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STATE-OF-THE-ART PAPER

Pathophysiological Basis and Clinical Application of T-Wave Alternans

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We review the contemporary understanding of the pathophysiology of repolarization alternans and present a perspective on the use of T-wave alternans (TWA) as a risk stratification marker of malignant ventricular arrhythmias. Several studies have demonstrated a high correlation of susceptibility to ventricular arrhythmias and sudden cardiac death with the existence of TWA. We describe a number of cellular and molecular alterations in the diseased heart that may provide a link between electrical and mechanical alternans and arrhythmia susceptibility. Repolarization alternans is likely the result of distinct and diverse cellular and molecular alterations that are associated with exaggerated regional repolarization heterogeneity, which renders the heart susceptible to malignant arrhythmias. (J Am Coll Cardiol 2002;40:207–17) © 2002 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) remains a major challenge in developed countries; it accounts for 11% of all deaths and approximately 50% of all cardiovascular deaths (1). In the U.S. alone, nearly 300,000 patients (1 to 2 per 1,000 population) experience SCD (2). The vast majority of these cases are due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Over the past two decades, tremendous progress has been made in the development of therapeutic modalities, such as the implantable cardioverter-defibrillator (ICD); however, similar progress in identifying patients at high risk has lagged behind. Large multicenter studies, such as the Multicenter Automatic Defibrillator Implantation Trial and the Multicenter Unsustained Tachycardia Trial (MUSTT), suggested that electrophysiologic (EPS) testing may be useful in identifying patients who would benefit from ICD therapy (3,4). The MUSTT suggested that EPS testing alone was not sensitive enough to identify broader groups of patients at risk for SCD (4). Moreover, noninvasive markers of risk-stratification, such as left ventricular ejection fraction (LVEF), frequent ventricular premature complexes and ventricular late potentials (LP), though sensitive, suffer from low specificity and positive predictive value (5,6). Determination of heart rate variability (HRV), especially in combination with LVEF, ventricular premature complexes and LP, has significantly improved risk prediction, but its positive predictive accuracy remains low (6).

The preceding discussion underscores the need for a screening procedure that is more sensitive and specific, with a higher predictive power for identifying patients at high risk of developing VT/VF. Recently, assessment of repolarization alternans (T-wave alternans [TWA]) in the electrocardiogram (ECG) has been suggested as a predictor of susceptibility to malignant ventricular arrhythmias (7–9). The TWA is characterized by changes in contour, amplitude or polarity of the T-wave, appearing with regular rhythmicity, usually every other beat, unaccompanied by gross changes in the cycle length.

This review discusses what is known about the cellular basis of cardiac (electrical and mechanical) alternans and the clinical relevance of repolarization alternans, with special reference to its prognostic efficacy in predicting arrhythmia susceptibility.

HISTORY OF CARDIAC ALTERNANS

Cardiac alternans has been divided into two general categories: electrical and mechanical; *electrical alternans* arises from a fundamental change in the electrical conduction pattern of the myocardium, and *mechanical alternans* arises from an alternation of the mechanical activity of the heart. Electrical alternans is a pattern of variation in the shape of ECG waveform that appears on an every-other-beat basis (10–21). Electrocardiographic alternans was first described in 1908 by Hering (10). Shortly thereafter, Thomas Lewis (11) recognized that cardiac alternans could occur in normal hearts as a result of marked acceleration of heart rate and also in the impaired or intoxicated myocardium. In 1948, Kalter and Schwartz (12) reviewed clinical ECGs from 6,059 patients and found five cases of macroscopically visible TWA, a frequency of 0.08%. Probably because of the very low incidence of visible TWA, it remained nothing more than an ECG curiosity for many decades.

In humans, visible (macroscopic) alternation in ventricular repolarization has been associated with increased vulnerability to ventricular arrhythmias under diverse pathophysiologic conditions (both experimental and clinical) such as

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Abbreviations and Acronyms

AP	= action potential
APD	= action potential duration
DCM	= dilated cardiomyopathy
ECG	= electrocardiogram
EPS	= electrophysiologic
FFT	= fast Fourier Transform
HCM	= hypertrophic cardiomyopathy
HRV	= heart rate variability
ICD	= implantable cardioverter-defibrillator
k	= alternans ratio
LP	= late potentials
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
MUSTT	= Multicenter Unsustained Tachycardia Trial
NSVT	= nonsustained ventricular tachycardia
RR	= relative risk
SAECG	= signal-averaged electrocardiography
SCD	= sudden cardiac death
SR	= sarcoplasmic reticulum
TWA	= T-wave alternans
V_{alt}	= alternans magnitude
VF	= ventricular fibrillation
VT	= ventricular tachycardia

myocardial ischemia (13–20), Prinzmetal's angina (21,22), states of altered autonomic tone (15,16,23,24), electrolyte abnormalities (22,25) and the long QT syndrome (26–28).

Microscopic TWA was first reported in 1982 (29). Subsequently, various studies have led to the development of the fast Fourier Transform (FFT) spectral method to detect microvolt-level TWA and the establishment of a relationship between TWA and VF threshold in animal studies and susceptibility to ventricular arrhythmias in humans undergoing EPS testing (30–32).

PATHOPHYSIOLOGY OF CARDIAC ALTERNANS

Ionic currents, calcium homeostasis and alternans. Several lines of evidence suggest that electromechanical alternans is linked to alterations in cellular Ca^{2+} homeostasis (33). Calcium homeostasis is not only important for excitation-contraction coupling but it also significantly influences the action potential (AP) profile and duration (APD). Excitation leads to the opening of voltage-gated L-type Ca^{2+} channels, allowing the entry of a small amount of Ca^{2+} into the cell. The small amount of Ca^{2+} that enters the cell through the L-type Ca^{2+} channel triggers a larger release of Ca^{2+} from the sarcoplasmic reticulum (SR) via Ca^{2+} release channels or ryanodine receptors (so-called calcium-induced calcium release), activating the myofilaments and leading to contraction. During relaxation, Ca^{2+} is sequestered in the SR by the SR Ca^{2+} adenosine triphosphatase and extruded from the cell by the sodium calcium exchanger. The change in intracellular Ca^{2+} during the cardiac cycle or calcium transient has direct and indirect effects on a number of ionic currents in ventricular myocytes, and therefore on the APD and profile. In addition to the profound effects on myocyte repolarization, intracellular Ca^{2+} influences cell-to-cell coupling and, thus, conduction of electrical impulses in the heart.

Altered electrophysiology of the heart or electrical remodeling is a recurring feature of myocardial failure, which has been associated with an increased risk of arrhythmic death (34). Furthermore, both electrical and mechanical alternans are easier to elicit by rapid pacing in animals with heart failure (35,36). This arrhythmogenic substrate is the result of a change in the functional expression of proteins responsible for repolarizing currents and Ca^{2+} homeostasis in the failing heart.

Both a concordant and discordant relationship between alternation of the calcium transient (and strength of contraction) and APD has been observed (37). Although the precise cellular mechanism of alternans either concordant or discordant is not established, it has been suggested that altered restitution of the calcium transient, a multistep process involving Ca^{2+} uptake into the SR, redistribution in the SR and release through the ryanodine receptor, may underlie alternans. Furthermore, an indication that electrical and mechanical alternans are mechanistically linked was provided by Orchard et al. (38), who observed mechanical alternans in voltage-clamped isolated myocytes, suggesting that AP alternans was rather due to calcium-transient alternans and not vice versa.

The profound cellular metabolic disturbances in ischemic hearts almost certainly play a role in the induction of mechanical and electrical alternans. In support of a theory that links the occurrence of cardiac alternans to decreased energy availability in the ischemic cell, Hüser et al. (39) suggest that the occurrence of alternans may be associated with the inhibition of adenosine triphosphate (ATP) production, thus affecting excitation-contraction coupling, perhaps on an every-other-beat basis.

Potassium channels may also play an important role in ischemia-induced TWA. The different spatial (epicardial vs. endocardial) sensitivity of K_{ATP} channel activation during ischemia (40) may be linked to repolarization alternans at the cellular level during regional ischemia (41–43). In a porcine model, acute ischemia shortened the APD and decreased the AP amplitude, velocity of depolarization and resting membrane potential. Alternans of AP amplitude was associated with alternation of ST segment, and alternans of upstroke velocity of the AP was associated with alternating QRS morphology (42).

Connexins are integral membrane ion channel proteins that govern cell-to-cell communication and conduction. Cellular uncoupling in hypoxia and ischemia has been shown to occur concomitantly with the onset of ischemic contracture (44), an increase in free cytoplasmic Ca^{2+} (44,45), rapid depletion of ATP (46) and acidification (47). This indicates that both depressed excitability and cellular uncoupling are likely to be inhomogeneous within an ischemic region and may contribute inhomogeneous impulse propagation, leading to excitation of alternating pop-

Table 1. Electrophysiologic Definitions

APD: time to 90% repolarization of the action potential
APD restitution: APD dependence on previous diastolic interval
Wave: cardiac excitation is viewed as an electrical wave
Wavefront: corresponds to the action potential upstroke (phase 0)
Waveback: corresponds to rapid repolarization (phase 3)
Wavelength: the distance between the wavefront and the waveback
Wavebreak: the break of single waves of electrical activity into multiple smaller waves
Concordant alternans: wavelengths of successive waves that alternate between long and short
Discordant alternans: two spatially discrete sites exhibiting APD alternans at opposite phases (Ref. 19)

APD = action potential duration.

ulations of cells or to alternation in the response to activation of individual cells. In support of this hypothesis, Pastore and Rosenbaum (48) have shown that electrotonic uncoupling of cells promotes the development of discordant alternans (for definition see Table 1), which in turn promotes marked gradients of repolarization and a substrate for functional re-entry.

In the failing human heart a decrease in the beta-adrenergic, activation-mediated protein phosphorylation of contractile proteins has been observed (49,50). A logical extension of such a case is the development of mechanical alternans. For example, reduced phosphorylation of cardiac troponin I, which leads to an increased affinity of troponin C for Ca^{2+} and thus an increased Ca^{2+} sensitivity of force development, could represent a link between the cytoplasmic Ca^{2+} (calcium transient) and mechanical alternans in the cardiac myocyte (51).

Repolarization alternans and arrhythmogenesis. Whether TWA is solely an effect or a cause linked to arrhythmogenesis has been an intriguing question. In both animal experiments and computer simulations (29,32) the presence of TWA is consistently associated with an increased susceptibility to VT/VF; thus, it has been hypothesized that, in addition to being a marker of vulnerability to ventricular tachyarrhythmias, TWA per se might be arrhythmogenic.

Suggested mechanisms of electrical alternans include excitation of alternating populations of cells in sequential beats (52), alternation of the AP waveform (53) and global movement of the heart within the chest (54). The proposed mechanisms of mechanical alternans include alternation of the loading of the heart (55), alternation in the contractile state of the heart through alternation in the number of cells involved in systole (56), or alternation in the strength of contraction of each cell (51).

Currently, there are two prevailing and closely linked hypotheses regarding the arrhythmogenic mechanisms associated with TWA. One is based on the concept that prolongation of repolarization favors re-entry when the prolongation is heterogeneous and dispersion of refractoriness is significantly enhanced (57). This dispersion-of-refractoriness hypothesis states that intrinsic dispersion of ventricular refractoriness prevents myocytes with the longest recovery times from depolarizing, or from depolarizing completely, every other cycle, resulting in a 2:1 behavior on the surface ECG. As a consequence, the resulting inhomogeneity in dispersion of recovery may lead to myocardial areas exhibiting prolonged recovery providing evanescent barriers to conduction (i.e., unidirectional block), which facilitate wavefront fractionation and reentry. Indeed, computer simulations using finite-element models have shown that with sufficient intrinsic dispersion of refractoriness some areas of the myocardium depolarize only partially every other beat (58), leading to repolarization alternans in the simulated surface ECG. Experimental support for this hypothesis is provided in ischemia models in which ECG alternans during regional ischemia was generated by alternating conduction block into the ischemic zone. In hypertrophic cardiomyopathy, which constitutes another form of structural heart disease, myocardial fiber disarray alone—which decreases cell-to-cell coupling and increases intraventricular conduction abnormalities—could lead to exaggerated dispersion of refractoriness and of conduction properties that could facilitate the occurrence of TWA and thus become a potential arrhythmogenic mechanism (59).

The second hypothesis suggests that AP alternans is the primary event in a series of events mechanistically linked to arrhythmogenesis (19,60). Recently, this hypothesis was further supported in a study by Pastore et al. (61) in Langendorff-perfused guinea pig hearts; they were able to show that increasing the pacing rate in the guinea pig ventricle consistently induced concordant repolarization alternans at a critical threshold heart rate, which led to the development of discordant epicardial APD alternans and to increased susceptibility to ventricular arrhythmias.

Though APD alternans may be the result of a wide variety of cellular conditions (see section titled "Ionic currents, calcium homeostasis and alternans"), at the whole-heart level changes in the relationship between the APD and the preceding diastolic interval (the restitution curve) affect AP alternans. The mechanism by which APD alternans could produce arrhythmias was clarified by Karma in 1993, (62) who showed that an APD restitution curve with slope greater than 1 could produce wave-break (for definition, see Table 1) in spiral wave re-entry. By reducing APD restitution steepness, in computer simulations Karma (62) and Weiss et al. (63) showed that spiral wave breakup can be prevented, and spiral wave behavior can be stabilized.

The mechanisms underlying induction of discordant alternans in the heart are unknown; however, it has been hypothesized that discordant alternans develops in structurally normal myocardium where large heterogeneities in cellular repolarization properties exist or in myocardium with a structural barrier that causes cell-to-cell uncoupling where minor heterogeneities exist (48). Discordant alternans markedly increases dispersion of refractoriness and increases the ability of a premature stimulus to cause localized wavebreak and induce reentry, even in completely

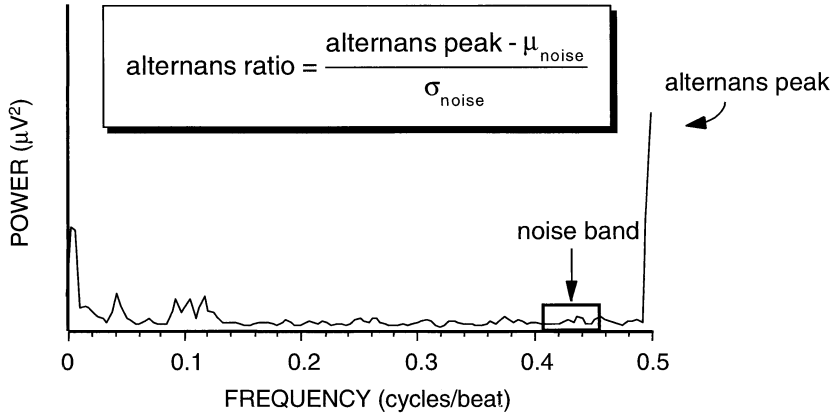

Figure 1. Representative example of power spectrum of beat-to-beat fluctuations in T-wave morphology. The alternans ratio is the amplitude of the spectrum at the alternans frequency (alternans peak) minus the mean background noise level (noise), divided by the standard deviation of the noise (noise) in the reference noise band plots. Reproduced with permission from Armoundas et al. (99).

homogeneous tissue. Furthermore, it is logical to speculate that factors known to modulate repolarization, such as transient ischemia (19,64), myocardial scar (32), premature ventricular depolarizations (61), or sympathetic stimulation (65), may trigger discordant alternans.

TECHNICAL ASPECTS

The FFT spectral analysis. Several algorithms have been developed to measure subtle beat-to-beat microvolt-level alternans. The most widely used procedure, termed the FFT spectral method, has been previously reported (32,66) and is briefly summarized here. It utilizes the vector magnitude ECG signal recorded from the three Frank orthogonal leads over at least 128 ECG beats. Fourier analysis is used to compute the power spectra of the beat-to-beat fluctuations in the amplitudes of corresponding sample points of the time-aligned QRST complexes. The power spectra corresponding to sample points within a given section of ECG complex (e.g., T-wave) are averaged. The presence of alternans is indicated by the presence of a peak at the last point in the averaged spectrum, corresponding to a frequency of 0.5 cycles per beat (Fig. 1). The analysis yields two measurements: the alternans magnitude (V_{alt}) and the alternans ratio (k). The V_{alt} represents the magnitude of the alternating variation in T-wave morphology compared to the mean T-wave. The alternans ratio is a measure of the statistical significance of the alternans compared to the standard deviation of the background noise. One of the inherent strengths of the FFT spectral method is its ability to differentiate between true alternans and nonspecific noise in the ECG.

A commercial instrument that can quantify microscopic TWA has recently received Food and Drug Administration approval as a noninvasive screening test to identify patients at risk for SCD (8). Using this system, the criteria for the interpretation of TWA tests have been reported by Bloomfield and Cohen (8). A positive TWA test is the presence of sustained alternans with an amplitude at least 1.9 μV and k $\geq$ 3.0 measured in a single-vector lead or two adjacent precordial leads (k $\geq$ 3.0 is required in only one of the two precordial leads). Alternans should be present for at least 1 min, including some period of artifact-free data, with an onset either at the resting heart rate or at a heart rate $\leq$110 beats/min (heart rate refers to a 128-beat averaged heart rate) during exercise (by means of treadmill or stationary bike). Artifact-free data are characterized by a frequency of ectopic beats $\leq$10%, and is collected when the stepping or pedaling rate is not at one-half the heart rate, the respiratory rate is not at one-fourth the heart rate, the heart rate is not changing more rapidly than 30 beats/min, and RR interval alternans of $\geq$2 ms is not present. A TWA test is usually defined as negative if it does not meet the criteria for a positive test and a maximum negative heart rate $\geq$105 beats/min is achieved (so-called A Rules). The maximal negative heart rate is defined as the highest heart rate at which at least 1 min of data is present without significant alternans, a noise level $\leq$1.8 μV in the vector magnitude lead and with fewer than 10% ectopic beats. The test may also be negative in patients who stop exercise due to fatigue or symptoms with a maximal negative heart rate $<$105 beats/min provided that the maximal negative heart rate is within 5 beats/min of the maximum heart rate and is $>$80 beats/min (B Rules). An indeterminate TWA test is a test that does not meet the criteria for being classified as positive or negative.

The sensitivity of TWA to predict the induction of sustained ventricular tachyarrhythmias is improved, with more than the typically used orthogonal X, Y, Z leads, but this is at the expense of specificity (67).

Other methods. Besides the above-described FFT-based spectral method, several other computerized methods have been applied for detection and quantification of TWA, such as autocorrelation techniques (68), complex demodulation (14) and autoregression techniques (69). The motivation for developing these techniques is the desire to detect rapid changes in alternans such as those observed during ischemia (65). Further

Table 2. Clinical Studies on the Predictive Power of T-Wave Alternans to Sustained Ventricular Tachyarrhythmias

Study	Patient Population	End Point	Indeterminate Tests	Predictive Power
Rosenbaum et al. (66)*	EPS (n = 83)	VT/VF	NA	RR = 5.2
Estes et al. (75)*	EPS (n = 51)	VT/VF	n = 24 (47%)	A = 80%
Hohnloser et al. (76)*	CAD, DCM, HCM (n = 95)	ICD discharge	n = 16 (18%)	RR = 2.5
	CAD (n = 71)			RR = 3.9
Ikeda et al. (83)*	Post-MI (n = 119)	AE	n = 17 (14%)	A = 64% RR = 16.8
Gold et al. (78)*	EPS (n = 313)	AE	n = 75 (24%)	RR = 10.9
Klingenheben et al. (82)*	CHF (n = 107)	AE	n = 22 (21%)	RR = ∞
Adachi et al. (81)*	DCM (n = 58)	VT	n = 10 (17%)	A = 77%
Hennersdorf et al. (80)†	NICM (n = 66)	AE	n = 6 (9%)	SENS = 65% SPEC = 98%
Tapanainen et al. (84)*	Post-MI (n = 379)	ACM	n = 178 (47%)	NS
Ikeda et al. (91)*	Brugada (n = 33)	VT/VF	n = 2 (6%)	A = 52%
Ikeda et al. (85)*	Post-MI (n = 834)	AE	n = 95 (12%)	RR = 11.4
Kitamura et al. (74)*	DCM (n = 104)	AE	n = 21 (20%)	RR = 7.4

*Prospective. †Retrospective.

A = accuracy; ACM = all-cause mortality; AE = arrhythmic event; CAD = coronary artery disease; DCM = dilated cardiomyopathy; EPS = electrophysiologic study presumed for ventricular arrhythmias; HCM = hypertrophic cardiomyopathy; MI = myocardial infarction; n = number of patients; NA = not applicable; NICM = nonischemic cardiomyopathy; NS = nonsignificant; RR = relative risk; SENS = sensitivity; SPEC = specificity; VF = ventricular fibrillation; VT = ventricular tachycardia.

investigation is needed to show that these alternative methods are equivalent to the FFT spectral method.

CLINICAL RESULTS

Importance of heart rate onset. Animal experiments have demonstrated that under physiologic conditions a critically short cycle length is required for induction of AP alternans (70,71), and that the heart rate onset required to elicit discordant alternans was significantly reduced in the presence of a structural barrier (48). Similarly in humans, a number of studies indicate that the magnitude of TWA is strongly dependent on heart rate (67,72–74), with an optimal heart rate for measuring microvolt-level TWA between 100 and 120 beats/min. However, interpretation of the TWA test must also take into account the dynamic variation of heart rate with exercise. For example, alternans that occurs episodically and does bear a consistent relationship to heart rate has not been associated with increased arrhythmic risk.

It does not appear to matter whether the threshold heart rate required to induce TWA is achieved by exercise or atrial pacing. In a comparison of exercise- and pacing-induced alternans, the average pacing rate at which TWA first became positive was 99 ± 9 beats/min, whereas the average heart rate at which TWA became positive during exercise in the same patients was 100 ± 13 beats/min. This suggests that it is the heart rate per se and not autonomic nervous system tone changes that appear to be the main factor of determining the onset of TWA (73). However, Hohnloser et al. (73) showed that, in patients with sustained alternans, the amplitude of alternans was greater at peak exercise than at the corresponding heart rate during atrial pacing (exercise TWA 11.4 ± 7.3 μV, right atrial pacing TWA 5.7 ± 1.8 μV). This suggests that sympathetic activation present at peak exercise modulates and tends to increase TWA, thus potentially influencing the sensitivity of the test.

A number of studies have measured TWA in different patient populations. Interpretation of these studies is complicated by different statistical metrics used to describe the changes in risk based on the outcome of the test. These clinical studies are summarized in the following sections and in Table 2.

TWA in patients at risk of VT/VF. The first human study revealing a statistically significant relationship between the outcome of EPS testing and the presence of repolarization alternans was conducted in 1988 (32). In another study of 83 patients undergoing EPS testing, microvolt TWA was correlated with inducibility of sustained VT or VF and inversely correlated with 20-month arrhythmia-free survival (Fig. 2) (66). A shortcoming of this study (66) was the invasive method employed (right atrial pacing) for eliciting TWA; nonetheless, a positive TWA test predicted arrhythmic events with an accuracy equivalent to that of programmed ventricular stimulation.

T-wave alternans can be elicited and measured noninvasively during bicycle exercise testing (75,76). In a prospective study, Hohnloser et al. (76,77) compared various conventional markers of arrhythmic risk in 95 high-risk patients who had undergone ICD implantation. The patient cohort comprised 75% with coronary artery disease, 17% dilated cardiomyopathy, 2% hypertrophic cardiomypathy, 5% no heart disease and 1% other. The end point of this

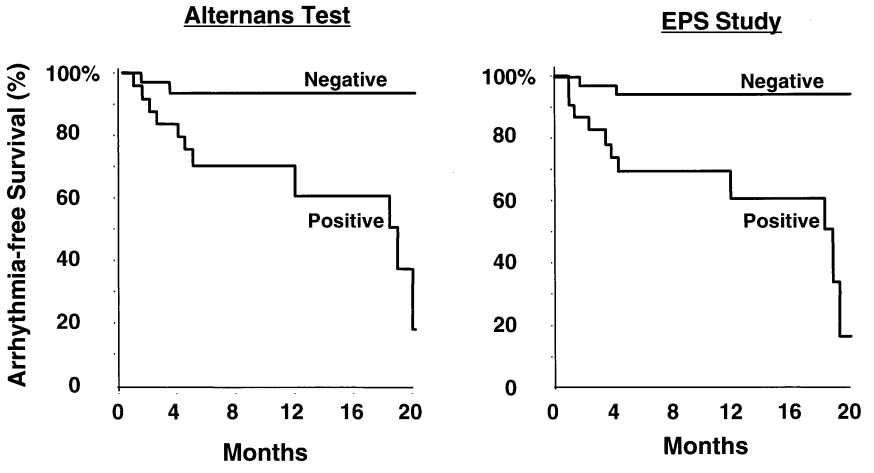

Figure 2. The relation between T-wave alternans and arrhythmia-free survival in 66 patients is shown in the **left panel**. Kaplan-Meier life table arrhythmia-free survival compared patients with and without T-wave alternans. In the **right panel**, arrhythmia-free survival in patients with a positive electrophysiologic (EPS) study is compared to survival in patients in whom ventricular arrhythmias were not induced in EPS study. Note that the predictive values of EPS study and T-wave alternans are essentially indistinguishable in these plots. Reproduced with permission from Rosenbaum et al. (66).

study (76) was the first appropriate ICD discharge documented by review of the stored electrograms. Forty-one patients (43%) had at least one documented arrhythmic event. Statistical analysis revealed that of the 10 risk markers included in the model, only a positive TWA result and a reduced LVEF were significant predictors of appropriate ICD discharges both in the entire study population and in the coronary artery disease subgroup. Notably, inducibility during EPS testing failed to achieve statistical significance in predicting appropriate ICD discharge.

In a prospective multicenter study of 313 patients, ventricular arrhythmia risk was assessed in patients undergoing EPS testing using TWA and signal-averaged electrocardiography (SAECG) (78). The indication for EP testing in this group was syncope or presyncope (41%), cardiac arrest (5%), sustained VT (14%), nonsustained ventricular tachycardia (NSVT) (4%) and supraventricular arrhythmias (31%). The primary end points of this study (78) were SCD, sustained VT, VF, appropriate ICD therapy or cardiac arrest. A composite secondary end point of any ventricular arrhythmia or all-cause mortality was also employed. Follow-up was obtained in 290 patients (92.6%) with a mean duration of 297 ± 103 days. A total of 22 patients experienced the primary end points, including 15 patients with ICDs. The relative risk for experiencing a primary end point was 10.9 for TWA, 7.1 for EPS testing and 4.5 for SAECG. In 27 patients with secondary end points, the relative risk (RR) was 13.9 for TWA, 4.7 for EPS testing and 3.3 for SAECG. Cox regression analysis revealed that TWA was the only independent statistically significant predictor of events.

However, in a study of 95 patients referred for EPS testing, the QT variability index was superior to TWA (measured during right atrial pacing), monomorphic VT inducibility at EPS study, SAECG, HRV and ejection fraction in identifying patients with prior sudden death (79). Univariate analysis reported that QT variability index was predictive of arrhythmia-free survival; however, this analysis was not reported for TWA (79).

TWA in cardiomyopathy. In a study of 60 patients with idiopathic dilated cardiomyopathy but nearly normal LVEF, 12 patients had positive TWA test (80). Ten of the 12 patients with positive TWA test had a prior ventricular tachyarrhythmia, while significantly fewer (6 of 48) TWA-negative patients experienced an arrhythmia. Three patients developed ventricular tachyarrhythmic events during a six-month follow-up period, and all had had a positive TWA test.

In a study by Adachi et al. (81) of 58 patients with dilated cardiomyopathy (DCM) (New York Heart Association functional class: 1.6 ± 0.8), TWA testing was positive in 23, negative in 25 and indeterminate in 10 patients. Analysis of a limited number of recorded ventricular arrhythmias including NSVT (≥3 consecutive premature ventricular beats, 14 episodes) or sustained VT (VT that lasted ≥ 30 s, three episodes) revealed that ventricular arrhythmias were more common in patients with a positive TWA test (the sensitivity, specificity and predictive accuracy rates of TWA to predict VT were 88%, 72% and 77%, respectively). Of course, predicting the presence of ventricular arrhythmias in a population with DCM is not a surrogate for predicting overall mortality or even cardiac events.

A study of 104 patients with nonischemic DCM, with 12 arrhythmic events during 21 ± 14 months of follow-up, showed that TWA in a subgroup of patients with an onset heart rate <100 beats/min (compared to the standard TWA heart rate onset) was the most significant predictor of arrhythmia-free survival (sensitivity: 75%; specificity: 78.9%; positive predictive value: 37.5%; negative predictive value: 94.9%; RR: 7.4). This is the first clinical study to elucidate the prognostic value of the heart rate onset of TWA in patients with DCM (74).

The prognostic value of noninvasively measured TWA was tested in a prospective study of 107 consecutive patients with congestive heart failure (New York Heart Association functional class II or III) and no history of sustained ventricular arrhythmias (82). During 18 months of follow-up, 13 patients had an arrhythmic end point. Of these, seven died suddenly, five had sustained VT, and one was resuscitated from VF. Additionally, three patients died from presumed pump failure. The TWA results were positive in 52 patients (49%), indeterminate in 22 patients (21%) and negative in 33 others (31%). Of the patients with an end point, 11 had a positive and 2 had indeterminate TWA results. There were no patients with a negative TWA result that experienced an arrhythmic event or SCD. Multivariate Cox regression analysis revealed that, of TWA, LVEF, NSVT, baroreflex sensitivity, HRV and SAECG, TWA was the only independent statistically significant predictor of arrhythmic events at 18 months of follow-up. These results suggest that TWA in patients with congestive heart failure may identify patients at increased risk of future cardiac events; however, this was based on a small number of events. Perhaps as importantly, minimally symptomatic patients with left ventricular dysfunction and a negative TWA test appear to have a low risk of significant cardiac events.

Studies of the role of TWA testing in patients with other types of cardiomyopathy are more scarce. A recent study demonstrated a positive TWA test in 61% of patients with hypertrophic cardiomyopathy (HCM) and only in 31% of patients with hypertensive left ventricular hypertrophy despite a nearly identical left ventricular mass index. In a subset of 12 HCM patients who underwent endomyocardial biopsy, TWA was greater in patients with more severe myofibril disarray and fibrosis, suggesting that the more severe histological changes are associated with greater electrical instability in the ventricular myocardium (59). However, no follow-up data or comparisons to other noninvasive predictors were provided.

TWA in patients with prior myocardial infarction. At present there are only a few studies regarding the prognostic utility of TWA in patients with a prior myocardial infarction (MI). T-wave alternans testing was performed in 102 patients with recent MI (20 ± 6 days after the MI) to test the hypothesis that the combination of LPs on the SAECG and TWA, as indices of depolarization and repolarization, respectively, would yield a higher positive predictive value for the risk of subsequent arrhythmic events than either test alone (83). There were a total of 15 sustained ventricular arrhythmic events, none of which were fatal. A positive TWA test exhibited the highest sensitivity, RR and negative predictive value but the lowest specificity, positive predictive value and predictive accuracy when compared to SAECG, LVEF and various combinations of all three tests. The main limitation of the study was the small number of events analyzed; however, consistent with TWA testing in other forms of structural heart disease, a negative test was associated with low risk of arrhythmic events (83). Recently, a larger cohort of 836 patients who underwent TWA testing 2.7 ± 5.4 months after MI revealed that TWA predicted sudden cardiac death or resuscitated VF with a risk hazard of 11.4 (85). In this study (85) the sensitivity, negative predictive value and risk hazard of TWA for predicting death or VF were higher than LVEF, SAECG and the presence of NSVT; however, the specificity and positive predictive value were indeed worse.

In a study of 379 consecutive post-MI patients with optimal medical management, sustained TWA was not present in any one of the 26 patients who died in follow-up (84). A number of variables, including an incomplete TWA test, increased HF-QRS duration on SAECG, increased QT dispersion, nondiagnostic baroreflex sensitivity and low wall-motion index, predicted all-cause mortality (84). However, an incomplete TWA test is a nonspecific end point; thus, the association with an increased RR of death is difficult to interpret. The investigators (84) suggest that the absence of sustained TWA in patients who subsequently died might be attributed to proximity of TWA testing to the MI (8.1 days vs. an optimal time of a few weeks later) or the high percentage of patients taking beta-blockers (97%) compared with other studies such as that by Ikeda et al. (83). However, the mortality rate after MI decreases with time, and any test that fails to predict SCD soon after infarction is limited in utility. If beta-blockers, the only agents known to reduce mortality post-MI, interfere with the predictive value of TWA testing, this represents a limitation in the largest population at risk for SCD. However, TWA is not a predictor of all-cause mortality (84) as the phenomenon reflects electrical instability associated with arrhythmic events and SCD.

These studies (83–85) suggest that the timing of TWA testing with respect to the MI is important. However, if a positive TWA test takes a long time to evolve, its utility may be limited immediately after the MI, the time when the risk for life-threatening arrhythmias and death is greatest. In summary, the utility of TWA testing for prognosis in patients with recent MI needs to be further clarified.

TWA in patients with the long QT and the Brugada syndromes. Macroscopic TWA has been observed in patients with idiopathic long QT syndrome (27,28,68,86–90). Prolongation and lability of the ventricular AP and QT interval, resulting from a reduction in repolarizing reserve, may reflect the presence of the EP substrate that predisposes to alternation of the QT interval and T-wave as well as to the polymorphic VT known as torsade de pointes. The prognostic value of microscopic TWA has not been assessed in patients (or their relatives) with congenital or acquired forms of the long QT syndrome, although case reports of the existence of microscopic TWA have appeared (27).

The existence of TWA in other inherited arrhythmias critically depends on the nature of the electrophysiologic substrate. In patients with presumed Brugada syndrome, TWA was no more frequent than in matched controls

(normal subjects), whereas LPs on the SAECG were significantly more frequent in patients compared to controls, suggesting that conduction disturbances may be the primary arrhythmogenic factor in patients with the Brugada syndrome (91). Obviously, the role of TWA testing in other inherited arrhythmias (e.g., arrhythmogenic right ventricular dysplasia) remains unexplored.

Effects of antiarrhythmic treatment. Because antiarrhythmic drug treatment may alter markers of risk, it would be important to know how antiarrhythmic drug therapy influences TWA. Procainamide (92), amiodarone (93) and beta-blockers (94,97,98) were reported on average to reduce the amplitude of TWA, whereas flecainide (95) tended to increase alternans.

In a published case report, dl-sotalol administration led to the conversion of a negative TWA test to positive in the setting of excessive prolongation of the QT interval (96). Recently, Klingenheben et al. (97) reported 54 patients with documented or suspected malignant ventricular tachyarrhythmias who underwent TWA testing and in whom the acute administration of metoprolol and dl-sotalol reduced overall TWA amplitude by 35% and 38%, respectively. Eight patients (five in the metoprolol group and three in the dl-sotalol group) became TWA negative after short-term administration of the drugs. Notably, the patients who became negative had a lower V_{alt} in the drug-free state compared to those patients who remained positive. This study indicates that TWA is modulated—at least in some patients—by sympathetic activity (97). The interpretation of the effect of beta-blockers on the clinical utility of TWA is complicated by at least two factors: blunting the chronotropic response to exercise, which may prevent some patients from reaching the specific TWA threshold heart rate, thus leading to an indeterminate test (84), and reducing the magnitude of V_{alt} (97). An unanswered question is whether the beta-blocker-induced reduction in V_{alt} is associated with a reduced risk of sudden death. The reduction in V_{alt} in patients treated with dl-sotalol suggests the unproven possibility of using TWA testing to guide therapy with class III antiarrhythmic drugs to minimize the risk of proarrhythmia. Because dl-sotalol has both beta-blocking (class II) and class III effects, such a study might be better suited to a drug with more pure AP prolongation.

In a recent study (98), selective autonomic blockade indicated that esmolol led to a statistically significant reduction of TWA (measured during atrial pacing) compared with a baseline measurement in 20 patients, whereas the number of positive TWA tests in the same patients was reduced by 50%. In the same study (98) parasympathetic blockade with atropine in 20 patients did not cause any change in the level of TWA compared with a baseline measurement.

Applicability of TWA testing. Several experimental and clinical studies have shown excellent reproducibility of TWA determined by the FFT spectral method (32,97). Thus far there have been only limited direct comparisons of TWA with other noninvasive measures of risk stratification, and a clear problem is that competitive tests have well-documented limitations as risk stratifiers. Both SAECG and measures of QT dispersion were either not statistically significant predictors of arrhythmic risk or were inferior to TWA testing (78,85,99,100). Similar results were obtained by Hohnloser et al. (76) in an exercise-induced TWA study as a predictor of EPS testing. However, in contrast to SAECG, which is usually assessed in the time domain, TWA testing can also be applied in patients with bundle branch block (99). Historically, other noninvasive risk stratifiers, such as LVEF, HRV, SAECG and NSVT on Holter monitoring, have individually tended to show moderately high sensitivity in a post-MI patient population, but rather low positive predictive value (101). Such comparisons with TWA must be made very cautiously, however, when testing is not performed on the same patient populations.

The predictive accuracy of arrhythmic events using a combined TWA and SAECG test was modestly better than TWA alone in a retrospective study of patients who underwent EPS testing for severe ventricular arrhythmias (78,99). However, when the combined effect of TWA and SAECG was examined in a larger population of patients with prior MI, SAECG appeared to have no additive prognostic power (85). It seems reasonable that TWA, which is a measure of repolarization, may contain different information, with respect to ventricular susceptibility to arrhythmias, than SAECG, which is an index of ventricular depolarization. Furthermore, one might expect nonoverlapping information in TWA and SAECG because TWA is a measure of beat-to-beat variability, whereas SAECG is a measure of mean QRS morphology. Conversely, the combination of TWA and LVEF increased the predictive power of TWA in patients with prior MI (85), and nonischemic DCM (74).

Limitations on the use of TWA testing. Although TWA assessed during exercise testing correlates well with measurement of TWA during atrial pacing, there are differences and potential pitfalls in measuring TWA during cycling (102). These limitations are both technical, including control of the patient's pedaling rate and meticulous skin preparation to improve signal-to-noise ratio, and biological, including differences in the activation of the sympathetic nervous system with exercise compared to pacing at similar rates.

Exercise-based TWA testing is particularly appealing because of its noninvasive nature, but it may be impossible in specific subgroups of patients who are not able to perform bicycle or treadmill testing, thus resulting in an indeterminate test (Table 2). In such cases, pharmacological stress testing using atropine or dopamine may be an alternative approach for TWA assessment.

In Table 2, we have included the number of indeterminate tests in patients for each study. This number includes all possible reasons for indeterminate TWA testing, such as the inability to achieve an adequate heart rate, excess noise,

frequent atrial or ventricular ectopy or atrial arrhythmias. However, the indeterminate rate of TWA testing may be reduced by prolonging the exercise protocol to reduce the likelihood that intermittent noise or ectopic beats will obscure the TWA data, by efforts to reduce noise, and by developing algorithms that enable one to measure alternans in the presence of a higher level of ectopy. It is anticipated that, by implementing these improvements, reported indeterminacy rates should decrease. Furthermore, the indeterminate rates are highly population dependent; they tend to be highest in patients with the lowest LVEF.

Atrial fibrillation and other frequent arrhythmias, such as frequent atrial and/or ventricular premature beats, limit the use of TWA testing, as they do in other noninvasive electrocardiographically based noninvasive tests that have been employed as risk stratifiers.

PERSPECTIVES

A major challenge, which is also the focus of a number of ongoing large clinical trials, is the prevention of SCD in patients with structural heart disease. Invasive testing (e.g., EPS testing) is impractical and has limited predictive power; noninvasive testing methods thus far lack specificity and predictive power. Implantation of defibrillators in all those at risk will place an unmanageable economic burden on the health care system. Refinement of selection criteria for patients who require the most aggressive therapy for sudden death prevention is as yet an elusive goal.

The clinical utility of TWA in predicting SCD appears promising, although still unproven, for patients with; 1) symptoms suggestive of ventricular arrhythmias (78); 2) congestive heart failure or ejection fraction $\leq$40% (74,82); and 3) a recent MI (TWA testing should be performed three to six weeks post-MI) (85). Because TWA has an excellent negative predictive value, patients who have a negative TWA test are at low risk for ventricular arrhythmias and SCD, whereas patients who test positive may be at significant risk and should be considered for invasive testing and prophylactic treatment.

T-wave alternans testing has shown promise as a noninvasive predictor of potentially lethal ventricular arrhythmias in initial studies of diverse patient populations with structural heart disease. The ultimate role of TWA testing in the armamentarium of noninvasive predictors of mortality awaits further large-scale prospective testing. Future studies should address the reproducibility of TWA, the effectiveness of ICD therapy using TWA testing in patients with a negative EPS test, the role of TWA in guiding therapy with beta-blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists and antiarrhythmic drugs.

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