REVIEW ARTICLE

Usefulness of T-Wave Alternans in Sudden Death Risk Stratification and Guiding Medical Therapy

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Visible T-wave alternans (TWA), a beat-to-beat alternation in the morphology and amplitude of the ST segment or T wave, has been observed for over a century to occur in association with life-threatening arrhythmias in patients with acute coronary syndrome, heart failure, and cardiac channelopathies. This compelling linkage prompted development of quantitative techniques leading to FDA-cleared commercial methodologies for measuring nonvisible levels of TWA in the frequency and time domains. The first aim of this review is to summarize evidence from more than a hundred studies enrolling a total of >12,000 patients that support the predictivity of TWA for cardiovascular mortality and sudden cardiac death.

The second focus is on the usefulness of TWA in guiding therapy. Until recently, TWA has been used primarily in decision making for cardioverter-defibrillator implantation. Its potential utility in guiding pharmacologic therapy has been underappreciated. We review clinical literature supporting the usefulness of TWA as an index of antiarrhythmic effects and proarrhythmia for different drug classes. Beta-adrenergic and sodium channel-blocking agents are the most widely studied drugs in clinical TWA investigations, with both reducing TWA magnitude; the exception is patients in whom sodium channel blockade discloses the Brugada syndrome and provokes macroscopic TWA. An intriguing possibility is that TWA may help to detect beneficial effects of nonantiarrhythmic agents such as the angiotensin II receptor blocker valsartan, which indirectly protects from arrhythmia through improving myocardial remodeling. We conclude that quantitative analysis of TWA has considerable potential to guide pharmacologic intervention and thereby serve as a therapeutic target.

Ann Noninvasive Electrocardiol 2010;15(3):276–288

T-wave alternans; sudden cardiac death; risk stratification; antiarrhythmic effects; proarrhythmia

Decreasing the incidence of sudden death, a leading cause of mortality in the industrially developed world, necessitates a reliable index of risk that reflects fundamental electrophysiologic properties underlying arrhythmogenesis in diverse forms of cardiac disease. Such a marker should be an integral component of the causal pathway of arrhythmogenesis and thereby serve as a therapeutic target. Moreover, as the propensity for arrhythmias changes across the natural course of cardiovascular disease or in response to an intervention such as pharmacologic therapy, this tool would ideally track the concomitant alterations in susceptibility to life-threatening arrhythmias.

As discussed below, T-wave alternans (TWA), a beat-to-beat alternation in the morphology and amplitude of the ST segment or T wave, reflects temporal-spatial heterogeneity of repolarization.[1] The evidence linking TWA with arrhythmias spans more than a century, dating from the pioneering

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Invited review for Revista Argentina de Cardiología and Annals of Noninvasive Electrocardiology.

Conflict of Interest: Dr. Verrier is co-inventor of the Modified Moving Average method for T-wave alternans analysis, with patent assigned to Beth Israel Deaconess Medical Center and licensed by GE Healthcare. Dr. Nieminen declares no conflicts of interest.

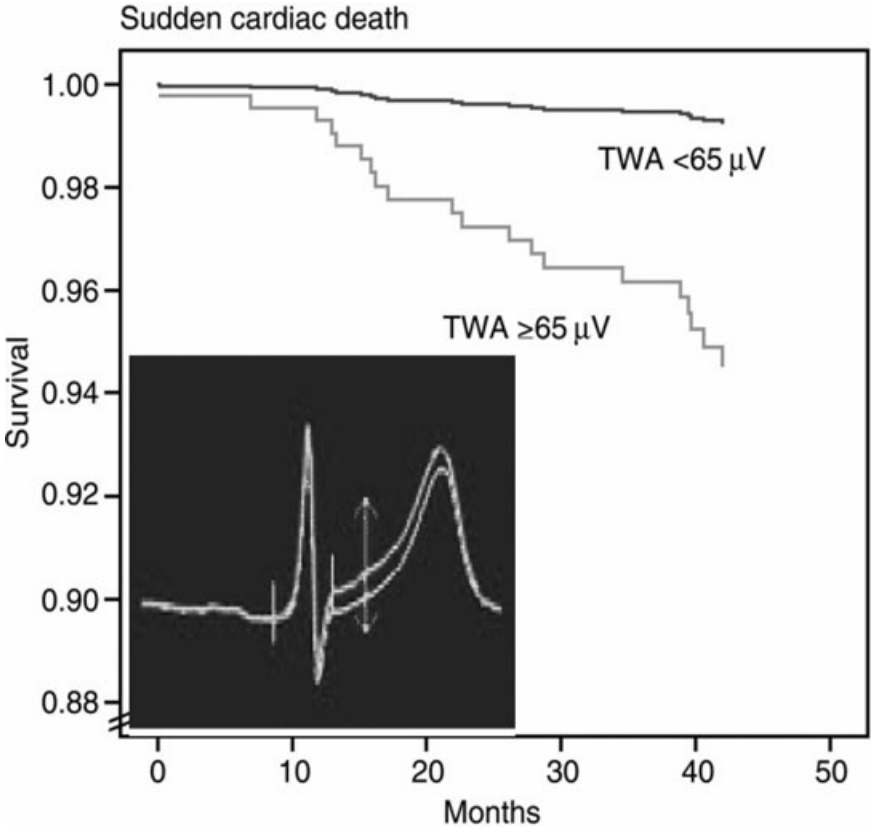

Figure 1. Survival curves from the Finnish Cardiovascular Study (FINCAVAS), which enrolled >1000 consecutive patients referred for routine exercise testing.[36] Inset is a high-resolution QRS-aligned template from a FINCAVAS patient illustrating T-wave alternans (TWA) as the separation between successive T waves.[2] TWA was measured by the Modified Moving Average method. (Reprinted with permission from Oxford University Press)

observations of Hering in 1908. Macroscopic levels of TWA have been detected under diverse clinical conditions in association with life-threatening arrhythmias, including acute myocardial ischemia and infarction, Prinzmetal's angina, heart failure, and channelopathies such as the Brugada and long QT syndromes. Although TWA is a unitary phenomenon, its morphology varies considerably as a function of the underlying pathology. In ambulatory patients with stable coronary heart disease, in whom ischemia is usually subendocardial, alternation is localized primarily in the first half of the T wave (Fig. 1).[2] TWA is particularly prevalent in congenital long QT syndrome patients, in whom the T wave frequently alternates above and below the isoelectric line without concomitant ST-segment changes[3] and heralds initiation of torsades de pointes.[4] In Brugada syndrome patients, the signature ST-T-wave pattern is the locus of alternation.[5] Collectively, these observations indicate that repolarization alternans is fundamentally linked to arrhythmogenesis but that the underlying pathophysiology differs, requiring that therapy be tailored to address the electrophysiologic derangement.

This review has two major aims. First, we will discuss the evidence based on more than a hundred investigations enrolling a total of more than 12,000 patients that TWA is a robust marker of risk of sudden cardiac death and cardiovascular mortality. The second focus will be on the literature demonstrating the applicability of TWA in evaluating the efficacy of antiarrhythmic drugs as well as agents with proarrhythmic potential.

PHYSIOLOGIC CONSIDERATIONS FOR TWA AS A MARKER OF VULNERABILITY TO VENTRICULAR FIBRILLATION

The fundamental link between TWA and arrhythmia vulnerability is underscored by the finding that TWA magnitude exhibits a parallel time course with the spontaneous occurrence of ventricular fibrillation and tachycardia during myocardial ischemia and reperfusion.[6]

Heterogeneity of Repolarization

The detailed electrophysiologic and ionic mechanisms underlying TWA have been recently reviewed.[7–10] Both experimental[1,11,12] and clinical evidence[13] indicates that TWA magnitude appears to parallel changes in temporal-spatial heterogeneity of repolarization, which is a critical factor in arrhythmogenesis arising in different cardiac pathologies associated with sudden death,[9] such as ischemic heart disease, heart failure, and cardiomyopathies including Chagas' disease.[14] The association between TWA and heterogeneity of repolarization is particularly evident during discordant TWA, wherein myocardial cells in neighboring regions alternate out-of-phase, thereby markedly enhancing heterogeneity of repolarization and establishing the preconditions for conduction block, reentry, and life-threatening arrhythmias.

Intracellular Calcium Cycling

The network of related ionic mechanisms is complex, but several lines of evidence from experimental investigations affirm that instabilities in calcium handling in the sarcoplasmic reticulum give rise to cellular alternation of Ca^{2+}, action potential duration (APD) alternans, and beat-to-beat alternation during repolarization. Calcium channel blockers and agents such as ryanodine, which blocks calcium release from the sarcoplasmic reticulum, have been shown to suppress pacing- and ischemia-induced APD alternans in ventricular muscle fibers.[15,16] Moreover, APD alternans was augmented by calcium channel agonist Bay K 8644, presumably secondary to changing amounts of calcium entering through the sarcolemmal calcium channel.[16] Adenoviral overexpression of SERCA2a enhanced calcium reuptake into sarcoplasmic reticulum and reduces calcium alternans in isolated cardiomyocytes[16] and ADP alternans in Langendorff-perfused hearts,[17] providing evidence that SERCA2a is a potential therapeutic target. Clusin[8] observed that ischemia-induced alternation in calcium transients was temporally correlated with APD alternans and TWA. Intrapericardial delivery of the classic nitric oxide donor nitroglycerin effectively and in parallel suppressed ischemia-induced ventricular fibrillation and TWA in intact porcines.[18] A follow-up study[19] determined the mechanism to be an improvement in calcium handling and reduction in T-wave heterogeneity. In a study of heart failure patients, Narayan and coworkers[20] reported that alternans of action potential amplitude, attributed to abnormalities of calcium cycling, strongly predicted ventricular tachycardia and fibrillation during a 2.6-year follow-up.

Heart Rate

Heart rate plays a role in TWA largely because of its impact on intracellular calcium cycling.[10] In patients with ischemic heart disease or heart failure, the capacity of the sarcoplasmic reticulum to reuptake calcium may be impaired, and TWA can be induced at low heart rates.[10] However, heart rate is not the sole determinant of TWA, as autonomic neurotransmitters and changes in myocardial substrate can provoke elevated levels of TWA during fixed rate pacing.[6,21] Pacing alone did not replicate the enhancement in TWA achieved by adrenergic stimulation or myocardial ischemia to a comparable heart rate.[21] In patients with a history of cardiac arrest, beta-adrenergic stimulation with isoproterenol elicited a 2.8-fold greater increase in TWA during electrophysiologic study compared to pacing to the same heart rate.[9,22]

Continuum of Electrical Instability

TWA magnitude reflects the continuum of cardiac electrical instability. The higher the level of TWA, the more likely is the onset of ventricular tachyarrhythmia. Both experimentally[23] and clinically,[24,25] life-threatening arrhythmias are preceded by a crescendo in the level of TWA. This continuum of instability underlies estimation of risk by quantitation of TWA[2,26] and the opportunity to monitor the efficacy of pharmacologic therapy.

CLINICAL MEASUREMENT OF TWA AND EVIDENCE OF PREDICTIVITY

Over the last two decades, evaluation of TWA has evolved from visual inspection of the ECG to the use of computerized analytical methods for detection of nonvisible TWA in the microvolt range. We summarize the two analytical approaches with FDA clearance in the United States.[27]

Spectral Method

Briefly, the Spectral Method employs the Fast Fourier Transform to analyze the ECG across 128 consecutive J-T segments in the frequency domain (Cambridge Heart, Inc., Tewksbury, MA, USA). The generated power spectrum at 0.5 cycle/beat, that is, occurring on every other beat, is defined as the alternans power. The test is usually conducted during bicycle or treadmill exercise. An alternans level $>1.9\ \mu V$ is considered a positive test, whereas test results below this level are negative. On account of relatively high incidence of indeterminate test results, between 20–40% of all cases, a new classification of "abnormal" due to patient factors has been introduced.[28] This classification is used when the test is associated with excessive ectopy, lack of capacity to reach a target rate of 105–110 beats/min, or nonsustained TWA. Abnormal test results due to these patient factors indicate the same level of risk as positive test results. Quantification of TWA with the Spectral Method provides additional insights[29] but is clearly less widely used than the binary approach.

Predictivity for sudden cardiac death and cardiovascular mortality by TWA analysis with the Spectral Method has been evaluated in >9000 patients with various types of cardiovascular disease, including ischemic heart disease, nonischemic cardiomyopathy, and heart failure. Overall, as reviewed in recent meta-analyses,[30,31] TWA testing with the Spectral Method exhibits valuable predictive capacity. However, concern about its suitability to guide ICD implantation has been raised based on the results of two trials in patients with implantable cardioverter defibrillators (ICDs). TWA stratified total mortality in the MASTER trial[32] but did not predict ICD discharge in MASTER or SCD-HeFT TWA substudy.[32,33] These results were disappointing in light of the fact that spectral TWA testing was advocated mainly to rule out the need for ICD devices, as the test performs particularly well in terms of negative predictive value, which is excellent, in the range of 97%.[30] A recent meta-analysis addressing this concern indicated that predictive accuracy was strong in the TWA studies enrolling relatively few patients with ICDs, with a composite hazard ratio for prediction of abnormal vs. negative TWA of 13.6 (95% CI 8.5–30.4), although predictive accuracy in studies with high ICD use was low at 1.6 (95% CI 1.2–2.1).[30] These findings suggest that use of ICD discharge as a surrogate end point for lethal arrhythmias may have underrepresented the utility of the test. As will be discussed, there is recurring evidence of the promise of spectral TWA analysis in evaluating antiarrhythmic agents, although this was not its primary application.

To date, only the Alternans Before Cardioverter Defibrillator (ABCD) trial[34] has tested TWA's capacity to guide prophylactic ICD implantation. The study enrolled 566 patients with coronary heart disease, ejection fraction $\leq 40\%$, and nonsustained ventricular tachycardia on Holter. All patients underwent both microvolt TWA testing and electrophysiology study, with ICD implantation mandated for patients in whom either test was positive. ICDs were also inserted in 67% of patients with both negative/indeterminate TWA and negative EP study results. Event rates at the prespecified primary time point of 1 year were significantly higher in patients with either a positive TWA (hazard ratio 2.1, $P = 0.03$) or a positive EP study (hazard ratio 2.4, $P = 0.007$) than in those with both tests negative/indeterminate. Moreover, the event rate at 1 year in patients with both negative TWA and EP studies was lower than in patients with two positive tests (2% vs. 12%; $P = 0.017$), suggesting synergy between the tests. The ABCD study was also the first to suggest that TWA predictivity is time dependent, as TWA predicted end point events at 1 year but not at 2 years.

Modified Moving Average Method

The time-domain Modified Moving Average (MMA) method is a more recently developed[35] and commercialized approach (GE Healthcare, Inc., Milwaukee, WI). This technique was designed to allow TWA analysis during routine exercise and ambulatory monitoring by circumventing the stationarity requirements of the Spectral Method, which mandates stabilization of heart rate for several minutes by a specialized exercise protocol

or pacing. The requirement for specialized electrodes is also eliminated through advanced noise-reduction software. The MMA algorithm continuously streams odd and even beats into separate bins and creates median complexes for each bin. These complexes are then superimposed, and the peak difference between the odd and even median complexes at any point within the JT segment is reported as the TWA value, which is updated every 10 to 15 seconds. The moving average allows control of the influence of new incoming beats on the median complexes with an adjustable update factor. A more rapid update factor provides greater sensitivity in detecting transient but clinically important surges in TWA. The recommended update factor is 1/8.

An essential component of MMA testing is the display of high-resolution QRS-aligned templates of the superimposed complexes, which permit visual examination to verify TWA's presence and magnitude (Fig. 1). Noise measurements are in part derived from mismatch of the median complexes outside the JT segment.

Predictivity by the two methods is comparable, consistent with the fact that they are measuring the same electrophysiologic property, although the TWA values reported with the MMA algorithm are consistently larger by a factor of 4 to 10. This difference is mainly attributable to the fact that the Spectral Method reports the average TWA level across the entire JT segment for 128 beats, whereas the MMA method reports the peak TWA level at any point within the JT segment.

Experience with the MMA TWA test, which has been used both during exercise testing and ambulatory ECG monitoring, extends to >3000 patients with preserved as well as with depressed ejection fraction (Table 1). In the initial investigation of 1000 consecutive patients referred for routine exercise testing in the Finnish Cardiovascular Study (FINCAVAS), Nieminen and coworkers[36] reported that MMA-based TWA had a high level of predictivity for cardiovascular mortality (relative risk 6.0, 95% confidence interval [CI] 2.8–12.8) and sudden cardiac death (relative risk 7.4, 95% CI 2.8–19.4, Fig. 1). These findings were subsequently confirmed in an extended database of 2000 patients.[2] In a prospective trial of ambulatory ECG-based TWA testing in 295 patients with left ventricular dysfunction, Sakaki, Ikeda, and colleagues[37] reported relative risks of 17.1 (95% CI 6.3–46.6, $P < 0.0001$) for cardiovascular mortality and 22.6 (95% CI 2.6–193.7, $P < 0.005$) for witnessed sudden death (Fig. 2).

CALCIUM CHANNEL BLOCKADE

Despite extensive experimental evidence suggesting the capacity of nondihydropyridine calcium channel blockers verapamil and diltiazem to suppress TWA in several experimental studies, no clinical studies regarding effects of this class of compounds on TWA have been published. In addition, definitive evidence that these agents reduce sudden cardiac death in humans is lacking. A potential explanation for this disparity is that inotropic interventions affecting interplay between uptake and release of calcium may influence cardiac outcomes by different mechanisms depending on the mechanical state of the heart. In the case of decompensated heart failure, depression of contractility by calcium channel blockade can lead to systemic hypotension, thereby reducing coronary perfusion and predisposing to myocardial ischemia and arrhythmias. In these patients, the negative inotropic effect of calcium channel blockers would be expected to overcome possible cardioprotective actions on electrophysiologic function. It is likely but untested that calcium sensitizers such as levosimendan, which is widely prescribed in Europe for acute heart failure and effectively improves pump function, might actually decrease repolarization alternans following attenuation of mechanical alternans. These surmises are based on results presented by the Multicenter Diltiazem Post-Infarction Trial Research Group,[38] who observed a diltiazem-related reduction in cardiac death (hazard ratio 0.77, 95% CI 0.61–0.98) for patients with preserved ventricular function but a significant diltiazem-related increase in cardiac death (hazard ratio 1.41, 95% CI 1.01–1.96) for those with pulmonary congestion. The increase in cardiac death rate was similar among patients with left ventricular ejection fraction <40%.

BETA-ADRENERGIC BLOCKADE

Beta-adrenergic blocking agents are well known to decrease incidence of sudden cardiac death, and they also reduce TWA with both acute and chronic use. These agents influence calcium handling through the cyclic nucleotide cascade and, in contrast to calcium channel blockers, improve

Table 1. Hazard Ratios Generated by MMA in Clinical Studies*

Test Setting	Patient Population (Disease, Enrollment)	Left Ventricular Ejection Fraction	Hazard Ratios for End Point at Follow-up Period
Routine Exercise Stress Testing			
• FINCAVAS (Minkkinen 2009)[2]	2119 consecutive patients referred for routine exercise testing	Mostly preserved	6.4 for CV death, 4.6 for SCD at 47 months
Exercise Recovery			
• REFINE/Exner 2007[75]	322 post-MI at 10–14 weeks after event	Moderately depressed (38–48%)	2.94 for CV death or resuscitated cardiac arrest at 47 months
• REFINE/FINCAVAS/ Slawnych 2009[26]	322 post-MI patients and 681 CAD patients	Moderately depressed (38–48%) and mostly preserved groups	2.5 for CV death at 48 months
• FINCAVAS/Leino 2009[76]	Consecutive patients referred for routine exercise testing in FINCAVAS database	Mostly preserved	3.5 for CV death at 48 months
Ambulatory ECG			
• ATRAMI/Verrier 2003[70]	Acute post-MI; Case control analysis (15 cases: 29 controls)	Moderately preserved (42 ± 3%)	4.2 to 7.9 for cardiac arrest or arrhythmic death at 21 months
• EPHESUS/Stein 2008[72]	Acute post-MI, LVEF ≤ 40%, and heart failure; Case control analysis (46 cases: 92 controls)	Depressed (34 ± 5%)	5.2 to 5.5 for sudden death at 16.4 months
• Sakaki 2009[37]	295 ischemic or nonischemic LV dysfunction	Depressed (34 ± 6%)	17.1 for CV death, 22.6 for witnessed SCD at 1 year
• Maeda 2009[73]	63 consecutive patients including 21 controls, 21 post-MI without VT, and 21 post-MI with VT	Depressed (36–43%) for post-MI group	6.1 for sustained VT/VF at 6 years
• Cardiovascular Health Study/Stein 2010[74]	Case-control (49 cases: 98 controls) analysis of patients ≥65 years old	Not tested, assumed preserved	4.8 for SCD at 14 years

*For comparison with the Spectral Method, the reader is referred to metaanalyses by Gehi et al.[30] and Hohnloser et al.[31]

cardiac mechanical function in patients with heart failure. Klingenheben and colleagues[39] found that infusions of metoprolol, a pure beta-blocker, or d,l-sotalol, a beta-blocker with Class III antiarrhythmic effects, diminished TWA magnitude in patients with documented or suspected malignant ventricular tachycardia during electrophysiologic testing. The reduction in TWA was comparable with metoprolol (by 35%, from 7.9 to 4.9 μV by spectral analysis, n = 25) and d,l-sotalol (by 38%, from 8.6 to 4.4 μV, n = 29) (Fig. 3).

Also during electrophysiologic testing, Rashba and colleagues[40] infused the beta-blocker esmolol (n = 20) in patients with ischemic cardiomyopathy and inducible sustained ventricular tachycardia. Esmolol significantly diminished the absolute values of TWA and diminished the number of TWA tests classified as positive by 50%. Komiya and coworkers[41] reported a greater decrement in TWA magnitude following propranolol infusion among patients with a history of ventricular tachycardia (n = 15) than among those with a history of

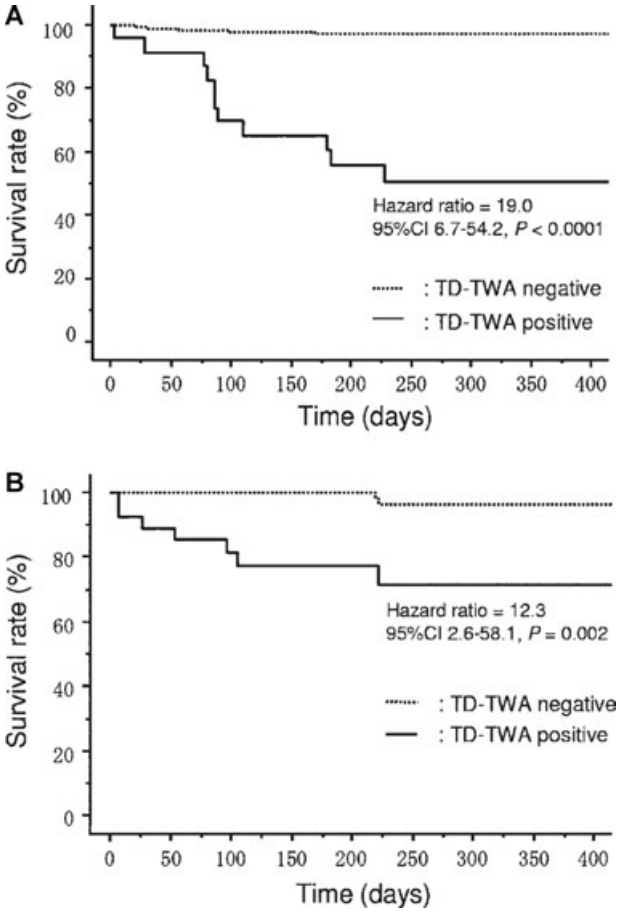

Figure 2. Event-free curves for cardiac mortality using maximal voltage of time-domain T-wave alternans (TD-TWA) from 24-hour Holter ECGs in ischemic (A) and nonischemic (B) study subgroups.[37] TWA was analyzed by the Modified Moving Average method. (Reprinted with permission from Elsevier, Inc.)

supraventricular tachycardia (n = 20). Despite this effect, TWA remained more sizeable in the ventricular tachycardia group than in the supraventricular tachycardia group during pacing at 110 beats/min, reflecting the greater level of cardiac electrical instability in the former group.

Murata and colleagues[42] reported a decrease in positive TWA test results along with improvement in several measures of sympathetic nerve activity and in left ventricular ejection fraction following a 3-month course of oral beta-adrenergic blockade. (123)I-metaiodobenzylguanidine (MIBG) imaging and echocardiography were performed at baseline and after beta-blocker therapy in 26 patients with nonischemic heart disease and positive TWA test results during rest or exercise. After treatment with metoprolol (mean dose 26 mg), carvedilol

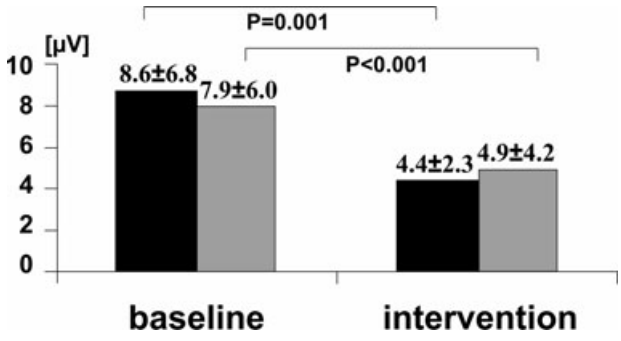

Figure 3. Changes in T-wave alternans (TWA) amplitude following drug administration in patients with d,l-sotalol (dark bars) and metoprolol (gray bars).[39] TWA was measured by the Spectral Method. (Reprinted with permission from Elsevier, Inc.)

(11 mg), bisoprolol (5 mg), or atenolol (5 mg), TWA became negative in eight patients but remained positive although decreased in magnitude in the remaining 18 patients.

A critical consideration in TWA test protocols is whether or not to withdraw beta-blocking agents prior to spectral TWA determination to allow patients to raise heart rates to target levels. Several investigators have advised, based on experience, against washing out antiarrhythmic medication prior to TWA testing.[39,43] A broader consideration is that this practice may lead to false positive test results, since beta-blockade in long-term use is protective against cardiovascular death.

SODIUM CHANNEL BLOCKADE

Kavesh and coworkers[44] reported that procainamide infusion decreased TWA magnitude by 43–65% during electrophysiologic study in 24 patients with inducible sustained ventricular tachycardia, but no outcomes were reported.

The prototypical late I_{Na} blocking agent ranolazine decreased ventricular vulnerability and TWA in a large animal model[45,46] and suppressed ventricular tachyarrhythmias in the MERLIN TIMI 36 clinical study.[47] Recently, Murdock and coworkers[48] reported parallel suppression of ventricular tachycardia and TWA with ranolazine in a patient with cardiomyopathy (Fig. 4).

Pharmacologic Testing to Disclose Brugada Syndrome

The Brugada syndrome is an autosomal-dominant ion channel disorder that predisposes

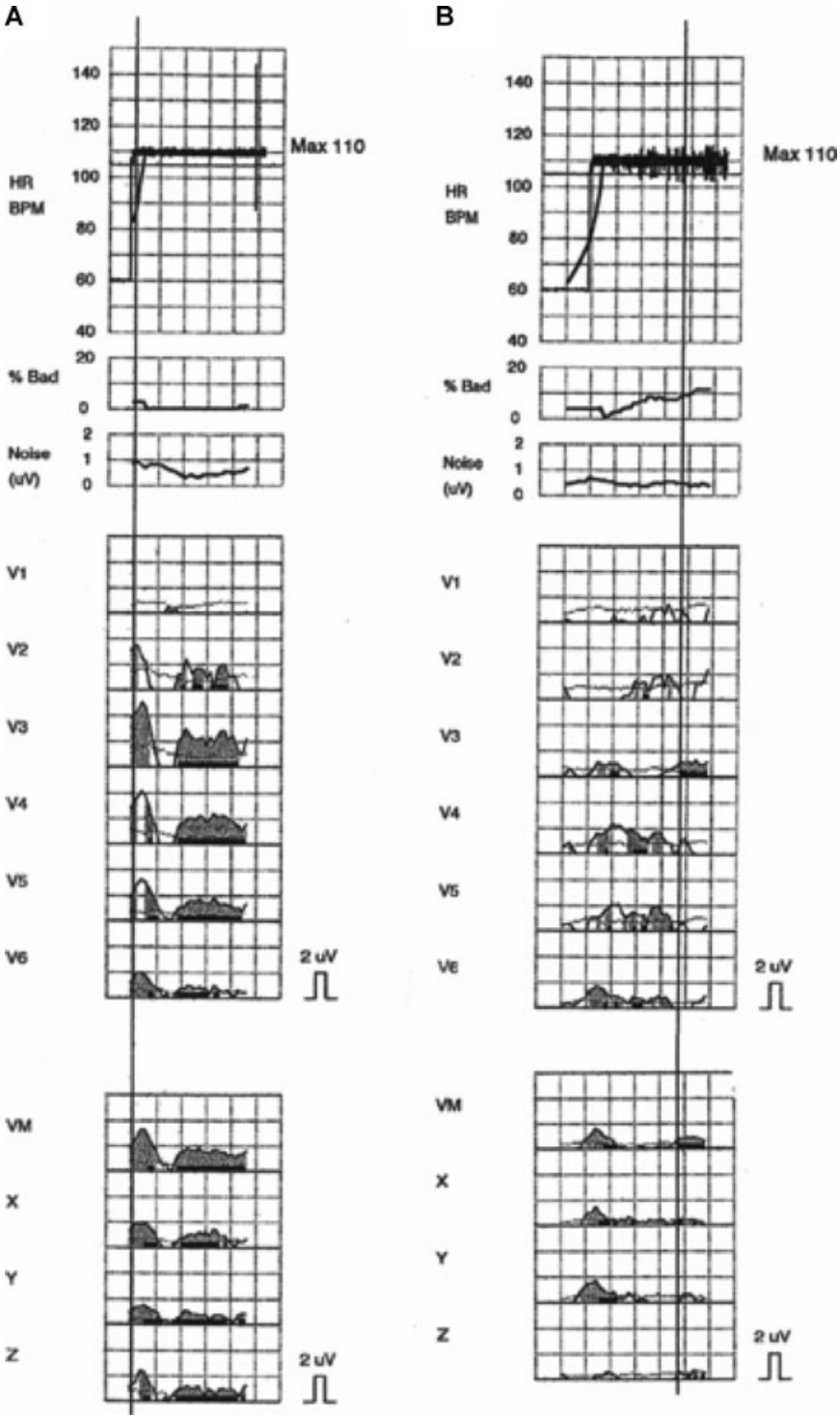

Figure 4. Significant microvolt T-wave alternans, determined by the Spectral Method, was present at 110 beats/min just before (A) but not after (B) ranolazine was restarted.[48]

individuals with structurally normal hearts to ventricular arrhythmias and sudden cardiac death. Guidelines indicate ICD implantation for primary or secondary prevention of cardiac arrest.[49] The spontaneous appearance of the Brugada ECG is diagnostic, namely distinct ST-segment elevation in the right precordial leads (V_1 to V_3) and incomplete or complete right bundle branch block. Visible TWA may also appear spontaneously.[50,51] As TWA is masked by exercise or atrial pacing in patients with this syndrome,[51] these platforms may be inappropriate for TWA-based risk assessment. Rather, provocative testing with pilsicainide, a Class Ic drug, can be used to disclose TWA along with the diagnostic Brugada ECG. Specifically, Morita and colleagues[52] administered pilsicainide orally or intravenously to 65 patients with Brugada syndrome during electrophysiologic study to evaluate the occurrence of TWA and ventricular arrhythmia. Prior to drug delivery, TWA was not visually detected. Pilsicainide provoked macroscopic TWA in 6 of 10 patients with drug-induced sustained polymorphic ventricular tachycardia or ventricular fibrillation but in only one of 55 patients without arrhythmia. Tada and colleagues[53] also investigated the association between ventricular fibrillation and TWA induced by intravenous pilsicainide. None of the patients exhibited TWA at baseline, but the agent provoked visible TWA in 17 (22.1%) of 77 Brugada patients. Patients with TWA also experienced a significantly higher incidence of spontaneous VF (52.9% vs 8.3%) and syncope (58.8% vs 26.7%) than their counterparts without TWA.

MULTICHANNEL BLOCKADE

Surprisingly, only limited experimental and clinical information is available regarding the effects of agents with multichannel actions, particularly amiodarone, on TWA, despite their clinical importance. Groh and colleagues[54] reported a decreased prevalence of TWA in ICD patients with ischemic or nonischemic cardiomyopathy and a history of ventricular tachycardia who were treated with amiodarone. Specifically, TWA test results were positive in only 1 (11%) of 9 patients treated with amiodarone as compared with 14 (64%) of 22 patients without the drug. Importantly, TWA status served as a predictor of appropriate ICD therapy over the follow-up of 0.9 ± 0.2 years.

Sakabe and colleagues[55] investigated whether use of antiarrhythmic therapy disrupts TWA's predictive capacity. They prospectively evaluated 49 patients with ischemic or nonischemic-dilated cardiomyopathy and history of sustained ventricular tachycardia or ventricular fibrillation. Amiodarone, prescribed for 28 (57%) patients, was the most common antiarrhythmic medication; additional medications included beta-blockade in 17 (35%) and angiotensin converting enzyme (ACE) inhibition in all 49 patients. TWA was measured only once, after 2–4 weeks with antiarrhythmics, and was positive in 61% of cases. During the 13 ± 11-month follow-up, the investigators found that TWA test results (negative/positive), but not left ventricular ejection fraction, significantly predicted the recurrence of tachycardia (Fig. 5). These

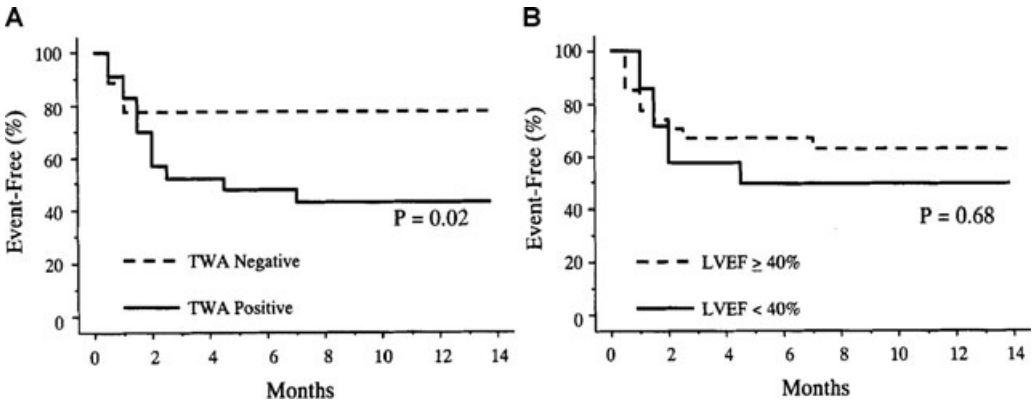

Figure 5. Kaplan-Meier event-free curves for ventricular tachyarrhythmias according to T-wave alternans (TWA) (Panel A) and left ventricular ejection fraction (LVEF) (Panel B).[55] TWA-positive patients had more frequent event recurrences than TWA-negative patients ($P = 0.02$), whereas LVEF $\leq$ 40% did not distinguish between patients with and without events ($P = 0.68$).

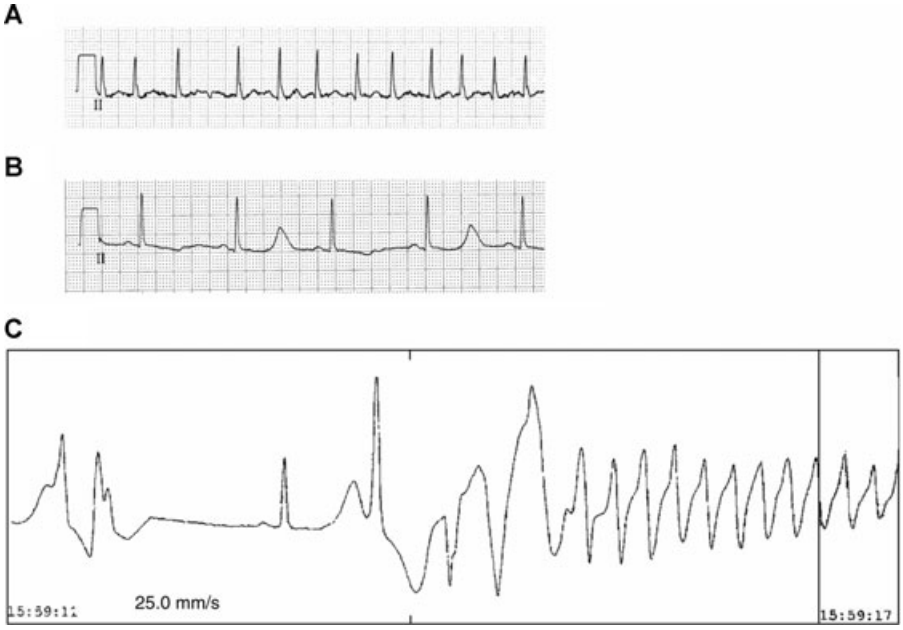

Figure 6. Case report of macroscopic T-wave alternans (TWA) heralding torsades de pointes induced by intravenous amiodarone in a 62-year-old male patient with new-onset atrial fibrillation and a rapid ventricular response. (A) Baseline ECG; (B) Prominent QT prolongation and macroscopic TWA appeared after restoration of sinus rhythm following 48 hours of drug exposure; and (C) Onset of torsades de pointes tachycardia that generated into ventricular fibrillation. The patient was resuscitated and QT interval normalized after amiodarone was discontinued. Genetic testing revealed a mutation at the KCNE2 gene, indicating congenital long QT syndrome VI, although the patient had no prior history of QT prolongation or ventricular tachyarrhythmias.[58] (Reprinted with permission from Oxford University Press.)

investigators concluded that TWA is capable of predicting recurrence of ventricular arrhythmias in patients receiving empirically guided pharmacologic therapy for sustained ventricular tachycardia or fibrillation.

Proarrhythmia

Case reports of macroscopic levels of TWA in association with proarrhythmia following amiodarone administration have appeared (Fig. 6).[56–58] Houltz and coworkers[59] reported visible TWA in association with torsades de pointes in patients receiving almokalant, another Class III agent, prescribed to revert atrial fibrillation or flutter. Torsades de pointes occurred in 6 of 100 patients, 3 of whom had exhibited visible TWA prior to drug infusion. Only 16 of the remaining 94 patients (17%) exhibited TWA without torsades de pointes.

DRUGS WITH "UPSTREAM" ANTIARRHYTHMIC EFFECTS

A number of agents that effectively reduce total mortality and sudden cardiac death are not, strictly speaking, "antiarrhythmic agents" but act on "upstream" events and processes to improve the electrical stability of the myocardial substrate in patients with atherosclerosis, hypertension, ischemic heart disease, or heart failure.[60] These agents may reduce ischemia and/or fibrosis and include statins, dihydropyridine calcium channel blockers, and drugs affecting renin-angiotensin-aldosterone system. Their proarrhythmic potential is limited as they do not act directly on cardiac ion channels, a focus that can slow conduction, predispose to reentrant tachycardias, or prolong the long QT interval, thereby conducing to torsades de pointes.

Recently, Kubo and colleagues[61] investigated whether TWA magnitude reflects the antifibrillatory potential of the angiotensin II receptor

antagonist valsartan. Sixteen of the 50 patients enrolled initially tested positive for TWA. Treatment with valsartan (80 mg/day, orally) for 3 days markedly decreased TWA from 6.1 ± 3.8 to 2.5 ± 1.9 μV (by spectral analysis), without accompanying changes in blood pressure, resting heart rate, or echocardiographic parameters.

PROARRHYTHMIA AND TWA WITH NONCARDIAC MEDICATIONS

Clinical reports concur that agents that markedly prolong the QT interval may also induce macroscopic levels of TWA that herald torsades de pointes.[56–59,62,63] QT interval prolongation sets the stage for increased spatial heterogeneity of repolarization across the ventricular wall,[64] leading to increased intracellular calcium levels and predisposing to afterdepolarizations.

CONCLUSIONS

The evidence cited in this review supports the pivotal role of this phenomenon in arrhythmogenesis and indicates the broad utility of TWA in sudden death risk evaluation and its potential for assessment of antiarrhythmic and proarrhythmic effects of diverse agents across differing pathologies. Although the focus of this review has been to discuss the value of TWA in guiding pharmacologic therapy, this marker may also prove to be useful in guiding nonpharmacologic approaches. The scope may include interventions such as rehabilitation following myocardial infarction, during significant substrate and neural remodeling[65,66] with changes in cardiac electrical instability potentially quantifiable by TWA. In heart failure patients, sleep apnea has been shown to result in high levels of TWA.[67] An intriguing question that deserves exploration is whether apnea treatment by CPAP and recent approaches such as resynchronization therapy may reduce susceptibility to cardiac arrhythmias reflected by reduction in TWA levels.[68] The recent availability of TWA testing based on ambulatory ECG recordings[24,37,69–74] is an important pragmatic advance, as this platform is routinely used in drug evaluation trials as well as in medical practice.

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