Journal of Arrhythmia 30 (2014) 485–490

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

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

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ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form
19 February 2014
Accepted 25 February 2014
Available online 13 April 2014

Keywords:
T-wave alternans
Recurrent ventricular tachyarrhythmias
Implantable cardioverter-defibrillator
shock therapy

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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http://dx.doi.org/10.1016/j.joa.2014.02.010
1880-4276/

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,