Clinical Implication of T-Wave Morphology Analysis as a New Repolarization Descriptor

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Background T-wave morphology analysis (TMA) quantifies irregularities of ventricular repolarization based on singular value decomposition of the 12-lead electrocardiogram (ECG). Furthermore, TMA is useful for risk stratification of patients with myocardial infarction (MI), although gender differences in TMA and the relationship between TMA and heart diseases are unknown. The aim of this study was to evaluate the significance of TMA in healthy individuals and patients with heart diseases.

Methods and Results Patients with heart disease and either with or without an implanted cardioverter defibrillator (ICD, n=33, 57±16 years; non-ICD, n=50, 67±10 years) were studied. Normal control ECGs (n=114) were selected from Marquette’s database (NC, 33±13 years) and the TMA descriptors, including T-wave morphology dispersion (TMD) and percentage of the loop area (PL), were calculated. TMD was significantly lower in group NC males than in the group NC females (11±5.9 vs 22±16, p<0.0001). PL was significantly higher in group NC than in the ICD and non-ICD groups (0.63±0.12 vs 0.53±0.15, p<0.0001). TMD of group NC was significantly lower than that of the ICD and non-ICD groups (14±11 vs 47±27, p<0.0001).

Conclusion There are gender differences in TMD. Abnormal values for TMA could reflect abnormalities of ventricular repolarization. (Circ J 2005; 69: 666–670)

Key Words: Gender difference; T-wave morphology analysis; Ventricular repolarization

Day et al1 reported that QT dispersion (QTd) reflects spatial differences in myocardial recovery time in long QT syndrome and this concept has extended to other heart diseases associated with ventricular arrhythmias, such as myocardial ischemia, cardiomyopathy, and congestive heart failure. Many studies have used QTd to stratify heart disease patients with respect to the presence of life-threatening arrhythmias and/or sudden death;2–6 however, it fails to identify high-risk patients, mainly because the measure of QTd has essential methodological limitations.7,8 The poor reproducibility of QT measurements indicates that there is an overlap of QTd values between healthy individuals and patients with heart disease.

It has been proposed that T-wave morphology analysis (TMA) may quantify the irregularities of ventricular repolarization based on singular value decomposition of the standard 12-lead electrocardiograms (ECG)9 All descriptors of TMA are measured and calculated automatically from the digitally recorded ECG, which solves the problem of determining the end of the T-wave when manually measuring the QT interval. Zabel et al identified the descriptors as the total cosine R-to-T (TCRT), the normalized T-wave loop area (PL) and T-wave morphology dispersion (TMD) for evaluating ventricular repolarization.10,11 TCRT reflects the spatial angle between depolarization and repolarization, in keeping with the concept of the ventricular gradient. PL measures the heterogeneity of the principal components of the T wave within its loop, and TMD reflects the inter-lead morphologic variation of the T-wave patterns within the surface ECG.

Although the basic characteristics of TMA have not yet been elucidated, several investigators have reported its clinical usefulness. Acar et al reported that TMD and TCRT clearly identify ECG abnormalities in patients with hypertrophic cardiomyopathy10 and TCRT is the only descriptor of TMA that is a strong and independent predictor of adverse outcome in patients with myocardial infarction (MI).12,13 In addition, Smetana et al demonstrated that TCRT is greater in women than in men14 However, the clinical significance of the TMA markers except TCRT for normal control and various heart diseases remains unknown. The aim of this study was to elucidate the basic characteristics of each of the TMA indices and to evaluate the clinical significance of each parameter in patients with organic heart diseases.

Methods

Subjects
Patients with an implanted cardioverter defibrillator (ICD) were recruited from the ICD clinic at St George’s Hospital (London, UK) from January to May 2000, and at Nippon Medical School Hospital (Tokyo, Japan) from February to April 2002 (group ICD: n=33, 23 males). Patients with heart disease who did not have an ICD were recruited from Nippon Medical School Hospital (Tokyo, Japan) and Yashio Heart Hospital (Saitama, Japan) from
June 2002 to February 2004 (group non-ICD: n=50, 32 males). Written informed consent was obtained from each subject at St George’s Hospital and verbally from each Japanese patient before inclusion in the study. Patients with permanent pacemakers, atrial fibrillation, or frequent ectopic beats were excluded. A normal control group was selected randomly from ECGs from the normal database from Marquette GE (Milwaukee, WI, USA) (group NC: n=114, 83 males (73%) NS).

**ECG Recordings and Analysis**

In all patients, a digital 12-lead surface ECG sampled at 250 Hz was recorded 10 times using a MAC-VU or MAC 5000 electrocardiographic system (GE Marquette Medical System, Milwaukee, WI, USA). All digital ECG files were sent to St George’s Hospital for automatic analysis in a blinded manner. Three TMA descriptors (TCRT, TMD, and PL) were calculated using a custom written software package. Details of the physiologic background and method of calculating TMA have been previously published. TCRT represents the difference between the orientation of the QRS loop and T-wave loop, and TMD represents the angle between all possible reconstructed T-wave vector pairs. Left ventricular ejection fraction (LVEF) was estimated by transthoracic echocardiography.

**Statistical Analysis**

We evaluated gender differences and the relationship between age and TMA descriptors in group NC, and in the heart disease group (group HD), which consisted of an ICD and a non-ICD group. In addition, we assessed the significance of the descriptors in patients at high risk for arrhythmias (group ICD), and compared that with group non-ICD. Clinical variables are presented as a percentage for categorical variables and mean value ± standard deviation for continuous variables. Statistical analysis was performed using StatView J-5.0 (SAS Institute, Cary, NC, USA). These data were analyzed with Student’s t-test, Mann-Whitney and chi-squared tests for unpaired variables and with Kruskal-Wallis test for multiple comparisons, as appropriate. The correlation between age and descriptors was analyzed by linear regression. A p-value of less than 0.05 was considered statistically significant.

**Results**

**Clinical Data**

The mean age of group NC was significantly younger than that of group HD (33±13 vs 61±14 years, p<0.0001). The characteristics of the patients are summarized in Table 1. The mean age of group ICD was significantly younger than that of group non-ICD (57±16 vs 67±10 years, p<0.005). The mean LVEF of group ICD was significantly lower than that of group non-ICD (43±14 vs 54±15%, p<0.005). The incidence of ventricular tachycardia (VT) in group ICD was significantly higher than in group non-ICD (p<0.0001). There were no differences in the history of ventricular fibrillation, non-sustained VT, or syncope between either group.

**TMA**

**Gender Differences**  The value for TMD was significantly lower in the group NC males than in the females (11±5.9 vs 22±16, p<0.0001, Fig 1) and in the same group the PL was significantly higher in the males than in females (0.65±0.09 vs 0.56±0.17, p<0.01), but there was no difference in TCRT between them. There were no differences in the values of any descriptor between males and females in group HD.

**Correlations Between Age and TMA Descriptors**

There were no correlations between age and the values of any of the TMA descriptors in either the NC or HD groups.

**NC Group vs HD Group**

The TMD of group NC was significantly lower than that of group HD (33±13 vs 61±14 years, p<0.0001, Fig 2). The TCRT and PL of group NC were significantly higher than in group HD (0.40±0.40 vs –0.04±0.63, 0.63±0.12 vs 0.53±0.15, p<0.0001, p<0.0001 for both, Figs 3,4).

**ICD Group vs Non-ICD Group**

The TMD of group ICD was significantly higher than
Fig 2. Comparison of TMD (T-wave morphology dispersion) between the normal control group (NC group) and patients with heart disease (HD group). HD group consisted of patients with and without an implanted cardioverter defibrillator.

Fig 3. Comparison of TCRT (the total cosine R-to-T) between the normal control group (NC group) and patients with heart disease (HD group). HD group consisted of patients with and without an implanted cardioverter defibrillator.

Fig 4. Comparison of PL (the normalized T-wave loop area) between the normal control group (NC group) and patients with heart disease (HD group). HD group consisted of patients with and without an implanted cardioverter defibrillator.

Fig 5. Comparison of TMD (T-wave morphology dispersion) between patients with and implanted cardioverter defibrillator (ICD group) and patients without (non-ICD).
that of group non-ICD (56±22 vs 42±28, p<0.05, Fig 5). PL of group ICD showed a tendency to be low in comparison with that of group non-ICD (0.50±0.15 vs 0.56±0.14, p=0.076). There was no difference in TCRT between the 2 groups (–0.14±0.62 vs 0.04±0.63, p=0.21).

**Discussion**

Although Smetana et al15 reported that the TCRT in women is greater than that in men, we did not find such a gender difference, although there were gender differences in TMD and PL in group NC, but not in group HD. Smetana et al focused only on TCRT and calculated them from 24-h Holter recording, which is a different method to that used in our study and could influence our results. The QT interval is generally longer in females than in males, but the interval from the peak to the QT end, which represents transmural dispersion of ventricular repolarization, is shorter in females than in males.16–18 The influence of estrogen on QT interval and dispersion in humans might protect women from arrhythmic events and/or sudden death.19 TMD and PL showed clinically similar gender differences to that of QT interval, but not of QT dispersion.

As there were no correlations between age and any of the TMA descriptors, we do not consider that aging influenced any results of this study. Therefore, we ignored differences in age in the comparison of the TMA indices.

The values of TMD, TCRT, and PL can distinguish normal control and the patients with various heart diseases, including cardiomyopathies, valvular diseases and ischemic heart disease. Acar et al analyzed the TMD, TCRT, and PL values of patients with hypertrophic cardiomyopathy (HCM) and normal controls, and found that the abnormal values could differentiate HCM from normal.20 Zabel et al, however, did not compare the values of TMD, TCRT, and PL between patients with MI and normal controls.11,12 This is the first report suggesting that repolarization abnormalities in patients with various heart diseases can be also detected by TMA analysis.

TMD is a measure of spatial T-wave variations and increases in the TMD value indicate greater inter-lead differences in T-wave morphology. Decreases in the PL value indicate heterogeneous temporal evolution of ventricular repolarization. Thus, increased TMD and decreased PL reflect heterogeneity in focusing of the T-wave shape on the 12-lead ECG in the ICD group.

Patients with an ICD are considered to be a population with a high incidence of life-threatening arrhythmias and/or sudden death. Zabel et al analyzed a database of 280 post-MI patients and found that TCRT is a strong independent predictor of adverse outcome.11 In our study, the mean values of TCRT in both the ICD and non-ICD groups were abnormal, but there were no differences between the 2 groups. TCRT is a marker for stratifying only those patients with MI. If patients with heart diseases other than MI are included, then TMD is superior to TCRT for differentiating normal and abnormal ventricular repolarization.

The pathophysiology responsible for the changes in TMD and PL has not been assessed in electrophysiologic terms. Batchvarov et al demonstrated a relationship between these descriptors and autonomic activity but the physiologic meaning is still uncertain. The concept of QT interval dispersion reflects ventricular repolarization only based on the duration of the QT interval. TMD and PL would allow for the evaluation of repolarization abnormalities based on variations of the T-wave shape. It is a new method and needs further physiologic examination.

**Study Limitations**

We utilized the Marquette database for the normal control ECG files, so there were different ethnic groups within this study. As an ethnic difference in the ECG measurements of women has been reported, we can not deny it might have had an effect, even partially, on our results.21 The study was not prospective, so we cannot determine whether TMD and PL can predict arrhythmic events. It might be clinically difficult to distinguish patients with or without an ICD by TMD because of their overlapping values, so the descriptors need to be more sensitive to changes in ventricular repolarization.

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