

# The problem of indeterminate microvolt T-wave alternans results in patients with left ventricular dysfunction referred for implantable cardioverter-defibrillator implantation in the primary prevention of sudden cardiac death

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## Abstract

**Background:** Microvolt T-wave alternans (MTWA) is a recommended noninvasive diagnostic test for predicting the risk of sudden cardiac death (SCD). However, about 6% to 41% of MTWA results are indeterminate. The causes, interpretation and clinical significance of these results have not been not clearly established.

**Aim:** To assess frequency, causes, and prognostic significance of indeterminate MTWA results in a group of patients with left ventricular dysfunction referred for implantable cardioverter-defibrillator (ICD) placement in the primary prevention of SCD.

**Methods:** Patients with left ventricular ejection fraction (LVEF)  $\leq$  35% underwent MTWA evaluation during a treadmill exercise test (CH2000 system, Cambridge Heart Inc. Bedford MA, USA). MTWA results (spectral analysis) were categorised as positive, negative, or indeterminate (MTWA<sub>pos</sub>, MTWA<sub>neg</sub>, and MTWA<sub>ind</sub>, respectively). Patients were followed up for the occurrence of SCD, ventricular tachycardia (VT), and ventricular fibrillation (VF).

**Results:** Mean age of participants (n = 93) was  $63 \pm 13$  years, an ischaemic cause of left ventricular dysfunction was present in 70 (75%) patients, and average LVEF was  $30 \pm 7\%$ . MTWA<sub>pos</sub> was found in 27 (29%) patients, MTWA<sub>neg</sub> in 41 (44%) patients, and MTWA<sub>ind</sub> in 25 (27%) patients. Causes of MTWA<sub>ind</sub> included inability to achieve a diagnostic HR in 12 (48%) patients, ventricular ectopy in 5 (20%) patients, nonsustained alternans in 3 (12%) patients, and technical factors (artifacts due to a high noise level) in 5 patients (20% of indeterminate results, 5.4% of the whole study group). During follow-up, 8 SCD/VT/VF events were noted (4 patients with MTWA<sub>pos</sub> and 4 patients with MTWA<sub>ind</sub> due to patient-related factors). The rate of SCD/VT/VF was 35% in patients with MTWA<sub>pos</sub> and 34.6% in MTWA<sub>ind</sub> due to patients-related factors, significantly higher compared to those with MTWA<sub>neg</sub> or MTWA<sub>ind</sub> due to technical factors ( $p < 0.05$ ).

**Conclusions:** Although the proportion of indeterminate MTWA results in patients with left ventricular dysfunction referred for ICD implantation in the primary prevention of SCD was high, the proportion of indeterminate MTWA results due to technical factors, probably of no prognostic significance, was small.

**Key words:** microvolt T-wave alternans (MTWA), implantable cardioverter-defibrillator (ICD), systolic dysfunction

Kardiol Pol 2012; 70, 8: 795–802

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Received: 12.08.2011 Accepted: 04.04.2012

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## INTRODUCTION

Primary prevention of sudden cardiac death (SCD) continues to be a major challenge in current cardiology practice [1]. In patients without a history of malignant ventricular arrhythmia, a clinically established predictor of sudden cardiac death (SCD) risk is left ventricular ejection fraction (LVEF) [2–4]. Current guidelines recommend implantable cardioverter-defibrillator (ICD) placement in all patient with  $LVEF \leq 35\%$  [3, 4].

In addition, search continues for new non-invasive predictors of risk that would help stratify SCD risk among patients with reduced LVEF. Candidate variables that have been tested for their potential to stratify the risk of ventricular arrhythmia include markers of autonomic nervous system function (heart rate variability [HRV], baroreceptor reflex sensitivity [BRS], and heart rate turbulence [HRT]), the presence of late potentials on a signal averaged electrocardiogram (ECG), and microvolt T-wave alternans (MTWA).

Of note, only MTWA testing currently holds a class IIa indication for risk stratification among patients with a history of, or at risk for ventricular arrhythmia, while testing for other non-invasive parameters has been given a class IIb indication [4]. Numerous studies have indicated that both positive and negative MTWA results have a large prognostic value [5–9]. MTWA measurements in patients with left ventricular (LV) dysfunction referred for ICD implantation in the primary prevention of SCD might help select patients who would benefit most from ICD therapy.

However, indeterminate MTWA results, reported in about 6% to 41% tests, are a significant but less well studied problem [10–17]. These non-diagnostic results may be related to both patient-related factors and technical issues, such as artifacts [18]. Differentiating between these causes seems clinically important, as artifacts are unlikely to have any prognostic value, while patient-related factors resulting in an indeterminate MTWA result may well be of such a value.

The aim of the present study was to evaluate frequency, causes, and prognostic significance of indeterminate MTWA results in a group of patients with LV dysfunction referred for ICD implantation in the primary prevention of SCD.

## METHODS

We studied patients with LV systolic dysfunction ( $LVEF \leq 35\%$ ) referred to our unit for consideration of ICD implantation in the primary prevention of SCD. Exclusion criteria included age below 18 years, history of sustained ventricular tachycardia, (VT), ventricular fibrillation (VF) or cardiac arrest, chronic atrial fibrillation or flutter, permanent second- or third degree atrioventricular block, New York Heart Association (NYHA) class IV heart failure, unstable angina, significant valvular heart disease, diabetes type 1 complicated by symptomatic peripheral neuropathy, difficulties with walking on the treadmill, and lack of patient consent.

## MTWA measurements

MTWA was measured during an exercise treadmill test performed in the morning hours. Patients continued to take their usual medications, including beta-blockers.

After skin preparation to minimise artifacts (cleansing using abrasion paper), high-resolution electrodes (High-Res, Cambridge Heart) were placed according to the orthogonal Frank system (three leads X, Y, and Z), along with the standard 12-lead configuration.

Exercise test was performed on a treadmill (Delmar Reynolds) using a protocol to measure MTWA, with gradual heart rate (HR) acceleration to 100–110 bpm followed by 110–120 bpm (for at least 2 min). MTWA analysis was performed using the spectral method (CH2000 system, Cambridge Heart, Bedford, MA, USA). Automatic analysis was verified by the physician performing the study.

The result was categorised as positive, negative or non-diagnostic (indeterminate) according to the criteria established in the literature [18].

**Positive MTWA (MTWApos)** was defined as sustained alternans (lasting for at least a minute) with an amplitude of  $\geq 1.9 \mu V$  in any orthogonal lead or two adjacent precordial leads, occurring at the HR of  $\leq 110$  bpm and persisting with continued exercise and further increase in HR, or present in resting conditions.

**Negative MTWA (MTWANeg)** was defined as lack of the positive MTWA criteria and no sustained alternans at the HR of  $\geq 105$  bpm.

**Indeterminate (MTWAnd)** was defined as a result that could be categorized neither as positive nor negative alternans.

In our analysis, we considered the following reasons for non-diagnostic MTWA results:

- non-diagnostic results due to patient-related cardiac factors (inability to reach HR of 105–110 bpm, frequent extrasystoles ( $> 10\%$  of the recording), unsustained alternans);
- non-diagnostic results due to technical reasons (artifacts related to a high noise level).

According to the current recommendations, every MTWA test that was found to be non-diagnostic due to technical reasons was immediately repeated [19, 20].

## Follow-up

All patients underwent outpatient follow-up in our unit, with follow-up visits every 3 months to evaluate clinical status of the patients and record any adverse events. The primary endpoint in the study included all occurrences of SCD, VT, VF, and appropriate high-voltage ICD interventions (due to  $VT \geq 170$  bpm or  $VF \geq 200$  bpm).

## Statistical analysis

Statistical analysis was performed using the STATISTICA 6.0 software. All data were presented as mean values  $\pm$  SD or as

numbers and percentages [n (%)]. Demographic and clinical data in SCD/VT/VF(+) and SCD/VT/VF(-) groups were compared using the Mann-Whitney test (due to non-normal data distribution) for quantitative data and the chi-square test with the Yates correction or the Fisher test (depending on the size of the compared samples) for qualitative data. Comparison of the occurrence of SCD/VT/VF events and MTWA result (negative vs. non-negative) was performed using the Fisher test. In addition, we evaluated the prognostic value of individual MTWA results (sensitivity, specificity, negative prognostic value [NPV], and positive prognostic value [PPV], with Wilson confidence intervals [CI]), and evaluated and compared the probability of SCD/VT/VF events during follow-up (Kaplan-Meier method, log-rank test).

## RESULTS

The study included 93 patients aged  $63 \pm 13$  (range 20–91) years with LVEF  $30 \pm 7\%$ . In a vast majority of patients, systolic dysfunction was of ischaemic origin. More than half of patients were in NYHA class II. Almost all patients were on chronic beta-blocker therapy, and several percent were on amiodarone therapy. These medications were continued during the MTWA measurements. Detailed demographic and clinical characteristics of the studied patients are shown in Table 1. In all patients, MTWA was measured during a treadmill exercise test. Figures 1 and 2 show examples of positive and negative MTWA results. Overall, a positive MTWA result was found in 27 patients, a negative result in 41 patients, and an indeterminate result in 25 patients (Fig. 3). When causes of indeterminate MTWA results were analyzed in detail, patient-related factors were found in 20 patients, including inability to achieve a diagnostic HR in 12 patients (in 10 patients due to chronotropic incompetence, and in 2 patients due to leg pain that necessitated termination of the exercise), frequent ventricular ectopy in 5 patients, and nonsustained alternans in 3 patients. In the remaining 5 patients, an indeterminate MTWA result was due to technical factors (high noise level). Initially, an indeterminate MTWA result was obtained in 9 patients, but immediately repeated testing allowed categorise 4 patients as having positive or negative MTWA. Overall, an indeterminate MTWA result due to technical factors was thus obtained in 5.4% of patients. Figure 4 shows distribution of specific causes of indeterminate MTWA results.

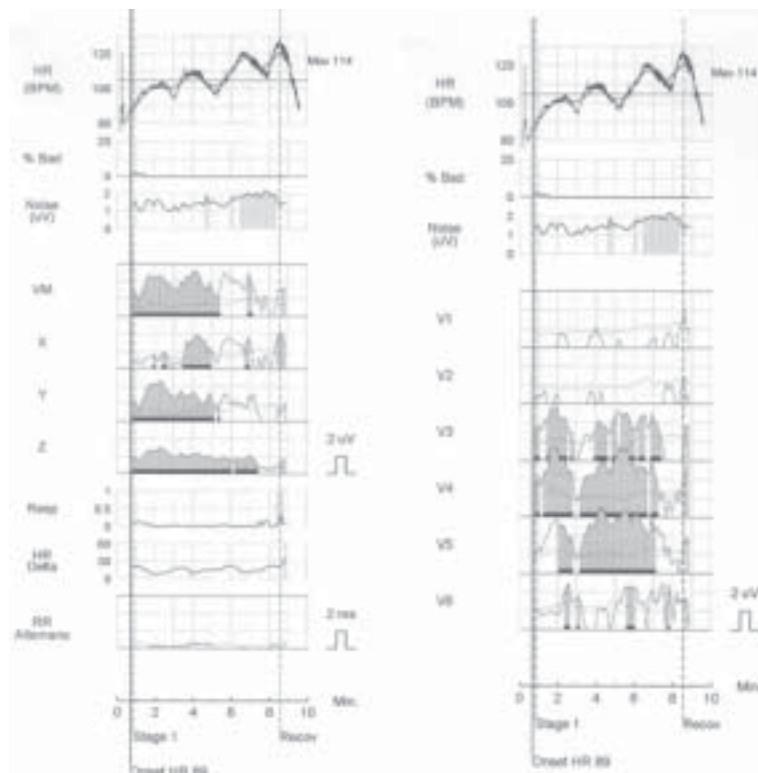
Follow-up duration was  $10 \pm 6$  months. During this time, ICD was implanted in 59 patients. During follow-up, 8 primary endpoint events (SCD/VT/VF) were noted, including 2 SCD events (in patients awaiting ICD implantations) and 6 appropriate ICD interventions due to rapid VT or VF (with appropriateness of the intervention verified by analysis of the electrograms stored in the ICD device memory). MTWAp<sub>os</sub> was found in 4 patients with the primary endpoint event, and MTWAnd in the remaining 4 patients in this group. Of note, no events were noted during the follow-up in 5 patients with

**Table 1.** Clinical characteristics of the study group (data presented as mean values  $\pm$  SD or as numbers and percentages)

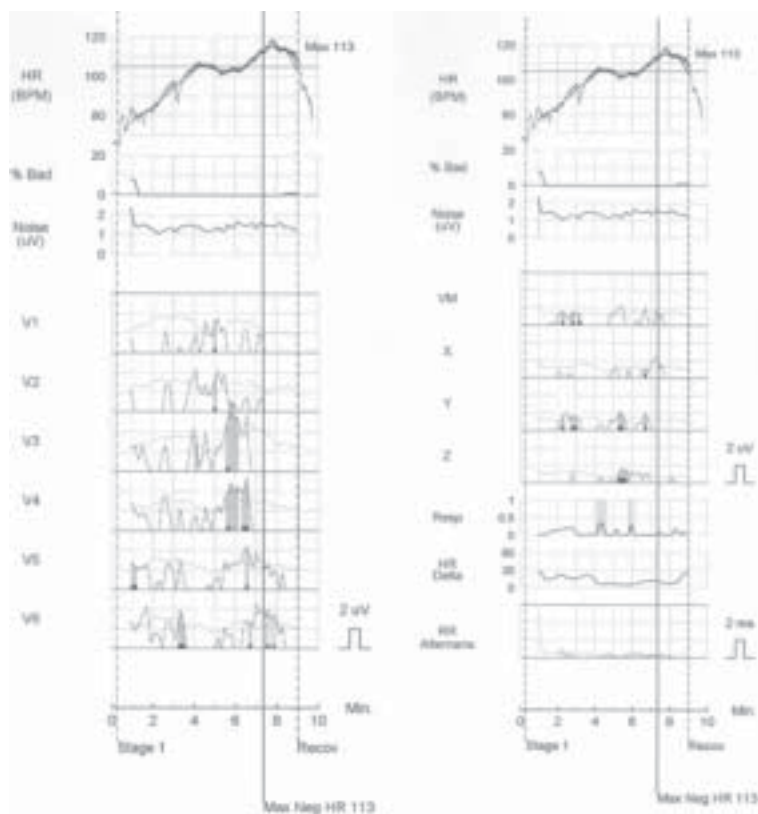
Number of patients	93
Age [years]	$63 \pm 13$
Men	84 (90%)
History of IHD	70 (75%)
History of MI:	
Number (%) of patients	63 (68%)
Time from infarction [years]	$7.1 \pm 8.3$
Previous PCI/CABG	62 (67%)
Non-ischaemic aetiology of HF	23 (25%)
LVEF [%]	$30 \pm 7$
NYHA class:	
I	19 (21)
II	59 (63)
III	15 (16)
Medications:	
Beta-blockers	90 (97%)
ACE-I/ARB	91 (98%)
Spironolactone/eplerenone	47 (51%)
Acetylsalicylic acid	75 (81%)
Vitamin K antagonist	16 (17%)
Amiodarone	11 (12%)
Statin	79 (85%)
Diuretic	52 (56%)
Concomitant disease:	
Hypertension	52 (56%)
Diabetes type 2	21 (23%)
Other characteristics:	
History of smoking	58 (62%)

IHD — ischaemic heart disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; HF — heart failure; LVEF — left ventricular ejection fraction; ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

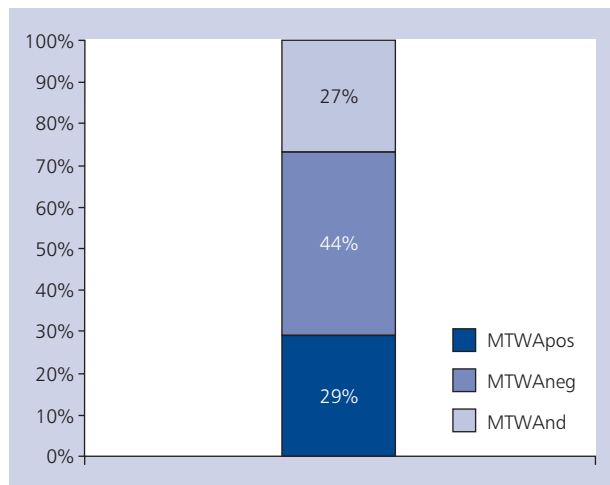
MTWAnd due to technical reasons. When we compared the SCD/VT/VF(+) and SCD/VT/VF(-) groups, no statistically significant differences were shown regarding demographic or clinical parameters (Table 2). However, a trend was found for more frequent occurrence of ischaemic heart disease in patients with SCD/VT/VF events. When patients with MTWAp<sub>os</sub> and MTWAnd were counted as having an abnormal MTWA results, sensitivity of MTWA was 100% (95% CI 67.56–100%), specificity 47.06% (95% CI 36.81–57.57%), PPV 15.09% (95% CI 7.85–27.05%), and NPV 100% (95% CI 91.24–100%). SCD/VT/VF events were significantly more frequent among patients with a non-negative MTWA result ( $p = 0.007$ ). The probability of having a SCD/VT/VF event was similar in MTWAp<sub>os</sub> and MTWAnd due to patient-related factors,



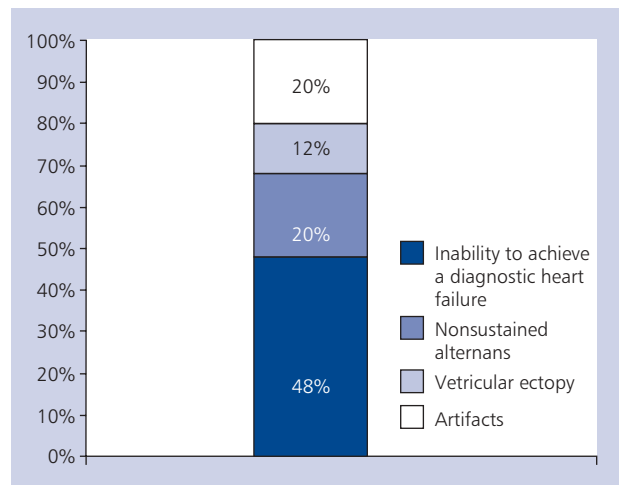
**Figure 1.** An example of a positive microvolt T-wave alternans result in one of our patients (patient O.R., age 61, with non-ischaemic dilated cardiomyopathy, left ventricular ejection fraction 25%)



**Figure 2.** An example of a negative microvolt T-wave alternans result in one of our patients (patient B.A., age 67, with two previous myocardial infarctions, left ventricular ejection fraction 33%)



**Figure 3.** Distribution of microvolt T-wave alternans positive (MTWAp0s), negative (MTWAneg), and indeterminate (MTWAnd) results in the study group

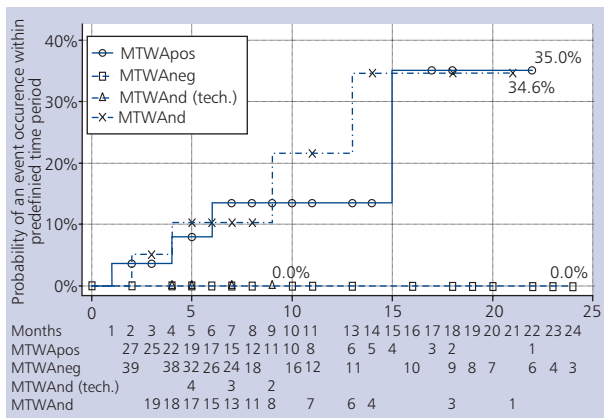


**Figure 4.** Distribution of causes of a indeterminate microvolt T-wave alternans results in the study group

**Table 2.** Comparison of demographic and clinical data in the SCD/VT/VF(+) and SCD/VT/VF(-) groups (data presented as mean values ± SD or as numbers and percentages).

	SCD/VT/VF (-); n = 85	SCD/VT/VF (+); n = 8	P
Age [years]	63 ± 13	67 ± 10	0.5
Men	50 (66%)	7 (88%)	0.2
History of IHD	62 (73%)	8 (100%)	0.09
History of MI:			
Nnumber (%) of patients	56 (63%)	7 (88%)	0.2
Time from infarction (years)	4.5 ± 7.5	6.6 ± 7.7	0.4
Previous PTCA/CABG	45 (62%)	4 (50%)	0.7
LVEF [%]	30 ± 6	28 ± 5	0.1
NYHA class:			
I	17 (20%)	2 (25%)	0.7
II	55 (65%)	4 (50%)	0.6
III	13 (15%)	2 (25%)	0.9
Medications:			
Beta-blockers	81 (95%)	8 (100%)	0.7
ACE-I/ARB	82 (96%)	7 (88%)	0.3
Spironolactone/eplerenone	44 (52%)	4 (50%)	0.6
Acetylsalicylic acid	68 (80%)	8 (100%)	0.2
Vitamin K antagonist	16 (19%)	0 (0%)	0.2
Amiodarone	11 (13%)	0 (0%)	0.4
Statin	72 (85%)	8 (100%)	0.3
Diuretic	47 (55%)	5 (63%)	0.5
Concomitant disease:			
Hypertension	47 (55%)	5 (63%)	0.5
Diabetes type 2	20 (24%)	1 (13%)	0.4
Other characteristics:			
History of smoking	40 (47%)	2 (25%)	0.2

SCD/VT/VF — sudden cardiac death/ventricular tachycardia/ventricular fibrillation event; PTCA — percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1



**Figure 5.** Kaplan-Meier curves illustrating the probability of a sudden cardiac death/ventricular tachycardia/ventricular fibrillation (SCD/VT/VF) event in relation to the microvolt T-wave alternans (MTWA) result, separately accounting for patients with indeterminate MTWA (MTWAnd) due to technical reasons. Two-year risk of SCD/VT/VF was 35% in patients with positive MTWA (MTWApos) and 34.6% among patients with MTWAnd due to patient-related factors. No significant differences were found between the curves for MTWApos and MTWAnd due to patient-related factors, and between the curves for negative MTWA (MTWANeg) and MTWAnd due to technical reasons, while such differences were found between MTWANeg and MTWApos and between MTWANeg and MTWAnd due to patient-related factors ( $p < 0.05$ )

but significantly higher compared to MTWANeg and MTWAnd due to technical factors (Fig. 5).

## DISCUSSION

Findings of the present study indicate that among patients with LV systolic dysfunction referred for ICD implantation in the primary prevention of SCD, despite a relatively large proportion of indeterminate MTWA results, the number of indeterminate MTWA results due to technical reasons, probably of no prognostic value, is small. This is a clinically important observation, as an indeterminate MTWA result due to patient-related factors may in fact have a prognostic value similar to that of a positive MTWA results, unlike an indeterminate MTWA result due to technical reasons. In addition, the studied group seems particularly important, as in such patients MTWA testing may be of potential use in clinical practice.

The proportion of indeterminate MTWA results depends on the studied population. Among patients with preserved LV systolic function, it was reported to range from 6% to 14% [13, 16, 17], while in patients with reduced LVEF it increases significantly to 20–28% in most studies [10–12], although it was even reported to exceed 30% in some studies [21] and even up to 41% in one study [14]. In our study, the propor-

tion of indeterminate MTWA results was 27%, similarly to the literature data.

When evaluating causes of indeterminate MTWA results, they are mostly due to patient-related factors. In a study among patients with LVEF  $\leq 40\%$ , Kaufman et al. [21] reported inability to achieve a diagnostic HR in more than 50% of 187 patients with an indeterminate MTWA result, frequent ventricular ectopy in more than 30% of these patients, and non-sustained alternans in about 10% of patients. In our study, the distribution of patient-related causes of indeterminate MTWA results was very similar.

In the study by Kaufman et al. [21], an indeterminate MTWA result due to technical reasons was reported very infrequently (12 out of 549 studied patients, or 2.2%). In our study among patients with LVEF  $\leq 35\%$ , the proportion of indeterminate MTWA results due to technical reasons was also low at 5.4%. According to the current recommendations regarding MTWA measurement methodology, a non-diagnostic test should be immediately repeated, as was done in our study in patients with an indeterminate MTWA result due to technical reasons. Repeating the exercise test in patients with frequent ventricular ectopy or exhausted after the initial test may be dangerous for the patient and often virtually impossible, as in case of 20 patients in our study group.

Distribution of MTWA results, and the proportion of indeterminate MTWA results may depend not only on LVEF but also on medications used [22–27]. Literature data indicated that inhibition of the sympathetic nervous system activity with beta-blockers may reduce alternans amplitude, decreasing the proportion of MTWApos and increasing the proportion of MTWANeg [22, 23, 26]. This was observed both in response to acute intravenous provocation and chronic oral therapy [22, 23, 26]. Also for amiodarone, literature data in patients with a history of VT/VF suggest a lower rate of MTWApos during amiodarone treatment [27]. Finally, chronic beta-blocker or amiodarone therapy may decrease the proportion of indeterminate MTWA results by reducing ventricular ectopy.

Of note, the most common cause of MTWAnd in our study group was inability to achieve a diagnostic HR, which is consistent with the literature data [21]. In a vast majority of patients (10 of 12), this resulted from chronotropic incompetence. As suggested by Witte et al. [28], chronic beta-blocker therapy may increase the proportion of patients with chronotropic incompetence. As nearly all patients in our study received beta-blockers, an 12% were treated with amiodarone, both exerting strong negative chronotropic effect, this might have affected the distribution of causes of non-diagnostic MTWA results. In contrast, Jorde et al. [29] reported that beta-blocker therapy did not increase the proportion of patients with chronotropic incompetence. Proportion of MTWA results in our study, including non-diagnostic results, is similar to the literature data from patients in whom beta-blocker was withdrawn before MTWA measurement. Regardless of these

considerations, it is currently recommended to continue previous drug therapy during MTWA measurement, as was the case in our study [24, 25].

When discussing non-diagnostic MTWA results, it should be noted that the predictive values of such results in patients with LV systolic dysfunction is similar to that of positive results [10, 11, 21]. This is of major clinical importance as it suggests that patients with both positive results and indeterminate results due to patient-related factors should be treated in the same way and may be combined into a single group with a so-called “non-negative” MTWA result. In terms of clinical practice, this increased the number of patients in whom MTWA measurement may be used in the stratification of SCD risk. As shown in many studies, abnormal (non-negative) MTWA result may predict episodes of malignant ventricular arrhythmia [5, 6, 8, 15], which has also been confirmed in the present study. Of note, indeterminate MTWA result has a predictive value for VT/VF and SCD only if it is due to patient-related factors, and not when it is due to technical reasons, as shown by Kaufman et al. [21] in their study in patients with LVEF  $\leq$  40%. In our study, we confirmed these observations in patients with LVEF  $\leq$  35%.

Regardless of these considerations, a limitation of MTWA measurement is the fact that not all patients potentially at risk of SCD may be tested using this method. Currently, MTWA measurement is not helpful in patients with chronic atrial fibrillation/flutter, or permanent second- or third degree atrio-ventricular block. MTWA assessment is also contraindicated in patients with severe heart failure, i.e. NYHA class IV. Thus, MTWA measurements, although useful and of large practical importance, may be used in only a limited subset of patients at risk of SCD who are candidates for ICD implantation.

## CONCLUSIONS

Although the proportion of indeterminate MTWA results in patients with LV dysfunction referred for ICD implantation in the primary prevention of SCD was high, the proportion of indeterminate MTWA results due to technical factors, probably of no prognostic significance, was small.

**Conflict of interest:** none declared

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# Problem wyników niediagnostycznych badania mikrowoltowej naprzemienności załamka T wśród pacjentów z dysfunkcją skurczową lewej komory kwalifikowanych do implantacji ICD w profilaktyce pierwotnej nagłej śmierci sercowej

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## Streszczenie

**Wstęp:** Ocena mikrowoltowej naprzemienności (alternansu) załamka T (MTWA) jest uznanym nieinwazyjnym badaniem diagnostycznym stosowanym w stratyfikacji ryzyka nagłej śmierci sercowej (SCD) pacjentów kardiologicznych. Jednak odsetek wyników niediagnostycznych tej metody jest wysoki (6–41%). Przyczyny, sposób interpretacji i znaczenie kliniczne takich wyników nie są w pełni sprecyzowane.

**Cel:** Celem pracy była ocena częstotliwości, przyczyn występowania i wartości prognostycznej wyników niediagnostycznych MTWA w grupie pacjentów z dysfunkcją skurczową lewej komory kwalifikowanych do implantacji kardiowertera-defibrylatora (ICD) w profilaktyce pierwotnej SCD.

**Metody:** Badaniem objęto chorych z frakcją wyrzutową lewej komory (LVEF)  $\leq 35\%$ . U każdego pacjenta wykonywano badanie MTWA (system CH2000, Cambridge Heart Inc. Bedford MA, USA) podczas próby wysiłkowej na bieżni ruchomej. Wynik badania MTWA (analiza spektralna) oceniano jako dodatni, ujemny lub niediagnostyczny (odpowiednio: MTWApos, MTWANeg, MTWAnd). Wszystkich pacjentów poddano obserwacji z uwzględnieniem wystąpienia epizodu SCD, częstoskurczu komorowego (VT) i migotania komór (VF).

**Wyniki:** Do badania włączono 93 osób w wieku  $63 \pm 13$  lat, z których 70 (75%) pacjentów miało niedokrwiennie podłoże dysfunkcji skurczowej, średnia wartość LVEF wynosiła  $30 \pm 7\%$ . Wyniki uzyskane w badaniu były następujące: MTWApos — 27 (29%) pacjentów, MTWANeg — 41 (44%), MTWAnd — (27%); przyczyny MTWAnd: u 12 (48%) osób — nieosiągnięcie wymaganego przyspieszenia częstotliwości rytmu serca, 5 (20%) — ekstrasystolia komorowa, 3 (12%) — nieutralony alternans, 5 (20% wśród wyników niediagnostycznych, 5,4% w całej grupie chorych) — przyczyny techniczne (artefakty na skutek wysokiego poziomu szumów). Epizody SCD/VT/VF zanotowano u 8 osób, z których u 4 pacjentów stwierdzono MTWApos, a u 4 osób — MTWAnd z przyczyn leżących po stronie chorego. Prawdopodobieństwo wystąpienia SCD/VT/VF wyniosło 35% w grupie MTWApos oraz 34,6% w grupie MTWAnd z przyczyn leżących po stronie chorego i było istotnie statystycznie wyższe w porównaniu z pacjentami z MTWANeg i MTWAnd z przyczyn technicznych ( $p < 0,05$ ).

**Wnioski:** Mimo stosunkowo dużego odsetka wyników niediagnostycznych badania MTWA wśród pacjentów z dysfunkcją skurczową lewej komory kwalifikowanych do implantacji ICD w ramach profilaktyki pierwotnej SCD liczba wyników niediagnostycznych z przyczyn technicznych, prawdopodobnie nieposiadających wartości prognostycznej, jest niewielka.

**Słowa kluczowe:** naprzemiennosc (alternans) załamka T, kardiowerter-defibrylator, dysfunkcja skurczowa

Kardiologia 2012; 70, 8: 795–802

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Praca wpłynęła: 12.08.2011 r. Zaakceptowana do druku: 04.04.2012 r.

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