No association between scar size and characteristics on T-wave alternans in post-myocardial infarction patients with relatively preserved ventricular function presented with nonsustained ventricular tachycardia

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Abstract

Objective: Microvolt T-wave Alternans (TWA) is associated with abnormal repolarization and predicts arrhythmic mortality in patients with previous myocardial infarction (MI). Infarct tissue size and heterogeneity characterized by cardiac magnetic resonance (CMR) has been shown to be associated with arrhythmogenic substrates and sudden cardiac death. Although both delayed enhancement-CMR (de-CMR) and TWA are useful in risk stratification of post-MI patients with preserved left ventricular function, the relationship between scar size and TWA has not studied yet. In this study, we aimed to study the relation between TWA and scar size and characteristics assessed with CMR in post-MI patients (pts) with relatively preserved systolic function presented with nonsustained VT.

Methods: This observational cross-sectional study was enrolled 36 post-MI patients with mild-systolic dysfunction and non-sustained ventricular tachycardia. Eight pts were excluded. Both TWA and contrast enhanced CMR were performed. Left ventricular ejection fraction (LVEF), dense scar, peri-infarct zone and total scar masses were assessed and these values to left ventricular (LV) mass ratios were calculated. Infarct ratios and characteristics were determined and compared among patients with negative TWA and those with positive TWA.

Results: For the positive (n=12) vs. negative (n=16) TWA patients there were no significant difference between LVEF (44.9±5.4% vs. 44.0±3.2%, p=NS) and LV masses (121.89±26.56 g vs. 106.14±21.16 g, p=NS). The ratio of scar core to LV mass (3.37±0.68% vs. 3.31±1.01%, p=NS), peri-infarct zone to LV mass (23.61±7.93% vs. 21.64±9.08%, p=NS), total scar to LV mass (26.98±7.86% vs. 24.96±9.62%, p=NS) were all similar.

Conclusion: There were no association between scar size and infarct heterogeneity and prevelance of TWA in post-MI patients with relatively preserved LVEF with non-sustained VT. Our data suggest that these two modalities may reflect different arrhythmogenic mechanisms in this cohort. *(Anadolu Kardiyol Derg 2014; 14: 442-7)*

Key words: T wave alternans, cardiac magnetic resonance, delayed enhancement, arrhythmogenic mechanisms

Introduction

Sudden cardiac death (SCD) due to malignant ventricular tachyarrhythmias is the most prevalent cause of death among adults in the industrialized world (1). Unfortunately, identifying individuals at risk of this fate remains challenging, as does the task of optimally identifying potential recipients of the implantable cardioverter-defibrillator (ICD). Although reduced systolic function (2) and heart failure (3) identify risk, they lack specificity. Using Left ventricular ejection fraction (LVEF) alone, a measure of impaired mechanical function, to predict electrophysiologic substrates for SCD is indirect and no doubt contributes to the relatively low specificity and large numbers needed to treat to reduce mortality from SCD. On the other hand, majority of sudden cardiac deaths occur in patients with moderately depressed or preserved LVEFs. It would be advantageous to incorporate risk markers that reflect specific arrhythmia substrates to better guide primary prevention of SCD (4). However, the specificity of different markers in probing the complex and varied substrates that underlie susceptibility to SCD is not well understood and represents a significant obstacle to implementation of risk stratification in clinical practice.

Although the exact mechanism underlying lethal ventricular arrhythmias is not clear, it has been demonstrated that scar tissue may serve as a substrate for these arrhythmias (5). Cardiac magnetic resonance is the gold standard imaging modality to as-

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Accepted Date: 19.07.2013 **Available Online Date:** 02.01.2014

DOI:10.5152/akd.2014.4918

sess both the size and the characterization of scar tissue. Dense scar and the peri-infarct tissue heterogeneity can be visualized by de-CMR. Several studies have evaluated the risk stratification potential of myocardial scar assessment by de-CMR. These reports showed that extent of the left ventricular scarring as well as the extent of the peri-infarct zone were independent predictors of ventricular tachyarrhythmia induciblity in ischemic cardiomyopathy. Also these scar characteristics have been linked to appropriate ICD shocks in this patient group (6-11).

The microvolt T-wave alternans (MTWA) test is a promising noninvasive test that predicts arrhythmic risk and mortality both in patients with cardiac dysfunction and in patients with preserved LVEF (12, 13). Although TWA is not traditionally considered to reflect structural heart disease, there is evidence that TWA reflects arrhythmic susceptibility related to structural nonuniformities (14). Although both de-CMR and TWA were tested in risk stratification of post-MI patients with preserved left ventricular function the relationship between scar size and TWA has not studied yet.

In this study, we hypothesized that scar size and characteristics would affect TWA results and tested this hypothesis in thirty-six patients with previous myocardial infarction, mild systolic dysfunction and nonsustained ventricular tachycardia who underwent CMR and TWA test.

Methods

Patients

For this cross-sectional study thirty-six patients (M:F=31:5) referred for risk stratification were prospectively and consequetively enrolled between March 2010 and September 2011 to İstanbul Faculty of Medicine, İstanbul University. The target population was patients with known history of coronary artery disease and prior myocardial infarction (>40 days), mild systolic dysfunction (LVEF between 40% and 50%) and non-sustained ventricular tachycardia (VT). Nonsustained ventricular tachycardia was diagnosed by Holter monitor (DMS Holter, Stateside, NV, USA). Patients with recent myocardial infarction (within 40 days) (4 patients), sustained ventricular tachycardia (1 patient), implanted devices (2 patients) or who have claustrophobia (1 patient) were excluded (Fig. 1). This study protocol was approved by local Ethics Community and all patients gave written informed consent.

CMR protocol

CMR was performed within a week of TWA test. Patients were placed supine in a 1.5-T whole-body MRI scanner (Philips Achieva Intera, Philips, Best, the Netherlands) fiberoptic electrocardiographic (ECG) leads were placed for scanner gating and a phased-array receiver coil was placed on the chest for imaging. All images were acquired using 10- to 15-s breath-holds. Short-axis slices were acquired from the base to apex, making sure to include the entire left ventricle using methods previously described (15, 16). A gadolinium-based contrast agent (0.1 to 0.2 mmol/kg, gadobutrol (Gadovist; Schering, Berlin, Germany) was administered intravenously, and images were obtained as described previously (17).

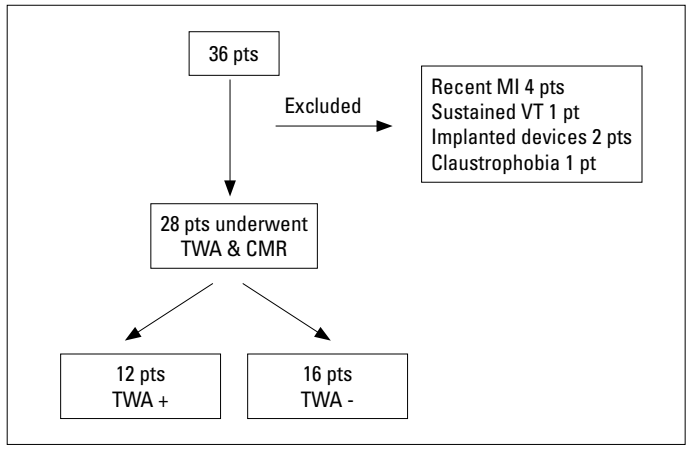

Figure 1. Enrollment of study patients
CMR - cardiac magnetic resonance, MI - myocardial infarction, pt - patient, TWA - T wave alternans, VT - ventricular tachycardia

CMR data analysis

All images were reviewed and analyzed by a custom software developed at our institution. Collection and interpretation of all imaging data were blinded to clinical data and T wave alternans test results. We manually traced the LV endocardial border on all short-axis cine images at the end-diastolic and end-systolic frames to determine the end-diastolic and end-systolic volumes, respectively. The endocardial and epicardial contours on delayed enhancement images were also outlined manually. Using a semiautomatic detection algorithm, we quantified the total scar (TS) size and divide it into the dense scar (DS) and the peri-infarct zone (PIZ) based on SI thresholds (>6 SDs and 2 to 6 SDs above remote normal myocardium, respectively). DS, PIZ and TS masses were calculated, these values to LV mass ratios were obtained (Fig. 2). All the patients underwent T wave alternans test for risk stratification within a week of CMR imaging. Infarct percents and characteristics were determined and compared among patients with negative TWA test and positive TWA test.

Measurement of T wave alternans

Treadmill exercise stress test (EST) (Cardiosoft GE Healthcare system, version 4.14, Freiburg, Germany) was carried out according to a standard symptom/sign limited Bruce protocol. Leads II, V2 and V5 were monitored continuously; a 12-lead ECG was printed at the end of each stage or when clinically indicated and at 1-min intervals in the recovery phase. Blood pressure was measured at baseline, at peak exercise, and during the last minute of each stage. ST-segment depression was considered significant if it was horizontal or down-sloping and at least of 1 mm at 0.08 s from the J-point.

T-wave alternans was assessed with the time-domain modified moving average (MMA) method, 16 using the software pro-

vided by the EST system manufacturer (GE CASE 8000, Milwaukee, WI, USA). Briefly, with this method a sequence of beats are separated into odd and even beats. Along the entire J-T segment, separated average morphologies of both the odd and even beats are calculated separately and continuously updated to every new incoming beat by a weighting factor of 1 of 8 in order to minimize the influence of noise on the TWA measurement and, then, to get a higher reliability of this method. The TWA value is calculated as the maximal difference between the averages of odd and even beats along one of the J-T-segment sampled points in any lead. T-wave alternans is analysed continuously during the entire stress test and the recovery phase up to heart rate of 125 bpm. Cut-off value for TWA was 65 μV for all three measurements as done in previous studies (18). The data were counted valid only if the noise level was less than 10 μV.

Statistical analysis

All statistical tests were performed with SPSS software, version 7.5 (IBM, Chicago, Illinois, USA). Continuous data are presented as mean±SD and cathegorical data are summarized as frequencies and percentages. Group percentages were compared with the use of the chi-square test or Fisher's exact test, as appropriate. Group means for variables with normal and non-normal distributions were compared with the use of Student's t-test for independent groups and the Mann-Whitney U, respectively. All tests were 2-sided, and $p<0.05$ was considered statistically significant.

Results

Table 1 summarizes the clinical characteristics and the CMR findings of the study population. Twelve of patients (42%) had positive T-wave alternans test, where as sixteen patients (58%) have negative test. Positive and negative groups had similar clinical characteristics (Table 1). All patients had abnormal delayed enhancement on LV indicating scar tissue. For the positive (n=12) versus negative (n=16) TWA patients there were no significant difference between LV ejection fractions and (44.9±5.4% vs. 44.0±3.2%, p=ns) and LV masses (121.89±26.56 g vs. 106.14±21.16 g, p=ns). The ratio of dense scar to LV mass (3.37±0.68% vs. 3.31±1.01%, p=ns), peri- infarct zone to LV mass (23.61±7.93% vs. 21.64±9.08%, p=ns), total scar to LV mass (26.98±7.86% vs. 24.96±9.62%, p=ns) were all statistically similar. Fig. 3 shows the comparison of the dense scar zone to LV mass, peri-infarction zone to LV mass and total scar to LV mass ratios among patients with positive and negative TWA study.

Discussion

Our study demonstrated that in post MI patients with non-sustained ventricular tachycardia; 1) T wave alternans by MMA method was positive in 42% of patients, 2) contrast enhanced CMR can determine both the size and characteristics of the scar, 3) scar percent of LV does not differ among T wave alternans positive and negative patients. Therefore these results support the concept that both repolarization alternans and scar size by CMR may reflect different arrhythmogenic mechanisms. To date, no prospective studies using CMR and TWA to predict arrhythmic end-points were done. Our study may smooth the pathway of studies combining these two modalities.

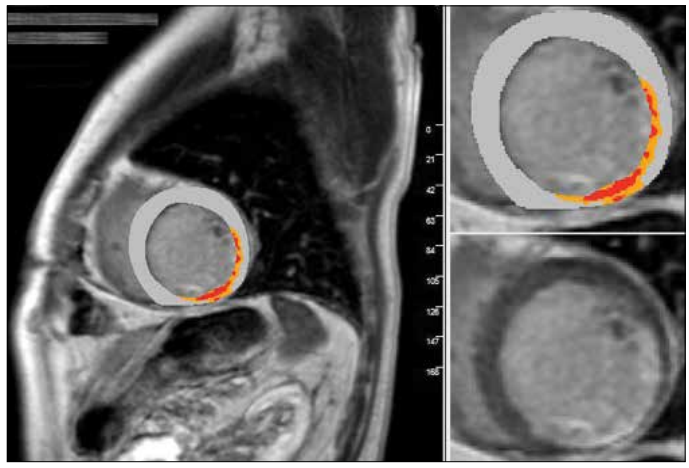

Figure 2. A custom developed software used for analyzing scar sizes. Red indicates the dense scar whereas, the yellow indicates peri-infarction zone

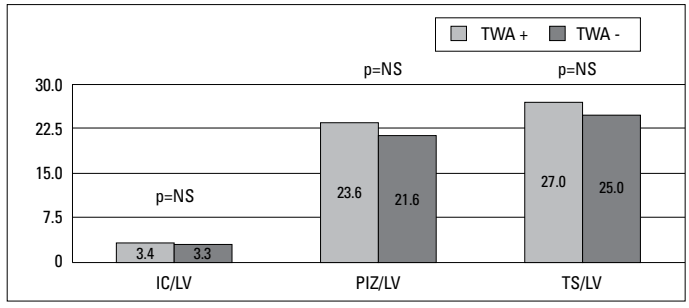

Figure 3. The graph shows the comparison of the dense scar zone to LV mass, peri-infarction zone to LV mass and total scar to LV mass ratios among patients with positive and negative TWA study

DS - dense scar; LV - left ventricle; NS - non-significant; PIZ - peri-infarction zone; TS - total scar; TWA - T wave alternans

Because the tachyarrhythmias that might lead to SCD are heterogeneous, including monomorphic ventricular tachycardia (VT), polymorphic VT, and ventricular fibrillation (VF), identifing the different substrates for responsible arrythmogenic mechanism may improve risk stratification.

The main mechanism responsible for ventricular arrhythmias causing sudden death is reentry and the ventricular tachycardia inducibility during electrophysiologic study is the only risk stratifying test that shows the presence of scar related-reentrant VT circuit. Contrast enhanced magnetic resonance may detect cardiac scar tissue as well as give useful information about characteristics of the myocardial scar. Imaging the substrate by CMR has provided to identify patients at higher risk. Several studies have recently focused on the relationship between scar size and heterogeneity determined by de-CMR and inducible and spontaneous VTs (6-11). Infarct surface area and mass predict monomorphic VT inducibility better than LVEF (6).

Table 1. Clinical characteristics and cardiac magnetic resonance parameters among patients with positive and negative TWA results

Variable	TWA- n=16	TWA + n=12	*P** value
Age, years	59.2±11.2	60.6±12.0	.26
Sex	16 male (100%)	11 male (91%)	.95
DM	2/16 (12%)	1/12 (8%)	.06
HT	10/16 (83%)	7/12 (58%)	.75
MI localization	11 Anterior (68%)	8 Anterior (66%)	.19
Creatinin, mg/dL	0.96±0.13	0.93±0.21	.18
ACE-I	15/16 (93%)	11/12 (91%)	.89
Beta blocker	14/16 (87%)	11/12 (91%)	.78
LV mass, gr	121.89±26.56	106.14±21.16	.11
Dense scar/LV mass %	3.37±0.68	3.31±1.01	.85
Peri-infarct zone/LV mass %	23.61±7.93	21.64±9.08	.55
Total scar/LV mass %	26.98±7.86	24.96±9.62	.55
LVEF%	44.9±5.4	44.0±3.2	.58
LVEDV, mL	132.75±44.43	135.05±62.6	.90
LVESV, mL	74.34±25.14	76.50±42.54	.91

Continuous data are presented as mean±SD and cathegorical data are summarized as frequencies and percentages. *The chi-square test or Fisher's exact test for group frequencies and percentages and Student's t-test of Mann-Whitney U test for group variables, as appropriate. ACE-I - angiotensin converting enzyme inhibitors; DM - diabetes mellitus; HT - hypertension; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume

In addition, a study also done by Bello's group (7) showed that LVEF and infarct mass by CMR were best predictors of mortality in patients with coronary artery disease. A newer concept, identification of peri-infarction zone or grey zone based on the spatial distribution of signal intensity was thought to increase sensitivity. For this purpose, semi-automated methods have been used. Yan et al. (8) identified a relatively large peri-infarct zone as a powerful predictor of mortality. Peri-infarct zone was defined as areas with an SI between 2 and 3 SD above SI of remote myocardium, normalized as a percentage of total infarct zone (area with an SI of 2 SD above remote myocardium). Schmidt et al. (9) could demonstrate that infarct tissue heterogeneity expressed by the extent of the infarct grey zone, but not total infarct size correlated with inducibility of monomorphic VTs at electrophysiological testing in patients with ischemic cardiomyopathy. In this study, the core infarct was defined as areas with SI 50% of maximal SI in the hyperenhanced area and the infarct grey zone as myocardium with SI peak SI of remote myocardium but, 50% of the maximum SI (9). In patients with relatively preserved left ventricular functions, we showed that patients with inducible VT have larger peri-infarction zone (10). Inducibility of VTs does not necessarily correlate with the occurrence of spontaneous VTs. Roes et al. (11) found that the infarct grey zone as a measure of tissue heterogeneity was the strongest predictor for spontaneous VTs. Measurement of peri-infarction zone due to different definitions among different studies and due to partial volume effect is controversial. In our study, we used areas with an SI between 2 and 6 SD above SI of remote myocardium as peri-infarction zone. Bernhardt et al.(19) studied the utility of CMR in predicting monomorphic VTs during follow-up. They enrolled 41 patients with ischemic cardiomyopathy and indication for ICD therapy underwent cine and late gadolinium enhancement CMR for quantification of left ventricular volumes, function and scar tissue before subsequent implantation of ICD device. During a follow-up period of 1184±442 days 68 monomorphic and 14 polymorphic types of ventricular tachycardia (VT) could be observed in 12 patients. Patients with monomorphic VT had larger scar volumes (25.3±11.3 vs. 11.8±7.5% of myocardial mass, than patients with polymorphic VT (19). This study indicates the role of CMR in identifying substrate for monomorphic VT.

T wave alternans is a noninvasive method that predicts future tachyarrhythmias in various types of heart diseases (12, 13). The Alternans Before Cardioverter Defibrillator (ABCD) trial compared the performance of an EPS-guided strategy with a TWA-guided strategy in predicting ventricular tachyarrhythmic events (VTEs) in low LVEF patients with coronary artery disease. The trial enrolled 566 patients with ischemic cardiomyopathy, LVEF <0.40, documented nonsustained VT, and no previous sustained ventricular arrhythmia. TWA provided 95% NPV for sustained arrhythmias and positive TWA gave a hazard ratio of 2.1. TWA complemented electrophysiologic testing (EPS), with a combined negative predictive value of 98% (20). An analysis of ABCD trial indicate that the TWA test predicts polymorphyic ventricular tachycardia and ventricular fibrillation better than stable monomorphyic ventricular tachyarrhythmias, whereas EPS does stable monomorphic VTs better (21). The mechanism linking TWA to arrhythmogenesis involves dynamic amplifications of refractory gradients that produce conditions favoring conduction block and reentry, without any requirement for scar or anatomic barriers (22). Therefore, TWA predicts a substrate at risk for conduction block, but not necessarily one that will support the stable reentrant rotors that underlie monomorphic VTs.

In the present study, we used modified moving average method to measure TWA. Predictivity of TWA analysis by the MMA method has been demonstrated in >4,800 patients, including those with coronary artery disease, recent or old myocardial infarction, congestive heart failure, or cardiomyopathy (23). In FINCAVAS (Finnish Cardiovascular Study), the largest investigation of TWA to date, TWA predicted sudden cardiac death and cardiovascular and total mortality in a general population of >3.500 low-risk patients referred for routine, symptom-limited exercise testing (23-25). REFINE study done by Exner et al. (26) demonstrated that MMA TWA may predict adverse events in post-MI patiets with moderately depressed left ventricular functions. Although experience with spectral method is more extensive, hazard ratios for arrhythmia prediction by the spectral and MMA methods are similar, whether in the same population or in studies overall (26). A study that investigates the relationship between scar extent and TWA by spectral method does not already exist. We don't consider the method of TWA measurement would affect the study results.

In our study, 42% of patients had positive T-wave alternans test. This may be considered as high rate for the group of patients with average LVEF 44%. Chronic myocardial infarction is a condition that increases T-wave alternans. Ren et al.(27) reported approximately 70% of post-MI patients have positive TWA by MMA from Holter recordings while only 9% of control group have positive results. Mollo et al. (28) used MMA TWA test in different patient groups with ischemic heart disease. Twenty-one percent of their patients with previous myocardial infarction had positive test. In patients with preserved left ventricular systolic functions, Ikeda et al. (13) reported 26% abnormal spectral TWA tests. To the best of our knowledge our study is the first study that using MMA TWA in post-MI patients with relatively preserved LVEF and nonsustained VT. We attribute our relatively high rates of positive TWA test results to the study patient group having nonsustained ventricular tachycardia.

Study limitations

We studied a relatively small patient group in a unicenter trial cross-sectional without follow-up. The present conclusion requires confirmation in larger study groups. Studies using TWA and CMR as risk stratifies with long follow-up duration are needed. In addition, larger studies may help to identify the best definition for characterization of the infarct gray zone.

Conclusion

There are no associations between scar size and charactestics and prevalence of TWA in post-MI patients with relatively preserved LVEF presented with non-sustained VT. Our data suggests that these two promising modalities for risk stratification may reflect different underlying mechanisms of lethal ventricular arrhythmias.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - K.Y., E.T., E.G.; Design - R.Y., M.D.; Supervision - K.A., A.K.B.; Resource - A.K.B., K.A, M.D.; Materials - K.Y., E.T., E.G.; Data collection&/or Processing - K.Y., E.T., E.G., K.A., A.K.B.; Analysis &/or interpretation - K.Y., E.T., E.G., R.Y., M.D.; Literature search - K.Y., E.G.; Writing - K.Y., E.G., R.Y.; Critical review - K.A., A.K.B.

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