The Usefulness of Microvolt T-Wave Alternans in the Risk Stratification of Patients with Hypertrophic Cardiomyopathy

Therese Fuchs MD[1] and Amram Torjman Msc[2]

[1]Arrhythmia Service, Assaf Harofeh Medical Center, Zerifin, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]College of Management, Rishon LeZion, Israel

ABSTRACT: **Background:** Patients with hypertrophic cardiomyopathy are prone to ventricular arrhythmias and sudden death. Identifying patients at risk of sudden death is difficult.

Objectives: To determine whether microvolt T-wave alternans detected during exercise or rapid atrial pacing can identify patients with HCM who are at risk of ventricular arrhythmias and sudden death.

Methods: This prospective observational study included 21 patients with HCM: the disease was abstructive in 11, non-obstructive in 9 and apical in 1. TWA was measured while the patients were on anti-arrhythmic medication.

Results: TWA was positive in 9 patients (43%) and negative in 12 (57%). Three patients were resuscitated after sudden death before their enrollment in the study and two patients developed ventricular tachycardia and fibrillation respectively during the study period. After combining the endpoint of sudden death from a ventricular arrhythmia and the presence of ventricular arrhythmias on a Holter monitor, there was no significant correlation between the presence of a positive TWA and the presence of ventricular arrhythmias on the Holter monitor or a history of sudden death.

Conclusion: TWA cannot be used as a non-invasive test for detecting patients with HCM and electrical instability. TWA is not useful for predicting sudden death in patients with HCM.

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KEY WORDS: T-wave alternans, hypertrophic cardiomyopathy, ventricular arrhythmias, sudden death

Hypertrophic cardiomyopathy is a genetic disease with a prevalence of 1 to 2 per 1000 in the general population. Patients with HCM are prone to atrial and ventricular arrhythmias [1]. The cumulative annual incidence of sudden death in a general HCM population is between 1% and 2%. Ventricular tachycardia or ventricular fibrillation appears to be the principal mechanism of sudden death in patients with HCM. However, it has been difficult to identify patients at risk of sudden death. A family history of sudden death, recurrent syncope, non-sustained VT, septum thickness of more than 30 mm, and an abnormal blood pressure response to exercise have been suggested as predictors for sudden death [1]. Holter monitoring, signal-averaged electrocardiography and QT dispersion have been used and were found to be inadequate [2-4]. Thus, there is a need for additional non-invasive tools to predict sudden death in patients with HCM.

TWA was found to be associated with cardiac electrical instability in patients with ischemic and dilated cardiomyopathy [5-8] and was present in high risk patients with HCM [9,10]. The purpose of the present study was to test the hypothesis that microvolt-level TWA detected during exercise or rapid atrial pacing can identify patients with HCM who are at risk of ventricular arrhythmias and sudden death.

HCM = hypertrophic cardiomyopathy
TWA = T-wave alternans

PATIENTS AND METHODS

The study group comprised 29 patients with HCM referred to Assaf Harofeh Medical Center during the period 16 November 2004 to 1 November 2006. All patients met the conventional clinical and echocardiographic criteria of HCM [11]. By means of echocardiography, patients were classified by the type of HCM: obstructive, b) non-obstructive, and c) apical. Beta-blockers were discontinued 24–36 hours before performance of the TWA study. Anti-arrhythmic drugs and calcium channel blockers were not discontinued. Informed consent was obtained from all study participants.

MEASUREMENT OF TWA

All subjects were prospectively evaluated for TWA by means of a treadmill exercise test and adherence to a manual protocol, or rapid atrial pacing via a pacemaker or an implantable cardioverter defibrillator. Measurements were obtained with the HearTwave™ system (Cambridge Heart Inc., Bedford, MA, USA), which uses the spectral method described by Smith et al. [6]. After careful skin preparation, 7 standard electrodes were placed in the standard 12-lead position and 7 multisegment special electrodes were arranged in a Frank orthogonal (XYZ) configuration. Alternans was measured at a heart rate of 100–110 and 110–120 beats/min.

Patients with a pacemaker or an ICD had their device temporarily programmed to the AAI mode and were paced at 105 beats/min and subsequently at 115 beats/min. The TWA test was automatically interpreted within the HearTwave™ system. The test was considered positive if the alternans voltage was ≥ 1.9 V and the alternans ratio ≥ 3 with an onset heart rate ≤ 110 beats/min during exercise or atrial pacing. The test was considered negative if alternans was absent during a sustained interval of exercise or atrial pacing at a heart rate ≥ 105 beats/min. If the result did not meet the positive or negative criteria it was considered indeterminate.

All patients underwent TWA testing at the beginning of the study period and had repeat TWA testing after 12 and 24 months. Additionally, patients were seen in the arrhythmia clinic every 6 months, and those with a pacemaker or an ICD had their devices interrogated and the device telemetry checked for possible arrhythmias. The list of the patients' medications was updated at each visit. The planned follow-up period was 36 months. The primary endpoints included cardiac arrest or a documented sustained ventricular arrhythmia. The secondary endpoints included syncope or NSVT on the Holter monitor. Patients whose baseline study was indeterminate due to inability to achieve an adequate heart rate or due to arrhythmias in their baseline study were excluded from the data analysis.

STATISTICAL ANALYSIS

We compared the parameters of patients with a positive TWA and of patients with a negative TWA. We used the chi-square test for categorical variables and the independent sample *t*-test for continuous variables. Results are presented as mean ± standard deviation. A *P* value < 0.05 was considered statistically significant [Table 1].

Table 1. Statistical analysis with the different variables

Baseline characteristics	TWA positive (N=9)		TWA negative (N=12)		*P* value
	No.	% (mean ± SD)	No.	% (mean ± SD)	
Age (yrs)	9	48.3 ± 21.2	12	52.5 ± 21.1	NS
Gender (male)	9	66.7%	12	66.7%	NS
T-wave magnitude	9	-2.67 ± 2.78	12	-3.17 ± 2.66	NS
ICD	9	55.6%	12	50.0%	NS
Sudden death	9	22.2%	12	25.0%	NS
Exercise test	9	55.6%	12	58.3%	NS
Atrial pacing	9	44.4%	12	41.7%	NS
Interventricular septum thickness	9	24.0 ± 7.6	11	21.7 ± 5.5	NS
Left posterior wall thickness	5	14.0 ± 2.0	7	12.3 ± 2.2	NS
Gradient	9	44.4%	12	50.0%	NS
Beta-blockers	9	55.6%	12	50.0%	NS
Calcium channel blockers	9	11.1%	12	16.7%	NS
Amiodarone	9	22.2%	12	33.3%	NS
Sotalol	9	11.1%	12	16.7%	NS
Follow-up events					
Holter (NSVT)	7	71.4%	12	50.0%	NS
Syncope	9	11.1%	12	16.7%	NS
ICD events	5	20%	6	33.33%	NS

ICD = implantable cardioverter defibrillator, NSVT = non-sustained ventricular tachycardia, NS = non-significant, SD = standard deviation.

RESULTS

Twenty-nine patients with HCM initially enrolled in this study. None of the patients had heart failure and none of the patients underwent septal alcohol ablation or myectomy. Six patients were unable to walk on the treadmill, one patient could not achieve a heart rate > 100 beats/min, and one patient had multiple atrial premature beats that interfered with TWA measurement. The study population thus comprised 21 patients; 11 had the obstructive type, 9 the non-obstructive type, and in 1 patient it was apical. Of the 19 patients with a Holter monitor 11 (58%) had episodes of NSVT. Eleven patients (52%) had an ICD and 1 patient had a permanent pacemaker. The ICD was implanted for primary prevention of sudden death in eight patients and for secondary prevention in three patients. Three patients had a syncopal episode, three were resuscitated from sudden death before their enrollment in the study, and two patients developed ventricular tachycardia and ventricular fibrillation respectively during the study period. These two patients were saved by their ICDs. Only one patient in this series had a family history of sudden cardiac death.

The TWA study was performed with an exercise test in 12 patients (57%) and with atrial pacing in 9 (43%). None of the patients had a bundle branch block on their baseline electrocardiogram. TWA was positive in 9 patients (43%) and negative in 12 (57%) during the study period of 24 months. The average vector magnitude, in the patients who were TWA positive, was 4.9 ± 2.8 microvolt and the average heart rate onset of TWA (the heart rate at which the TWA became positive) was 102 ± 7 beats per minute. Fourteen of the 21 patients (66%) had a repeat TWA study at 12 months follow-up and 10 patients (47%) at 24 months follow-up [Table 2]. The mean follow-up was 33 ± 11 months. After combining the endpoint of sudden death from a ventricular arrhythmia and the presence of ventricular arrhythmias on a Holter monitor, there was no significant correlation between the presence of a

ICD = implantable cardioverter defibrillator
NSVT = non-sustained ventricular tachycardia

Table 2. Follow-up TWA testing with different anti-arrhythmic agents

Patient no.			
Sudden death	**Baseline TWA**	**12 months TWA**	**24 months TWA**
1	Negative/Amiodarone	Negative/Amiodarone	–
2	Positive	Positive	Negative
3	Negative/Amiodarone	Negative/Amiodarone	Negative/Amiodarone
4	Negative/ Verapamil	Negative	Negative
5	Negative	Negative	Positive (Flecainide+Pace)
Non-sudden death			
6	Negative/Sotalol	Negative/Sotalol	Positive
7	Negative	Negative	Negative
8	Negative/ disopyramide, verapamil	Indeterminate/ disopyramide, verapamil	Negative/disopyramide, verapamil
9	Negative/Sotalol	Negative/Sotalol	Negative/Sotalol
10	Negative/Amiodarone	Negative/Amiodarone	Negative/Amiodarone
11	Negative	–	–
12	Positive/Amiodarone	–	–
13	Positive	–	–
14	Negative/Sotalol	–	–
15	Negative/Amiodarone	Positive/Amiodarone	–
16	Positive	Negative	–
17	Positive	Positive	–
18	Negative	–	–
19	Negative	–	–
20	Positive	–	–
21	Negative	Negative	Positive

– = no data

positive TWA and the presence of ventricular arrhythmias on the Holter monitor or a history of sudden death.

DISCUSSION

Sudden death is a well-known complication of HCM. The most common cause of sudden death in patients with HCM is VT/VF. ICD therapy offers a reasonable chance of improving prognosis in patients with HCM. On the other hand, it represents a lifelong commitment to repeated procedures and significant exposure to potentially catastrophic complications including the risk of infection and inappropriate ICD shocks [12-15]. Therefore, there is a need for a non-invasive test that can identify patients who are at high risk of ventricular arrhythmias and sudden death.

VT = ventricular tachycardia/ventricular fibrillation

Microvolt TWA is a relatively new non-invasive method for identifying patients at increased risk of sudden cardiac death from ventricular arrhythmias [5]. It measures subtle beat-to-beat fluctuations in T-wave amplitude. TWA is heart rate dependent and can be measured during an exercise stress test, during pharmacological stress, or during cardiac pacing [16]. Clinical studies have shown a good correlation between TWA and the results of electrophysiological studies in patients with ischemic heart disease [5]. More recent studies have shown mixed results regarding the capacity of TWA to predict sudden death, sustained ventricular arrhythmias, or appropriate ICD discharges [17-21].

Momiyama and co-workers [9] were the first to study TWA in patients with HCM [9]. Their study included 14 patients; alternans was found in 5 of the 7 high risk patients and in none of the 7 low risk patients. The high risk group included only one patient with VT/VF and three patients with fractionated paced ventricular electrograms, and the rest of the patients had NSVT on their Holter or had a family history of sudden death.

Kuroda et al. [10] studied 53 patients with HCM [10]. They found that ECG, echocardiographic parameters, family history, and genetic abnormalities did not significantly differ between the TWA-positive and the TWA-negative groups. The percentage of patients with NSVT and myocardial disarray score in the TWA-positive group were significantly higher than those in the TWA-negative group. In these two studies, beta-blockers, calcium antagonists and anti-arrhythmic agents were discontinued before the investigation.

Our study was different. We repeated the TWA testing every 12 months and patients were followed for an average of almost 3 years, whereas in the two studies described above patients had an isolated TWA measurement and no follow-up. Additionally, it was neither feasible nor safe to discontinue anti-arrhythmic drugs in our patients for the purpose of the study. Therefore, our study represents a real-life scenario. One drawback was that the use of amiodarone or sotalol by many of our patients made our data more difficult to interpret. Interestingly, the study by Sakabe et al. [22] of patients with dilated cardiomyopathy showed that TWA significantly predicted the recurrence of ventricular arrhythmias even while the patients were on anti-arrhythmic pharmacotherapy. In contrast, Groh and collaborators [23] showed that amiodarone can cause TWA to be negative. Sotalol can probably also make the TWA turn negative since it has beta-blocker and class III properties similar to amiodarone. Calcium channel blockers and caffeine were shown to inhibit alternans in a canine model [24]. In our study, unlike that of Kuroda et al. [10], there was no significant correlation between the presence of ventricular arrhythmias on the Holter monitor and the presence of a positive TWA in patients with HCM.

To our knowledge, this is the first prospective study reporting on repeat TWA testing during a follow-up of 1–2 years. All

the studies in the literature report isolated TWA testing, except for the study of Oliviera and team [18] who reported repeat TWA testing in patients after a myocardial infarction.

In our study, three patients who were TWA negative on baseline and 12 months follow-up became TWA positive in the 24 months follow-up study [Table 2]. One patient, who was a sudden death survivor, was TWA positive at baseline and at 12 months follow-up but became TWA negative at the 24 months follow-up study. A repeat study was performed at 36 months and was found to be negative [Figure 1]. Another patient was TWA positive in the baseline study on no medication; her repeat TWA was negative. We have no explanation for this phenomenon of conversion of TWA positive to negative over time. We can speculate that the myocardium is constantly subject to changes in the electrical milieu, which determines the patient's susceptibility to develop an arrhythmia at a specific time. From the data collected in this small series of patients with HCM, it seems that TWA is not a permanent finding in a specific patient. No relationship was found between the risk of sudden death and a positive TWA in our study population.

STUDY LIMITATIONS

This series of patients is small. It was difficult to enroll a larger number of patients because they had atrial premature beats, were unable to walk on a treadmill or were unable to increase their heart rate while they were on anti-arrhythmic medication. Many patients were taking anti-arrhythmic drugs when TWA was measured. We could not perform the test in a drug-free state because of the fear that patients may develop recurrent ventricular arrhythmias. Three patients who had suffered sudden death and were resuscitated before their enrolment in the study were also included in this series, because sudden death can recur and therefore we tried to use TWA as a risk stratifier for recurrent sudden death in these patients as well. We do not have a follow-up TWA study in all patients.

CONCLUSIONS

In patients with HCM, TWA does not correlate with the presence of ventricular arrhythmias on the Holter monitor and is not useful for predicting sudden death. TWA is not a fixed phenomenon and can change over time in patients with HCM.

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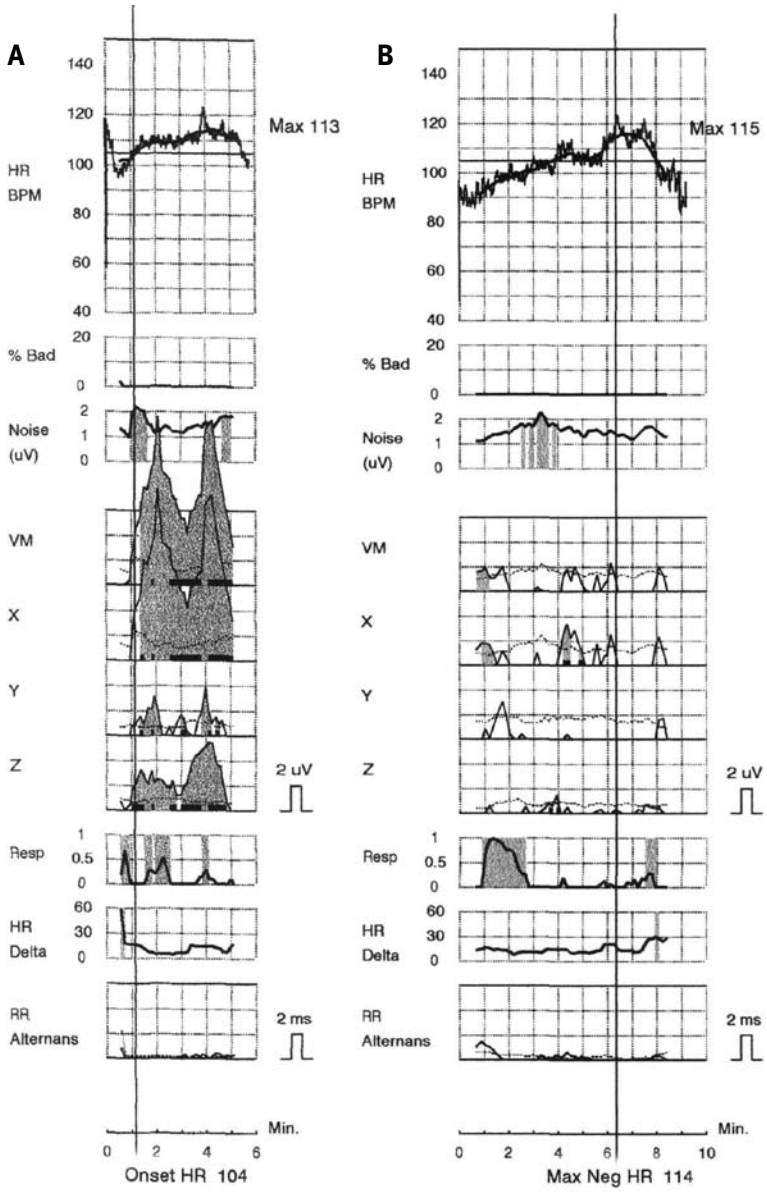
Correspondence:
Dr. T. Fuchs
Arrhythmia Service, Assaf Harofeh Medical Center, Zerifin 70300, Israel
Phone: (972-3) 616-4042
Fax: (972-77) 328-0001
email: therese@fuchs.org

Figure 1. T wave alternans tracings in the baseline study and the 24 months follow-up study in a sudden death survivor. **[A]** Baseline study showing positive TWA. **[B]** Follow-up study showing negative TWA.



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