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Long-term reproducibility of microvolt T-wave alternans in patients after cardioverter-defibrillator implantation

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Abstract

Background: *Microvolt T-wave alternans (MTWA) is a promising method for noninvasive assessment of arrhythmic risk. Recent studies have shown good immediate reproducibility of T-wave alternans. Little is known about it during the long term. The aim of the study was to prospectively evaluate the long-term reproducibility of MTWA in a group of patients after ICD implantation.*

Methods: *The study group consisted of 22 patients: 21 male and 1 female, aged 63.0 ± 7.6 years. Nineteen of them had a history of myocardial infarction and 3 had non-ischemic cardiomyopathy. Ejection fraction was 34.7 ± 10.0. T-wave alternans was measured during treadmill tests and additionally in 6 patients during implantation cardioverter-defibrillator device pacing. We received 30 reports of MTWA available for analysis. The second test was performed after 11.8 ± 3.3 months (range 7–16) using the same protocol.*

Results: *Of the 30 tests, 12 were positive, 2 negative and 9 indeterminate in both tests. The results were concordant in 23 tests (76.66%) (Kappa 0.602). Of the initial positive tests, only one became negative in the second test and 4 became indeterminate. Of the initial negative tests, none became positive and none became indeterminate. Of the initial indeterminate tests, one became positive and one negative. At the same time, there were no significant differences between QRS, QTc and ejection fraction between the first and second tests. Only the heart rate in the second test was greater than in the first.*

Conclusions: *The results suggest that microvolt T-wave alternans measurement is stable over a long period. It is probably not worth examining the status of MTWA after several months, at least if patients are in the chronic stage of their disease.* (Cardiol J 2007; 14: 561–567)

Key words: T-wave alternans, reproducibility, sudden death

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Introduction

T-wave alternans (TWA) is an electrocardiographic pattern in which the morphology of the T-wave alternates on an 'every-other beat' basis. Visible alternans in the electrocardiogram is a rare finding associated with the variety of pathophysiological conditions which are in turn associated with increased risk of ventricular arrhythmias such as acute ischaemia, Prinzmetal's angina, electrolyte abnormalities and long QT syndrome [1–6]. Thanks to advancement in signal processing methods, it has become possible to measure microvolt T-wave alternans (MTWA) which cannot be detected by visual inspection of the electrocardiogram [7]. Electrophysiological mapping studies have demonstrated that TWA is caused by localized alternation in the duration of the action potential. Localized action potential alternans leads, in turn, to spatial dispersion of recovery leading to the fractionation of depolarization wave fronts and the development of re-entrant arrhythmias — ventricular tachycardia and fibrillation [8–10].

A number of excellent studies have shown that TWA is an effective noninvasive predictor of risk of ventricular tachyarrhythmias and sudden death, with an efficacy that appears at least comparable to invasive electrophysiological testing [11–14]. The latest recommendations, according to ACC/AHA/ /ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death class IIa with level of evidence A, pointed out that 'it is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life threatening ventricular arrhythmias' [15].

Many other studies have shown different methodological aspects of TWA measurement. Hohnloser et al. [16] have shown the equivalence of measurement during atrial pacing and bicycle exercise. Others try to resolve questions concerning how to measure TWA when the QRS complex is altered due to bundle brunch block or ventricular pacing [17–20]. Another important question concerns the appropriate time for TWA evaluation after acute myocardial infarction. Hohnloser et al. [21] found that T-wave alternans evolved substantially between 5 and 21 days and from 28 to 56 days after myocardial infarction. The concordance rate between determinate TWA in the two periods was only 67%. Tapanainen et al. [22] studied 379 patients with a mean period of 8.1 days after myocardial infarction and did not find a statistically significant elevation of cardiac deaths among patients who tested positive for TWA. These studies showed that T-wave alternans evolves rapidly during the acute post-infarction period and it is now suggested that TWA be measured not earlier than 6 weeks after myocardial infarction.

There are only a few papers assessing the reproducibility of TWA, showing the dilemma of whether this localized action potential alternans is stable over time. Bloomfield et al. [23] has shown that TWA measured during bicycle exercise tests had an acceptable reproducibility when measurements were made during two sequential exercise tests performed within a short period of time (one after another) and additionally, that repeating the test could significantly reduce the proportion of patients with indeterminate test results. Until now only Klingenheben et al. [24] have evaluated the long-term reproducibility of TWA in a group of patients after myocardial infarction.

The aim of this prospective study was to evaluate the long-term reproducibility in a group of patients who underwent the cardioverter defibrillator implantation (ICD).

Methods

The study group consisted of 22 patients who are participating in our own prospective program of evaluating risk factors in secondary and primary prevention after ICD implantation. There were 21 men and 1 woman. Nineteen of them had a history of myocardial infarction and 3 had non-ischaemic cardiomyopathy. The clinical characteristics of the study group are shown in Table 1.

The algorithm of evaluating T-wave alternans based on the spectral method was described previously [25]. In brief, the analysis is based on the measurement of the differences between odd and even cycles in a sequence of 128 beats, applying a fast Fourier transform. Tests were classified as positive, negative or indeterminate [26]. We classified alternans as positive when the onset heart rate (HR), the specific heart rate above which sustained alternans is present, was less than 110 beats/min. A negative test was when the criteria for positive were not fulfilled and when maximal negative heart rate was ≥ 105 beats/min. The indeterminate test was when we could not classify it as positive or negative. The details of classification are described in the references [25, 26]. After careful skin preparation, microvolt T-wave alternans was measured during treadmill tests. If the test was indeterminate, it was immediately repeated. Additionally, 6 of the

Table 1. Clinical characteristics of the patients.

Patients (male)	22 (21)
Age	63.0 ± 7.6
Ejection fraction (%)	34.7 ± 10.0
Etiology:	
Ischemic	19
Cardiomyopathy	3
Reason for cardioverter-defibrillator implantation:	
History SCD (reversible)	9
History of sustained ventricular tachycardia	10
Electrophysiological study (positive) + low EF (< 35%)	1
Sudden cardiac death of unknown reason	1
Syncope of unknown reason + low EF	1
Low EF + no sustained ventricular tachycardia in Holter monitoring	1
Medication:	
Beta-blocker (first/second test)	22/22
Amiodarone (first/second test)	10/8

SCD — sudden cardiac death; EF — ejection fraction

patients with indeterminate tests due to the insufficient heart rate had atrial or/and atrioventricular pacing using an ICD device to reach it. According to the measurement protocol, to obtain the necessary heart rate we increased the pacing heart rate every 10 beats for at least 1 minute starting from 70/beats/min up to 110/beats/min. We evaluated MTWA using the commercially available Cambridge Heart 2000 System.

The second test was performed after 11.8 ± ± 3.3 months, range 7–16 months, according to the same protocol. Finally, we received 30 reports of MTWA which could be compared: those performed on the treadmill with each other and those performed during ICD stimulation with each other, respectively. Standard ECG with evaluation of HR, QRS complex and corrected QT interval and echocardiography with evaluation of ejection fraction (EF) were performed before each MTWA test for all of the patients. All patients had received beta-blockers and the treatment had not been discontinued before the tests. All of them where screened every three months for ICD discharge.

We obtained local ethics committee agreement, and all patients had agreed to participate in the study.

Statistical analysis

The main analysis of the data was created to establish the long-term reproducibility of T-wave alternans. We have obtained 2 kinds of results — determinate (positive or negative) and indeterminate, so we analyzed all the results together as well as determinate results separately.

The reproducibility of the results was determined by a statistical measure of agreement called the Kappa statistic. A Kappa statistic between 0.4 and 0.7 means good, above 0.7 is excellent and less than 0.4 is a poor agreement of results. The clinical data were analyzed by Wilcoxon paired test.

Results

Of the 30 tests, 12 were positive, 2 were negative and 9 were indeterminate in both tests. The results were concordant in 23 tests (76.66%) (Kappa 0.602). For determinate tests the reproducibility was 73.6%. Examples of the reproducibility of the results of MTWA are shown in Figures 1 and 2.

Of the initial positive tests, only one became negative in the second test and four became indeterminate. Of the initial negative testsn none became positive and none became indeterminate. Of the initial indeterminate tests, one became positive and one negative. The reproducibility of MTWA is shown in Table 2.

At the same time, there were no statistical differences between onset HR of MTWA in the first and second tests in the group of both positive tests. There were no differences between supine ECG parameters such as QRS or QTc and between the EF before the first and second tests. Only the supine heart rate before the second test was greater than the first: 62.96 ± 8.84 *vs*. 65.58 ± 12.39 beats/ /min ($p = 0.024$). At same time, there were no differences in onset HR between the two tests. The results are shown in Table 3.

During this prospective observation, 11 of 22 patients had appropriate ICD discharge. In this group, 5 had both tests positive, 2 had the first test positive and second indeterminate, 2 had both tests indeterminate and 1 had the first test positive whereas the second was negative. Only 1 patient with negative first and second test had the appropriate discharge.

Discussion

The study showed good reproducibility (76.6%) of all the results (Kappa 0.602). This is the first study which has shown the long-term reproducibility of MTWA in a group of patients in the stable

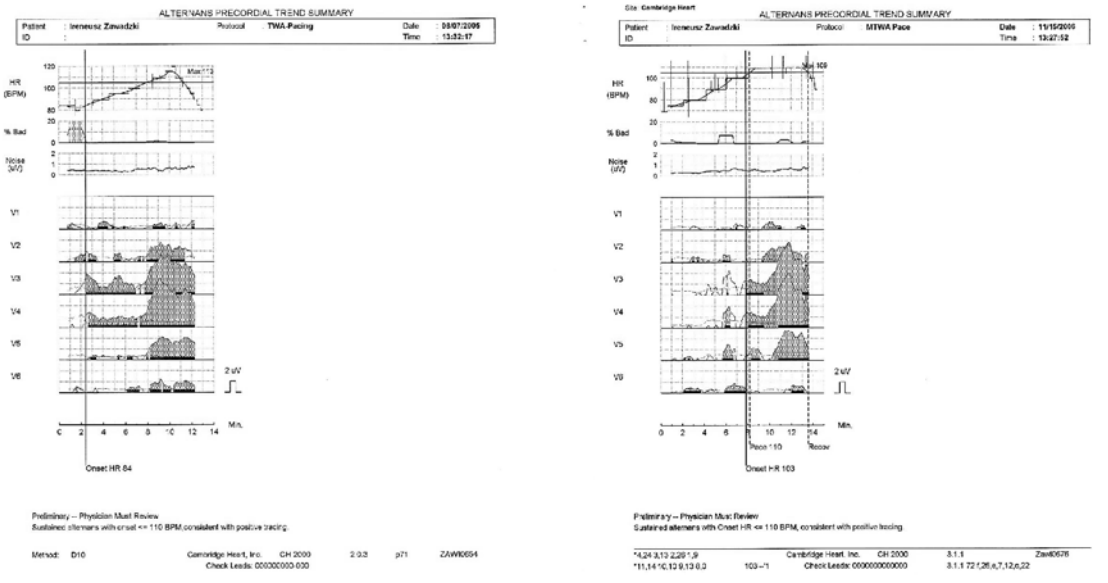

Figure 1. Reproducibility of microvolt T-wave alternans (MTWA) in precordial leads (V1, V2, V3, V4, V5, V6); HR (BPM) — continuous heart rate trend, %Bad — the percentage of bad beats, defined as those more than 10% premature or with correlation coefficient < 0.9, Noise [μV] — the mean noise in the vector magnitude (VM), Resp — the measure of the respiration at the frequency of 0.25 cycles per beat, HR Delta — the measure of the difference between the highest and lowest instantaneous heart rate in a 128 beat interval, RR Alternans — the alternans level in the RR interval, expressed in milliseconds [ms], Onset HR — the lowest heart rate at which sustained alternans is present, Max Neg HR — the highest interval HR of all intervals having no significant alternans or artefact.

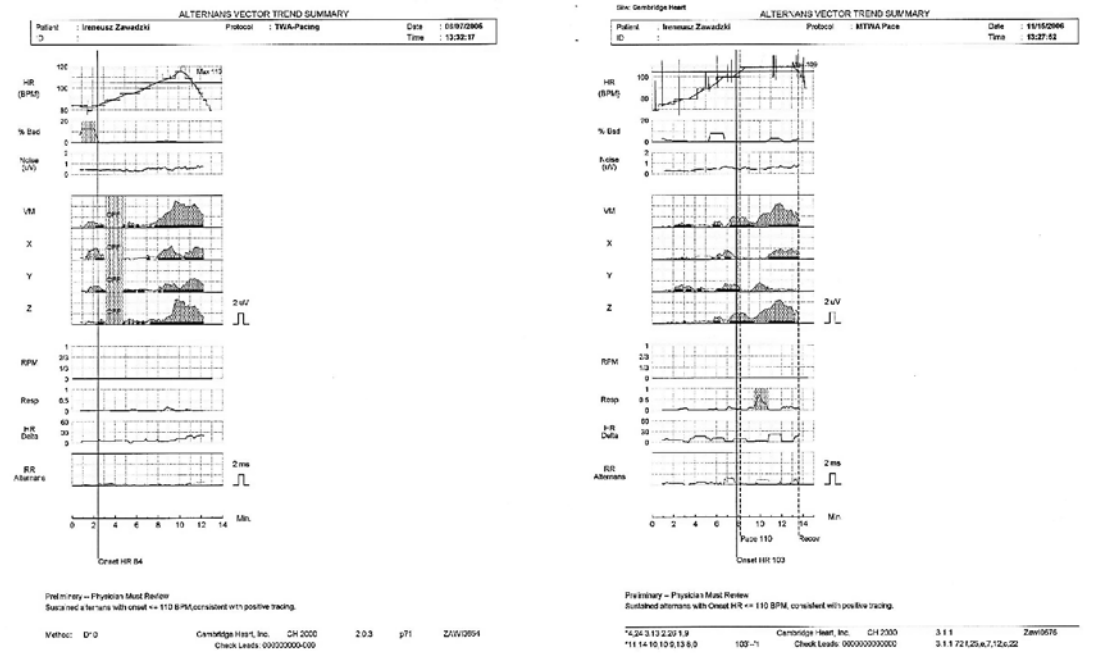

Figure 2. Reproducibility of microvolt T-wave alternans (MTWA) in vector leads; VM — vector magnitude; X, Y, Z — Frank leads, HR (BPM) — continuous heart rate trend, %Bad — the percentage of bad beats, defined as those more than 10% premature or with correlation coefficient < 0.9, Noise [μV] — the mean noise in the vector magnitude (VM), Resp — the measure of the respiration at the frequency of 0.25 cycles per beat, HR Delta — the measure of the difference between the highest and lowest instantaneous heart rate in a 128 beat interval, RR Alternans — the alternans level in the RR interval, expressed in milliseconds [ms], Onset HR — the lowest heart rate at which sustained alternans is present, Max Neg HR — the highest interval HR of all intervals having no significant alternans or artefact.

Table 2. Reproducibility of microvolt T-wave alternans.

Initial test	Second test		
	Positive	Negative	Indeterminate
Positive	12	1	4
Negative	0	2	0
Indeterminate	1	1	9

Table 3. Clinical parameters.

Parameter	Initial test	Second test	P
Onset HR [beats/min]	92.35 ± 10.02	94.61 ± 8.90	0.422
HR [beats/min]	62.96 ± 8.84	65.58 ± 12.39	0.024
QRS [ms]	125.33 ± 36.45	127.51 ± 37.43	0.607
QTc [ms]	457.06 ± 35.14	448.24 ± 48.62	0.133
EF (%)	34.70 ± 10.07	35.07 ± 8.11	0.281

Onset HR — the lowest heart rate at which sustained alternans is present, HR — supine heart rate, QRS — time of QRS complex duration, QTc — corrected QT interval, EF — ejection fraction

period of the disease. Klingenheben et al. [24] also tested the reproducibility of TWA over a long period, but their group of patients were early after myocardial infarction. The reproducibility was 58% of all and 82% of determinate results. The weaker reproducibility for all the results was probably due to the shift from indeterminate to determinate tests in the unstable early phase of myocardial infarction (8 ± 6 days after) compared to one year of follow-up. Now it is recommended that T-wave alternans tests be performed at least 6 weeks after the acute phase of myocardial infarction [21, 22], which is concordant with guidelines to implant the ICD not earlier than 40 days after myocardial infarction.

Reproducibility in a short period, which means immediate reproducibility, has also been the aim of several other studies which have shown 82% and 93% reproducibility for determine results in Bloomfield et al. [23] and Turitto et al. [27] groups, respectively. However, reproducibility of the results of the short period was outside our field of interest. We were obliged to obtain determinate results, so we had to repeat the test only when the initial result had been indeterminate. When the second test was indeterminate, mainly due to insufficient heart rate or for other reasons such as ventricular arrhythmia [25], we considered it as a final result.

However, the determinate results are the most important for risk stratification, and we would like to stress that in this analysis we have shown the reproducibility of an electrocardiographic pattern — the alternans and the overall result of this. We reached 73.6% reproducibility for determinate results, so the score was very similar to the reproducibility for all the results. This means that the pattern called alternans is reproducible and independent under the stable conditions of the examination, even if the results are indeterminate. On the other hand, there is increasing information that indeterminate results should be treated as positive. Therefore, if we assume that indeterminate results are equal to positive ones, we could obtain much better results of reproducibility.

We obtained a high percentage of indeterminate results mainly due to insufficient heart rate, which in turn was caused by beta-blocker treatment. We could say that if we use beta-blockers, and if even it does change the TWA appearance and we received indeterminate results, it should be put into one group together with the positive results, as non-negative TWA. We now also know that even if beta-blockers decrease the appearance of MTWA, when determining cardiovascular factors in high-risk patients, it is recommended that T-wave alternans be performed on beta-blockers [28–30].

We have also shown that onset HR is stable with time. Turitto et al. [27] has shown in her study that not only the onset HR is stable when T-wave alternans is appearing, but also the magnitude of TWA (the amplitude) and the number of leads showing T-wave alternans is unchangeable.

Finally, we would like to stress that the clinical status of our patients was stable during the follow-up period. The reason we concluded this, as well as careful investigation, is that we did not notice differences between such parameters of ECG as duration of QRS complex and duration of corrected QT interval. Ejection fraction was unchangeable during follow up as well.

On the basis of our results and references, we would like to draw an algorithm of the performance and timing of T-wave alternans measurement: 1. It should be performed during stable status of the disease, at least six weeks after myocardial infarction; 2. It should be done during exercise testing to receive determinate results. If the result is indeterminate, it is necessary to repeat it immediately. Atrial pacing protocol as a priority or atrioventricular pacing could be used if available; 3. It is not recommended to repeat the TWA testing after a longer period if the status of the disease of the patient is unchanged.

Conclusions

The results suggest that microvolt T-wave alternans measurement is stable over long periods. This means that the presence and absence of MTWA is reliable. It is probably not worth repeating the test after several months to examine the status of MTWA of the patients, at least if they are in the chronic stage of their disease.

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