Assessment of the relationship between the ambulatory electrocardiography-based micro T-wave alternans and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy

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ABSTRACT

Objective: Micro T-wave alternans (MTWA) has been associated with poor arrhythmic prognosis in various cardiac disorders. The aim of this study was to assess the relationship between the presence of MTWA and the predicted 5-year risk of sudden cardiac death (HCM Risk-SCD) among patients with hypertrophic cardiomyopathy (HCM).

Methods: A total of 117 consecutive HCM patients were included in this prospective observational study. Patients were divided into two groups, according to the presence [MTWA (+) group (n=44)] or absence [MTWA (−) group (n=73)] of MTWA on ambulatory (Holter) electrocardiography.

Results: The risk of HCM Risk-SCD (%), the rate of high-risk patients (HCM Risk-ECG >6%), the requirement for cardiopulmonary resuscitation, and implanted cardioverter defibrillator therapy, the percentage of some clinical, echocardiographic, and Holter findings were all statistically higher in the MTWA (+) group than in the MTWA (−) group (all p<0.05). Both in the univariate and multivariate analyses, T-wave alternans (+) and the New York Heart Association's functional classification assigned that the HCM Risk-SCD is an independent predictor of high risk. In the receiver operating characteristic curve analysis, the HCM Risk-SCD >4.9% was identified as an effective cutoff point in the MTWA (+) for HCM. The HCM Risk-SCD value of more than 4.9 yielded a sensitivity of 93.2% and a specificity of 84.5%.

Conclusion: The presence of the MTWA on ambulatory electrocardiogram seems to be significantly associated with increasing percentages of the predicted HCM Risk-SCD score in patients with HCM. The MTWA was determined as an independent high-risk indicator for HCM Risk-SCD. *(Anatol J Cardiol 2018; 20: 165-73)*

Keywords: hypertrophic cardiomyopathy, ambulatory electrocardiography, sudden cardiac death, score

Introduction

Hypertrophic cardiomyopathy (HCM) is defined as a heart muscle disorder characterized by left ventricular (LV) and/or right ventricular hypertrophy, and it is an important cause of death in patients of all ages, especially in the young (1). Although most of these patients remain asymptomatic or experience only paroxysmal manifestations (2), others die suddenly due to ventricular tachycardia (VT) or fibrillation (3). In such cases, the implantable cardioverter-defibrillator (ICD) is the first-line treatment for HCM. Identification of patients who are at high risk of ventricular arrhythmias (VA) or sudden cardiac death (SCD) is of paramount importance when selecting patients for ICD implantation. Inadequate evaluation in this regard may cause a lack of adequate attention to patients who really need an ICD, or cause unnecessary ICD insertion in patients who will never benefit from it. The European Society of Cardiology (ESC) Guidelines recommend the use of a risk stratification model when deciding which patient will be treated with an ICD. The predicted 5-year risk of SCD (the HCM Risk-SCD) is an HCM SCD risk model that assesses risk stratification and helps to identify high-risk patients who require an ICD (HCM Risk-SCD of >6%) (4).

The microvolt T-wave alternans (MTWA) consists of microscopic alternans measured in microvolts on every heartbeat and is evidenced in the amplitude or the morphology of the T-wave. A positive MTWA test is associated with a poor arrhythmic prognosis in various cardiac disorders and has emerged as an im-

portant tool for stratifying the risk of potentially lethal VA (5). The TWA has been approved by the Food and Drug Administration as a noninvasive method to evaluate the need for ICD implantation in post-myocardial infarction and LV dysfunction of ischemic or non-ischemic etiology (6, 7). However, only a few studies have analyzed the TWA in HCM (6). There are no studies investigating TWA in HCM by the Modified Moving Average (MMA) method on ambulatory electrocardiography.

The aim of the study was to assess the relationship between the presence of MTWA and the absolute value of the HCM Risk-SCD.

Methods

Patient population

This study included 117 consecutive patients with HCM who presented to the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital and Bezmialem Vakıf University, School of Medicine. Study data were obtained evaluating the patients from these two hospitals using the devices in a single hospital. This study was conducted as a prospective observational study between December 2012 and March 2016. The study was approved by the Ethics Committee in the Bezmialem Vakıf University, School of Medicine. All patients signed informed consent forms. This study was conducted in compliance with the Declaration of Helsinki.

The study inclusion criteria were the following: Patients whose echocardiography (ECHO) revealed HCM, or HCM defined as a maximum LV wall thickness ≥15 mm in one or more LV myocardial segments with unexplained abnormal loading conditions (1); with lesser degrees of wall thickening; a family history, positive gene mutations, and electrocardiogram (ECG) abnormalities; and apical hypertrophy assessed by cardiac magnetic resonance (CMR) imaging. The patients, especially those in who Anderson-Fabry disease was suspected, were screened (35 patients), and none of them was positive. These evaluations identified adult patients (>17 years) with a high possibility of HCM for inclusion in the study.

In this study, we included only those patients who were evaluated for the ICD treatment for primary protection.

Exclusion criteria

We excluded patients with a prior history of ICD for secondary protection, or prior cardiac arrest and sustained VT, and we excluded from our analysis patients with prolonged uncontrolled hypertension, renal failure, a history of coronary artery disease, aortic valve stenosis, atrial fibrillation, previous permanent pacemaker implantation, metabolic storage disease, and other moderate-to-severe valve diseases.

Patients with a body mass index (BMI) over 30 kg/m² were also excluded. Competitive athletes, pediatric patients, and pa-

tients with a LV wall thickness ≥35 mm were not included. The final study population consisted of 117 patients.

Electrocardiography

A 12-lead surface ECG was obtained in all patients in the supine position. The ECG records were taken using a Nihon Kohden-Cardiofax S instrument (ECG-1250 K, filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, at a speed of 25 mm/s and an amplitude of 10 mm/mV; Nihon Kohden, Tokyo, Japan). We assessed the rhythm, speed, and presence or absence of a fragmented QRS on ECG.

Echocardiography

Upon hospital admission, a transthoracic echocardiography (ECHO) study was performed using a Vivid S5 system (General Electric Vivid S5; GE Vingmend Ultrasound AS, Horten, Norway) with a 1.7/3.4 MHz phased-array transducer. All ECHO parameters were measured offline, and an average of three cardiac cycles was used. The biplane Simpson method was used for the calculation of the LV ejection fraction (LVEF) (8). The LV wall thickness, LV end diastolic diameter (LVEDD), and LV end systolic diameter (LVESD) were measured in the parasternal long axis. The LV outflow tract obstruction gradient (LVOTOG) was measured in the apical five chambers. In addition, the LV end diastolic volume, end systolic volume, left atrial (LA) diameter, LA volume, LA volume index (LAVI), and LV mass in grams were calculated from M-mode echocardiograms according to the formulas described by Devereux et al. (9). We calculated the LV mass and the LV mass index with CMR in patients with markedly asymmetric or apical hypertrophy. The LV mass was indexed to body surface area as the LV mass index (LVMI) in g/m². The mitral valve regurgitation and the relative wall thickness index (RWTI) were also evaluated.

Ambulatory ECG-based microvolt T-wave alternans

The Spectral and the MMA methods are two contemporary techniques used for risk stratification of arrhythmias by microvolt-level TWA. In this study, we used the MMA method for the evaluation of MTWA (7). Twelve-channel records of ambulatory Holter monitoring were used for the analyses during daily activity. Ambulatory ECG recordings (DMS 300-7 Holter Reader; DSM, Stateline, NV, USA) were obtained for 24 hours in all patients at the admission and follow-up. Evaluations of TWA were obtained during the admission. The TWA was reported at the predetermined times associated with cardiovascular stress, including the maximum heart rate and maximum ST segment deviation. Prior to an automatic analysis of the tapes with the Holter program (CardioScan 12.0DM software, DSM), the recordings were evaluated for rhythm anomalies, and the TWA value was measured at a maximum heart rate <120 beats/min. The MARS PC software was used to identify the possible TWA periods according to the MMA algorithm, which is a time-domain-based method that bifurcates the beat stream to generate
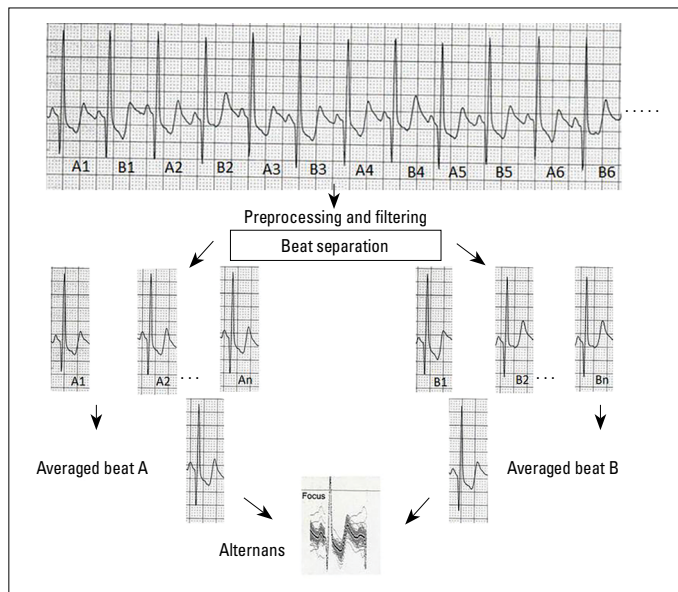
Figure 1. Flow diagram of major components for the modified moving average (MMA) method used in the TWA analysis

separate moving average templates for odd versus even beats (10). The average values were updated using a weighting factor of 1/8 of the difference of the ongoing average and the current pair of beats. The magnitude of the TWA was calculated per every 15 seconds of data, and it was analyzed as a continuous variable. The effects of noise and artifacts were minimized, and 20 µV was adopted as the noise level in the system configuration. The highest TWA value observed in either one of the channels was considered as the maximum TWA value. Based on previous studies, a TWA ≥65 µV was considered to be positive (5) (Fig. 1).

Statistical analysis

The study population was divided into two groups based on the admission MTWA: the first group (n=44) [MTWA (+)] and the second group (n=73) [MTWA (−)]. Qualitative variables were expressed as percentages (%), and quantitative variables as the mean value±standard deviation (SD). The normally distributed continuous variables were assessed using the Kolmogorov–Smirnov test. A comparison of the parametric values between the two groups was performed with a two-tailed Student's t-test. Categorical variables were compared with the likelihood ratio (chi) 2 or Fisher's exact test. Pearson's correlation coefficient was used for correlation comparisons between groups. A backward stepwise multiple logistic regression analysis, which included variables with a p-value less than 0.1, was performed to identify independent predictors of high risk (over 6%). The accuracy of relevant variables from the regression analysis to differentiate between the groups was assessed with receiver operating characteristic curves to determine the area under the curve and optimal sensitivity and specificity. A p-value less than 0.05 was considered statistically significant. All statistical

studies were carried out using the SPSS program (version 15.0, SPSS, Inc., Chicago, IL, USA).

Study end-point and follow-up

In this study, the mean follow-up period was 31.7±12.7 months. The patients' medical histories, family history of SCD, syncope, and a questionnaire on lifestyle and risk factors were taken. Patients were regularly followed-up in an outpatient clinic at regular 3-month intervals. Any change in the patient's clinical status was noted. Holter monitoring was performed at least once in all patients and at least twice in those with more than one risk factor for SCD. Holter monitoring was also performed when patients had any possible arrhythmic symptoms, including dizziness, palpitations, and syncope. The primary end-point for the study was mortality and sustained ventricular tachyarrhythmias requiring ICD interventions. The secondary end-point was the occurrence of major arrhythmic events. The follow-up for clinical end-points was performed by telephone interviews and a review of outpatient and inpatient medical records.

Results

Baseline characteristics and micro T-wave alternans results

The baseline and clinical characteristics of all patients are shown in Table 1. The mean age of the 117 patients was 46.6±15.2 years. Of those 117 patients, 71 (60.6%) were male. The functional capacity was New York Heart Association (NYHA) II in 53 and NYHA III in 25 patients. A total of 49% of the patients had HCM in their first-degree relatives. During the follow-up, 36% experienced presyncope, and 12% experienced syncope. A total of 33 patients were admitted to the hospital with heart failure (HF) symptoms. A total of 12 patients had paroxysmal atrial fibrillation (PAF), 24 had NSVT attacks, 14 patients needed CPR, ICD implantation was performed in 12 patients, and a two-chamber pacemaker was implanted in 1 patient. A total of 8 patients with ICD had appropriate shock, 6 patients underwent myectomy, and 1 patient underwent alcohol septal ablation. β blockers were administered in 107, amiodarone in 4, calcium channel blockers in 5, and dysopropamid in 8 patients.

A comparison of the results between the MTWA (+) (n=44) and the MTWA (−) (n=73) groups is shown in Table 1. No statistically significant correlation was found in terms of age (years), gender, BMI (kg/m²), diabetes mellitus (%), HT (%), hyperlipidemia (%), syncope (%), LVEF (%), RWTI, the LVOTO gradient (mm Hg), and PAF (%), in the MTWA (−) and MTWA (+) groups (all p>0.05). The rate of family history (57%; 33%), presyncope (47%; 20%), HCM Risk-SCD (9.1±4.3; 3.6±2.3), HCM Risk-SCD (>6%) (88%; 8%), VT (43%; 8%), CPR (25%; 4%), ICD implantation (23%; 3%), shock (18%; 0%), and admittance with HF (48%; 16%) were higher in the MTWA (+) group than in the MTWA (−) group, and all results were statistically significant (all p<0.05). The LAAPD (mm) (43.2±4.4; 41.5±4.2), LAV (ml) (59.4±16.2; 48.8±14.2), LAVI

Table 1. Baseline and clinical characteristics of all patients

Variabilities	All (n=117)	MTWA(+) (n=44)	MTWA(-) (n=73)	P
Age (years)	46.6±15.2	43.8±14.4	48.3±15.4	0.120
Gender				
Male (%)	71 (60.6%)	32 (72)	39 (53)	0.081
Female (%)	46 (39.4%)	12 (28)	34 (47)	
Body mass index (kg/m^2)	26.7±3.5	26.4±3.2	26.9±3.6	0.478
Diabetes mellitus (%)				
(+)	7	3 (7)	4 (5)	1.000
(-)	110	41 (93)	69 (95)	
Hypertension (%)				
(+)	5	3 (7)	2 (3)	0.363
(-)	112	41 (93)	71 (97)	
Family history (%)				
(+)	49	25 (57)	24 (33)	0.013
(-)	68	19 (43)	49 (67)	
HL (%)				
(+)	23	9 (20)	14 (19)	1.000
(-)	94	35 (80)	59 (81)	
Cigarettes (%)				
(+)	22	10 (23)	12 (16)	0.466
(-)	95	34 (77)	61 (84)	
Presyncope (%)				
(+)	36	21 (47)	15 (20)	0.003
(-)	81	23 (53)	58 (80)	
Syncope (%)				
(+)	12	8 (18)	4 (5)	0.055
(-)	105	36 (82)	69 (95)	
NYHA (%) class				
I	39 (32)	8 (18)	31 (42)	
II	53 (47)	18 (41)	35 (47)	<0.001
III	25 (21)	17 (41)	8 (11)	
Beta blockers (%)				
(+)	107	41 (93)	66 (90)	0.741
(-)	10	3 (7)	7 (10)	
Amiodarone (%)				
(+)	4	3 (7)	1 (2)	0.149
(-)	113	41 (93)	72 (98)	
Dysopyramide (%)				
(+)	8	5 (11)	3 (4)	0.150
(-)	109	39 (89)	70 (96)	

Table 1. Cont.

Variabilities	All (n=117)	MTWA(+) (n=44)	MTWA(-) (n=73)	*P*
Calcium channel blocker (%)				
(+)	5	3 (7)	2 (3)	0.363
(-)	112	41 (93)	71 (97)	
The HCM Risk-SCD (%)	5.7±4.1	9.1±4.3	3.6±2.3	<0.001
The HCM Risk-SCD				
(>6%) (%)	42	36 (82)	6 (8)	<0.001
(<6%) (%)	75	8 (18)	67 (92)	
LAAPD (mm)	42.1±4.3	43.2±4.4	41.5±4.2	0.042
LAV (ml)	52.8±15.8	59.4±16.2	48.8±14.2	<0.001
LAVI (ml/m²)	29.6±8.9	32.7±9.7	27.8±7.8	0.004
LV EF (%)	66.6±7.1	66.8±6.6	66.4±7.4	0.804
IVST (mm)	21.8±4.4	23.9±4.9	20.6±3.7	<0.001
LVPWT (mm)	12.8±3.1	13.1±3.8	12.5±2.5	0.329
LVM (g)	332.3±87.1	371.2±98.5	309.1±70.6	<0.001
LVMI (g/m²)	180.1±54.1	200.1±65.9	168.1±41.8	0.002
RWTI	0.61±0.22	0.64±0.29	0.60±0.18	0.394
LVOTOG (mm Hg)	25.7±29.8	30.8±32.8	22.7±27.7	0.162
Paroxysmal atrial fibrillation (%)				
(+)	12	7 (16)	5 (7)	0.209
(-)	105	38 (84)	67 (93)	
Ventricular tachycardia (%)				
(+)	24	19 (43)	6 (8)	<0.001
(-)	91	25 (57)	66 (92)	
Cardiopulmonary resuscitation (%)				
(+)	14	11 (25)	3 (4)	<0.001
(-)	103	33 (75)	70 (96)	
ICD implantation (%)				
(+)	12	10 (23)	2 (3)	<0.001
(-)	105	34 (77)	71 (97)	
Shock (%)				
Apropriate	8	8 (18)	0	0.001
inappropriate	3	2 (4)	1 (1)	
Admitted with heart failure (%)				
(+)	33	21 (48)	12 (16)	0.001
(-)	84	23 (52)	61 (84)	
Sudden death/VT-VF (+), appropriate shock (+) group				
(+)	29	22 (50)	7 (11)	<0.001
(-)	88	22 (50)	66 (89)	

Values are the mean±standard deviation or number (%).
EF - ejection fraction, HCM - hypertrophic cardiomyopathy, HCM Risk-SCD - predicted 5-year risk of sudden cardiac death in HCM patients, ICD - implantable cardioverter defibrillator, IVST - interventricular septum thickness, LAAPD - left atrium anterior–posterior dimension, LAV - left atrium volume, LAVI - left atrium volume index, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVM - left ventricular mass, LVMI - left ventricular mass index, LVPWT - left ventricular posterior wall thickness, LVOTO - left ventricular outflow tract obstruction, NYHA - New York Heart Association, RWTI - relative wall thickness index, SCD - sudden cardiac death

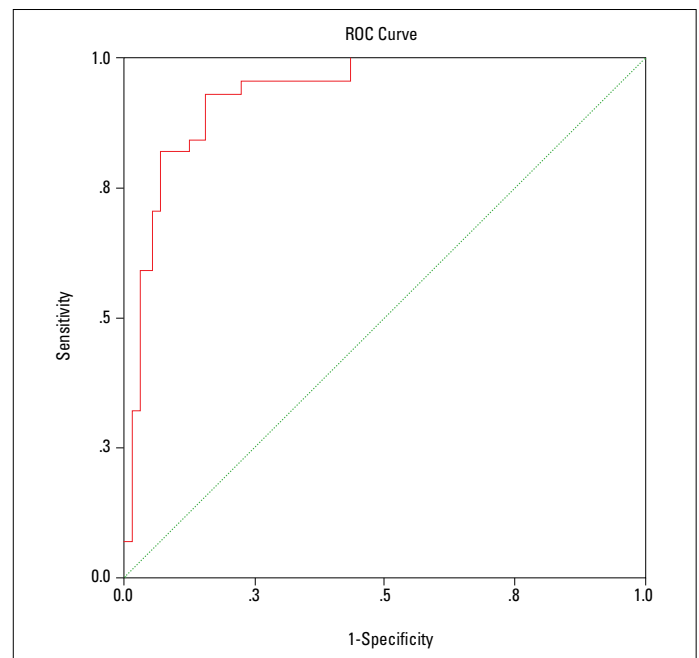**Table 2. Correlations coefficients of the relationship between T-wave alternans and other parameters**

Variable	T-wave alternans (+)	
	r	P
Age (years)	-0.145	0.120
Gender	-0.175	0.057
Body mass index (kg/m^2)	-0.066	0.478
Family history (%)	0.285	0.011
Presyncope (%)	0.285	0.002
Syncope (%)	0.203	0.028
NYHA (%) class		
I	0.358	<0.001
II		
III		
The HCM Risk-SCD (%)	0.632	<0.001
The HCM Risk-SCD (>6%) (%)	0.759	<0.001
LAAPD (mm)	0.189	0.042
LAV (ml)	0.325	<0.001
LAVI (ml/m^2)	0.267	0.004
LV EF (%)	0.023	0.804
IVST (mm)	0.348	<0.001
LVPWT (mm)	0.092	0.329
LVM (g)	0.287	0.002
LVMI (g/m^2)	0.346	<0.001
RWTI	0.081	0.394
LVOTOG (mm Hg)	0.131	0.162
PAF (%)	0.138	0.138
Ventricular tachycardia (%)	0.411	<0.001
CPR (%)	0.342	<0.001
ICD implantation (%)	0.353	<0.001
Admitted heart failure (%)	0.341	<0.001
Appropriate shock (%)	0.304	0.001

Values are the mean±standard deviation or number (%).
CPR - cardiopulmonary resuscitation, EF - ejection fraction, HCM - hypertrophic cardiomyopathy, HCM Risk-SCD - predicted 5-year risk of sudden cardiac death in HCM patients, HF - heart failure, ICD - implantable cardioverter defibrillator, IVST - interventricular septum thickness, LVPWT - left ventricular posterior wall thickness, LAAPD - left atrium anterior–posterior dimension, LAV - left atrium volume, LAVI - left atrium volume index, LVM - left ventricular mass, LVMI - left ventricular mass index, LVOTO - left ventricular outflow tract obstruction, NYHA - New York Heart Association, PAF - paroxysmal atrial fibrillation, RWTI - relative wall thickness index, SCD - sudden cardiac death, VT - ventricular tachycardia

Figure 2. In a ROC curve analysis, an HCM Risk-SCD >4.9 was identified as an effective cutoff point in the MTWA (+) for HCM (area under curve=0.932, 95% CI=0.887-0.978, P<0.001)

shock (n=29, 24.7%), and those who did not (n=88, 75.3%). The HCM-SCD risk score was 10.0±5.3 in the group with VT-VF and appropriate shock. The HCM-SCD risk score was 4.3±2.4, p-value <0.001, in the non-group. The sudden death/VT-VF (+), appropriate shock (+) group (n=29, 24.7%), were higher in the MTWA (+) group than in the MTWA (−) group, and results were statistically significant (p<0.001) (Table 1).

Correlation between micro T-wave alternans and other parameters

A statistically significant correlation was established between the MTWA and the rate of family history (r=0.285; p=0.011), presyncope (r=0.285, p=0.002), syncope (r=0.203, p=0.028), the NYHA class (r=0.358, p<0.001), the HCM Risk-SCD (r=0.632, p<0.001), the HCM Risk-SCD (>6%) (r=0.759, p<0.001), the LAAPD (r=0.189, p=0.042), LAV (r=0.325, p<0.001), LAVI (r=0.267, p=0.004), IVST (r=0.348, p<0.001), LVM (r=0.287, p=0.002), LVMI (r=0.346, p<0.001), percentage of VT (r=0.411, p=0.001), CPR (r=0.342, p<0.001), and ICD implantation (r=0.353, p<0.001), admittance for HF (r=0.341, p<0.001), and appropriate shock (r=0.304, p<0.001). There was no statistically significant correlation found between the MTWA and the other parameters (Table 2).

Results of the logistic regression analysis

Univariate (UVA) and multivariate analyses (MA) of the independent predictors of high risk for HCM Risk-SCD are shown in Table 3. Both in the UVA and MA, MTWA (+) [UVA: odds ratio (OR): 59.400, confidence interval (CI): 18.091–195.030, p<0.001; MA: OR: 79.741, CI: 13.685-464.687, p<0.001] and the NYHA (UVA: OR: 0.196, CI: 0.098–0.394, p<0.001; MA: OR: 0.300, CI: 0.096–0.941, p=0.039)

(ml/m^2) (32.7±9.7; 27.8±7.8), IVST (mm) (23.9±4.9; 20.6±3.7), and LVM (g) (371.2±98.5; 309.1±70.6), and LVMI (g/m^2) (200.1±65.9; 168.1±41.8) were statistically significantly higher in the MTWA (+) group compared to the MTWA (−) group (all p<0.05).

Patients were divided into two groups: those who had experienced sudden death/VT-ventricular fibrillation (VF), appropriate

Table 3. Univariate and multivariate analyses for independent high-risk predictors HCM Risk-SCD score

	Univariate			Multivariate		
	OR	**CI**	**P**	**OR**	**CI**	**P**
Micro T-wave alternans (+)	59.400	18.091-195.030	<0.001	79.741	13.685-464.687	<0.001
New York Heart Association	0.196	0.098-0.394	<0.001	0.300	0.096-0.941	0.039
Paroxysmal atrial fibrillation	4.242	1.192-15.100	0.026	-	-	-
Left atrium volume	0.961	0.936-0.988	0.004	-	-	-
Ventricular tachycardia	9.788	3.473-27.585	<0.001	-	-	-
Left atrium volume index	0.937	0.895-0.982	0.007	-	-	-
Interventricular septum thickness	0.846	0.768-0.932	0.001	-	-	-
Left ventricular mass	0.995	0.990-0.999	0.027	-	-	-
Presyncope	4.130	1.793-9.513	0.001	-	-	-
Admitted with heart failure	6.778	2.771-16.580	<0.001	-	-	-

CI - confidence interval, HCM - hypertrophic cardiomyopathy, OR - odds ratio, SCD - sudden cardiac death

assigned that the HCM Risk-SCD is an independent predictor of high risk. In a ROC curve analysis, the HCM Risk-SCD >4.9 was identified as an effective cutoff point in the MTWA (+) for HCM (area under curve=0.932, 95% CI=0.887-0.978, p<0.001). A HCM Risk-SCD value of more than 4.9 yielded a sensitivity, specificity, positive, and negative predictive values of 93.2%, 84.5 %, 86%, and 89%, respectively (Fig. 2).

Discussion

Ventricular malignant arrhythmias and SCD are well-known complications of HCM. VT/VF are the most common cause of SCD in patients with HCM. The ICD therapy is an important treatment option for preventing SCD and improving prognosis. However, ICD hardware may become seeded and lead to infective endocarditis and inappropriate ICD shocks. Moreover, self-perpetuating procedures such as requirement for subsequent generator changes are disadvantages of this treatment (11, 12). For these reasons, it is important to choose the patient who really needs the ICD treatment.

Recently, even if microvolt TWA seems like a promising test for the identification of sudden death in various heart diseases, data to support the use of TWA to withhold or delay the ICD implantation are yet insufficient. In addition, intracardiac repolarization alternans plays an important pathogenetic role in the formation of malignant arrhythmias in channelopathies. There is no previous study to show that the TWA analysis assesses the arrhythmic risk in patients with Brugada syndrome or long QT (13, 14). In the present study, we investigated whether the MTWA could be a potential predictor of cardiac events, focusing on arrhythmic events and the predicted HCM Risk-SCD in patients with HCM. The most important findings of this study are as follows: The number of patients with a predicted HCM Risk-SCD

greater than 6% was significantly higher, and the percentage of VT and the necessity for CPR and ICD therapy and appropriate shock were significantly higher in the MTWA (+) group. Patients describing the NYHA class III HF symptoms and the incidence of hospitalization due to the general impairment caused by deficiency were significantly higher in the MTWA (+) group. There was a significant relationship between positive MTWA and IVST, LVM, LVMI, LAAPD, LAV, and LAVI. A positive MTWA and an increased level of NYHA functional classification were found to be independent high-risk predictors for the HCM Risk-SCD.

The MTWA is a non-invasive method for identifying patients at increased risk of SCD from VA (15, 16). On the other hand, the test's alternative usefulness appears to be the detection of a group of patients with low risk for the development of malignant VA, because a negative test result strongly predicts freedom from VT-VF (17). This would help to separate these patients from those who are more likely to benefit from the ICD use. Otherwise, a significant proportion of these patients will never have access to these devices (18). The alternation of T-waves in patients with HCM may possibly be explained as a result of the following mechanisms. First, abnormal cell-to-cell conduction may contribute to the inhomogeneous action potential propagation and heterogeneous repolarization, which result in the alternans of T-wave in HCM. Second, fibrous tissue replacement of both RV and LV, an important characteristic of HCM, may delay cell-to-cell conduction and facilitate the development of re-entrant ventricular arrhythmias (19). Previous studies have shown that re-entry is the main mechanism responsible for ventricular arrhythmias causing sudden deaths (20). Third, myocardial ischemia may be one of the causes of the MTWA positivity. Myocardial ischemia due to microvascular dysfunction (MD) and supply-demand mismatches in coronary blood flow (21) occurring in HCM, is an important pathophysiologic component of the disease process, and leads

to heterogeneous repolarization gradients between myocytes. The discordant alternans establish heterogeneous repolarization gradients, which are thought to be highly arrhythmogenic (22). Furthermore, MD promotes the LV myocardial scarring and remodeling (23) by acting as a facilitator for excessive myocardial fibrosis. Slower conduction, which may initiate a re-entry circuit, occurs as a result of all these pathological mechanisms, and beat-to-beat alternation in the amplitude or morphology of the ECG recording of the ST segment and T-wave. In the present study, IVST, LVM, and LVMI were significantly higher in patients with positive MTWA.

Microvascular dysfunction, which is thought to play a role in the pathological mechanism of the TWA formation, has been advanced as a predictor of a long-term outcome and HF death (23). In most patients, there is a lifelong process of progressive and adverse cardiac remodeling characterized by myocardial fibrosis and wall thinning (24, 25). In the early stages of this process, patients are often asymptomatic, and conventional non-invasive indices of cardiac performance are within the normal range. Progression to severe functional limitation with preserved LV systolic function NYHA III–IV is infrequent (3). In this study, a significant relationship was observed between an increasing functional classification and the TWA positivity. Admission to the hospital with HF symptoms was correlated with positive MTWA.

As is well known, the most feared complication of HCM is SCD, and it is often the initial clinical manifestation of the disease, occurring commonly in asymptomatic individuals. ICD is the best available therapy for patients with HCM who have survived SCD or who are at high risk of life-threatening ventricular arrhythmias (26). The NSVT, severe hypertrophy, unexplained syncope, a family history of SCD, and an abnormal blood pressure response to exercise (27) have been used in clinical practice for a long time; however, these approaches provide a very crude estimate of the relative risk of SCD, and they fail to account for the differences in the size of the effects of individual risk factors. The ESC Guidelines for HCM recommend a practical risk prediction model in line with the requirement absolute value for the risk of SCD (1). According to this model, the HCM Risk-SCD ≥6% is considered to be a high risk for SCD, and an ICD treatment is recommended for this patient group. In the present study, the rate of patients with an SCD risk of over 6% was significantly higher in the MTWA (+) group, and a positive MTWA significantly correlated with the HCM Risk-SCD ≥6%. A positive MTWA was found to be an independent high-risk predictor for the risk of 5-year SCD. According to these results, the MTWA evaluation in patients with HCM may especially help in predicting the HCM Risk-SCD in patients who are in the high-risk group for HCM.

Study limitations

This study is not an epidemiological or randomized study exploring new associations with SCD. A relatively small sample size of HCM patients was included in this study. So, our study is a preliminary study, and it is needed to be reproduced in a larger population. The mean follow-up period of the study was not long enough. A quantitative LGE assessment with CMR was not performed in all patients. Thus, the relationship between the LGE and MTWA could not be assessed clearly. We performed genetic tests in 3 patients and a screening test for Anderson-Fabry disease in 35 patients. Some 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 the patients might develop recurrent ventricular arrhythmias. We did not characterize TWA by the quantitative model.

Conclusion

We demonstrated that the presence of MTWA on ambulatory ECG seems to be significantly associated with increasing percentages of the predicted HCM Risk-SCD score in patients with HCM. The MTWA was determined as an independent high-risk indicator for the HCM Risk-SCD. Ventricular arrhythmias, requirement for CPR and ICD therapy, and some ECHO parameters were significantly higher in the HCM patients with positive MTWA.

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