T wave alternans for ventricular arrhythmia risk stratification

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Identifying patients at high risk of sudden cardiac death is an important goal, given the magnitude of this problem. In this regard, T wave alternans (TWA) is a heart-rate–dependent measure of arrhythmia vulnerability. The predictive accuracy of this test is maximal at heart rates between 100 and 120 bpm, which are usually achieved with exercise or atrial pacing. TWA has been shown to predict inducibility of ventricular tachycardia with programmed stimulation and to predict spontaneous arrhythmic events. This test has been applied to diverse populations, including patients with coronary artery disease, nonischemic cardiomyopathy, congestive heart failure, and status post implantable defibrillators. Despite these encouraging results, the role of TWA to guide clinical therapy still must be better elucidated. Curr Opin Cardiol 2002, 17:1–5

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Current Opinion in Cardiology 2002, 17:1–5

Abbreviations

EF	ejection fraction
EPS	electrophysiologic study
FFT	fast Fourier transformation
ICD	implantable cardioverter defibrillator
SAECG	signal averaged electrocardiogram
SCD	sudden cardiac death
TWA	T wave alternans
VT	ventricular tachycardia

ISSN 0268–4705

Sudden cardiac death (SCD) is one of the leading causes of mortality, claiming approximately 350,000 lives annually in the US. Several classes of medications, including beta blockers, ACE inhibitors, aspirin, and statins reduce cardiac mortality either directly or indirectly. Unfortunately, antiarrhythmic drugs have been disappointing as primary or secondary prevention of SCD. In contrast, the implantable defibrillator (ICD) is now primary therapy for preventing SCD. However, most SCD victims have not experienced a preceding symptomatic arrhythmic event. Accordingly, accurate arrhythmia risk stratification is needed to justify this expensive and invasive prophylactic therapy. In this regard, electrophysiology studies (EPS) using programmed ventricular stimulation identify a cohort with ischemic heart disease, left ventricular systolic dysfunction and ambient arrhythmia or syncope who benefit from ICDs. Unfortunately, these studies are costly, invasive and imperfect, so further less-invasive risk stratification is needed [1].

Several noninvasive markers have been studied and compared with EPS. Left ventricular ejection fraction (EF), spontaneous nonsustained ventricular tachycardia, measures of heart rate variability, baroreflex responses, and signal-averaged electrocardiography (SAECG) have been used alone or in different combinations to identify high-risk patients after a myocardial infarction. None of these techniques have become standard in clinical practice because of low positive predictive values. In patients with nonischemic cardiomyopathy, risk stratification is even more problematic. More recently, attention has been directed toward measures of repolarization to identify high-risk cohorts for SCD.

Historical background

TWA was first described in 1909; it is the variation in vector and amplitude of the T wave that occurs on an alternating beat basis [2]. In a review by Kalter in 1948, 46 patients were identified with macroscopic TWA, and they had a 60% mortality at 24 hours [3]. Several clinical syndromes have been identified in which TWA is associated with arrhythmia vulnerability, such as in Long QT Syndrome [4,5], ischemia and vasospastic angina [6,7], marked electrolyte abnormalites [8], and hypertrophic cardiomyopathy [9]. More recently, techniques were developed to measure more subtle microscopic TWA, which is undergoing extensive evaluation.

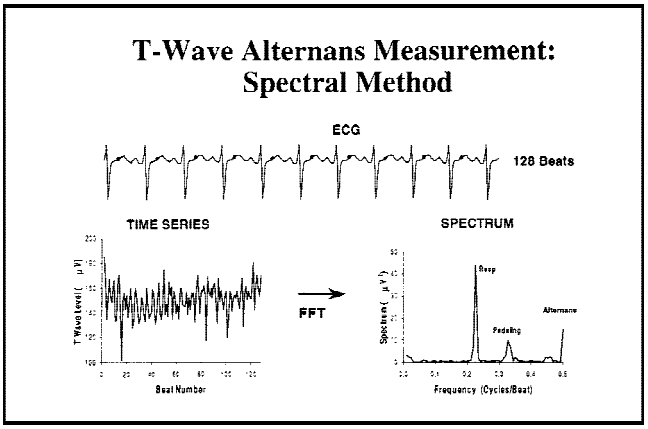
Pathophysiology

Optical mapping studies of isolated perfused hearts have shown that TWA is caused by localized alternation in action potential duration. This in turn leads to spatial dispersion of repolarization. Above a critical heart rate threshold, the repolarization of the membrane of adjacent tissue may alternate in opposite phase (discordant alternans) creating large spatial gradients in repolarization and TWA. Under these conditions, the depolarizing wavefronts become fractionated, allowing for the development of ventricular reentrant arrhythmias [10]. At the cellular level, there is increasing evidence that electrical alternans may be linked to alterations in cellular calcium control.

Technique

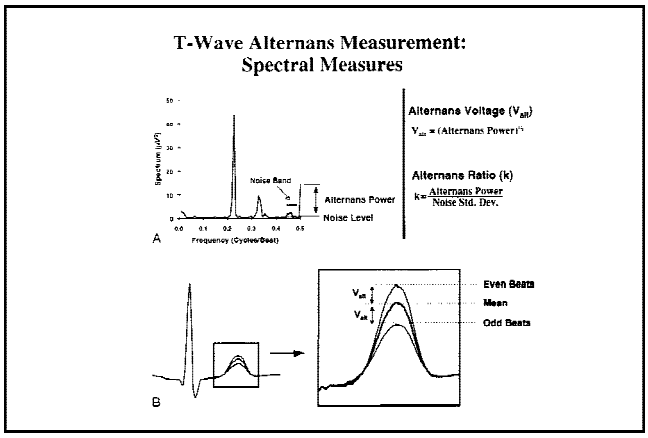
Detection of beat-to-beat microvolt fluctuation of the T wave has been made possible with the use of advanced signal processing techniques and high-resolution electrodes to reduce ambient noise. A large number of beats, generally 128, are sampled and the voltage of multiple corresponding points on the T waves is computed and averaged. Through fast Fourier transformation (FFT), these consecutive amplitudes are displayed spectrally, yielding several frequency peaks (Fig. 1). These peaks correspond to respiratory variation, pedaling (if bicycle exercise is performed), and noise. The peak at 0.5 beats is due to TWA if present [11]. The alternans magnitude, Valt, represents the difference between the even or odd beat and the mean amplitude, in microvolts (Fig. 2). A conventional threshold of 1.9 uV is used for significance. The alternans ratio (k) is another parameter measured and represents the ratio of the alternans amplitude to the standard deviation of the background noise. It is required to be greater than 3 for significance. Finally, to be significant, TWA must be sustained for more than one minute.

Figure 1. Spectral method for assessment of T wave alternans



A time series of 128 amplitudes of corresponding points on the T wave are processed by Fast Fourier Transformation to yield the spectral display with the various peaks. Reprinted with permission [18].

Figure 2. Derivation of the alternans voltage (V alt) and the alternans ratio (k) from the spectral display of T wave alternans



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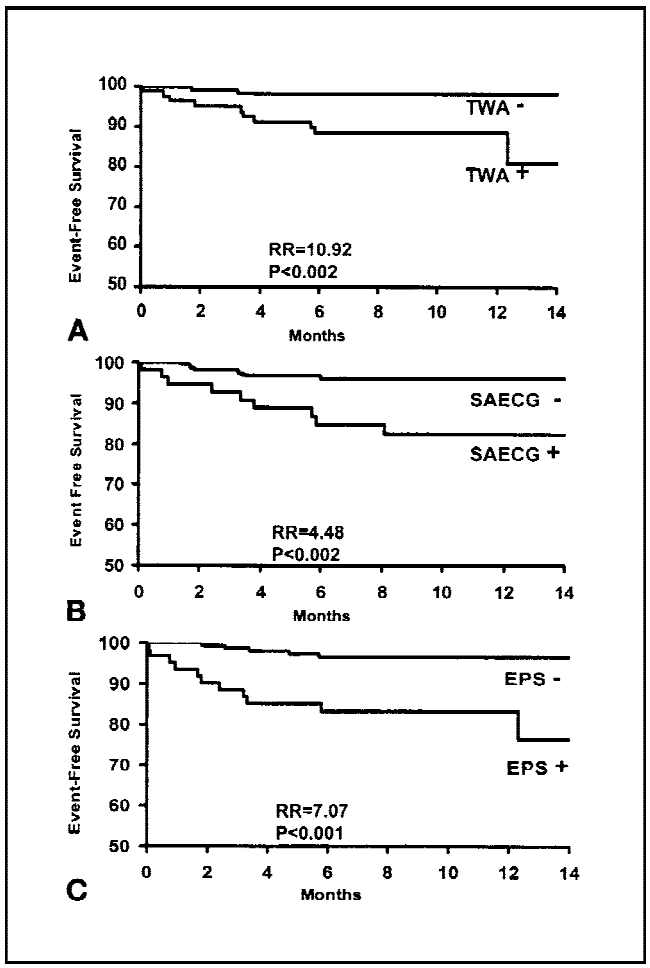
TWA is highly rate dependent, with even low-risk populations developing significant alternans at elevated heart rates. It has been shown that the onset heart rate is lower in patients with structural heart disease and history of sustained ventricular arrhythmia than in patients with no structural disease or arrhythmia history [12]. In a study of 200 patients, 42% of whom had organic heart disease and 15% had history of sustained VT, patients with both of these criteria had a lower onset heart rate of TWA than the other groups [12]. Kavesh *et al.* [13] showed that TWA increases and false positive results increase with heart rate. An onset heart rate less than 110 beats per minute is a conventional requisite for positivity.

The initial studies of TWA were performed with atrial pacing. Testing with exercise, either bicycle or treadmill, is now possible with the use of high-resolution electrodes and advanced noise reduction algorithms. A small study of 30 patients with a history of ventricular tachyarrhythmias reported a concordance rate for TWA of 84% between pacing and exercise, suggesting that heart rate and not autonomic changes are the main determinant of the onset of TWA [14]. However, we have shown a marked decrease in TWA with acute beta blockade independent of paced heart rate. In this study of patients with inducible VT, beta blockade was achieved with intravenous esmolol [15]. We postulate that this effect may be one of the mechanisms for the beneficial effect of beta blockers in reducing arrhythmias and sudden death. On the other hand, atropine does not affect TWA measurements [16].

Further technical considerations for the interpretation of tests include the presence of less than 10% ectopic beats during the recording, low noise level, and the absence of other artifactual alternans such as that caused by pedaling or respiration. Approximately 20 to 25% of studies performed are indeterminate secondary to the previously

Figure 3. Comparison of TWA, SAECG, and EPS



A comparison of (**A**) TWA, (**B**) SAECG, and (**C**) EPS to predict arrhythmic events in patients referred for electrophysiology study. Kaplan-Meier event curves are shown for each test. Reprinted with permission [18].

mentioned criteria or because of failure to achieve target heart rate. Patients with atrial fibrillation are excluded because of variability of repolarization due to fluctuating RR intervals.

Clinical applications

The first large clinical study of TWA was performed by Rosenbaum and colleagues [17•], who observed 83 patients undergoing both EPS and TWA measured during atrial pacing. Over a 20- month follow-up period, ventricular tachyarrhythmic events occurred in 81% of TWA positive patients, compared with only 6% of those who were negative (RR 5.2, $P < 0.001$). TWA was equivalent to EPS as a predictor of events, with almost superimposable survival curves.

More recently, Gold *et al.* [18••] reported on a multicenter study of TWA measured noninvasively with bicycle exercise testing in 313 patients referred for EPS. Structural heart disease was present in 70% of subjects including 34% of with congestive heart failure. However, 31% of patients presented for EPS with supraventricular arrhythmias. SAECG was also measured at the time of TWA and before EPS, and patients were observed clinically for 297+ days [18••]. The predictive value of TWA and EPS for arrhythmic events was comparable (relative risks 10.9 *vs* 7.1, *P*s = 0.01), and better than SAECG (Fig. 3). Cox regression analysis revealed that TWA was the only significant independent predictor of events in this heterogeneous population. Combining TWA and SAECG results appeared to enhance the value of noninvasive testing to predict the results of EPS as well as spontaneous arrhythmias.

Several other studies evaluated TWA in more homogeneous, high-risk populations as described below.

Post MI

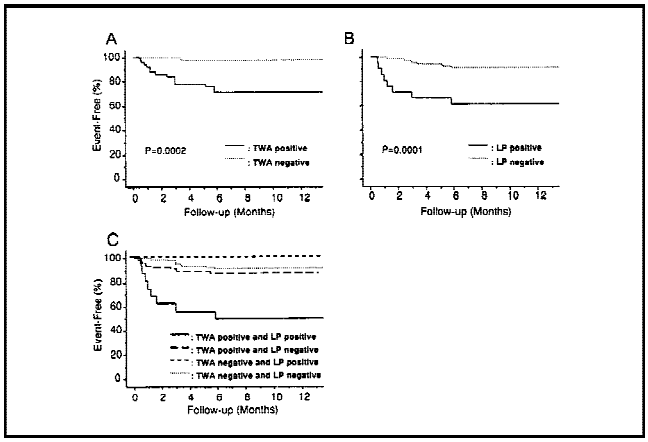
Ikeda and colleagues studied 102 patients post MI who underwent testing for TWA, SAECG, and measurement of EF [19]. In this population, TWA showed the highest individual relative risk for arrhythmic events (16.8 *vs* 5.7 and 4.7 for SAECG and low EF respectively, *P*s < 0.05) (Fig. 4). With multivariate analysis, however, the combination of TWA and SAECG yielded the most significant predictor (RR 19.9, CI 3.2–125.3). Interestingly, Gold and colleagues also noted a potential enhanced diagnostic value of combining TWA and SAECG results.

Left-ventricular dysfunction

Klingenheben *et al.* [20] studied 107 patients with a mean EF of 28 ± 7% and no prior sustained ventricular arrhythmia. During 18 months of follow-up review, all events occurred in the TWA positive group, rendering TWA a highly significant predictor of ventricular tachyarrhythmias.

In a study of nonischemic cardiomyopathy, a syndrome in which EPS is generally not regarded as useful for

Figure 4. Kaplan-Meier event curves for TWA and SAECG



Kaplan-Meier event curves for TWA and SAECG separately or in combination after acute myocardial infarction. Reprinted with permission [19].

arrhythmic risk stratification, TWA also correlated well with the occurrence of ventricular arrhythmias [21].

Our lab is observing patients with ischemic cardiomyopathy who underwent EPS and TWA for the endpoints of sustained VT, cardiac arrest, appropriate ICD therapy, or death. We have shown that TWA is a strong independent predictor of arrhythmia vulnerability in this high-risk population [22].

Post ICD

The role of TWA to predict ICD discharges has also been evaluated. TWA, EPS, EF, baroreflex sensitivity, SAECG, ambient arrhythmias, and QT dispersion were all measured in 95 high-risk patients in this study [23]. TWA was found to be the only significant predictor of appropriate ICD therapy with multivariate analysis, whereas EPS failed to achieve statistical significance (Fig. 5).

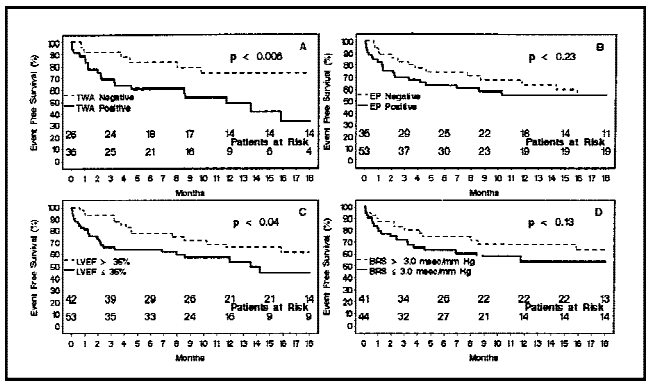
Limitations

Exercise testing, by bicycle or treadmill, while allowing TWA to be used noninvasively, has introduced certain limitations. Attention to cycling rate to avoid contamination of the alternate beat spectral analysis is mandatory. In our experience exercise testing is associated with increased noise, which can confound data interpretation. In addition, some patients are unable to reach appropriate heart rates with exercise due to chronotropic incompetence, deconditioning, or concomitant drug therapy.

Conclusion and future directions

TWA is a promising new technique for arrhythmic risk stratification. Despite the encouraging results noted previously, the role of this test in clinical management remains to be defined. All clinical studies have been observational and the outcomes of groups treated based on TWA have not been evaluated. Better definition of the clinical role of this test will be achieved with the results of the ongoing ABCD trial (Alternans Before Cardioverter Defibrillator), in which patients with ischemic cardiomyopathy will undergo ICD implantation if they have abnormal EPS or TWA results. Further improvement in technique should increase the rate of determinate results. Finally, the current conventional thresholds for positivity should be reassessed and validated in prospective trials, possibly with the use of population specific criteria, to maximize the predictive value of this test. Hopefully, with a better understanding of the factors influencing changes of repolarization and the results of prospective outcome studies, TWA can be used as part of strategies to reduce SCD.

Figure 5. Predictors of appropriate shocks in high-risk population of ICD recipients



Kaplan-Meier event curves are shown for (**A**) TWA, (**B**) EPS, (**C**) left-ventricular EF, and (**D**) baroreceptor sensitivity. Reprinted with permission [14].

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