Microvolt T-wave alternans for the risk stratification of dangerous ventricular arrhythmias in patients with previously implanted automatic cardioverter-defibrillator

Maciej Lewandowski¹, Irmina Kossuth¹, Joanna Zielonka¹, Maciej Wielusiński¹, Arkadiusz Kazimierczak², Zdzisława Kornacewicz-Jach¹, Krzysztof Przybycień¹, Robert Kaliszczak¹

¹Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
²Vascular Surgery Department, Pomeranian Medical University, Szczecin, Poland

Abstract

Background: Sudden cardiac death (SCD) is the main cause of death in patients with reduced left ventricular ejection fraction (LVEF). Implantation of an automatic cardioverter-defibrillator (ICD) significantly reduces mortality of these patients. T-wave alternans (TWA) analysis is a relatively new method of SCD risk stratification. However, its prognostic role in patients with ICD has not yet been fully established.

Aim: To assess the predictive value of TWA in patients with previously implanted ICD.

Methods: The study included 67 patients with properly functioning ICD (54 men and 13 women, aged 62.2 ± 8.4 years). All patients underwent TWA analysis on the treadmill using the Cambridge Heart 2000 system. Results were considered as positive, negative or indeterminate. Each patient had at least 1 clinical control visit with ICD interrogation during the 12 ± 6 months of follow-up. The recurrence of sustained ventricular arrhythmias: ventricular tachycardia (VT) or ventricular fibrillation (VF) was analysed.

Results: No significant relationship was found between previous infarction (p = 0.810), aetiology (p = 0.768), LVEF (p = 0.413) or age (p = 0.562) and the incidence of arrhythmia during follow-up. The results of TWA were not significantly different between patients with or without VT or VF. The TWA analysis identified patients with arrhythmia recurrences with a sensitivity of 62%, specificity of 49%, negative predictive value of 81%, and positive predictive value of 28%. The TWA performance was better in patients with non-ischaemic than ischaemic cardiomyopathy (negative predictive value: 100%, positive predictive value: 75%).

Conclusions: The TWA alternans was moderately effective for identification of patients with ICD and ventricular arrhythmia recurrences. The test was most useful for identification of patients with non-ischaemic cardiomyopathy who are of low arrhythmic risk.

Key words: microvolt T-wave alternans, implantable cardioverter-defibrillator

INTRODUCTION

The main immediate cause of death in patients with reduced left ventricular ejection fraction (LVEF) is sudden cardiac death (SCD), usually due to life-threatening ventricular arrhythmias (ventricular tachycardia — VT or ventricular fibrillation — VF). Implantation of a cardioverter-defibrillator (ICD) in patients with reduced LVEF (≤ 30–40%, depending on the study criteria), significantly reduces the mortality of such patients when com-
pared to medical treatment [1, 2] and this holds true for primary as well as secondary prevention. However, a major problem remains, i.e. the extensive cost of treating the entire population at risk (especially in primary prevention). This represents a major limitation of the widespread ICD use. For this reason, continuous research is being carried out, aiming at reliable risk stratification methods in the population at risk.

One of the relatively new methods of risk stratification is the assessment of T-wave alternans (TWA). It is a non-invasive method based on computerised analysis of the electrocardiogram obtained at the threshold heart rate [3, 4]. Microvolt TWA (MTWA) allows for detection of variations at a level of 0.1 μV. The presence of a positive or indeterminate (non-negative) test result has been found to correlate with increased serious ventricular arrhythmias whereas absence of this electrocardiographic phenomenon is related to a more favourable prognosis (negative results are false negatives rarely — ca 3.5%) [5].

The MTWA method has a highest (IIa) recommendation in the current guidelines of the European Society of Cardiology (ESC) [6]. Despite that, it is not commonly adopted, and its role in the risk stratification in the patients implanted with an ICD is not fully established [4, 7].

The aim of the study was to assess the prognostic value of MTWA in the group of ICD patients.

METHODS

Study group

This was a prospective study approved by the local bioethical committee of the Pomeranian Medical University. Sixty-seven patients with a previously implanted, properly functioning ICD were included. All the patients expressed their written informed consent for the participation in the study, were able to perform exercise testing and were haemodynamically stable with no known triggers of arrhythmia (i.e. acute coronary syndrome or electrical storm within 3 months prior to inclusion). Study population consisted of 54 men and 13 women aged 62.2 ± 8.4 years. The group consisted of 55 ICD/VVI patients and 12 patients with ICD/DDD.

MTWA testing

All the patients underwent treadmill exercise test on a Cambridge Heart 2000 system with MTWA analysis capability (MTWA Ex). The test was considered positive if the alternans voltage was 1.9 μV or higher and if it lasted for over one minute, with the onset heart rate lower than 110/min in whichever of the orthogonal X, Y, Z leads or 2 consecutive precordial leads. If at the rate higher than 105/min the alternans of 1.9 μV or higher was not recorded, the result was considered negative. If neither negative or positive result criteria were met, the test result was considered indeterminate. The indeterminate tests together with the positive were defined as non-negative. All the patients who had been on β-blockers, were advised to skip or reduce the dose for 12–24 h prior to the MTWA testing. During the study or immediately after, no adverse effects or significant arrhythmias were recorded. In 2 (3%) of the patients, premature ventricular contractions were noted, and in 1 (1.5%), atrial fibrillation (AF) was recorded. In all these patients the MTWA results were considered indeterminate.

Clinical follow-up and arrhythmia assessment

Each patient subsequently had at least one follow-up visit combined with ICD check-up within 12 ± 6 months of the MTWA testing. The primary end-point was serious ventricular arrhythmia, adequately identified by the device. Ventricular fibrillation as well as sustained ventricular tachycardia (sVT) were identified based on an algorithm stored in the device’s memory. According to standard criteria, sVT was identified as ventricular arrhythmia of over 170 bpm, consisting of more than 16 cycles (according to the 16/20 algorithm), causing adequate detection and therapy triggering (anti-tachycardia pacing [ATP], or intra-cardiac cardioversion). The limits for VF detection were set at 200 bpm and the arrhythmia was terminated by intra-cardiac defibrillation. The study group was then stratified by LVEF, NYHA class, aetiology of cardiac disease and amiodarone therapy.

Statistical methods

The statistical analysis was performed with Statistica PL package. Initially, the proportion of patients with arrhythmia in subgroups was compared by χ² or Fisher’s exact test (where the patient numbers were lower than 5) and Yates correction was introduced for patient numbers higher than 5. The test choice was additionally justified by subgroup size of less than 25 patients. Quantitative data were compared between arrhythmia and no arrhythmia groups by the Mann-Whitney U test. This test was used due to non-normal data distribution in the groups. After initial identification of factors related to arrhythmia occurrence, a discriminational analysis was carried out (Wilk’s lambda) in order to eliminate factors which correlated with each other more closely than with arrhythmia itself. The results were considered significant at p level < 0.05. A multivariable analysis of the factors correlating with arrhythmia was carried out. Variables for which Wilk’s lambda test reached p < 0.05 were included in the model.

RESULTS

The MTWA exercise test (MTWA Ex) was positive in 16 (24%) patients, negative in 32 (48%), and indeterminate in 19 (28%). The patients were then divided into 2 groups: with negative (32 pts) and non-negative (positive + indeterminate, 35 pts) MTWA test result. Baseline characteristics of the two group did not differ significantly and are presented in Table 1.

During follow-up no deaths were recorded. On the follow-up visit at 12 ± 6 months, ventricular arrhythmias including either sVT or VF (VT/VF+) were found recorded in the Holter memory of the device in 16 patients, and no arrhythmia was found in 51 patients (VT/VF−).
Data analysis did not show any significant relationship between such factors as history of infarction, type of cardiomyopathy, LVEF or age and arrhythmia occurrence in the long-term follow-up. It turned out, however, that in women ventricular arrhythmia was significantly more common than in men (54% vs 17%). These results are summarised in Table 2.

Similarly, no significant relationship was noted between the MTWA Ex test result and the occurrence of arrhythmia in the device’s memory (Table 3). Moreover, the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the MTWA Ex test for identification of patients with life-threatening ventricular arrhythmias (sVT, VF) were estimated (Table 4). The MTWA performed better in patients with non-ischaemic rather than ischaemic cardiomyopathy, with the sensitivity and NPV values approaching 100%. A weak independent effect of amiodarone on arrhythmia reduction was found. There was no relationship between MTWA Ex test and arrhythmia occurrence (Table 5).

**DISCUSSION**

Despite substantial number of publications, consistent and unequivocal results with regard to the non-negative MTWA result as a predictor of arrhythmias are not as yet available. The results of studies to date remain discordant. In earlier studies [8] it was shown that reduced EF as well as TWA result were significant and independent risk factors of serious arrhythmia (based on adequate ICD intervention). The major role of TWA testing is attributed to arrhythmic event prediction in patients with low LVEF.

In the group of patients with LVEF ≤ 45% in NYHA class II or III, TWA result represented a significant risk factor for ventricular arrhythmia or sudden death, and patients with negative TWA result had low risk of arrhythmic events [9]. Cantillon et al. [10] found a significant prognostic value of MTWA for overall survival (78% for a negative test and 56% for a non-negative test) and arrhythmia-free survival (75% for a negati-

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**Table 1. Patient characteristic according to MTWA result**

<table>
<thead>
<tr>
<th>MTWA Result</th>
<th>Negative MTWA</th>
<th>Non-negative MTWA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Men/women</td>
<td>27/5</td>
<td>27/8</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>62 ± 8</td>
<td>63 ± 8</td>
</tr>
<tr>
<td>NYHA class:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ICD implantation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>38 ± 11</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>IHD</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>History of MI</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

All differences NS; MTVA — microvolt T-wave alternans; NYHA — New York Heart Association; IHD — ischaemic heart disease; MI — myocardial infarction; ACE — angiotensin-converting enzyme; ARB — angiotensin receptor blockers.

**Table 2. Comparison of the occurrence of demographic and clinical parameters between patients with or without VT/VF**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>VT/VF (-)</th>
<th>VT/VF (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Male sex</td>
<td>54</td>
<td>45</td>
<td>83</td>
</tr>
<tr>
<td>Female sex</td>
<td>13</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>67</td>
<td>61.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>18</td>
<td>14</td>
<td>78</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>49</td>
<td>37</td>
<td>76</td>
</tr>
<tr>
<td>History of MI</td>
<td>50</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>No history of MI</td>
<td>17</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>21</td>
<td>15</td>
<td>71</td>
</tr>
<tr>
<td>No amiodarone</td>
<td>46</td>
<td>27</td>
<td>59</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>58</td>
<td>44</td>
<td>76</td>
</tr>
<tr>
<td>Non-ischaemic cardiomyopathy</td>
<td>9</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>EF 20–39%</td>
<td>45</td>
<td>34</td>
<td>76</td>
</tr>
<tr>
<td>EF ≥ 40%</td>
<td>22</td>
<td>17</td>
<td>77</td>
</tr>
</tbody>
</table>

VT — ventricular tachycardia; VF — ventricular fibrillation; MI — myocardial infarction; EF — ejection fraction.
Microvolt T-wave alternans for the risk stratification of dangerous ventricular arrhythmias

ve test and 40% for a non-negative test) during 60-month follow-up of patients with EF < 35%. In a meta-analysis of 19 studies, the positive predictive value of the test was found to be 19.3% (95% CI 17.7–21) [11].

The usefulness of the method has also been questioned by other investigators, who suggested that MTWA result should not be taken into consideration in the clinical decision-making in patients with symptomatic LV dysfunction, either ischaemic or of non-ischemic aetiology [12, 13]. They found no significant differences in the combined end-point including arrhythmic death, sVT/VF, adequate ICD intervention between patients with negative and non-negative MTWA (HR 1.28, 95% CI 0.65–2.53, p = 0.46). The results of the CARISMA study are in concordance with these reports [14]. In another study, the MTWA carried out in 768 patients with ischaemic cardiomyopathy seemed to have a substantial prognostic value, sustained for over a year after the test (the risk of death or ventricular arrhythmia during follow-up was doubled) [15].

A separate, interesting and underinvestigated population, as opposed to the post-infarction population, is the group of patients with non-ischaemic cardiomyopathy [16–20]. The results of the ALPHA study (T-Wave Alternans in Patients With Heart Failure) (HR 3.44, p = 0.008) [20], as well as the results of a meta-analysis carried out by De Ferrari et al. [21] suggested, that in the group with non-ischaemic aetiology (8 studies, almost 1.5 thousand patients) abnormal MTWA result was related to significantly higher risk of death or serious ventricular arrhythmias (RR 2.99; 95% CI 1.88–4.75), and that patients with a negative MTWA result had favourable good prognosis. As opposed to contradictory data concerning the clinical usefulness of a positive result, the negative MTWA result has high predictive value, a consistent finding in the majority of studies to date. Hence, this is a group that can derive greater benefit from MTWA testing. It is even more important in view of the lack of usefulness of programmed ventricular stimulation in the identification of patients at highest risk within this group. In the clinical practice, this can lead to the reduction of ICD implantation in patients who would derive no benefit of the device.

Table 3. The relationship between MTWA test result and ventricular arrhythmia occurrence at 12 ± 6 month follow-up

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>VT/VF (–)</th>
<th>VT/VF (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>MTWA Ex (+)</td>
<td>35</td>
<td>71</td>
<td>10</td>
</tr>
<tr>
<td>MTWA Ex (–)</td>
<td>32</td>
<td>81</td>
<td>6</td>
</tr>
</tbody>
</table>

VT — ventricular tachycardia; VF — ventricular fibrillation; MTVA — microvolt T-wave alternans; MTWA Ex — the MTWA exercise test

Table 4. Sensitivity, specificity, positive and negative predictive value of the MTWA test in patient subgroups

<table>
<thead>
<tr>
<th>Overall</th>
<th>MTWA Ex in selected patient subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>67 (100)</td>
<td>62</td>
</tr>
<tr>
<td>45 (67)</td>
<td>75</td>
</tr>
<tr>
<td>22 (33)</td>
<td>43</td>
</tr>
<tr>
<td>9 (13)</td>
<td>100</td>
</tr>
<tr>
<td>58 (86)</td>
<td>60</td>
</tr>
<tr>
<td>50 (75)</td>
<td>59</td>
</tr>
<tr>
<td>17 (25)</td>
<td>60</td>
</tr>
</tbody>
</table>

NPV — negative predictive value; PPV — positive predictive value; rest abbreviations as in Tables 1 and 2

Table 5. Multifactorial analysis of the effects of sex, amiodarone therapy and MTWA result on life threatening arrhythmia occurrence

<table>
<thead>
<tr>
<th>Female sex p = 0.0098</th>
<th>Amiodarone p = 0.1079</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTWA Ex (+)</td>
<td>p = 0.7749</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 3

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It is difficult to explain why MTWA performed better in non-ischaemic than ischaemic cardiomyopathy patients. It could be related to the more localised arrhythmia substrate in patients with ischaemic cardiomyopathy (local alterations in action potential resulting from ischaemia) what can translate to lower diagnostic utility of the test (due to its “macroscopic” nature, i.e. the fact that the net electrical instability of the myocardium is detected). However, this statement should be used with caution as there are studies in which high NPV was also found in patients with ischaemic cardiomyopathy [11].

An interesting finding is that recurrence rate of arrhythmia in female patients during follow-up was higher than in men. It is known that SCD is 4–7 times more frequent in men. However, above the age of 60 this difference becomes less pronounced, and disappears in more advanced age-groups. Women participating in our study were older (63.5 vs 61.9 years), had lower LVEF (33% vs 37%), more of them had a history of myocardial infarction (85% vs 71%) and were on amiodarone therapy less frequently (23% vs 33%). None of these differences showed statistical significance, but they might have some effects on arrhythmia occurrence. Moreover, arrhythmia has smaller prognostic value for SCD in women than in men [24–26].

Also, one should mention the influence of β-adrenergic drugs and their effect on MTWA result, which has not been agreed upon. The majority of authors recommend the discontinuation of β-blockers 24–36 h before the test in order to enhance the possibility of MTWA occurrence, as well as to increase chances for achieving target heart rate [27, 28]. Further studies should be carried out to elucidate the effects of β-blockers on MTWA results.

**Limitations of the study**

The limitations include the relatively small study group and the putative influence of drugs, especially amiodarone, on the study results.

**CONCLUSIONS**

Based on the study results, the authors conclude that MTWA test has a high NPV for life-threatening ventricular arrhythmias, especially in patients with non-ischaemic cardiomyopathy.

**Conflict of interest:** none declared

**References**

Mikrowoltowy alternans załamka T w stratyfikacji ryzyka groźnej arytmii komorowej u chorych z uprzednio implantowanym automatycznym kardiowerterem-defibrylatorem

Maciej Lewandowski¹, Irmina Kossuth¹, Joanna Zielonka¹, Maciej Wielusiński¹, Arkadiusz Kazimierczak², Zdzisława Komacewicz-Jach, Krzysztof Przybycień¹, Robert Kaliszzczak¹

¹Klinika Kardiologii, Pomorski Uniwersytet Medyczny, Szczecin
²Klinika Chirurgii Naczyniowej, Pomorski Uniwersytet Medyczny, Szczecin

Streszczenie

Wstęp: Podstawową, bezpośrednią przyczyną zgonu wśród pacjentów z obniżoną frakcją wyrzutową lewej komory (LVEF) jest nagły zgon sercowy. Implantacja automatycznego kardiowertera-defibrylatora (ICD) istotnie redukuje śmiertelność tych osób w porównaniu z chorymi leczonymi zachowawczo. Do stosunkowo nowych sposobów stratyfikacji ryzyka należy ocena alternansu załamka T (TWA), czyli występowania naprzemiennnej różnicy wysokości załamka T w kolejnych zespołach QRST. Ujemny wynik tego badania (brak występowania alternansu) uważa się za cechę wskazującą na lepsze rokowanie pacjentów. Jednak mimo dostępnego licznie piśmiennictwa zagranicznego i rekomendacji badania w zaleceniach ESC, w Polsce metoda ta jest mało znana, niedostępna w wielu ośrodkach i rzadko brana pod uwagę; brakuje również oryginalnych publikacji opartych na polskim materiale.

Cel: Celem pracy było określenie wartości rokowniczej mikrowoltowego TWA (MTWA) wśród pacjentów z ICD.

Metody: Badaniem objęto 67 pacjentów z implantowanym uprzednio, prawidłowo działającym ICD. Populacja badana składała się z 54 mężczyzn i 13 kobiet w wieku 62,2 ± 8,4 roku. W grupie tej znalazło się 55 pacjentów z ICD VVI i 12 z ICD DDD. U wszystkich osób wykonano test na bieżni ruchomej, wykorzystując system Cambridge Heart 2000 z możliwością analizy MTWA (MTWA Ex). Uzyskane wyniki określano jako dodatnie, ujemne i nieokreślone. U każdego pacjenta następnie przeprowadzono co najmniej 1 kontrolę kliniczną połączoną z kontrolą ICD w czasie 12 ± 6 miesięcy od wykonania testu. Głównym ocenianym parametrem było wystąpienie groźnej arytmii komorowej (sVT, VF), prawidłowo wykryte przez urządzenie. Następnie grupę badaną podzielono pod względem wartości LVEF, klasy wg NYHA, etiologii uszkodzenia serca i przyjmowania bądź niestosowania amiodaronu.

 Wyniki: Analiza danych nie wykazała istotnej zależności między takimi czynnikami, jak przebyty zawał serca (p = 0,810), rodzaj kardiomiopatii (p = 0,768), wartość LVEF (p = 0,413) lub wiek (p = 0,562) a częstością wystąpienia arytmii w obserwacji klinicznej. Nie odnaleziono również istotnej zależności między wynikiem testu MTWA Ex a obecnością arytmii w badaniu kontrolnym (p = 0,512). Oszacowano czułość (62%), swoistość (49%), negatywną wartość prognoistyczną (NPV, 81%) i pozytywną wartość prognoistyczną (PPV, 28%) testu MTWA Ex dla wystąpienia groźnej arytmii komorowej (sVT, VF), których wartości były szczególnie wysokie w grupie pacjentów z kardiomiopatią inną niż niedokrwieni (NPV 100%, PPV 75%).

Wnioski: Na podstawie przeprowadzonego badania autorzy stwierdzili, że MTWA charakteryzuje się wysoką negatywną wartością predykcyjną w stosunku do występowania zagrażających życiu arytmii komorowych, szczególnie wśród pacjentów z kardiomiopatią inną niż niedokrwieni.

Słowa kluczowe: mikrowoltowy alternans załamka T, implantowany kardiowerter-defibrylator

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