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Original Article

Prognostic value of T-wave alternans in survivors of ventricular fibrillation or hemodynamically unstable ventricular tachycardia

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ABSTRACT

Background: T-wave alternans is useful for predicting the occurrence of ventricular tachyarrhythmias and sudden cardiac death in various heart diseases. However, little is known about the clinical significance of T-wave alternans measurement in survivors of ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT).

Methods: We studied 28 patients with organic heart disease who survived VF or hemodynamically unstable VT (20 males, mean age 63 years). Echocardiography, electrocardiogram (QRS duration and QTc intervals), and Holter monitoring (heart rate variability, heart rate turbulence and T-wave alternans) were performed before implantable cardioverter-defibrillator (ICD) implantation. Positive T-wave alternans was defined as $>65\,\mu V$. During the follow-up period (10.2 ± 6.2 months), ventricular tachyarrhythmias requiring appropriate shock therapy occurred in eight patients (29%). The subjects were divided into two groups, based on whether appropriate shock therapy was required ($n=8$, Group A) or not ($n=20$, Group B). Parameters from echocardiography, electrocardiogram, and Holter monitoring were compared between the two groups in order to investigate their relationship with the incidence of shock therapy after ICD implantation.

Results: The prevalence of positive T-wave alternans was significantly higher in Group A than in Group B (88% vs. 15%, $P=0.004$). Univariate Cox proportional hazard analysis showed that, among the variables measured, only T-wave alternans had predictive power for recurrent ventricular tachyarrhythmias (hazard ratio, 13.17; 95% confidence interval: 1.606–108.1, $P=0.016$).

Conclusions: These results suggest that T-wave alternans by Holter monitoring is useful for predicting recurrent ventricular tachyarrhythmias in survivors of VF or hemodynamically unstable VT.

1. Introduction

Ventricular fibrillation (VF) is the most common cause of sudden cardiac death [1]. Survivors of VF require more careful post-resuscitation care, because this arrhythmia is associated with a high rate of recurrence and a poor prognosis after successful resuscitation. Therefore, the implantable cardioverter-defibrillator (ICD) for the secondary prevention of VF has already become an essential treatment to reduce the risk of sudden cardiac death and improve survival [2–4]. On the other hand, it has been shown that ICD shock therapy itself is linked with a deterioration in cardiac function, and may lead to high cardiac mortality [5]. Thus, the recurrence of ventricular tachyarrhythmias after ICD implantation is a critical problem in patients who have previously experienced lethal ventricular tachyarrhythmias. In order to improve patients' survival after ICD implantation, an effective means of predicting which of them are at high risk for sudden cardiac death is required in the clinical setting.

Recently, T-wave alternans (TWA) has been shown to be useful for predicting the prevalence of fatal ventricular tachyarrhythmias and sudden cardiac death in various heart diseases [6–9]. TWA is analyzed by the conventional power spectral method, using an exercise stress protocol, or by the time-domain modified moving average method, using Holter monitoring [10]. From the point of view of risk assessment, TWA by the time-domain modified moving average method has been demonstrated to be equivalent to the conventional spectral method in the long-term prediction of cardiac death [11]. However, the clinical significance of TWA measurement in survivors of VF or hemodynamically unstable ventricular tachycardia (VT) has not been fully elucidated.

Therefore, using the time-domain modified moving average method, we investigated the prognostic value of TWA as a predictor

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of recurrent ventricular tachyarrhythmias requiring shock therapy in patients with organic heart disease who had survived VF or hemodynamically unstable VT.

2. Material and methods

The study subjects were 28 consecutive patients with organic heart disease who underwent ICD implantation for the secondary prevention of sudden cardiac death, based on the indications for ICD implantation in the European Society of Cardiology's guidelines [12]. The reason for ICD therapy in these patients was previously documented VF or hemodynamically unstable VT requiring electrical shock therapy. The exclusion criteria were the presence of atrial fibrillation, idiopathic VF (including Brugada syndrome), and acute coronary syndrome. Ischemic patients had a history of coronary intervention, including balloon angioplasty or stenting, and they were in stable condition at enrollment.

An electrocardiogram was recorded (QRS duration and QTc intervals) and Holter monitoring (heart rate variability, heart rate turbulence, and TWA) was performed before ICD implantation. At the same time, blood samples were taken for measurement of B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF) was assessed using echocardiography, and New York Heart Association functional class was determined based on the clinical history. During the follow-up period (10.2 ± 6.2 months), ventricular tachyarrhythmias requiring appropriate shock therapy occurred in eight patients (29%). The subjects were divided into two groups based on whether appropriate shock therapy was required ($n=8$, Group A) or not ($n=20$, Group B). Parameters from echocardiography, electrocardiogram, and Holter monitoring were compared between the two groups, in order to investigate their relationship with the incidence of shock therapy after ICD implantation.

Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University (approval number: 1656, approval date: 22 April, 2013).

2.1. Twelve-lead electrocardiogram analysis

We used a standard 12-lead electrocardiogram tracing at 25 mm/s paper speed and 10 mm/mV amplitude (FCP-7541, Fukuda Denshi, Tokyo, Japan). QRS durations and heart rate were reported on the electrocardiogram recording. The QT interval was measured manually and corrected (QTc) using Bazett's formula [13].

2.2. Holter monitoring

In a manner similar to that used in routine Holter-based ST-segment analysis, the greatest TWA magnitudes were examined separately for each of the two leads (the bipolar modified V_1 and V_5 leads). TWA voltage was analyzed by the time-domain modified moving average method using a MARS PC Holter Monitoring and Review System (version 7, GE Healthcare, Milwaukee, WI, USA). The modified moving average method has been described in a previous study by Nearing et al. [14]. In brief, the algorithm continuously streams odd and even beats into separate bins and creates average complexes for each bin. Average morphologies of both the odd and even beats are continuously updated by a weighting factor of one-eighth of the difference between the ongoing average and the new incoming beats. TWA voltage is calculated as the maximum difference in amplitude between the odd and even median complexes from the J point to the end of the T-wave for each 15 s beat stream. A TWA voltage $>65\ \mu V$ is useful for predicting fatal ventricular arrhythmia in various heart diseases [10].

In the present study, we defined a positive TWA as $>65\ \mu V$. TWA voltages at heart rates >120 beats/min or those with high noise levels $>20\ \mu V$ were excluded from the analysis. Positive TWA was analyzed in the modified V_1 and V_5 leads; of these two leads, the one with the higher TWA voltage was termed the higher lead. The maximum TWA voltage and the prevalence of positive TWA were compared between the two groups.

In heart rate variability analysis, the standard deviation of all R–R intervals and the standard deviation of the 5-min mean R–R intervals were calculated by time-domain analysis. In this study, as no recordings had $>15\%$ noise or ectopic beats during the 24-h period, TWA and heart rate variability were measured in all patients. Heart rate turbulence parameters included turbulence onset and turbulence slope, which were determined according to a previous study [15].

The total number of single ventricular premature complexes was determined over a single day. In addition, the presence of non-sustained VT, defined as more than 3 repetitive ventricular premature complexes with a heart rate >100 beats/min, was determined, since a previous study [16] reported that the presence of non-sustained VT in Holter monitoring was an independent marker for higher overall mortality and incidence of sudden death.

2.3. Long-term follow up

The study subjects were implanted with Medtronic devices (Secura® or Protecta®; Medtronic Inc., Minneapolis, MN, USA) or St. Jude Medical devices (Current® or Fortify®; St. Jude Medical, St. Paul, MN, USA). These devices were dual-chamber ICDs. During the follow-up period (10.2 ± 6.2 months) after ICD implantation, patients were followed-up according to a scheduled protocol, with regular visits at 1, 3, and 6 months, and every 6 months thereafter. Detected episodes were classified as ventricular tachyarrhythmias, supraventricular tachyarrhythmias, or other events, according to established criteria. We investigated the prevalence of fatal ventricular tachyarrhythmias requiring appropriate shock therapy, since a recent study has reported that the occurrence of at least one appropriate ICD shock is associated with a poor prognosis [5].

2.4. Statistical analysis

Statistical analyses were performed using SPSS (version 17, SPSS Inc., Chicago, IL, USA). Data are presented as mean $\pm$ SD. Differences between the two groups were assessed by the unpaired Student t-test for continuous variables, and categorical variables were assessed by Fisher's exact test. A value of $P<0.05$ was considered statistically significant. Univariate Cox proportional hazard analysis was used to investigate the association between covariates and the prevalence of ventricular tachyarrhythmias requiring appropriate shock therapy. Receiver-operating characteristic (ROC) analysis for the identification of ventricular tachyarrhythmias was performed to calculate the sensitivity, specificity, areas under the ROC curve, and the optimal cutoff value. The event-free survival of patients with ventricular tachyarrhythmias was evaluated by the Kaplan–Meier method and analyzed using a log-rank test.

3. Results

3.1. Clinical characteristics of study subjects

Table 1 shows the baseline clinical characteristics of the study subjects. The study population consisted of 28 patients (71% men,

Table 1
Clinical characteristics ($n=28$).

Age (years)	63.7 ± 15.8
Male (*n*, %)	20 (71%)
Etiology	
Ischemic heart disease (*n*, %)	13 (46%)
Dilated cardiomyopathy (*n*, %)	10 (36%)
Hypertensive heart disease (*n*, %)	3 (11%)
Valvular heart disease (*n*, %)	2 (7%)
BNP (pg/mL)	176.6 ± 177.8
LVEF (%)	46.3 ± 14.1
NYHA functional class	2.0 ± 0.5
Medication	
β Blockers (*n*, %)	19 (68%)
ACE-inhibitors/ARBs (*n*, %)	20 (71%)
Amiodarone (*n*, %)	11 (39%)
Reason for ICD implantation	
VF (*n*, %)	20 (71%)
Hemodynamically unstable VT (*n*, %)	8 (29%)

BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE-inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; and VT, ventricular tachycardia.

mean age 63.7 ± 15.8 years) who had previously documented VF (71%) or hemodynamically unstable VT (29%) that required electrical shock therapy. The patients had either ischemic heart disease ($n=13$), or non-ischemic heart disease ($n=15$) including dilated cardiomyopathy ($n=10$), hypertensive heart disease ($n=3$), and valvular heart disease ($n=2$). Cardiac function judged from BNP levels (mean 176.6 pg/mL) or LVEF (mean 46.3%) indicated mild depression. Most patients were receiving optimal medical therapy, as evidenced by the 68%, 71%, and 39% usage rates for β blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers and amiodarone, respectively.

3.2. Ventricular tachyarrhythmias requiring shock therapy during follow up

During the follow-up period (10.2 ± 6.2 months), 8 (29%) patients had ventricular tachyarrhythmias requiring appropriate shock therapy. Among these 8 patients, 3 (38%) patients died of cardiac causes, despite frequent treatment modifications, and 3 (38%) patients underwent radiofrequency ablation for the recurrence of ventricular tachyarrhythmias, despite drug treatment modifications and the optimization of antiarrhythmic ICD intervention protocols.

3.3. Comparison of patients with or without recurrent ventricular tachyarrhythmias

As shown in Table 2, the prevalence of positive TWA and the maximum TWA voltage was significantly higher in Group A than in Group B (positive TWA: 88% vs. 15%, $P=0.004$; maximum TWA voltage: 79.8 ± 21.7 μV vs. 58.6 ± 19.1 μV, $P=0.018$). In addition, the use of β blockers was significantly higher in Group A than in Group B (100% vs. 55%, $P=0.029$). Other parameters did not differ between the two groups.

We next investigated the relationship between the covariates and incidence of shock therapy (Table 3). Univariate Cox proportional hazard analysis showed that the prevalence of positive TWA and the maximum TWA voltage had predictive power for the recurrence of ventricular tachyarrhythmias requiring shock therapy (positive TWA: hazard ratio [HR] 13.17, 95% confidence interval [CI]: 1.606–108.1, $P=0.016$; maximum TWA voltage: HR 1.026, 95% CI: 1.003–1.049, $P=0.028$).

Table 2
Clinical characteristics of recurrent and non-recurrent ventricular tachyarrhythmias.

	Group A Shock therapy ($n=8$)	Group B Non-shock therapy ($n=20$)	*P*-value
Age (years)	62.1 ± 19.8	64.3 ± 14.5	0.744
Male (*n*, %)	6 (75%)	14 (70%)	1.000
Underlying cardiac disease			
Ischemic (*n*, %)	2 (25%)	11 (55%)	0.221
Non-ischemic (*n*, %)	6 (75%)	9 (45%)	0.221
BNP (pg/mL)	205.5 ± 270.9	164.4 ± 128.9	0.594
LVEF (%)	42.2 ± 12.5	48.0 ± 14.5	0.326
NYHA functional class	2.2 ± 0.6	1.9 ± 0.5	0.179
Medication			
β Blockers (*n*, %)	8 (100%)	11 (55%)	0.029
ACE-inhibitors/ARBs (*n*, %)	7 (88%)	13 (65%)	0.371
Amiodarone	5 (62%)	6 (30%)	0.200
Electrocardiogram			
Heart rate (bpm)	74.3 ± 9.8	67.9 ± 9.2	0.113
QRS duration (ms)	120.7 ± 25.7	114.5 ± 28.7	0.601
QTc interval (ms)	440.4 ± 22.1	449.8 ± 33.6	0.496
Holter monitoring			
VPCs	2036.2 ± 3018.9	610.3 ± 1011.3	0.071
NSVT	5 (62%)	9 (45%)	0.678
Maximum TWA voltage (μV)	79.8 ± 21.7	58.6 ± 19.1	0.018
TWA > 65 μV	7 (88%)	3 (15%)	0.004
SDNN (ms)	100.6 ± 31.7	113.6 ± 26.1	0.277
SDANN (ms)	86.8 ± 38.1	94.8 ± 21.6	0.494
TO (%)	−0.21 ± 1.59	−0.62 ± 2.04	0.621
TS (ms/RRI)	2.66 ± 3.11	7.06 ± 8.47	0.174

VPCs, ventricular premature complexes; NSVT, non-sustained ventricular tachycardia; TWA, T-wave alternans; SDNN, standard deviation of all R–R intervals; SDANN, standard deviation of the 5-min mean R–R intervals; TO, turbulence onset; and TS, turbulence slope.

Table 3
Univariate Cox proportional hazard analysis of predictors of recurrent ventricular tachyarrhythmias requiring shock therapy.

	Odds ratio (95% confidence interval)	*P*-value
BNP (pg/mL)	1.002 (0.998–1.006)	0.367
LVEF (%)	0.975 (0.928–1.025)	0.327
Electrocardiogram		
Heart rate (bpm)	1.068 (0.985–1.158)	0.113
QRS duration (ms)	1.007 (0.983–1.032)	0.585
QTc interval (ms)	0.992 (0.968–1.016)	0.510
Holter monitoring		
NSVT	1.882 (0.448–7.907)	0.388
Maximum TWA values (μV)	1.026 (1.003–1.049)	0.028
TWA > 65 μV	13.17 (1.606–108.1)	0.016
SDNN (ms)	0.986 (0.960–1.012)	0.278
SDANN (ms)	0.990 (0.964–1.017)	0.483
TO (%)	1.084 (0.774–1.520)	0.639
TS (ms/RRI)	0.890 (0.732–1.082)	0.242

Abbreviations as in Table 2.

3.4. Cutoff values of T-wave alternans for predicting recurrent ventricular tachyarrhythmias

The best operating TWA cutoff value determined by ROC analysis for predicting the recurrence of ventricular tachyarrhythmias was 70.5 μV. Comparisons of TWA values between Group A and Group B are shown in Fig. 1. High TWA values (≥ 70.5 μV) were found in 7 (87.5%) patients of Group A and 2 (10.0%) of Group B. The area under the ROC curve for predicting recurrent ventricular tachyarrhythmias was 0.816 (Fig. 2). The sensitivity and

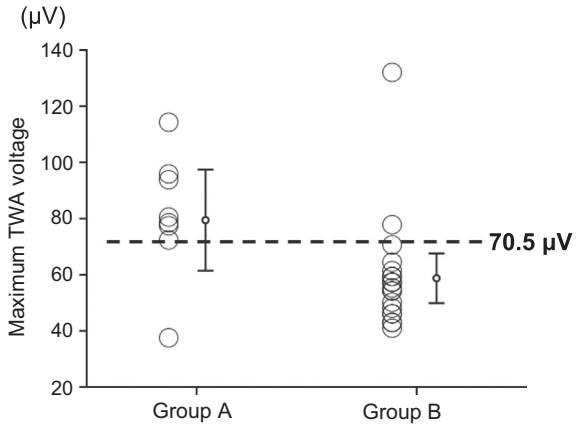

Fig. 1. Comparison of T-wave alternans (TWA) values between Group A and Group B. There were 7 (87.5%) patients with high TWA value (≥ 70.5 μV) in Group A and 2 (10.0%) in Group B.

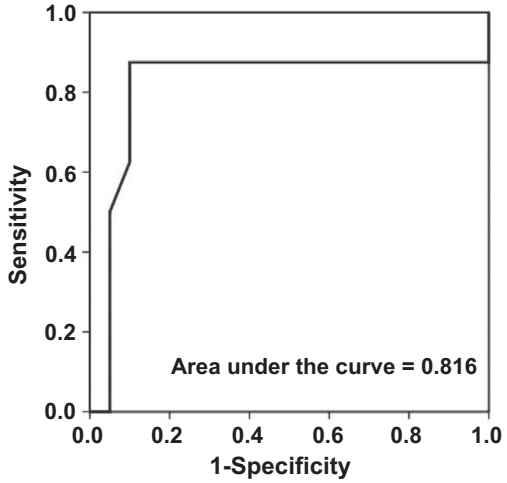

Fig. 2. Receiver-operating characteristic curve analysis for predicting recurrent ventricular tachyarrhythmias. The optimal threshold value for T-wave alternans (TWA) was 70.5 μV (sensitivity 87.5%, specificity 90.0%, and area under the curve 0.816).

specificity of TWA values (70.5 μV) in predicting recurrent ventricular tachyarrhythmias were 87.5% and 90.0%, respectively.

For the conventionally proposed cutoff value of TWA (65 μV), the sensitivity and specificity in the prediction of recurrent ventricular tachyarrhythmias were 87.5% and 85.0%, respectively.

3.5. Association of T-wave alternans with recurrent ventricular tachyarrhythmias

To evaluate the TWA voltage as a predictor for recurrent ventricular tachyarrhythmias requiring shock therapy, the study subjects were divided into two groups according to the TWA voltage cutoff of 70.5 μV. Of the 28 patients, 9 (32%) had a TWA voltage ≥ 70.5 μV (high TWA group) and 19 (68%) had a voltage < 70.5 μV (low TWA group). During the follow-up period (10.2 ± 6.2 months), recurrent ventricular tachyarrhythmias requiring appropriate shock therapy occurred more frequently in the high TWA group than in the low TWA group (78% vs. 5%, $P < 0.001$), as shown in Fig. 3. Fig. 4 shows the overall event-free probabilities for recurrent ventricular tachyarrhythmias according to the TWA voltage. The Kaplan–Meier curves for recurrent ventricular tachyarrhythmias differed significantly between the two groups ($P < 0.001$). High TWA voltage was recognized as a

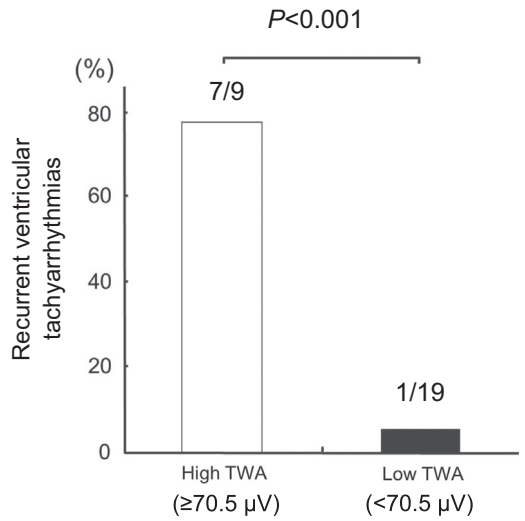

Fig. 3. Recurrence of ventricular tachyarrhythmias requiring shock therapy between high T-wave alternans (TWA) voltage and low TWA voltage. Appropriate shock therapy was delivered more frequently in the high TWA group than in the low TWA group (78% vs. 5%, $P < 0.001$).

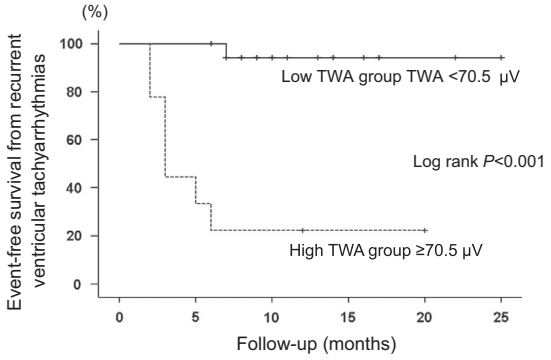

Fig. 4. The Kaplan–Meier analysis of T-wave alternans (TWA) in predicting the recurrence of ventricular tachyarrhythmias (low TWA group: solid line vs. high TWA group: dotted line). Event-free curves between the two groups differed significantly ($P < 0.001$) by log-rank test.

predictor for recurrent ventricular tachyarrhythmias requiring shock therapy, compared with low TWA voltage.

4. Discussion

This is the first study to show that TWA measured by the time-domain modified moving average method is an effective predictor of recurrent ventricular tachyarrhythmias requiring shock therapy in survivors of VF or hemodynamically unstable VT. High values of TWA were associated with recurrent ventricular tachyarrhythmias, whereas other noninvasive parameters had no significant association.

4.1. TWA and ventricular tachyarrhythmias after ICD implantation

TWA is considered to represent ventricular repolarization abnormalities [17,18]. High TWA is known to be associated with cardiac electrical instability, and TWA increases acutely prior to VT or VF [19–21]. TWA is analyzed by the conventional power spectral method using an exercise stress protocol, or by the time-domain modified moving average method using Holter ECG recording. It is sometimes impossible to perform TWA analysis by the power spectral method, because treatment with β blockers or other medications prevents the patients from increasing their heart rate

appropriately during exercise. On the other hand, TWA by the time-domain method might be helpful in evaluating the risk of recurrent ventricular tachyarrhythmias under treatment with β blockers or other medications. Thus, in the present study we investigated the risk for recurrent ventricular tachyarrhythmias using TWA by the time-domain method.

Hoshida et al. reported that the average TWA voltage was 29 ± 20 μV in mildly depressed cardiac function judged by LVEF ($47 \pm 11\%$), while TWA voltage > 65 μV was associated with fatal arrhythmic events [22]. In the patients of the present study, with equivalently depressed cardiac function, the average TWA voltage (64 ± 21 μV) was high compared to that in the study by Hoshida et al. This may have been because our study subjects had the arrhythmogenic substrate for ventricular tachyarrhythmias as a result of their previous lethal ventricular tachyarrhythmias. In the present study, ROC curve analysis for predicting recurrent ventricular tachyarrhythmias indicated an optimal TWA value threshold of 70.5 μV (sensitivity, 87.5%; specificity, 90.0%). Nieminen et al. [10] reported that TWA voltage > 65 μV was useful for predicting fatal ventricular arrhythmias and sudden cardiac death in various heart diseases. At the same time, they showed that the TWA cutoff value of 65 μV had low sensitivity (35%) and high specificity (92%) for predicting sudden cardiac death. However, A TWA cutoff value of 65 μV in our study had both high sensitivity (87.5%) and high specificity (85.0%) for predicting recurrent ventricular tachyarrhythmias. Thus, a TWA threshold modification based on patient background may provide more accurate identification of patients who are likely to suffer lethal ventricular tachyarrhythmias.

4.2. Other noninvasive parameters and ventricular tachyarrhythmias after ICD implantation

Other than the measurement of TWA, previous studies [9,15,23–26] have reported some predictors for the prevalence of ventricular tachyarrhythmias, such as prolonged QRS duration and QTc interval [24], the impairment of autonomic nervous control [15,25], and left ventricular dysfunction [26]. There is ample evidence for predicting sudden cardiac death in patients with ischemic heart disease [15,23,25] or left ventricular systolic dysfunction [23,27,28]. At present, however, little is known about the predictive value of these markers in patients with non-ischemic heart disease [27,29,30]. In the present study, with the exception of TWA, noninvasive parameters were not identified as predictors for recurrent ventricular tachyarrhythmias requiring shock therapy. Possible considerations to be taken into account regarding our results were that the cardiac function of our study subjects judged by LVEF was mildly depressed, and that 15 (54%) subjects were patients with non-ischemic heart disease.

4.3. Clinical implications

If a high value of TWA is related to recurrent ventricular tachyarrhythmias requiring shock therapy, TWA-guided therapy might be effective in reducing the prevalence of ventricular tachyarrhythmias in the clinical setting. TWA abnormality can be improved by treatment with β blockers [31]. Hreybe et al. [32] reported that β blockers increased the 1-year shock-free survival from 65% to 79% after ICD implantation for secondary prevention. Despite medical treatment with β blockers in the present study, ICD shock therapy was required and the maximum TWA voltage was high. It might be difficult to prevent the recurrence of ventricular tachyarrhythmias requiring shock therapy using β blockers only. Further investigation of improvements in ventricular repolarization abnormalities could lead to the development of effective therapeutic strategies.

4.4. Limitations

Our study has some limitations. First, patients with atrial fibrillation were excluded, because the association between a high value of TWA and atrial fibrillation was uncertain. Atrial fibrillation is common in patients with depressed cardiac function [33], and depressed cardiac function leads to a prevalence of ventricular tachyarrhythmias [26]. It is necessary to clarify the relationship between atrial fibrillation and the risk of recurrent ventricular tachyarrhythmias. Second, the present study was a retrospective study; a prospective study will be needed in the future. Third, the signal-averaged electrocardiogram and baroreceptor sensitivity are also important for prediction of sudden cardiac death [9]. However, we did not examine the signal-averaged electrocardiogram and baroreceptor sensitivity for all the patients in the present study. To improve patients' survival after ICD implantation, we should conduct additional research that includes these markers.

5. Conclusion

The measurement of TWA by Holter monitoring is useful for predicting recurrent ventricular tachyarrhythmias requiring shock therapy in survivors of VF or hemodynamically unstable VT. The maximum TWA voltage is high in patients who have survived VT or VF. Thus, a modification of the TWA threshold based on patient background may provide more accurate identification of patients likely to suffer fatal ventricular tachyarrhythmias.

Conflict of interest

We received no financial support for this study. The Department of Arrhythmia and Cardiac Pacing is supported by St. Jude Medical Japan Co., Ltd., Biotronik Japan, Japan Lifeline Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd.

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