Clinical Significance of T-Wave Alternans in Hypertrophic Cardiomyopathy

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The clinical significance of T-wave alternans (TWA) in hypertrophic cardiomyopathy (HCM) is unclear, so SV1+RV5 and QT dispersion on 12-lead electrocardiograms (ECG), the parameters of the left ventricle on echocardiography and the family history of HCM and sudden death were investigated in 53 patients with HCM who experienced TWA. The maximal numbers of successive ventricular ectopic beats (max VE) and nonsustained ventricular tachycardia (NSVT) were measured by Holter monitoring. In 13 patients, genetic abnormalities were examined. In 22 patients, the hypertrophy of myocytes, disarray and fibrosis were histopathologically examined using a scoring method. TWA was positive in 27 patients (TWA+ group), negative in 14 (TWA– group) and indeterminate in 12. The ECG and echocardiographic parameters, family history and genetic abnormalities did not significantly differ between the TWA+ and TWA– groups. Max VE, the percentage of patients with NSVT and disarray score in the TWA+ group were significantly higher than those in the TWA– group (3.6±3.6 vs 1.3±0.7, 37% vs 0%, 1.9±1.1 vs 0.7±0.5; p<0.05). TWA in HCM correlates with histopathological changes, especially disarray and ventricular tachyarrhythmia, and measuring it may be a noninvasive means of detecting high-risk patients with HCM. (Circ J 2002; 66: 457–462)

Key Words: Disarray; Hypertrophic cardiomyopathy; T-wave alternans; Ventricular tachyarrhythmia

Hypertrophic cardiomyopathy (HCM) is a cardiac disorder characterized by increased left ventricular wall thickness in the absence of any other cause of increased cardiac mass. The natural history of patients with HCM is a slow progression with a 5-year survival rate of approximately 90%,2–5 but death from HCM is usually sudden. A family history of sudden death, recurrent syncpe, nonsustained ventricular tachycardia and an abnormal response of blood pressure to exercise have been cited as predictors for sudden death6 and therefore identifying these high-risk patients is of the utmost importance.

Noninvasive tools are needed to predict sudden cardiac death in patients with HCM. The signal-averaged electrocardiogram (SAECG),7 QT dispersion (QTd)8 and 24-h Holter monitoring9 have been used, but none of these is regarded as suitably powerful. T-wave alternans (TWA) is associated with cardiac electrical instability and ventricular arrhythmias in ischemic heart disease10 and dilated cardiomyopathy.11 Momiyama et al12 first reported TWA in 14 patients with HCM in 1997; they classified them high risk or non-high-risk according to the episodes of sustained VT or ventricular fibrillation, or a family history of sudden death and they found that 71% of patients in their high-risk group were TWA positive. In the present study, we examined the relationship between TWA and not only the conventional noninvasive risk predictors of sudden death, but also histopathological changes and genetic abnormalities, to determine the clinical significance of TWA in patients with HCM.

Methods

Patients

The study group consisted of 53 patients with HCM referred to the Kobe University Hospital and clinically diagnosed with idiopathic HCM according to the criteria of the World Health Organization.13 Cardiac catheterization and echocardiography were performed, and coronary heart disease, valvular disease and cardiac hypertrophy because of hypertension were excluded. Patients were classified by the type of HCM using the echocardiography: (i) non-obstructive type (HNCM) (n=37), (ii) obstructive type (HOCM) (n=4) and (iii) apical hypertrophy (APH) (n=12). The purpose of the study was explained to all participants, who gave their consent. Beta-blockers, calcium antagonists and antiarrhythmic agents were discontinued for more than 5 times their respective half-lives before the investigation.

Measurement of TWA

TWA was measured at rest and during controlled bicycle exercise using a CH2000 system (Cambridge Heart Inc, Bedford, MA, USA),14 based on the spectral method described by Smith et al15 If the alternans voltage (Valt) was ≥1.9μV and the alternans ratio (R) was ≥3 with an onset heart rate ≤110 beats/min during exercise, the test was positive. If alternans was absent during a sustained interval of exercise without an artifact at a heart rate ≥105 beats/min, the test was negative. If a result did not meet the positive or negative criteria, it was considered indeterminate.
Other Measurements 
All patients underwent the following noninvasive examination and the following parameters were evaluated. On a 12-lead standard electrocardiograms (ECG) with a paper speed of 25 mm/s, we assessed the SV1+RV5, as an indicator of hypertrophy, QT dispersion (QTd) at rest, and ST-T depression over 0.1 mV during exercise (Ex ST-dep). We manually measured the QT interval in all leads. The end of the T wave was defined as a return to the isoelectric line. In the presence of the U wave, the QT interval was measured to the nadir between the T and U waves. Those leads in which the end of the T wave could not be measured because of a flat T wave or excessive noise were excluded. QTd was defined as the difference between maximal and minimal QT intervals. We also examined the presence of late potential (LP) in SAECG (FDX-6521, Fukuda Denshi, Tokyo, Japan) as described.14 The thickness of the interventricular septum (IVS) and posterior wall (PW), and the end-diastolic and end-systolic diameters of the left ventricle (LVDd, LVDs) were measured by echocardiography (UCG). IVS, the ratio of IVS to PW (IVS/PW), LVDd and percent fractional shortening (%FS) were used as analytical parameters. Patients with HNCM and HOCM were classified by the type of hypertrophy according to the classification of Maron16 using UCG. Total ventricular ectopic beats (VE), the maximal number of successive VE (max VE) and nonsustained ventricular tachycardia (NSVT ≥5 VEs) were evaluated by 24-h Holter monitoring, which was recorded a few days before the TWA assessment. We also investigated any family history of HCM (FH-HCM) or sudden death (FH-SD).

Statistical Analysis 
We compared all parameters between the patients with a positive TWA (TWA+ group) and the patients with negative TWA (TWA– group). ECG at rest, UCG and 24-h Holter monitoring data are expressed as means ± SD and were compared using an unpaired t-test between the TWA+ and TWA– groups. Other parameters were compared by the χ² test. Probability was considered significant at p<0.05.

Results 

T-wave alternans was positive in 27 (51%) and negative in 14 (26%) patients, and indeterminate in 12 (23%) because of too much noise or inadequate increase in heart rate. We excluded the indeterminate results from further analysis. The TWA+ and TWA– groups did not significantly differ in terms of age, sex, ECG and UCG parameters, and SAECG (Table 1).
Three of 5 patients who had experienced syncope were TWA+, but NSVT was not observed on Holter monitoring. The total VE did not significantly differ between the 2 groups, but max VE in the TWA+ group was significantly higher than that in the TWA– group (3.6±3.6 vs 1.3±0.7; p<0.05) (Table 1). Sustained VT and ventricular fibrillation were not observed. The ratio of patients with NSVT in the TWA+ group was also significantly higher than in the TWA– group (10/27, 37% vs 0/14, 0%; p<0.01). Therefore, the sensitivity, specificity, positive and negative predictive values, and predictive accuracy of TWA for NSVT were 100%, 45%, 37%, 100% and 59%, respectively. Those of QT dispersion ≥80 ms for NSVT were 50%, 35%, 20%, 69% and 39%, and those of LP were 10%, 87%, 20%, 75% and 68%, respectively.

**Family History**

Eight of 13 patients (62%) with a FH-HCM and 5 of 6 (83%) with a FH-SD were TWA+, but the incidence of FH-HCM and FH-SD did not significantly differ between the 2 groups (Table 1). Fig 1 shows representative data from a 66-year-old male patient. The IVS thickness was 18 mm and %FS was 42%. The 24-h Holter monitoring detected NSVT (max VE, 23), but he did not have a family history of HCM or sudden death. He was TWA+ with an onset heart rate of 98 beats/min. Histopathological assessment revealed mild myocytic hypertrophy with severe disarray and fibrosis.

**Genetic Analysis**

Table 2 shows the genetic analysis and clinical variables: 7 of 13 patients had genetic abnormalities (54%). The β-myosin heavy chain (MYHC), cardiac muscle binding protein C (CMBPC) and troponin I (cTnI) were abnormal in 5, 1 and 1 patients, respectively. Case nos. 2 and 10 were brothers who did not have NSVT, but one was TWA+; nos. 7 and 13 were father and son, neither of whom had a genetic abnormality in the present analysis, but the son (case no. 7), who did not have NSVT, was TWA+; case nos.3 and 9 both had NSVT and genetic abnormalities and both were TWA+. Of the patients with genetic abnormalities, only 1 (no. 10) was TWA+ without NSVT and the other 3 (nos. 2, 8, 11 and 12) did not have NSVT and were either TWA– or indeterminate. One patient with both a family history of sudden death and a genetic abnormality was TWA+ (no. 9).

**Discussion**

Using noninvasive methods of identifying high-risk patients with HCM is an important priority. In the majority
of studies of late potential (LP) using SAECG, the prevalence of LP was approximately 10%, with a higher incidence in patients with documented VT, although a significant correlation was not found.20–22 The prevalence of LP in those studies differed according to the filters and criteria used in the analysis; Chang et al suggested that the inability of SAECG to risk-stratify patients with HCM was probably because diffuse left ventricular hypertrophy masked the LP, or that sudden death in HCM is not caused by reentrant ventricular arrhythmias.22 The QT dispersion (QTd) and prolongation23,24 have also been reported in HCM: Buja et al reported that QT interval and QTd were significantly prolonged in HCM with ventricular tachyarrhythmia,8 but Fananapazir et al suggested that prolongation of both the QT interval and QTd was a common finding in patients with HCM and may not be of prognostic significance in the absence of syncope or cardiac arrest.24

The difficulty of determining the end of the T wave in HCM because of negative or biphasic T waves may be also limit its usefulness as a predictor. We found that TWA was a more powerful method of identifying patients with VT than LP and QTd. Momiyama et al first reported TWA in patients with HCM, although the study population was extremely small and the correlation between TWA and the clinical variables of family history, cardiac function and histopathological change was not clarified.12 Kon-No et al evaluated TWA in 12 patients with APH, and left ventricular hypertrophy (LVH), and reported that TWA may be related to abnormal myocardial arrangement (disarray) and/or fibrosis, although it was unclear how they determined the severity of fibrosis and disarray.25 We evaluated the relationship between TWA and the histopathological changes quantitatively in 22 patients and also found that TWA correlated with myocardial disarray.

The present study evaluated the relationship between TWA and the conventional noninvasive risk predictors of sudden death and examined the clinical significance of TWA in 53 patients with HCM. Of the ECG variables, SV1+RV5 was higher in the TWA– group than in the TWA+ group, which we think is because several patients with complete right bundle branch block were included in TWA+ group. Maximal VE and NSVT on 24-h Holter monitoring closely correlated with TWA. A family history of HCM or sudden death weakly correlated with TWA. Therefore, TWA is a valuable tool for predicting sudden death in patients with HCM.

The present study also evaluated the TWA from the viewpoint of histopathological and genetic abnormalities. Patients with HCM and severe histopathological changes were TWA+, and of the histopathological changes that we examined, disarray closely correlated with TWA. Pastore et al reported that TWA is related to discordant alternans, which arises from the heterogeneity of the prolonged action potential in each myocyte.26 Maron et al27,28 and McKenna et al29 suggested that disorganized cells dispersed throughout the left ventricular wall are predisposed toward disordered electrical depolarization and repolarization, and constitute an arrhythmogenic myocardial substrate. If a discordant area arises in the presence of disarray or fibrosis, then TWA will easily become positive. Yutani et al suggested that disarray was a characteristic histopathological change in HCM, involved in the decreasing diastolic function.30 Thus, TWA could reflect histopathological changes, especially disarray, and provide useful information about the severity of HCM.

Apical hypertrophy is a type of HCM with good prognosis in which arrhythmia and decreased wall motion at the apex are observed rarely.31 When our analyses excluded the 12 patients with APH, the results were same. Three of the APH patients had NSVT, 4 had a family history of HCM, and 3 had a family history of sudden death apparently caused by HCM. Therefore patients with APH should be evaluated for TWA.

The prognostic of familial HCM differs according to the genetic abnormalities and mutations.32 For example, in families carrying the MYH6 gene, the Arg603Gln, Arg653Cys, Arg719Trp and Gly716Arg mutations are associated with a high incidence of sudden death in the young, whereas the Leu908Val and Val606Met mutations are associated with a near normal life expectancy.33–35 The prognosis of families with MBPC is better than that of families with a malignant mutation in MYH7. In families carrying cTnT, Arg92Trp and Ala104Val are associated with sudden death, although the hypertrophy is mild.36,37
183 del mutation is associated with sudden death at any age and dilated cardiomyopathy-like features in those aged over 40.\textsuperscript{38} We detected 6 different mutations in 7 patients, and TWA was positive in 2 patients with NSVT (\textsuperscript{35}MYHC and MBPC) and in 1 without NSVT (\textsuperscript{35}MYHC). One patient with an arginine mutation of \textsuperscript{35}MYHC, which reportedly has a malignant prognosis, was TWA+, as was another with both a family history of sudden death and a genetic abnormality. The genetic abnormalities we found differed from those so far reported. The TWA+ patients without a genetic abnormality may have other unknown gene abnormalities. The relationship between TWA and genetic abnormalities remains unclear in these patients, and we need to carefully follow the changes in their clinical variables by Holter monitoring, UCG and TWA.

**Study Limitations**

Thirty-seven (78\%) of the patients did not have obstructive HCM with which an abnormal blood pressure response, which is considered to be a predictor of a high risk of sudden death in HCM, is frequently associated. Prognosis is worse in the obstructive type; so malignant and high-risk patients may not have been included in our study population because HCM patients with the severe obstructive type were excluded.

In addition, the relationship between a high risk of sudden death and genetic abnormalities remains unclear, especially with respect to the occurrence of ventricular tachyarrhythmia, and needs to be followed up in such patients.

**Conclusions**

In patients with HCM, TWA closely correlated with histopathological changes, especially disarray, and ventricular tachyarrhythmia, and may be a useful noninvasive marker for high-risk patients.

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**References**


