.04
HCM, n (%)	35 (37.6)	9 (24.3)	26 (46.4)	.03
ARVC, n (%)	4 (4.3)	2 (5.4)	2 (3.6)	.67
Sarcoidosis, n (%)	6 (6.5)	3 (8.1)	3 (5.4)	.60
Others, n (%)	2 (2.2)	0 (0.0)	2 (3.6)	.25
Past medical history				
Hypertension, n (%)	27 (29.0)	9 (24.3)	18 (32.1)	.42
Diabetes, n (%)	25 (26.9)	9 (23.1)	16 (29.6)	.65
Dyslipidemia, n (%)	43 (46.2)	16 (43.2)	27 (48.2)	.64
Chronic kidney disease, n (%)	39 (41.9)	19 (51.4)	20 (35.7)	.13
CVA, n (%)	14 (15.1)	6 (16.2)	8 (14.3)	.80
Atrial Fibrillation, n (%)	24 (25.8)	12 (32.4)	12 (21.4)	.24
Medication				
ACEI/ARB, n (%)	64 (68.8)	28 (75.7)	36 (64.3)	.25
β blocker, n (%)	85 (91.4)	34 (91.9)	51 (91.1)	.89
Aldosterone blocker, n (%)	37 (39.8)	13 (35.1)	24 (42.9)	.46
Amiodarone, n (%)	33 (35.5)	15 (40.5)	18 (32.1)	.41
Sodium channel blocker, n (%)	5 (5.4)	0 (0)	5 (8.9)	.06
Sotalol, n (%)	5 (5.4)	3 (8.1)	2 (3.6)	.34
Diuretics, n (%)	46 (49.5)	24 (64.9)	22 (39.3)	.02
Statin, n (%)	43 (46.2)	17 (46.0)	26 (46.4)	.96
Calcium channel blocker, n (%)	23 (24.7)	8 (21.6)	15 (26.8)	.57

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; CVA, cerebrovascular attack; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NICM, nonischemic cardiomyopathy.

Event was defined as a primary endpoint. Chronic kidney disease was defined as estimated glomerular filtration rate $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$.

the event-positive group and event-negative group. The study population included 61 (65.6%) NICM patients (dilated cardiomyopathy, $n = 14$; hypertrophic cardiomyopathy, $n = 35$; arrhythmogenic right ventricular cardiomyopathy, $n = 4$; cardiac sarcoidosis, $n = 6$; and Emery-Dreifuss muscular dystrophy, $n = 2$). The usage of diuretics was more frequent in the event-positive group than in the event-negative group.

Electrocardiographic and echocardiographic findings are provided in Table 2. Less negative TAaVR was observed in up to 95% of cases in the event-positive group. The frequency of patients with less negative TAaVR was significantly higher in the event-positive group than in the event-negative group ($p < .05$). Not-surprisingly, echocardiographic parameters, such as LVEF, LVDD, and LVDs, demonstrated remarkable discriminative ability between the two groups ($p < .05$).

Table 3 demonstrated the results of univariate and multivariate Cox regression analysis for the primary endpoint. Multiple Cox

regression analysis provided information that less negative TAaVR was the only independent factor associated with a primary endpoint (hazard ratio [HR], 3.75; 95% confidence interval [CI], 1.09–23.7; $p = .04$).

Figure 2 shows a Kaplan–Meier Curve analysis of the primary endpoint in patients with TAaVR $< -0.1 \text{ mV}$ and those with less negative TAaVR. Patients with less negative TAaVR demonstrated a worse survival rate than did those with TAaVR $< -0.1 \text{ mV}$ ($p < .05$). Three-year event-free survival rates in patients with TAaVR $< -0.1 \text{ mV}$ and in those with less negative TAaVR were 85.2% and 45.8% respectively.

Figure 3 represents Kaplan–Meier Curve analyses of secondary endpoints. A significant difference in event-free survival rate was observed in MVAE ($p < .01$), while no remarkable differences were observed in cardiac death ($p = .26$) and HHF ($p = .15$). In terms of cardiac death, no events were observed in patients without less negative TAaVR.

TABLE 2 Electrocardiographic and Echocardiographic findings

	Total, n = 93	Event (+), n = 37	Event (−), n = 56	p value
Electrocardiography				
Heart rate, bpm	61 (56–68)	61 (56–69)	61 (56–67)	.95
CRBBB, n (%)	11 (11.8)	4 (10.8)	7 (12.5)	.81
QRS width, ms	112 (98–133)	114 (107–138)	109 (97–126)	.08
QT interval, ms	437 (412–478)	436 (412–469)	447 (411–478)	.48
QTc interval, ms	441 (424–473)	440 (420–468)	444 (425–478)	.55
QRS axis, degree	24 (−36 to 62)	12 (−42 to 59)	31 (−17 to 63)	.28
T-wave axis, degree	97 (44–120)	103 (45–120)	90 (32–119)	.33
V1S + V5R, mV	2.4 (1.5–3.5)	2.3 (1.4–3.2)	2.6 (1.6–4.0)	.21
Abnormal Q wave, n (%)	28 (30.1)	15 (40.5)	13 (23.2)	.07
T wave inversion, n (%)	64 (68.8)	25 (67.6)	39 (69.6)	.83
Left ventricular hypertrophy	24 (25.8)	7 (18.9)	17 (30.4)	.22
Fragmented QRS, n (%)	48 (51.6)	20 (54.1)	28 (50.0)	.7
TA in lead I <0 mV	43 (46.2)	17 (46.0)	26 (46.4)	1.00
TA in lead II <0 mV	21 (22.6)	10 (27.0)	11 (19.6)	.45
Less negative TAaVR	74 (79.6)	35 (94.6)	39 (69.6)	<.01
Echocardiography				
LVEF, %	43 (30–64)	37 (26–50)	49 (35–69)	<.01
LVDd, mm	57 (48–65)	63 (54–67)	55 (47–63)	.01
SWT, mm	10 (8–13)	9 (8–12)	11 (8–13)	.16

AVB, atrioventricular block; CRBBB, complete right bundle branch block; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; SWT, end-diastolic ventricular septal wall thickness; TA, T wave amplitude, TAaVR, T wave amplitude in lead aVR.

Less negative TAaVR was defined as $-0.1 \text{ mV} \leq \text{TAaVR} < 0 \text{ mV}$ and $0 \text{ mV} \leq \text{TAaVR}$.

4 | DISCUSSION

This study provides two major findings. First, less negative TAaVR was an independent predictor for the primary endpoint. Second, less negative TAaVR was significantly associated with MVAE in secondary endpoints.

An upright T wave (TAaVR > 0 mV) is generally accepted to be a useful ECG parameter for cardiac events in males, in patients following a myocardial infarction, and in hemodialysis patients (Jaroszyński et al., 2015; Tan et al., 2008; Torigoe et al., 2012). However, high-risk patients were appropriately excluded when the cut-off value was set at −0.1 mV, as was done in the present study and as was shown in previous studies (Okuda et al., 2011). Okuda et al. (2011) enrolled heart failure patients with a narrow QRS complex in their study and, in doing so, revealed that less negative TAaVR was an independent predictor of mortality. Similarly, in our study, most patients that experienced complications with chronic heart failure were at high risk for cardiovascular events. Therefore, −0.1 mV is considered to be an appropriate cut-off value in ICM or NICM patients with ICD.

In modern ECG machines, aVR is not measured but calculated using leads I and II; $aVR = -1/2 (I + II)$. Therefore, less negative T wave amplitude in aVR reflects the presence of T wave inversion in at least leads I and/or II. Although, less negative TAaVR was significantly associated with the primary endpoint in this study, T wave amplitude in leads I and II did not predict the primary endpoint. These findings suggest that a single lead did not have enough predictive value for the primary endpoint, but that averaging the T wave amplitudes in leads I and II (aVR) could provide enough predictive power to predict the primary endpoint. This could be partly because TAaVR may provide information on a wide range of electrophysiological activities in the inferolateral part of the left ventricle compared to each lead, I and II, thus, less negative TAaVR or upright T wave might reciprocally reflect ST-segment depression and/or T wave inversion in the inferolateral regions (Tanaka et al., 2016). Additionally, compared to other ECG variables, TAaVR has the unique advantage of being a single lead that can provide sufficient information regarding the entirety of the heart with the exception of the anterior regions. This characteristic feature of TAaVR on a simple and

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age ≥ 60 years	1.30	0.65–2.82	.47	–	–	–
Male	2.23	0.95–6.55	.07	1.51	0.62–4.52	.38
2nd prevention	1.86	0.79–5.45	.16	–	–	–
NICM	0.77	0.40–1.54	.45	–	–	–
Heart rate ≥ 60 bpm	0.75	0.39–1.45	.39	–	–	–
Atrial fibrillation	1.45	0.70–2.84	.30	–	–	–
QRS width ≥ 120 ms	1.41	0.73–2.71	.30	–	–	–
QTc ≥ 440 ms	0.90	0.47–1.73	.75	–	–	–
QRS axis, degree	1.00	0.99–1.00	.54	–	–	–
T-wave axis, degree	1.00	1.00–1.01	.13	–	–	–
Abnormal Q wave	2.01	1.02–3.88	.045	1.07	0.50–2.27	.86
T wave inversion	0.95	0.49–1.95	.88	–	–	–
V1S + V5R, mV	0.54	0.26–1.17	.12	–	–	–
Fragmented QRS	1.17	0.61–2.26	.64	–	–	–
TA in lead I < 0 mV	0.95	0.49–1.82	.88	–	–	–
TA in lead II < 0 mV	1.13	0.52–2.27	.74	–	–	–
Less negative TAaVR	5.28	1.61–32.5	$<.01$	3.75	1.09–23.7	.04
LVEF $\leq 40\%$	2.67	1.38–5.43	$<.01$	2.07	0.96–4.59	.07
Chronic kidney disease	1.72	0.90–3.31	.102	–	–	–
BNP ≥ 200 pg/ml	1.40	0.73–2.72	.32	–	–	–

CI, confidential interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NICM, nonischemic cardiomyopathy; TA, T wave amplitude; TAaVR, T wave amplitude in lead aVR.

FIGURE 2 Kaplan-Meier curve analysis of the primary endpoint. The event-free survival rate at the primary endpoint was compared between the two groups (i.e., patients with TAaVR < -0.1 mV and patients with less negative TAaVR, -0.1 mV $\leq$ TAaVR < 0 mV and 0 mV $\leq$ TAaVR). Patients with less negative TAaVR showed significantly worse outcomes compared to those with TAaVR < -0.1 mV ($p < .01$). Three-year event free survival rates in patients with TAaVR < -0.1 mV and those with less negative TAaVR were 85.2% and 45.8%, respectively

cost-effective ECG may enable us to identify high-risk ICM or NICM patients with ICD.

For predicting secondary endpoints, less negative TAaVR was successful in predicting the event-free survival rate of MVAE (Figure 3). Previous reports have demonstrated that TAaVR is

strongly associated with cardiac death or sudden cardiac death that is presumably caused by MVAE (Jaroszyński et al., 2015; Okuda et al., 2011; Tan et al., 2008), which is consistent with our data. Meanwhile, Shinozaki, Tamura, & Kadota (2011) reported that TAaVR is associated with left ventricular remodeling, but this parameter did

FIGURE 3 Kaplan–Meier curve analysis of secondary endpoints. The effects of cardiac death, major ventricular arrhythmic events (MVAE), and hospitalization due to heart failure (HHF) on event-free survival were evaluated. A remarkable distinction was observed in MVAE ($p < .01$). Conversely, significant differences were not detected in cardiac death ($p = .26$) and HHF ($p = .15$)

not predict the occurrence of HHF in our study population. The main reason for this discrepancy includes the involvement of patients who previously experienced myocardial infarction with severe left ventricular remodeling and left ventricular systolic impairment in the study by Shinozaki et al. (2011). In addition, this discrepancy might be explained by the lack of statistical power for detecting significant difference between the two groups due to the small number of our study population.

There are several limitations to this study. First, the study population in our study was heterogeneous. We enrolled ICM and NICM patients with ICD in this study. For example, patients with ICM constituted 35.5% of the study population. This percentage indicates a significant etiological difference between cardiomyopathy in patients in Japanese and Western countries (Group JJW, 2013). Furthermore, most patients underwent ICD implantation for secondary prevention (76.3%). Therefore, it might be difficult to apply our results to the general ICM and NICM population or to patients who received ICD for primary prevention. Additionally, patients with continuous ventricular pacing and left bundle branch block were excluded from this study. Nonetheless, multiple Cox regression analyses suggested that less

negative TAaVR could be a useful marker for cardiac events despite our heterogeneous cardiomyopathy population. Second, the sample size was small. The significant correlations between less negative TAaVR and cardiac events observed in this study should be validated in a larger cohort. This validation would also address the limitations inherent to a retrospective study design. Indeed, future studies that prospectively evaluate the utility of TAaVR measurements would provide clarification of the appropriateness of this risk stratifications strategy. In addition to the small sample size, we treated the study population as both the training and test sets. Further study is warranted to validate our observation.

5 | CONCLUSION

Our findings suggest that TAaVR can be used to predict cardiac events in ICM and NICM patients with ICD implantation. We strongly recommend that TAaVR should not be neglected in the assessment of high-risk patients given its high sensitivity and negative predictive value for predicting cardiac events.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- Das, M. K., Khan, B., Jacob, S., Kumar, A., & Mahenthiran, J. (2006). Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation*, 113, 2495–2501.
- Das, M. K., Suradi, H., Maskoun, W., Michael, M. A., Shen, C., Peng, J., ... Mahenthiran, J. (2008). Fragmented wide QRS on a 12-lead ECG: A sign of myocardial scar and poor prognosis. *Circulation Arrhythmia and Electrophysiology*, 1, 258–268.
- Fujita, T., Konno, T., Yokawa, J., Masuta, E., Nagata, Y., Fujino, N., ... Hayashi, K. (2015). Increased extent of myocardial fibrosis in genotyped hypertrophic cardiomyopathy with ventricular tachyarrhythmias. *Journal of Cardiology*, 66, 63–68.
- Gold, M. R., Sommer, T., Schwitter, J., Al Fagih, A., Albert, T., Merkely, B., ... Investigators EMS (2015). Full-body MRI in patients with an implantable cardioverter-defibrillator: Primary results of a randomized study. *Journal of the American College of Cardiology*, 65, 2581–2588.
- Goldberger, J. J., Subačius, H., Patel, T., Cunnane, R., & Kadish, A. H. (2014). Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. *Journal of the American College of Cardiology*, 63, 1879–1889.
- Group JJW (2013). Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS 2011). *Circulation Journal*, 77, 249–274.
- Jaroszyński, A., Jaroszyńska, A., Siebert, J., Dąbrowski, W., Niedziątek, J., Bednarek-Skublewska, A., ... Schlegel, T. T. (2015). The prognostic value of positive T-wave in lead aVR in hemodialysis patients. *Clinical and Experimental Nephrology*, 19, 1157–1164.
- Kireyev, D., Arkhipov, M. V., Zador, S. T., Paris, J. A., & Boden, W. E. (2010). Clinical utility of aVR-the neglected electrocardiographic lead. *Annals of Noninvasive Electrocardiology*, 15, 175–180.
- Konno, T., Fujino, N., Hayashi, K., Uchiyama, K., Masuta, E., Katoh, H., ... Yamagishi, M. (2007). Differences in the diagnostic value of various criteria of negative T waves for hypertrophic cardiomyopathy based on a molecular genetic diagnosis. *Clinical Science (Lond)*, 112, 577–582.
- Konno, T., Hayashi, K., Fujino, N., Nagata, Y., Hodatsu, A., Masuta, E., ... Yamagishi, M. (2014). High sensitivity of late gadolinium enhancement for predicting microscopic myocardial scarring in biopsied specimens in hypertrophic cardiomyopathy. *PLoS ONE*, 9, e101465.
- Konno, T., Shimizu, M., Ino, H., Yamaguchi, M., Terai, H., Uchiyama, K., ... Mabuchi, H. (2004). Diagnostic value of abnormal Q waves for identification of preclinical carriers of hypertrophic cardiomyopathy based on a molecular genetic diagnosis. *European Heart Journal*, 25, 246–251.
- Okuda, K., Watanabe, E., Sano, K., Arakawa, T., Yamamoto, M., Sobue, Y., ... Ozaki, Y. (2011). Prognostic significance of T-wave amplitude in lead aVR in heart failure patients with narrow QRS complexes. *Annals of Noninvasive Electrocardiology*, 16, 250–257.
- Pedersen, C. T., Kay, G. N., Kalman, J., Borggrefe, M., Della-Bella, P., Dickfeld, T., ... Savelieva, I. (2014). EHRA/HRS/APHR expert consensus on ventricular arrhythmias. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 11, e166–e196.
- Poole, J. E., Johnson, G. W., Hellkamp, A. S., Anderson, J., Callans, D. J., Raitt, M. H., ... Reddy, R. K. (2008). Prognostic importance of defibrillator shocks in patients with heart failure. *New England Journal of Medicine*, 359, 1009–1017.
- Riera, A. R., Ferreira, C., Ferreira Filho, C., Dubner, S., Barbosa Barros, R., Femenía, F., & Baranchuk, A. (2011). Clinical value of lead aVR. *Annals of Noninvasive Electrocardiology*, 16, 295–302.
- Salles, G. F., Xavier, S. S., Sousa, A. S., Hasslocher-Moreno, A., & Cardoso, C. R. (2004). T-wave axis deviation as an independent predictor of mortality in chronic Chagas' disease. *American Journal of Cardiology*, 93, 1136–1140.
- Sapp, J. L., Wells, G. A., Parkash, R., Stevenson, W. G., Blier, L., Sarrazin, J. F., ... Tang, A. S. (2016). Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *New England Journal of Medicine*, 375, 111–121.
- Scott, P. A., Rosengarten, J. A., Curzen, N. P., & Morgan, J. M. (2013). Late gadolinium enhancement cardiac magnetic resonance imaging for the prediction of ventricular tachyarrhythmic events: A meta-analysis. *European Journal of Heart Failure*, 15, 1019–1027.
- Shinozaki, K., Tamura, A., & Kadota, J. (2011). Associations of positive T wave in lead aVR with hemodynamic, coronary, and left ventricular angiographic findings in anterior wall old myocardial infarction. *Journal of Cardiology*, 57, 160–164.
- Sokolow, M., & Lyon, T. P. (1949). The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *American Heart Journal*, 37, 161–186.
- Tan, S. Y., Engel, G., Myers, J., Sandri, M., & Froelicher, V. F. (2008). The prognostic value of T wave amplitude in lead aVR in males. *Annals of Noninvasive Electrocardiology*, 13, 113–119.
- Tanaka, Y., Konno, T., Yoshida, S., Tsuda, T., Sakata, K., Furusho, H., ... Hayashi, K. (2016). T wave amplitude in lead aVR as a novel diagnostic marker for cardiac sarcoidosis. *Heart and Vessels*, 32, 352–358. [Epub ahead of print].
- Torigoe, K., Tamura, A., Kawano, Y., Shinozaki, K., Kotoku, M., & Kadota, J. (2012). Upright T waves in lead aVR are associated with cardiac death or hospitalization for heart failure in patients with a prior myocardial infarction. *Heart and Vessels*, 27, 548–552.
- Verma, V. K. A. A. (2003). Can an upright T-wave in lead aVR be a clinical marker for underlying myocardial disease? *Chest*, 124, 155S.
- Yan, A. T., Yan, R. T., Kennelly, B. M., Anderson, F. A., Budaj, A., López-Sendón, J., ... Investigators G (2007). Relationship of ST elevation in lead aVR with angiographic findings and outcome in non-ST elevation acute coronary syndromes. *American Heart Journal*, 154, 71–78.
- Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer*, 3, 32–35.

How to cite this article: Tanaka Y, Konno T, Tamura Y, et al. Impact of T wave amplitude in lead aVR on predicting cardiac events in ischemic and nonischemic cardiomyopathy patients with an implantable cardioverter defibrillator. *Ann Noninvasive Electrocardiol*. 2017;22:e12452. <https://doi.org/10.1111/anec.12452>