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Basis for Sudden Cardiac Death Prediction by T-Wave Alternans from an Integrative Physiology Perspective

Richard L. Verrier, Ph.D., F.A.C.C., Kapil Kumar, M.D., and Bruce D. Nearing, Ph.D.

Harvard Medical School, Beth Israel Deaconess Medical Center, Department of Medicine, Cardiovascular Institute, Boston MA

Abstract

Detection of microvolt levels of T-wave alternans (TWA) has been shown to be useful in identifying individuals at heightened risk for sudden cardiac death. The mechanistic bases for TWA are complex, at the cellular level involving multiple mechanisms, particularly instabilities in membrane voltage (i.e., steep action potential duration restitution slope) and disruptions in intracellular calcium cycling dynamics. The integrative factors influencing TWA at the systemic level are also multifold. We focus on three main variables, namely, heart rate, autonomic nervous system activities, and myocardial ischemia. Clinically, there is growing interest in extending TWA testing to include ambulatory ECG monitoring as well as exercise. The former modality permits assessment of the influence of diverse provocative stimuli of daily life, including circadian factors, mental stress, and sleep-state related disturbances in respiratory and cardiovascular function. Two major emerging concepts in clinical TWA testing are discussed, namely, quantitative analysis of TWA level, to complement the current binary classification scheme, and risk stratification of patients with preserved left ventricular function, the population with the largest absolute number of sudden cardiac deaths.

Keywords

T-wave alternans; sudden cardiac death; cardiac arrest; ventricular fibrillation; ventricular tachycardia; risk stratification

INTRODUCTION

Identification of individuals who are at risk for sudden cardiac death (SCD), which claims an estimated 325,000 Americans annually, remains an elusive challenge. The mainstay contemporary noninvasive marker of elevated risk is left ventricular ejection fraction (LVEF).¹ However, LVEF has limited sensitivity, as the majority of SCDs occur in patients with relatively preserved mechanical function. In addition, LVEF has limited specificity, since all patients with depressed LVEF do not have the same risk for SCD and thus do not gain the same benefit from an implantable cardioverter-defibrillator (ICD).

Corresponding author: Richard L. Verrier, Ph.D., F.A.C.C., Associate Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Harvard-Thorndike Electrophysiology Institute, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Room 148, Boston MA 02115, Phone: 617-667-0730; FAX: 617-975-5270, Email address: E-mail: rverrier@bidmc.harvard.edu.

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The need for more reliable prognostic indicators has prompted extensive investigations of electrocardiographic markers, particularly T-wave alternans (TWA), defined as a beat-to-beat fluctuation in the morphology and amplitude of the ST segment and/or T wave. The present review will focus on physiologic principles derived from intact animal studies and clinical investigations to discuss the scientific underpinnings for the use of TWA as a SCD risk stratification tool.

Basic Cellular Electrophysiologic Mechanisms Underlying TWA

The underlying cellular mechanisms of TWA have been reviewed in detail elsewhere.^{2–7} Here we briefly summarize some of the highlights. TWA on the surface ECG arises from beat-to-beat alternation of action potential duration (APD) at the level of the cardiac myocyte. Two major conceptual frameworks, namely, APD restitution and calcium cycling dynamics, have been advanced. According to the first, dynamic instabilities in the form of TWA can result from changes in membrane voltage (V_m) due to steep APD restitution (the relationship between APD and the preceding diastolic interval).^{5,8} Flattening the APD restitution curve pharmacologically or otherwise is expected to diminish the propensity for tachyarrhythmias⁹ by reducing the likelihood of progression from spatially concordant TWA to discordant TWA, in which APD alternates out-of-phase in adjoining regions.¹⁰

Discordant alternans is thought to be highly arrhythmogenic because it establishes steep, heterogeneous repolarization gradients and is conducive to reentry and wavebreak.¹¹ It is facilitated by changes in APD and conduction velocity restitution, premature beats, and functional and anatomically based gradients in APD. Among the most important clinically significant anatomical barriers is myocardial scar associated with ischemic heart disease and infarction. In patients with hypertrophic cardiomyopathy, abnormal myocardial fiber orientation and/or fibrosis may constitute potentially arrhythmogenic anatomical barriers, as a positive TWA test has been linked to the severity of histopathological changes.¹²

Alterations in intracellular calcium cycling are an important basis for repolarization alternans.⁷ In normal ventricular myocytes, Ca^{2+} is released from the sarcoplasmic reticulum (SR) through the ryanodine receptor type-2 (RyR2) complex to initiate myocardial contraction. Relaxation develops upon reuptake of Ca^{2+} into the SR by the Ca^{2+} -adenosine triphosphatase (SERCA2a), regulated by phospholamban, and extrusion of Ca^{2+} to the external medium through the action of the Na^+/Ca^{2+} exchanger and the plasma membrane Ca^{2+} ATPase. The Na^+/Ca^{2+} exchanger removes Ca^{2+} from the cytosol, with an exchange of 3 Na^+ in per each Ca^{2+} out, leading to a net positive charge in. As a result, during normal conditions and heart rates, the amount of Ca^{2+} released from the SR equals SR reuptake by SERCA2a. Repolarization alternans can occur whenever the myocyte's capabilities to maintain the balance between release and reuptake is compromised, such as when heart rate is elevated. Even in the normal heart, rapid pacing can elicit concordant TWA with progression to discordant TWA, wherein long/short APDs alternate out of phase with neighboring APDs.

Physiologic influences on TWA

Diverse physiologic interventions have been shown to alter TWA magnitude in parallel with their influence on vulnerability to ventricular tachyarrhythmias. Specifically, these include elevations in heart rate, coronary artery occlusion and reperfusion,^{13,14} and sympathetic nerve stimulation,¹³ as previously reviewed.¹⁵ Conversely, vagus nerve stimulation, blockade of beta-adrenergic receptors, sympathetic denervation, and spinal cord stimulation,¹⁶ which reduce susceptibility to ventricular tachyarrhythmias,¹⁵ have been shown to decrease TWA magnitude.^{15,17} These series of observations underscore the fundamental link between TWA and vulnerability to lethal arrhythmias, which underlies the utility of this parameter in assessing

propensity for life-threatening ventricular arrhythmias. Because of their clinical importance, the roles of heart rate, the autonomic nervous system, and myocardial ischemia are reviewed.

Roles of heart rate and autonomic factors

Heart rate is an integral factor in TWA both experimentally¹⁰ and clinically.¹⁸ However, as will be discussed, heart rate is not the sole determinant, as autonomic neurotransmitters can exert a heart-rate independent influence on TWA magnitude.

Changes in autonomic nervous system activity, particularly beta-adrenergic activation and blockade, can significantly alter the magnitude of TWA. During myocardial ischemia in anesthetized canines, quantifiable increases in TWA are inducible by left stellate ganglion stimulation and ameliorated by surgical interruption of tonic influences of the two ganglia.¹³ Importantly, the sympathetic nervous system results were independent of the effect of heart rate, which was maintained constant by right atrial pacing. In conscious animals, elicitation of an angerlike state significantly increased TWA with and without concurrent myocardial ischemia, and this effect was significantly lessened by acute beta-adrenergic blockade with intravenous metoprolol.¹⁹ Heart-rate independence from adrenergic influences was underscored by the demonstration that rapid pacing alone to a comparable level did not replicate the enhancement in TWA.

In humans, Kaufmann and colleagues¹⁸ compared the effects of increasing heart rate by pacing to ~100 beats/min to beta-adrenergic stimulation with isoproterenol to the same heart rate on TWA test results in normal subjects, in patients with monomorphic ventricular tachycardia, and in patients with a history of sudden cardiac arrest. The results of the combined group analysis, which suggested no difference in TWA positivity between the two protocols, led the investigators to conclude that increased heart rate rather than sympathetic activation is responsible for TWA. However, a rate-independent effect of beta-adrenergic stimulation is evident in the fact that in all of the patients with a history of cardiac arrest, although not in the other groups, beta-adrenergic stimulation with isoproterenol elicited a 2.8-fold increase in TWA magnitude (means from 4.44 to 12.44 μ V) compared to pacing alone. This finding is consistent with the results of electrophysiologic studies conducted by Klingenhoben and coworkers²⁰ with metoprolol and by Rashba et al²¹ with esmolol. They demonstrated that beta-blockade significantly reduced both the number of positive tests and the mean TWA magnitude, further implicating adrenergic factors in TWA in humans. Finally, either by anger recall or by mental arithmetic, mental stress can elicit prognostically significant, elevated TWA in patients with an ICD.^{22,23} By comparison, mental stress exerted only minor changes in TWA magnitude in age-matched healthy volunteers.²² The increase in TWA in both groups occurred with only mild changes in heart rate (<15 beats/min) and therefore was unlikely to be accounted for solely by chronotropic changes.

The mechanisms responsible for the heart-rate independent increase in TWA during beta-adrenergic activation have not been sufficiently studied. It is reasonable to anticipate that there may be indirect influences as a result of increased metabolic demands, which exacerbates myocardial ischemia, decreasing supplies of circulating fatty acids and glucose. As a consequence, cellular ATP levels, which are critical for calcium reuptake by the ATP-dependent SERCA2a pump, would be reduced. No doubt, other complex changes occur.⁵

The effects of parasympathetic nerve activation on TWA are less studied. Pilot data indicate that direct electrical stimulation of the vagus nerve, which decreases susceptibility to ventricular fibrillation, reduced myocardial ischemia-induced TWA in canines during fixed rate pacing.¹⁵ In humans, Rashba and coworkers²¹ have shown that parasympathetic nerve blockade with atropine did not affect a positive or negative TWA determinations during atrial pacing in patients undergoing electrophysiologic testing. However, in this anxiogenic

environment, vagal tone may have been low, and its blockade may underestimate the capacity of vagus nerve activity to influence TWA.

Myocardial ischemia

Extensive evidence in animals during coronary artery occlusion^{13, 14} and in humans during angioplasty¹⁴ indicates that provocation of myocardial ischemia can increase TWA magnitude. In experimental studies in which heart rate was maintained constant, it was demonstrated that myocardial ischemia provokes increases in TWA magnitude in parallel with increased susceptibility to ischemia-induced ventricular fibrillation.¹⁴ This crescendo in TWA was accompanied by marked parallel changes in T-wave complexity and heterogeneity (Fig. 1).^{24,25} The progression in electrical instability was orderly, with a transition from concordant to discordant TWA.

The ionic bases for these changes are not well understood. It is likely although unproven that derangements in both calcium cycling and conduction are involved. It is germane that Clusin and coworkers^{6,26} using luminescent dyes demonstrated both concordant and discordant alternation in calcium transients during myocardial ischemia (Fig. 2). The potential involvement of calcium is also suggested by the observation that calcium channel blockade reversed ischemia-induced TWA in parallel with suppression of arrhythmia in anesthetized canines.²⁷

Potassium channels also appear to be involved in TWA during ischemia, with different spatial (epicardial vs. endocardial) sensitivity of K_{ATP} channel activation.²⁸ Alternans of action potential amplitude was associated with alternation of ST segment, and alternans of action potential upstroke velocity was associated with alternating QRS morphology.

Exercise-Based TWA Prediction of SCD

Most clinical TWA studies for prediction of sudden cardiac death have utilized exercise as a provocative stimulus in diverse patient populations including those with ischemic heart disease, heart failure, or ischemic or nonischemic cardiomyopathy.^{29–34} The basic rationale is that physiologic factors associated with exercise, namely increased heart rate, workload, and sympathetic nerve activity, with concurrent withdrawal of parasympathetic tone, help to disclose latent electrical instability within the vulnerable substrate. The main analytical approach introduced by Cohen, Smith, Rosenbaum and their coworkers and employed for more than a decade is the spectral method, which applies a Fast Fourier Transform to compute the average TWA magnitude throughout the JT interval and in comparison to a mean beat over 128 beats at a constant heart rate during exercise or fixed rate pacing to meet data stationarity requirements.³⁵

Gehi and coworkers performed an extensive meta-analysis to summarize the results of numerous prospective, observational studies with the spectral method, which demonstrated that TWA is a powerful predictor of cardiovascular and arrhythmic mortality with a hazard ratio of 3.77 (95% CI: 2.39–5.95).²⁹ These studies enrolled patients with coronary artery disease, preserved or depressed LVEF, congestive heart failure, and non-ischemic cardiomyopathy. Although most studies using spectral analysis of TWA have concluded that it is valuable in estimating risk for SCD and ventricular tachyarrhythmias, the negative outcome of the recent sizeable MASTER I trial in ICD-treated patients with left ventricular ejection fraction $\leq 30\%$ and history of myocardial infarction has raised questions.³⁶ This study found that the rate of appropriate ICD shocks was not different in patients who were TWA negative compared to those who were non-negative. Two significant limitations of that study could account for this lack of predictivity. These include adoption of ICD shocks as a surrogate endpoint for SCD, despite the facts that shocks have been shown to overestimate arrhythmic

mortality by a factor of two and that the devices themselves may potentially be proarrhythmic. Hohnloser and coworkers³⁷ performed a meta-analysis of studies enrolling nearly 6,000 patients to address the potential confounding influence of ICDs on TWA's predictivity. In prospective primary prevention studies in which ICD use was high, including the MASTER I trial and the recently published TWA substudy of Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),³⁸ they found that the hazard ratio for predicting SCD including appropriate ICD therapies was low, 1.6 (95% CI: 1.2–2.1). By contrast, in studies in which ICD use was low and a low percentage of ICD treatments were employed as endpoints, the predictive capacity of TWA for SCD was high, with a hazard ratio of 13.6 (95% CI: 8.5–30.4). Hohnloser and coworkers concluded that ICD therapy appears to be an unreliable surrogate endpoint for SCD, and this fact may in part account for TWA's apparent lack of predictivity in studies with high use of ICDs.

Recently, interest has developed in applying the time-domain modified moving average (MMA) method to analyze TWA during both routine exercise and ambulatory ECG monitoring.³⁹ The technique is based on the powerful noise-rejection principle of recursive averaging, and respiration and motion artifacts have been further reduced by cubic alignment and other filters. MMA computes TWA as the peak difference between A and B beats in an ABAB beat stream at any point within the JT interval. The predictive capacity of this technique during exercise has been examined in consecutive patients referred for exercise testing enrolled in the Finnish Cardiovascular Study (FINCAVAS).^{32,33} The main indications for the exercise test were to confirm suspicion of coronary heart disease (frequency 46%), test vulnerability to arrhythmia during exercise (18%), and evaluate work capacity (19%) and adequacy of the CHD treatment (24%), as well as to obtain an exercise test profile prior to an invasive operation (13%) or after an MI (10%). Nieminen and coworkers³² found in multivariate analysis in this low-risk population that the relative risk of $TWA \geq 65 \mu V$ for SCD was 7.4 (95% CI, 2.8–19.4; $P < 0.001$), for cardiovascular mortality was 6.0 (95% CI, 2.8–12.8; $P < 0.001$), and for all-cause mortality was 3.3 (95% CI, 1.8–6.3; $P = 0.001$), indicating that TWA exhibits specificity for SCD.

Pathophysiologic Rationale and Clinical Evidence for AECG-Based TWA Prediction of SCD

Until a few years ago, TWA was primarily assessed in conjunction with exercise testing.^{29,31} However, factors other than exercise can trigger arrhythmias during daily activities, in particular, circadian factors, mental stress, and sleep states, which can function as an autonomic stress test for the heart due to adrenergic surges during rapid eye movement (“REM”) sleep⁴⁰ and the occurrence of sleep apnea. Approximately 15% of SCDs occur at night, and patients with disturbed nighttime breathing, particularly 50% of advanced heart failure patients, are at increased risk. Certain channelopathies, including LQT3⁴¹ and Brugada syndromes,⁴² are associated with an increased risk of arrhythmic events during sleep, when reduced heart rates expose the arrhythmogenic effects of their channel defects. AECG monitoring may be advantageous, as these specific disruptions in autonomic and respiratory patterns, which may lead to nocturnal SCD, are not replicated during an exercise test. Moreover, AECG-based TWA testing provides an opportunity for assessment of patients who cannot perform an exercise test.

The utility of AECG monitoring for TWA testing with MMA was examined in two case-control studies of post-myocardial infarction patients. The Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study⁴³ enrolled patients with preserved LVEF. The odds ratios were calculated based on an *a priori* cutpoint at the 75th percentile of TWA magnitude in ATRAMI patients without events during followup. Risk of lethal arrhythmia or cardiac arrest was elevated by 4- to 7-fold when TWA exceeded this cutpoint during peak heart rate, potentially reflecting the influence of enhanced physical and mental activity, and at 8:00 a.m., coinciding with the circadian period of elevated risk for SCD. The MMA-based 47 μV TWA

cutpoint was recently validated in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study, as receiver-operator characteristic curves determined that this TWA magnitude resulted in the most significant separation between hospitalized heart failure patients with left ventricular dysfunction who died suddenly or survived during followup, with relative risk exceeding 5.⁴⁴ Recently, Exner and colleagues determined that the spectral method assessed during exercise and the MMA method monitored during the recovery phase yielded significant odds ratios, 2.75 and 2.94, respectively, in post-myocardial infarction patients with moderately depressed LVEF but without ICDs.⁴⁵

FUTURE OF TWA-BASED ASSESSMENT OF CARDIAC ELECTRICAL INSTABILITY

Quantitative TWA testing

TWA's capacity to predict SCD rests on sound physiologic principles, as this ECG phenomenon reflects the degree of heterogeneity of repolarization, a fundamental trigger of arrhythmias in diverse disease conditions. Accordingly, TWA magnitude can provide a measure of the extent of vulnerability to ventricular fibrillation within the continuum of cardiac electrical instability. Experimental^{13,14,39} and clinical studies using either the spectral method^{20,48} or MMA^{32,33,43,44} reveal that higher TWA magnitudes indicate increased risk for ventricular tachyarrhythmias. Klingenhöfen and colleagues found in patients with infarct-related or nonischemic cardiomyopathy that TWA magnitude, not just its presence, was associated with tachyarrhythmic complications (Fig. 3).⁴⁶ In a recent analysis of the expanded 2000+-patient FINCAVAS database, Minkinen and coworkers found that the risk for SCD and cardiovascular mortality rose sharply when the *a priori* 46 μ V TWA cutpoint was exceeded (Fig. 4).³³ Analysis of AECG recordings from ambulatory subjects⁴⁷ as well as hospitalized patients⁴⁸ reveals a crescendo in the TWA magnitude prior to onset of life-threatening ventricular tachyarrhythmias. These observations lend credibility to employing quantitative analysis, as independent of the analytical methodology, information on TWA magnitude can complement the results of a single cutpoint for a positive TWA test.

Progressing from the current binary all-or-nothing approach to incorporate quantitative TWA testing carries important advantages in terms of gauging risk and guiding therapy. These include the possibility of tracking changes in risk over time, as patients recover and the myocardium remodels, or as cardiac disease or heart failure status are altered. The magnitude of TWA also reflects the effects of pharmacologic therapy without reducing the phenomenon's predictive capacity. The finding that beta-adrenergic blockade with metoprolol, an agent known to reduce SCD, substantially reduces TWA magnitude without affecting its prognostic utility^{20,21,49} is illustrative. As with most clinical measures, such as blood pressure, lipid levels, and LVEF, knowing TWA values within a range can be important in evaluating the patient's status, the urgency of intervention, and effectiveness of therapy.

Quantitative TWA analysis may also prove useful in developing ICD-based therapy for preemptive interventions. Intracardiac recordings both in animals^{13,14} and humans^{50–52} have demonstrated that marked increases in TWA magnitude herald the development of ventricular tachyarrhythmias. Thus, there is interest in developing algorithms for incorporation into implantable devices to monitor TWA magnitude with the goal of device-initiated therapy,^{51, 52} including burst-pacing, activation of autonomic pathways by vagal or spinal cord stimulation,^{16,17,53} or administration of antifibrillatory agents.

Risk Stratification in Patients with Preserved Ejection Fraction

An important frontier for TWA lies in improving arrhythmia risk stratification among patients with preserved LVEF. This is the population in which the majority of SCDs occur although

the incidence is low. Ikeda and colleagues employing the spectral method⁵⁴ and the FINCAVAS and ATRAMI investigators using MMA^{32,33,43} have provided encouraging evidence that TWA can identify individuals at heightened risk for SCD whose LVEF is preserved and whose risk is not indicated by other factors. TWA has high negative predictive value of $\geq 98\%$, but, as is typical for markers in low-risk populations, its positive predictive value is 8–10%.^{32,33,54} To address this concern, there is growing interest in pursuing a combination of noninvasive parameters, particularly autonomic measures, such as heart rate turbulence,⁵⁵ which stratifies risk of cardiovascular death in its own right and fits within the mechanistic framework of SCD as resulting from transient triggers acting on a vulnerable substrate, with cardiac electrical instability quantifiable by TWA.^{14,33,46,47} This approach has gained support from improved prediction with the combination of TWA, heart rate turbulence, and LVEF in the recent investigation by Exner and coworkers.⁴⁵

Thus, TWA testing is based on sound physiologic underpinnings and has an intriguing future in helping to address the elusive challenge of SCD risk stratification and development of mechanistically based anti-SCD therapy.

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ABBREVIATIONS

AECG	ambulatory ECG
APD	action potential duration
ICD	implantable cardioverter defibrillator
LQT	long QT
LVEF	left ventricular ejection fraction
MI	myocardial ischemia
MMA	modified moving average
SCD	sudden cardiac death
SR	sarcoplasmic reticulum
TWA	T-wave alternans

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Fig. 1.

Progression of T-wave complexity in electrograms monitored from a 4-electrode plaque preceding ventricular fibrillation is paralleled by the increasing magnitude of T-wave heterogeneity, assessed by analysis of second central moment, a measure of variance in T-wave morphology among the electrodes.²⁸

Fig. 2. Calcium transients from selected pixels after 4 minutes of ischemia in a blood-perfused heart showing pairs of pixels where alternans is out of phase.²⁹

Fig. 3. Spectral Method TWA output in a patient with nonischemic cardiomyopathy with a positive test. Note the high TWA level in precordial leads V3 (22 μ V) and V4 (24 μ V).⁴⁹

Fig. 4.

Top: Representative ECG tracing (left upper panel) and high-resolution QRS-aligned superimposed waveforms with baseline wander removal and noise filtering (right upper panel) illustrating exercise-induced TWA of $124\mu\text{V}$ in lead V4 in a patient from the Finnish Cardiovascular Study (FINCAVAS) who experienced cardiovascular death at 12 months following the exercise stress test.³⁶ The bidirectional arrow refers to the point of maximum TWA. Bottom: Representative rhythm strip (left lower panel) and QRS-aligned superimposed MMA waveforms (right lower panel) for the maximum TWA ($65\mu\text{V}$) in lead V3 from a patient enrolled in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study.⁴⁷ Note the lack of separation between the superimposed beats in the isoelectric PQRS complex, indicating the low level of noise. The ABAB separation is concentrated within the JT segment, as observed experimentally.^{6,16}