

# MICROVOLT T-WAVE ALTERNANS : A NEW METHOD TO EVALUATE THE RISK OF SUDDEN CARDIAC DEATH

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## REZUMAT

Microalternanța undei T (mAT) este o nouă metodă clinică pentru evaluarea riscului de moarte subită cardiacă. Alternanța undei T este rezultatul alternanței potențialului de acțiune la nivelul celulei miocardice. Mecanismele celulare ale alternanței sunt legate de perturbările cineticii intracelulare a ionilor de calciu și schimbului Na-Ca sarcolemal. Alternanța discordantă, în care două regiuni miocardice învecinate prezintă alternanță în opoziție de fază, crează o dispersie marcată a refractarității miocardice și substratul electrofiziologic al reintrării. Testul mAT este pozitiv când alternanța este susținută pentru cel puțin 1 minut, cu un voltaj mai mare de 1,9 uV. Studiile clinice publicate prezintă mAT ca pe un marker important al riscului de aritmii ventriculare.

**Cuvinte cheie:** microalternanța undei T, moarte subită cardiacă, aritmii ventriculare

## ABSTRACT

Microvolt T Wave Alternans (MTWA) is a new clinical method for the risk evaluation of sudden cardiac death (SCD). The T wave alternans is the result of the action potential alternans at the level of ventricular myocyte. The cellular mechanisms of alternans are related to alterations of the intercellular kinetics of calcium ions and the Na-Ca sarcolemal exchange. Discordant alternans, in which two neighboring myocardial regions present alternans in an opposite phase, creates a marked dispersion of repolarisation and the electrophysiological substrate of reentry. The MTWA test is positive when the alternans is sustained for at least 1 minute, with a voltage higher than 1,9 uV. Available clinical studies present MTWA as an important marker of risk of ventricular arrhythmias.

**Key Words:** microvolt T wave alternans, sudden cardiac death, ventricular arrhythmias

## INTRODUCTION

Sudden cardiac death (SCD) remains a major problem of human communities, even in the highly economical developed countries, where it represents approximately 11% of the total deaths, and almost 50% of all cardiac deaths. The number of SCD in USA is estimated to approximately 350000 annually. The relative failure of antiarrhythmic drug treatment in primary or secondary prophylaxis of SCD has determined the increasing use of implantable cardioverter defibrillator (ICD). The high price of the device imposes a rigorous selection of patients. The electrophysiological study (EPS) is invasive, expensive

and, as the MUSTT trial has shown, not perfect. The classical, noninvasive markers of arrhythmic risk have low specificity and low positive predictive value. Recently, a new noninvasive method, Microvolt T Wave Alternans (MTWA), has been introduced in clinical practice to evaluate the risk of SCD. In the USA, the method has received the Food and Drug Administration approval, for the evaluation of SCD risk in the year 2000.

## HISTORY

MTWA represents a type of electrical alternans in which, the morphology of the T wave, changes from one beat to another in a ABABAB succession. The first observations about MTWA belong to Hering, in the year 1908.<sup>1</sup> In 1913, Windle<sup>1</sup> described pulsus alternans in patients with severe cardiomyopathy and concluded that alternans always adds to the gravity of the prognosis. In the year 1988, Smith introduced the spectral analysis method in the study of the MTWA, which allows the detection of electrical alternans at the microvolt level.<sup>2</sup> In 1997 was published the first study, in which the MTWA evaluation was performed noninvasively.<sup>3</sup>

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### The electrophysiological basis of MTWA

Optical mapping studies have demonstrated that the mechanism that generates the appearance of the MTWA is the localized alternation in the action potential duration (APD). The APD alternans appears when the slope of the restitution curve (APD expressed as a function of the previous diastolic interval) is more than 1 at the current value of the diastolic interval.<sup>4</sup> The localized alternation of the APD reflects on the ECG in MTWA. The optical mapping studies of Pastore and Rossenbaum have shown that the MTWA on the surface ECG is synchronous with APD alternans.<sup>5</sup>

### Cellular and subcellular mechanisms

The ionic mechanisms of the alternans are in interdependence with the intercellular recycling of calcium ions, reflecting the abnormal functioning of the sarcoplasmic reticulum. The spatial heterogeneity of the intercellular calcium alternans correlates with the APD dispersion at the time of MTWA.<sup>6</sup>

### Discordant alternans: the arrhythmogenic mechanism

The alternans in APD is not an uniform process in the myocardium. When in two contiguous myocardial regions, the APD alternans is in opposition of phase, a marked dispersion of the refractoriness is produced, which creates the favorable conditions for reentry. This electrophysiopathological mechanism was named discordant alternans (DA). In the experimental model described by Rosenbaum, the DA presence was a prerequisite condition for the initiation of ventricular arrhythmias.<sup>6</sup>

**Ischemia, cardiac frequency and the level of the sympathetic tonus** are the main factors that can modulate MTWA. The APD alternans can be seen as an intrinsic property of the ischemical myocardium.<sup>7</sup> The evaluation of intrinsic arrhythmic risk through MTWA has to be done only after the exclusion of an ischemical cause of MTWA. It is important to underline the fact that there is no evidence that MTWA associated with a high risk of ventricular arrhythmia is, in some way, dependent on the presence of myocardial ischemia.<sup>6</sup>

In general, an increase in sympathetic tone determines an increase in the level of MTWA. Administration of beta blockers decreases the level of alternans. There are divergent opinions concerning the necessity of the interruption of beta blockers before the MTWA testing. The alternans is dependent on the heart rate (HR). Even persons without cardiac disease may present

significant MTWA at high heart rates, usually over 120 beats/min.

It has been shown that onset heart rate (OHR) of MTWA is reduced in patients with structural cardiac disease and antecedents of ventricular arrhythmias, in comparison with patients without a cardiac disease or arrhythmic antecedents. The false positive results increase at a HR higher than 120 beats/min. The essential condition for a positive test is that the OHR of MTWA is under 110 beats/min.

### Interpretation, classification

The spectral analysis method, developed by the group of researchers led by Richard J. Cohen, from M.I.T., Cambridge, USA is used in clinical practice. This group has introduced the technique for the standard evaluation of MTWA through the exercise stress testing. The apparatus is commercialized under the name HEARTWAVE and is property of CAMBRIDGE HEART. In our country, PHILIPS holds the distribution rights for the apparatus. (Fig.1)



Figure 1. Heartwave Apparatus

128 measurements, done at the level of the corresponding points to 128 consecutive T waves, are used to calculate a spectrum.

The resulting frequencies are expressed in cycles/cardiac beat (instead of cycles/sec). The point from the spectrum, corresponding to exactly 0,5 cycles/beats indicates the level of detection of MTWA. The results of the analysis are expressed as indices:<sup>8</sup>

- alternans power: measures the real physiological level of the MTWA;

- alternans voltage, expressed in mV, represents the square root of the alternans's power;
- alternans report, or the K score calculated as the report between the MTWA power and the standard deviation of the noise in the reference frequency band.

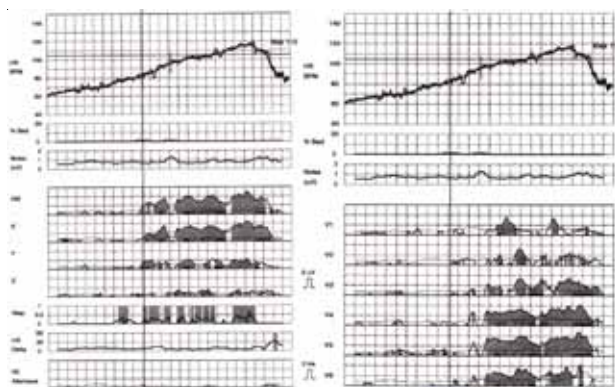
MTWA is considered significant if the index K is  $> 3$ .

**The classification of the MTWA registrations:<sup>8</sup> Sustained alternans:**

MTWA that is constantly present at heart rates higher than onset heart rate, with at least one minute with  $V_{alt} - 1,9 V$  and index  $K > 3$ ; in any of X, Y, Z derivations or VM (vector magnitude lead) or one of the precordial derivations, confirmed by an adjacent precordial derivation (with  $V_{alt} - 1,9 V$ ). The alternans may be considered sustained even if the magnitude decreases at HR - 120 b/min.

**Classification criteria:**

*Positive test:* sustained alternans: MTWA with an OHR  $< 110$  beats/min or sustained MTWA at a resting HR, even if this is  $> 110$  beats/min.<sup>8</sup> (Fig. 2)



**Figure 2.** Positive MTWA Test

*Negative test :*

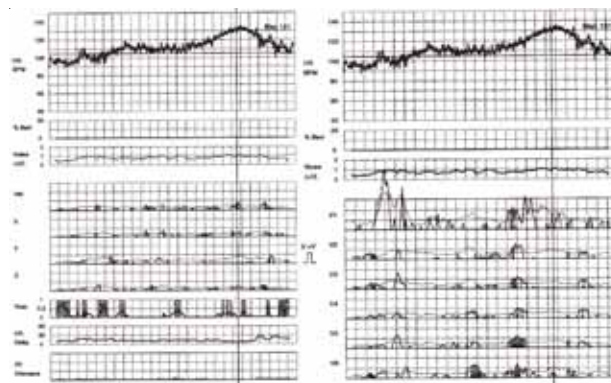
Rules A: 1). The test does not fulfil the criteria to be positive and 2) the maximum negative cardiac frequency is  $> 105$  beats/min.

Rules B : the test is also classified as negative if at the time of maximum exercise, the maximum HR is  $> 80$  beats/min and maximum negative HR  $> (\text{max. HR} - 5 \text{ beats/min})$ . *Indetermined test:* the test cannot be finally classified as positive or negative. Because rules B have been clinically, prospectively and retrospectively tested, Bloomfield recommends their adoption in clinic, on the considerent of reducing the number of equivocal tests.<sup>8</sup> (Fig. 3)

**Counter-indications** for MTWA testing: atrial fibrillation, frequent atrial extrasistoles, premature ven-

tricular beats (PVB), ventricular stimulated rhythms.

Short-term **reproducibility** of MTWA recordings is satisfying. Turitto compares the successive recordings of MTWA, taken at intervals of 4 hours. From 42 patients with 2 successive recordings, 39 (93%) have shown concordant results.<sup>9</sup>



**Figure 3.** Negative MTWA Test

## CLINICAL RESULTS

**Patients with ventricular arrhythmia,** e.g. ventricular Tachycardia (VT), ventricular Fibrillation, VF). Rosenbaum published in 1994, the first clinical study, in which 83 patients were diagnosed with MTWA, through atrial pacing, simultaneously with the electrophysiological study (EPS).<sup>10</sup> In the group of 32 patients with positive EPS, the MTWA was a predictor of VT inductibility with a 81% sensitivity and 84% specificity. As a predictive value, MTWA was equivalent to the EPS. Later on, clinical studies have proved the predictive value of the MTWA for the risk of ventricular arrhythmia. Relevant is the fact that, after Gold's study, FDA approved MTWA for the SCD risk evaluation in the USA.<sup>11-14</sup>

**Patients with left ventricular dysfunction.** Recent clinical studies have shown that MTWA can be used for the evaluation of arrhythmic risk in patients with congestive cardiac failure and dilated cardiomyopathy. In cardiac failure, patients with MTWA (+) have had a 10% mortality at two years in contrast to only 1% mortality in patients with negative MTWA.<sup>16</sup> The excellent negative predictive value of the MTWA is clinically useful in MADIT II patients: recent data show that in post-myocardial infarction patients with EF  $< 30\%$  and a negative MTWA test, the prophylactic ICD implantation is not necessary.<sup>15-20</sup>

**Patients with syncope.** Bloomfield,<sup>21</sup> analyzing the MTWA results in patients with ischemic heart disease and syncope, comes to the conclusion that MTWA

can identify at least as well as EPS a subgroup of patients with high risk of SCD or ventricular arrhythmias. Patients with MTWA (-) have an excellent prognosis and most of the times, they don't require additional investigations. Marangoni suggested that using the MTWA as a screening test in patients with ischemic heart disease and syncope can significantly reduce the hospitalization costs.<sup>22</sup> The arguments were the following:

- the MTWA method has the sensitivity and specificity similar to the EPS, but it is 10 times cheaper and without any risk to the patient;

- due to the fact that in all clinical trials (2000 patients) the negative predictive value is almost 90% (almost no patient with a negative MTWA test has presented SCD in the next 15 months), it is economically justified to hospitalize only the patients with a positive MTWA test.

#### **Patients with prior myocardial infarction.**

Ikeda has done the largest MTWA study in the world. In 850 patients with previous MI, the author finds the MTWA test to be the best predictor of arrhythmic risk: a positive MTWA test indicates an approximately 20% risk for the appearance of SCD, VF or VT in the next 2 years.<sup>23</sup>

**The MTWA implications for the selection of patients with ICD implant indication.** Because the MTWA test is useful in stratifying the ventricular arrhythmic risk, it can be used to identify a subgroup of patients which can be addressed to EPS and benefit from the ICD implantation.

The test may accurately identify patients with minimum risk, who don't need prophylactic ICD implantation. Ezekowitz analyses the efficiency of the ICD implantation in patients with high risk of SCD, underlining that the decisions concerning the allocation of the ICD resources depend on the accurate stratification of the patients with arrhythmic risk.<sup>24</sup> The authors sum up the results of 8 trials including 4909 patients: AVID, CASH, CIDS, MADIT, CABG patch, MUSTT, MADIT II, CAT. ICD has reduced the relative risk for SCD by approximately 50%, independent from basal risk. The analysis shows a large variability of the cost efficiency reports with values between 17,700 and 138,800\$ per year of life saved. The large variability in the cost efficiency reports shows the importance of an accurate stratification of the arrhythmic risk, in determining the patients with maximum benefit from the ICD treatment.

Today, 2 prospective studies try to establish the value of MTWA for the ICD implant indication. The

ABCD (The alternans before cardioverter defibrillator) trial, sponsored by St. Jude Medical Company, which made its debut on May, 8, 2001, compare MTWA with EPS for the establishment of ICD implant indication. The trial has the purpose to establish if the noninvasive MTWA test is comparable to invasive EPS in the prediction of the severe ventricular arrhythmias risk and the establishment of indication for ICD implant. A second study, the MASTER trial (Microvolt T-Wave Alternans Testing For Risk stratification of post MI patients), sponsored by Medtronic Company will include 600 patients who fulfil the MADIT II (previous MI and EF < 30%) criteria. A second group, of 1200 patients, with EF between 30 and 40% will be evaluated in a separate register. The study takes place in 50 centers from all over the world and its completion is expected at the end of the year 2005.

## **CONCLUSIONS**

MTWA is a noninvasive test, indicated for the analysis of risk of SCD and ventricular arrhythmias. Its positive predictive value, is variable from 25% to 80%, depending on the basal disease process. In some clinical situations, the positive predictive value may be increased through the correlation of the MTWA with ventricular late potentials and EPS results. The negative predictive value is higher than 99%. The ABCD and MASTER trials results are expected, to see if MTWA can substitute EPS in the establishment of indication for the cardioverter defibrillator implantation.

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