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Scar tissue and microvolt T-wave alternans

Karin Kraaier · Marlon A. G. M. Olimulder · Michel A. Galjee ·
Pascal F. H. M. van Dessel · Job van der Palen · Arthur A. M. Wilde ·
Marcoen F. Scholten

Abstract Microvolt T-wave alternans (MTWA) is an electrocardiographic marker for predicting sudden cardiac death. In this study, we aimed to study the relation between MTWA and scar assessed with cardiac magnetic resonance imaging (CMR) in patients with ischemic cardiomyopathy (ICM) or dilated cardiomyopathy (DCM). Sixty-eight patients with positive or negative MTWA and analysable CMR examination were included. Using CMR and the delayed enhancement technique, left ventricular ejection fraction (LVEF), volumes, wall motion and scar characteristics were assessed. Overall, positive MTWA (n = 40) was related to male gender ($p = 0.04$), lower LVEF ($p = 0.04$) and increased left ventricular end-diastolic volume (LVEDV) ($p < 0.01$). After multivariate analysis, male gender ($p = 0.01$) and lower LVEF remained significant ($p = 0.02$). Scar characteristics (presence, transmurality, and scar score) were not related to MTWA (all $p > 0.5$). In the patients with ICM (n = 40) scar was detected in 38. Positive MTWA (n = 18) was related to higher LVEDV ($p = 0.05$). In patients with DCM (n = 28), scar was detected in 11. Trends were found between positive MTWA (n = 15) and male gender ($p = 0.10$), lower LVEF ($p = 0.10$), and higher LVEDV ($p = 0.09$). In both subgroups, the presence, transmurality or extent of scar was not related to MTWA (all $p > 0.45$). In this small study, neither in patients with ICM or DCM a relation was found between the occurrence of MTWA and the presence, transmurality or extent of myocardial scar. Overall there was a significant relation between heart failure remodeling parameters and positive MTWA.

Keywords Microvolt T-wave alternans · Cardiac magnetic resonance imaging · Ischemic cardiomyopathy · Dilated cardiomyopathy · Implantable cardioverter defibrillator

K. Kraaier (✉) · M. A. G. M. Olimulder ·
M. A. Galjee · M. F. Scholten
Department of Cardiology, Thoraxcentrum Twente, Medisch
Spectrum Twente, Haaksbergerstraat 55, 7513 ER Enschede,
The Netherlands
e-mail: k.kraaier@mst.nl

M. F. Scholten
e-mail: marcoen.scholten@mst.nl

P. F. H. M. van Dessel · A. A. M. Wilde
Department of Cardiology, Academic Medical Center,
Amsterdam, The Netherlands

J. van der Palen
Department of Epidemiology, Medisch Spectrum Twente,
Enschede, The Netherlands

J. van der Palen
Department of Research Methodology, Measurement and Data
Analysis, University of Twente, Enschede, The Netherlands

Introduction

Microvolt T-wave alternans (MTWA) is a promising electrocardiographic risk marker for predicting sudden cardiac death (SCD) and life threatening ventricular arrhythmia (VA). Previous studies have demonstrated that MTWA screening in patients with ischemic and dilated cardiomyopathy is effective in identifying patients the level of risk for SCD or all cause mortality [1, 2]. In the current and ACC/AHA/ESC guidelines for management of patients with VA and prevention of SCD, there is a class IIa indication for MTWA testing to improve the diagnosis and risk stratification in patients with ischemic and non-ischemic dilated cardiomyopathy [3].

MTWA is a phenomenon of beat-to-beat change in amplitude of the T-wave. This reflects temporal heterogeneity or dispersion in the ventricular repolarization. The exact cellular pathophysiological mechanism underlying MTWA remains unclear. At this moment, there are two hypothesis: (1) the action potential duration restitution hypothesis, and (2) the calcium cycling hypothesis [2, 4]. Recently it has been suggested that MTWA could also be related to an anatomic fibrotic substrate [5–7]. Experimental models have shown the influence of structural barriers on the occurrence of MTWA [6]. In clinical research, the relation between myocardial disarray, fibrosis and MTWA was demonstrated by Kon-No et al. [5] in a group of patients with hypertrophic cardiomyopathy. Recently Narayan et al. demonstrated a spatial correlation between MTWA and wall motion abnormalities due to myocardial infarct [7]. Using cardiac magnetic resonance imaging (CMR) and the delayed enhancement (DE) technique, it is possible to identify and characterize areas of scar or fibrosis in both patients with ischemic and non-ischemic cardiomyopathy [8–10].

The purpose of this study is to evaluate the influence of scar tissue on MTWA in patients with ischemic (ICMP) or non-ischemic dilated cardiomyopathy (DCM).

Methods

Study population

The study was conducted at the Medisch Spectrum Twente (Enschede, The Netherlands) as part of the Twente ICD Cohort Study (NL13939.044.06). In this study, the role of several non-invasive risk markers in predicting SCD and life threatening VA in patients with an ICD are studied. All patients received an ICD following current guidelines for primary and secondary prevention. [3] LVEF was measured using echocardiography or nuclear imaging. After obtaining informed consent, MTWA testing and CMR were performed before implantation, both test were performed within a month. In this analysis, patients with DCMP or ICMP who received an ICD following current guidelines for primary and secondary prevention were included. Patients with indeterminate MTWA results, or poor image quality were excluded from analysis. Ischemic origin of cardiomyopathy was defined as a history of prior myocardial infarction, or coronary abnormalities >70 % and/or coronary interventions.

Microvolt T-wave alternans

All MTWA tests were performed with the HearMTWAve system II (Cambridge Heart Inc., Bedford, Massachusetts,
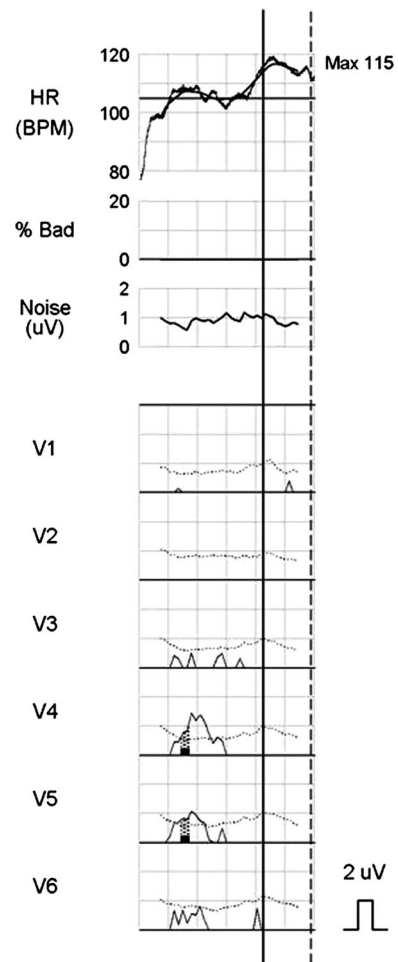

Fig. 1 Example of MTWA. From *top* till *bottom*: heart rate (HR) profile, ectopy (% bad beats), noise level and alternans magnitude (microvolts µV) in the precordial leads (V1–V6) demonstrates no significant sustained alternans

USA) using the spectral analysis method and an exercise protocol. After gradually increasing the workload to achieve a constant heart rate, a target heart rate between 100 and 110 beats per minute was attained and kept stable for 2.5 min. Subsequently during 1.5 min, a target heart rate between 110 and 120 beats per minute was attained. The MTWA tests were read and interpreted by two trained physicians and in case of disagreement a third physician was consulted. Each MTWA report was classified as positive, indeterminate, or negative using accepted criteria [11]. A test was defined positive if the MTWA voltage was ≥1.9 µV for at least 1 min with an onset heart rate <110 bpm or at rest in any of three orthogonal leads (X, Y or Z), or in two adjacent precordial leads. If the recording did not prove positive and the heart rate was >105 bpm for at least one minute, the MTWA test was defined negative (Fig. 1). A MTWA test was considered indeterminate if the test did not meet the criteria for being classified as positive or negative. Patients continued their medication, including

beta blocking agents and amiodarone, and therefore represent a real life population.

Cardiac magnetic resonance imaging

CMR examination was performed on a 1.5-T whole body scanner (Achieva scan, Philips Medical System, Best, The Netherlands) using commercially available cardiac CMR software. For signal-reception a five-element cardiac synergy coil was used. Electrocardiogram (ECG) triggering was done with a vector-ECG set-up. Subjects were examined in the supine position. Morphologic images in the cardiac short axis, four chamber long axis, three chamber, and two chamber long axis, and left ventricular outflow tract views were acquired by using fast field echo cine images. Myocardial scar and/or fibrosis was assessed on DE multislice (without interslice gap) short- axis, long-axis and four -chamber views, obtained approximately 10 min after the peripheral bolus injection of gadolinium (Shering AG, Berlin, Germany; 0.2 mmol/kg of body weight). All CMR data were analyzed on a workstation using dedicated software for cardiac analysis (Philips MR workspace. Release 2.5.3.0 2007-12-03). All analyses were performed by two trained investigators who were blinded from the MTWA test results, in case of disagreement, a third investigator was asked.

Left ventricular end-diastolic volume (LVEDV), end systolic volume, stroke volume, left ventricular ejection fraction (LVEF), cardiac output and cardiac mass were calculated from contiguous short-axis loops by segmentation of endocardial and epicardial borders on each frame. Papillary muscles were regarded as part of the ventricular cavity. As an internal control for estimation of stroke volume and LVEF, the stroke volume over the aortic valve was estimated (on condition that no mitral insufficiency is present).

Scar was defined as the zone of hyper enhancement on the late gadolinium-enhanced images, in contrast with the dark-gray signal of the normal myocardium. Since scar patterns differ between patients with ICM and DCM (Fig. 2) [8], different definitions of scar were used. In patients with ICM, scar was divided into an infarct core and—border zone. After outlining thye myocardiale segment containing the region with high signal intensity, the maximum signal intensity (SI) within the infarct region was determined. Infarct core was defined as myocardium with SI $\geq$50 % of the maximal SI [12]. The border zone was defined as myocardium with SI $\geq$35 % of the maximal SI and <50 % of maximal SI. Total scar was defined as the summation of infarct core and border zone [13]. In patients with DCM, no difference was made between core and border zone. In these patients, scar was defined as myocardium with SI >50 % of the maximal SI.

After qualitative assessment of scar. The wall motion score in the left ventricular wall regions were scored quantitatively using a standardized 17 segment model. Wall motion of all 17 separate segments was assigned the following scores: normal wall motion was 0, hypokinesia 1, severe hypokinesia 2, akinesia 3, and dyskinesia 4. The wall motion score index (WMSI) was calculated by dividing the sum of scores in each segment by the total number of segments (17 segments). WMSI of 0 was considered as normal, 0–1 as moderate, 1–2 as poor, and >2 as bad.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD, categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between MTWA positive and negative patients were analyzed using Students t test or Mann–Whitney U-test, as appropriate, if continuous, or Chi square or Fisher exact test if categorical. All variables that were significant at $p < 0.15$ were entered in a multivariate logistic regression analysis. Subsequently, non-significant variables were removed from the model, based on -2 log likelihood tests. All tests were 2-sided, p values of 0.05 were considered statistically significant.

Results

From our TICS-database, 68 patients were included. All these patients had a positive or negative MTWA-test and a good quality CMR prior to implantation. Baseline characteristics of the 68 included patients are listed in Table 1. The mean age was 60 years, 79 % were men and the average LVEF was 26 %. Fifty-five patients received an ICD as primary prevention therapy; the remaining 13 patients as secondary prevention therapy.

Patients with positive MTWA were predominantly male, had lower LVEF, higher LVEDV, and used more often aldosteron antagonists. Scar was identified in 43 patients, with different patterns in patients with ICM and DCM. Overall, no relation was found between the presence of scar, its transmurality, and scar score (Table 1). In the multivariate analysis, only male gender and lower LVEF remained significant predictors of a positive MTWA.

Patients with ischemic heart disease

There were 40 patients with ICM included in the analysis (Table 2). MTWA was positive in 18 patients. In 38 patients scar was identified. In the two patients without scar, no clinical myocardial infarction had been documented but revascularization had been performed due to
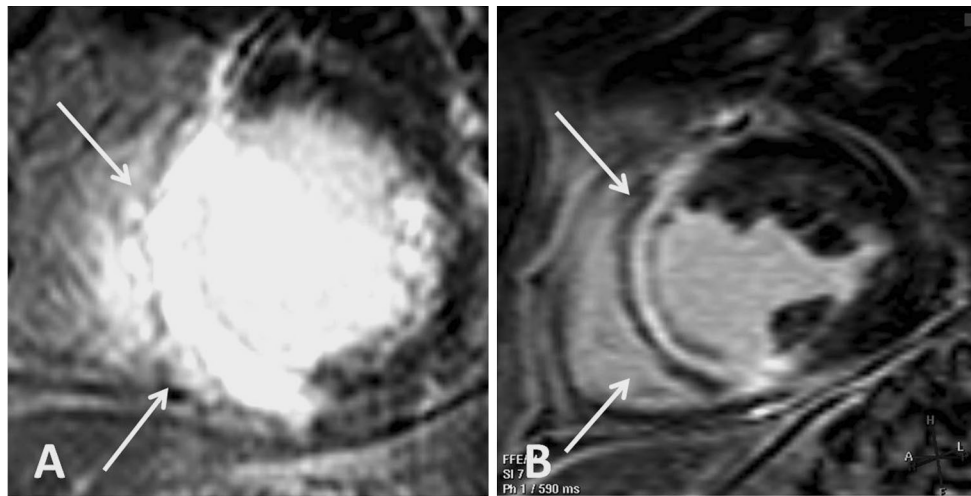
Fig. 2 Example of delayed enhancement magnetic resonance image. Example of a patient with an ischemic cardiomyopathy (**a**) and non-ischemic dilated cardiomyopathy (**b**). In patient A, transmural enhancement is seen in the anteroseptal, septal and inferoseptal area with a high signal intensity (*arrow*). In patient B, midwall enhancement with a lower signal intensity (*arrow*), without transmurality, is seen in the anteroseptal, septal and inferoseptal area

Table 1 Patient characteristics

	Overall	MTWA positive	MTWA negative	p_{uni}	p_{multi}
Patients, n	68	33	35		
Men	54 (79)	30 (91)	24 (69)	0.02	0.01
Age, years (± SD)	60 ± 11	61 ± 10	59 ± 13	0.35	
Etiology					
Ischemic	40 (59)	18 (54)	22 (63)	0.49	
Dilated	28 (41)	15 (46)	13 (37)		
Indication ICD					
Primary	55 (81)	28 (85)	27 (77)	0.42	
Secondary	13 (19)	5 (15)	8 (23)		
NYHA ≥3	14 (21)	7 (21)	7 (20)	0.90	
LVEF, % (±SD)	26 ± 13	23 ± 10	29 ± 14	0.04	0.02
LVEDV, ml/m^2 (±SD)	137 ± 39	146 ± 41	128 ± 37	<0.01	NS
QRS >120 ms	45 (66)	21 (64)	24 (69)	0.67	
Co morbidity					
Hypertension	17 (25)	8 (24)	9 (26)	0.89	
COPD	3 (4)	2 (6)	1 (3)	0.52	
DM	9 (13)	3 (9)	6 917)	0.33	
Medication					
Beta-blocker	56 (82)	26 (79)	30 (86)	0.45	
Diuretics	49 (72)	27 (82)	22 (63)	0.08	NS
ACE-i/AT-II antagonist	58 (85)	29 (88)	29 (83)	0.56	
Scar characteristics					
Scar	49 (73)	22 (67)	27 (79)	0.24	
Transmural	20 (29)	9 (24)	12 (34)	0.36	

All values are numbers (percentage) unless otherwise specified

ICD implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end diastolic volume, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *ACE-I* Ace-inhibitor, *AT-II ant* Angiotensin-II antagonist

[a] Median (range)

angina pectoris with significant stenosis in the coronary arteries. Including or excluding these patients from analyses did not influence the results. There was no relation between presence of scar and MTWA ($p = 0.27$).

Transmural scar was identified in 50 % of the patients, with no statistical difference between MTWA positive and negative patients ($p = 0.53$). Total infarct size was 20.4 g in the MTWA positive patients and 21.0 gram in the

Table 2 Ischemic heart disease

| | MTWA test result | | p_{uni} |
	Positive	Negative	
Patients	18	22	
Men	17 (94)	17 (77)	0.13
Age, years ($\pm$ SD)	64 $\pm$ 9	63 $\pm$ 11	0.69
Indication ICD			
Primary	14 (78)	17 (77)	0.97
Secondary	4 (22)	5 (23)	
NYHA $\geq$3	15 (83)	18 (82)	0.90
LVEF, % ($\pm$SD)	24 $\pm$ 8	28 $\pm$ 13	0.23
LVEDV, ml/m^2 ($\pm$SD)	140 $\pm$ 33	124 $\pm$ 35	0.05
EDWM, g ($\pm$SD)	149 $\pm$ 41	138 $\pm$ 37	0.37
QRS >120 ms	11 (61)	17 (77)	0.27
Co morbidity			
Hypertension	5 (28)	6 (27)	0.97
COPD	0 (0)	1 (5)	0.36
DM	2 (11)	5 (23)	0.34
Medication			
Beta-blocker	13 (72)	20 (91)	0.12
Diuretics	14 (78)	15 (68)	0.50
ACE-i/AT-II antagonist	16 (89)	19 (86)	0.81
Scar characteristics			
Scar	17 (95)	21 (100)	0.27
Infarct age, years (range)	12.5 $\pm$ 10.0	7.5 $\pm$ 7.8	0.14
Transmural	8 (44)	12 (55)	0.53
Total infarct	20.4 $\pm$ 12.9	21.0 $\pm$ 7.5	0.88
Core	11.2 $\pm$ 8.1	11.4 $\pm$ 6.2	0.92
Border zone	9.3 $\pm$ 5.6	9.5 $\pm$ 3.3	0.84
Wall motion score	1.9 $\pm$ 0.6	1.8 $\pm$ 0.5	0.56

All values are numbers (percentage) unless otherwise specified

ICD implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end diastolic volume, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *ACE-I* Ace-inhibitor, *AT-II ant* Angiotensin-II antagonist

[a] Median (range)

Table 3 Dilated Cardiomyopathy

| | MTWA test result | | p_{uni} | p_{multi} |
	Positive	Negative		
Patients	15	13		
Men	13 (67)	7 (54)	0.10	0.04
Age, years ($\pm$SD)	58 $\pm$ 10	52 $\pm$ 13		
Indication ICD				
Primary	14 (93)	10 (77)	0.31	
Secondary	1 (7)	3 (23)		
NYHA $\geq$3	4 (27)	3 (23)	1.00	
LVEF, % ($\pm$SD)	22 $\pm$ 12	31 $\pm$ 17	0.10	0.06
LVEDV, ml/m^2 ($\pm$SD)	155 $\pm$ 50	134 $\pm$ 41	0.09	NS
EDWM, g ($\pm$SD)	188 $\pm$ 71	154 $\pm$ 75	0.23	
QRS >120 ms	10 (67)	7 (54)	0.70	
Co morbidity				
Hypertension	3 (20)	3 (23)	1.00	
COPD	2 (13)	0 (0)	0.48	
Diabetes	1 (7)	1 (8)	1.00	
Medication				
Beta-blocker	13 (87)	10 (77)	0.64	
Diuretics	13 (87)	7 (54)	0.10	
ACE-i/AT-II antagonist	13 (87)	10 (77)	0.64	
Scar characteristics				
Scar	5 (33)	6 (46)	0.70	
Transmural	0 (0)	0 (0)	1.00	
Total scar size	10.3 $\pm$ 15.9	2.3 $\pm$ 4.44	0.09	NS

All values are numbers (percentage) unless otherwise specified

ICD implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end diastolic volume, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *ACE-I* Ace-inhibitor, *AT-II ant* Angiotensin-II antagonist

[a] Median (range)

MTWA negative patients (ns, $p = 0.88$). There was also no difference in core size (11.2 vs 11.4; $p = 0.94$), border zone size (9.3 vs 9.5, $p = 0.84$) or wall motion score (1.9 vs 1.8, $p = 0.56$). LVEDV was significantly higher in MTWA positive patients (140 vs 124 ml/m^2, $p = 0.05$).

Patients with dilated cardiomyopathy

Twenty-eight patients were included in the analysis (Table 3). Positive MTWA was found in 15 patients. In 11 patients, scar was detected on the LGE-CMR, which predominantly showed a midwall enhancement pattern and more diffuse spread. In none of the patients transmurality was seen. There were no statistically significant differences between the positive tested and negative tested group regarding presence of scar. There was a trend for larger scar size in patients with a positive MTWA test (10.3 vs 2.3 g; $p = 0.09$) There was also trends for higher LVEDV (155 vs 137 ml/m^2; $p = 0.09$), lower LVEF (22 vs 31 %; $p = 0.10$) and more male gender (67 vs 54 %; $p = 0.10$) in the MTWA positive patients. After the multivariate analysis, male gender was associated with MTWA positivity, and a trend was seen for a association between lower EF and positive MTWA.

Discussion

This is the first study aimed to relate MTWA to the presence and extent of myocardial scar and/or fibrosis using LGE-CMR. Neither in patients with ICM or DCM a relationship was found between MTWA result and the

presence, transmurality or extent of myocardial scar as assessed by LGE-CMR.

Both in patients with ischemic and non-ischemic CMP, myocardial scar can act as an anatomical substrate for re-entry tachycardia which can lead to potentially lethal arrhythmias. Using LGE-CMR, it is possible to visualize these scars. The patterns of scar differ between ICM and DCM [8]. In patients with ICM, areas of scar involve the subendocardium and extend up to the epicardium, resulting in a transmural scar. In contrast, in patients with DCM, scar has a more diffuse pattern, is most commonly located in the midwall, and is unrelated to a coronary artery territory. The relation between scar size and the spontaneous occurrence of SCD or potential life-threatening VA was shown in several CMR studies. The relation was both found in patients with ICM and DCM [13–15].

In the past years, MTWA has been associated with susceptibility to VA and SCD. However, its exact pathophysiological mechanism remains unknown. Besides the action potential duration restitution hypothesis and the calcium cycling hypothesis it has been suggested that MTWA might be relate to the extent of fibrosis or scar tissue.(5–7) Our present study does not support this last hypothesis, since we were not able to find a relation between the presence, transmurality or extent of myocardial scar and MTWA. However, MTWA appears to have a relation with heart failure remodelling parameters (low LVEF, large LVEDV). Male gender was also related to positive MTWA, this can be explained by higher incidence of SCD in male patients [16].

In our study, older infarct age was related to presence of MTWA in patients with prior myocardial infarction. This is supported by earlier studies which showed increased arrhythmogenesis of myocardial scar with a peak 4-12 years after the index myocardial infarction [17, 18].

Limitations

An important limitation of this study is its small study size. Caution is required when interpreting the results and present conclusions require confirmation in larger study groups. Patients with DCM have smaller scars with lower signal intensities; therefore, utilization of the semi-automatic thresholding technique can lead to overestimating of scar score due to difficulties to differentiate scar from remote myocardium and artifacts (22). The question whether MTWA, CMR or its combination have additional value in predicting SCD or potentially life threatening arrhythmia can only be answered after sufficient follow up data have been obtained.

Conclusion

In this relatively small study, no relation was found between the occurrence of MTWA and the presence, extent or characteristics of myocardial scar as assessed by LGE-CMR in patients with ICM and DCM. Overall there was a relation between heart failure remodeling parameters and positive MTWA.

Conflicts of interest   None.

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