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How to do exercise-induced T-wave alternans testing using the spectral method

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Abstract

The present review summarizes current aspects on how to perform noninvasive microvolt T-wave alternans (mTWA) testing in clinical practice. The focus is on methodologic issues such as patient-related, or technical aspects, and interpretation of the results. Special attention is given to the different sources of noise that may interfere with mTWA assessment. The role of beta-blocker therapy and its potential effect on mTWA is discussed as well. In the first clinical studies of mTWA, a high rate of indeterminate test results was observed. In this respect, patient-related indeterminacy has been demonstrated to be associated with an increased mortality and such tests are thus regarded as "abnormal" whereas technically inadequate tests are classified as indeterminate. Since mTWA evolves over time in patients with structural heart disease, the "optimal timing" for mTWA assessment is rather in the chronic phase than in the acute setting of heart disease. (Cardiol J 2008; 15: 288–292)

Key words: arrhythmia risk stratification, microvolt T-wave alternans, methodology

Introduction

Several studies have recently proven that primary preventive therapy of sudden arrhythmogenic death is possible in selected patients with congestive heart failure, particularly in the setting of ischemic cardiomyopathy [1, 2]. However, many clinicians agree that more accurate identification of patients at arrhythmogenic risk is warranted. Microvolt level T-wave alternans (mTWA) has recently been proposed to assess abnormalities in ventricular repolarization favoring the occurrence of reentrant arrhythmias [3, 4]. In 1994, a first clinical study [5] convincingly demonstrated that mTWA is closely related to arrhythmia induction in the electrophysiology laboratory as well as to the occurrence of spontaneous ventricular tachyarrhythmias during follow-up [5]. More recently, a number of clinical studies has examined its clinical application [6–14].

However, several methodological issues have been a matter of debate, including interpretation and potential consequences of so-called "indeterminate" test results as well as the question of repetitive re-testing of patients who may be at high risk according to their reduced ejection fraction but have a negative mTWA test.

The present review summarizes currently available clinical data on mTWA with a particular focus on how to perform the test and how to interpret its results.

Definition and pathophysiological aspects of mTWA

T-wave alternans is defined as 2:1 beat-to-beat changes in the amplitude of the T-wave. Whereas

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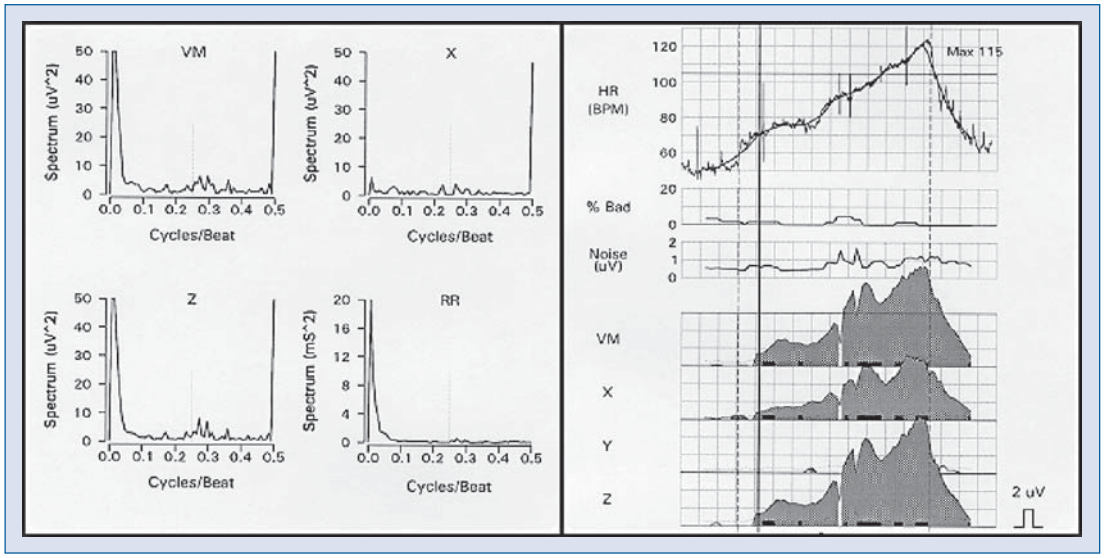

Figure 1. Alternans voltage in a patient with moderately reduced left ventricular function and a history of syncope following myocardial infarction. Note the increase of T-wave alternans voltage with increasing heart rate (HR).

visible "macroscopic" T-wave alternans (TWA) has been associated with a high risk of ventricular tachyarrhythmias in patients with the congenital long QT syndrome [15] or other clinical disorders, this phenomenon is rarely observed in clinical practice [16, 17]. With the development of new computer processing techniques, the phenomenon of *micro*-volt level TWA was first demonstrated in an experimental study by Adam, Smith and coworkers [3, 18]. Recent experimental and clinical studies have provided new insights into the genesis of this phenomenon [4, 19–21]. Briefly, with increasing heart rate, action potential duration shows discordant prolongation in different regions of the myocardium finally resulting in repolarization alternans with opposite phase between neighboring cells (so-called discordant alternans). This creates increased spatial dispersion of repolarization associated with unidirectional conduction block, reentry, and finally the occurrence of ventricular fibrillation [4]. On the cellular level, TWA is accompanied by inhomogeneities in the calcium transient indicating that Ca^{2+} ions play a key role in the genesis of TWA [22–24].

Methodology of mTWA

The spectral methodology of mTWA analysis involves a graded increase of heart rate in order to provoke this electrophysiological phenomenon. In general, heart rate elevation is performed using bicycle or treadmill exercise. Some investigators have performed mTWA assessment using infusion of positive chronotropic agents or cardiac (atrial) pacing [25, 26]. In detail, during increasing heart rate, sequential ECG cycles are aligned to their QRS complex and the amplitude of the T waves at a predefined point *t* are measured. Subsequently this beat-to-beat series of amplitude fluctuations — devided in 128-beat segments —– are subjected to spectral analysis using fast Fourrier transformation. Using different time points of the T-wave, multiple spectra are generated and then averaged to a composite spectrum. The alternans voltage (unit: μV) represents the square root of the alternans power, and represents the voltage difference between the overall mean beat and the even (or odd) numbered mean beats. The alternans ratio (K score) is a measure of the significance of alternans and is calculated as the ratio of alternans power divided by the standard deviation of the noise [27]. TWA manifests itself as a pronounced peak which is visible in the power spectrum at 0.5 cycles/beat. The greater the power, the higher is the alternans voltage. An alternans voltage exceeding 1.9 μV with the alternans ratio K (indicator of the significance of the measurement) being ≥ 3 min is defined significant. To be defined as positive, alternans has to be sustained for ≥ 2 min. A typical example for a positive mTWA test is depicted in Figure 1.

Preparation for "successful" mTWA assessment

The quality of the data collected is pivotal in the precise and correct interpretation of the test results. Specialized electrodes have, therefore, been

developed that are devided in multiple segments for recording of ECG signals as well as measurement of impedance and respiratory activity (Microvolt Alternans Sensors™, Cambridge Heart Inc., Bedford, MA, USA). Through an adaptive averaging method, noise can be cancelled and a composite low-noise ECG signal is produced. In addition, careful skin preparation prior to electrode placement has been shown to significantly reduce artifact noise levels by decreasing electric impedance; this preparation includes shaving hair and slight skin abrasion resulting in reduction of skin-to-lead impedance. Further artifact reduction can be obtained by placing the arm electrodes away from the pectoral muscles with the patients loosely resting their arms instead of "cramping" to the hand grips. Careful attention should be given to the exercise protocol: the increase in heart rate should be slow, particularly in the heart rate window between 90 and 110 bpm — which should last 3–5 min in order to have 2 min with the heart rate between 105 and 110 [27, 28].

Classification of mTWA test results

The classification of mTWA is based on its magnitude, its relationship to heart rate, the alternans ratio, and assessment of potential artifacts. Based on these measures, the test is classified as positive (= pathological), negative (= normal) or indeterminate; the latter means that the test cannot be classified as positive or negative for several potential reasons: (1) there is alternans, but it is not sustained, (2) noise levels are too high and may obscure the mTWA result, (3) there are too many "bad beats". Bad beats are defined as either premature beats (> 10%), or beats with a different morphology (correlation < 0.9) compared to normal template QRS complexes. To better classify the mTWA test, different rules have been developed which are based on the different criteria mentioned above [28]. The so-called B-rules have recently been used as the standard classification system by most investigators (Fig. 2).

Potential problems in classifying mTWA

There are some situations, in which determination of mTWA may be challenging. These include: rapid changes in heart rate leading to artifactual alternans; RR interval alternans; ECG lead malfunction; too rapid increase in heart rate during exercise; respiration; pedaling artifacts; noise from musculature; excessive number of ectopic beats. All of these can result in artifacts and produce "artifactual alternans" which may be depicted in the trend report as sustained alternans. A case collection of different mTWA recordings including those with different sources of noise/artifacts is presented in an excellent paper by Bloomfield et al. [28].

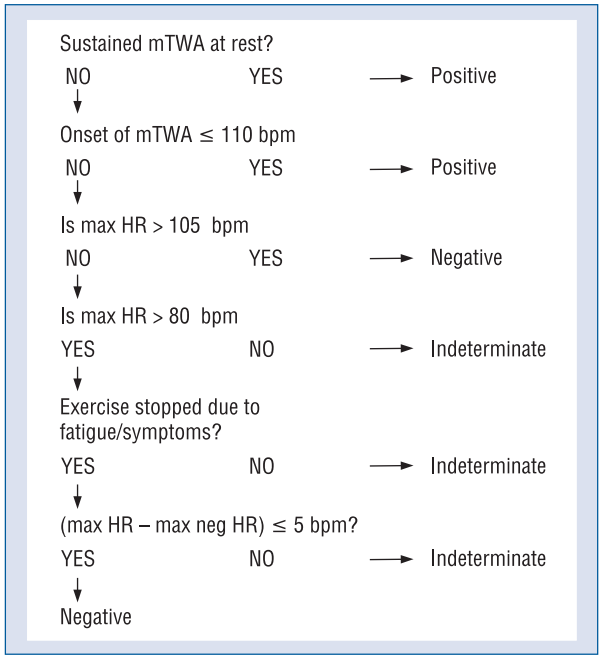

Figure 2. Classification rules of microvolt T-wave alternans (mTWA); HR — heart rate (modified from [12])

The "indeterminate" mTWA test result

In the first clinical studies the rate of indeterminate (i.e. not positive and not negative) test results averaged about 25%. It also has been demonstrated that depending on the cause of indeterminacy, the test may have a prognostic value which has led to categorize patients with positive and indeterminate tests as "non-negative" or "abnormal", being at higher risk than mTWA-negative patients ("normal" test result) [29]. The reason for classifying a test as indeterminate is, however, of importance. Whereas an increased number of ventricular premature beats as well as inability to achieve the target heart rate (also referred to as "incomplete" test) may be a harbinger of worse outcome and therefore puts a patient in a higher risk category [28–30], the occurrence of (muscle) artifacts or electrode noise — referred to as "technically indeterminate" has no prognostic value *per se*. It has thus recently been proposed that in case of an indeterminate result the test should be repeated immediately, since a significant proportion of patients will have a classifiable test; such a protocol has been applied in the ABCD and MASTER-I trials [31, 32].

Medication, bundle branch block, and mTWA

The influence of certain conditions such as antiarrhythmic/antiadrenergic medication or intraventricular conduction delay on mTWA have been and remain a matter of debate. In fact, some studies have demonstrated the effect of autonomic tone on mTWA [33–35]. It could be demonstrated that alternans voltage amplitude is reduced following IV administration of metoprolol or sotalol [35] — this is primarily due to the attenuated heart rate increase during exercise. However, in most cases a positive test will not become negative. In several studies, beta-blockers were not withheld prior to mTWA testing and in these studies mTWA was predictive of ventricular tachyarrhythmic events. It is not known at present whether a decrease in mTWA voltage translates into a better clinical outcome with respect to endpoint events. However, since risk stratification should be performed in the patients "clinical reality", i.e. on full protective medication, the authors propose to perform mTWA testing on beta-blockers. Another methodologic controversy relates to the effect of bundle branch block on mTWA [36, 37]. A recently published prospective study in 386 patients with ischemic cardiomyopathy and non-sustained ventricular tachycardia demonstrated that patients with bundle branch block are at high risk irrespective of mTWA results. However, mTWA was highly predictive of arrhythmic events in patients with a narrow QRS complex [37].

Is there optimal timing of mTWA assessment?

In several studies of patients with chronic heart diseases and left ventricular dysfunction or chronic heart failure — both of ischemic and non-ischemic origin — mTWA has been shown to be of high predictive value with respect to arrhythmic events or mortality. In contrast, there are several studies in the early (7 days to 3 weeks) post myocardial infarction period, that consistently showed (1) a high rate of indeterminate test results, and (2) that mTWA did not yield significant predictive power [38]. From the data of one well controlled pilot study of serial mTWA measurements in post-myocardial infarction patients [39] it can be postulated that the arrhythmogenic substrate evolves over time and thus the optimal time frame for mTWA testing may be something like 3–6 months after an acute myocardial infarction. But even then, a substantial proportion of patients who initially will test mTWA negative may turn to a positive test result later during the course of their disease. Although there are currently no prospective data to support this, is seems prudent to assess mTWA in high-risk patients on a regular (e.g. 6-monthly) basis. Further studies are needed in order to define the optimal timing and the usefulness of repetitive mTWA testing after myocardial infarction as well as in patients with depressed left ventricular function.

Future of mTWA — new methods

The alternative to exercise-induced spectral mTWA is the modified moving average (MMA) analysis [40]. This is a Holter-based method using a time-domain analytic approach. Basically, MMA is based on averaging odd and even beats and constructing a T-wave template for each group which are then compared for TWA. The MMA method has first been used in different smaller patient populations and recently in two large cohort studies and seems to provide similar predictive value as compared to the spectral method [41, 42]. In the recently published REFINE study both methods have been compared in 322 post myocardial infarction patients. With respect to the primary endpoint of cardiac death or resuscitated cardiac arrest, both methods yielded similar predictive value; in combination with an autonomic marker (either heart rate turbulence or baroreflex sensitivity) the hazard ratio for an endpoint event increased significantly [42]. The Holter-based MMA method offers the potential of mTWA assessment independently from an exercise test; however, since there is only modest correlation between the two methods, further studies are warranted to compare both approaches with regard to pathophysiological as well as methodological issues and to clarify their role in screening patients with respect to prophylactic therapy with implantable cardioverter-defibrillators.

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