

STATE-OF-THE-ART PAPERS

T-Wave Alternans and
the Susceptibility to Ventricular Arrhythmias

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T-wave alternans (TWA) reflects beat-to-beat fluctuations in the electrocardiographic T-wave, and is associated with dispersion of repolarization and the mechanisms for sudden cardiac arrest (SCA). This review examines the bench-to-bedside literature that, over decades, has linked alternans of repolarization in cellular, whole-heart, and human studies with spatial dispersion of repolarization, alternans of cellular action potential, and fluctuations in ionic currents that may lead to ventricular arrhythmias. Collectively, these studies provide a foundation for the clinical use of TWA to reflect susceptibility to ventricular arrhythmias in several disease states. This review then provides a contemporary evidence-based framework for the use of TWA to enhance risk stratification for SCA, identifying populations for whom TWA is best established, those for whom further studies are required, and areas for additional investigation. (J Am Coll Cardiol 2006;47:269–81) © 2006 by the American College of Cardiology Foundation

Sudden cardiac arrest (SCA) claims over 400,000 lives per year in the U.S. alone, predominantly from ventricular tachycardia (VT) or ventricular fibrillation (VF) (1). Although prophylaxis with the implantable cardioverter defibrillator (ICD) is extremely effective (2–4), identifying individuals who should receive such therapy remains challenging. Certainly, reduced systolic function (4) and heart failure (5,6) are sensitive indices of SCA risk, yet they identify populations in whom arrhythmic event rates may be low (7). From an individual as well as a public health perspective, there is therefore an urgent need for more accurate indices of lethal ventricular arrhythmias.

T-wave alternans (TWA) is a promising electrocardiographic (ECG) index that measures beat-to-beat alternation in T-wave shape, amplitude, or timing. Decades of research now link TWA with inducible (8–10) and spontaneous (11–13) clinical ventricular arrhythmias, and with basic mechanisms leading to their initiation (14). This bench-to-bedside foundation makes TWA a very plausible index of susceptibility to SCA, and motivates the need to define optimal conditions for its detection and clinical populations in whom its potential can be realized.

PHENOMENOLOGY AND HISTORY OF TWA

“T-wave alternans” refers to alternation of the ECG ST-segment (9,15), T- and U-wave (16), and is also termed repolarization alternans (10,17). T-wave alter-

nans refers to *primary* T-wave fluctuations as opposed to T-wave fluctuations *secondary* to electrical alternans totalis (alternans of all ECG components, such as in pericardial effusion) or QRS alternans. Visible TWA was first reported in the early 1900s during tachycardia and ischemia in remarkable observations by Hering (18) and Sir Thomas Lewis (19). Subsequently, visible TWA of increasing subtlety (Figs. 1A to 1C) has been reported in patients with ischemia (11), long QT syndrome (LQTS) (20), electrolyte disturbances, and conversion from tachycardia (21), and consistently linked with ventricular arrhythmias (22,23).

The contemporary use of TWA relies upon microvolt-level fluctuations (Fig. 1D) that are invisible to the unaided eye yet revealed by computerized signal processing methods (8,15,24).

TWA: A SYSTEMS-LEVEL APPROACH

Conceptually, electrical stability of the ventricle lies along a spectrum from regular rhythms to VF. It is now felt that VF, rather than being random, exhibits features of chaotic systems because it is sensitive to initiating conditions and demonstrates characteristic scaling properties (25). In this context, alternans of repolarization (the T-wave) may be considered to be a bifurcation point (26,27) preceding VF. Moreover, when canine hearts are paced under proarrhythmic conditions (norepinephrine administration), they show period doubling (TWA) (26) and, with ischemia, further multippling to higher-order T-wave oscillations imminently preceding VF (28) (Fig. 2). Under such conditions, therefore, repolarization alternans may represent one step in an “orderly” transition to VF.

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Abbreviations and Acronyms

APD	= action potential duration
DI	= diastolic interval
ECG	= electrocardiography
EPS	= electrophysiologic study
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter-defibrillator
LQTS	= long QT syndrome
LV	= left ventricular
LVEF	= left ventricular ejection fraction
MADIT	= Multicenter Automatic Defibrillator Trial
MASTERS	= Microvolt T-wave Alternans Testing for Risk Stratification of post-MI patients
MI	= myocardial infarction
MMA	= Modified Moving Average
MUSTT	= Multicenter Unsustained Tachycardia Trial
NICM	= non-ischemic cardiomyopathy
RR	= relative risk
SAECG	= signal-averaged ECG
SCA	= sudden cardiac arrest
TWA	= T-wave alternans
VF	= ventricular fibrillation
VT	= ventricular tachycardia

PATHOPHYSIOLOGY OF TWA

Work in many preparations has shown that TWA reflects spatial (29) or temporal (14) dispersion of repolarization (Fig. 3), both of which may precede VF (25,30), although the precise pathophysiology underlying microvolt TWA in

humans has not been delineated. In particular, it is unclear how microvolt TWA relates to visible TWA preceding VT or VF (Fig. 1B), although they seem analogous in some studies (14,31).

SPATIAL DISPERSION OF REPOLARIZATION AND TWA

Spatial variations in repolarization (action potential duration [APD], or shape) (29) or conduction velocity (32,33) may prevent depolarization in myocytes that are still repolarizing from their last cycle (Fig. 3 left, region 1). Not only may this cause 2:1 behavior (alternans) and TWA (14), but unidirectional block may occur at sites of delayed repolarization, thus facilitating re-entry. Importantly, proarrhythmic events such as ischemia (34) and extrasystoles (14) have been shown to cause repolarization alternans by exaggerating spatial gradients in repolarization. Under critical conditions, ischemia (34) or extrasystoles (34,35) may reverse the phase of cellular alternans in one tissue region, causing discordant alternans (that is, out-of-phase between regions) and leading to unidirectional block and VF (14).

TEMPORAL DISPERSION OF REPOLARIZATION, APD ALTERNANS, AND TWA

T-wave alternans may also result from the complementary mechanism of temporal dispersion of repolarization, or alternans of action potential shape or APD (Fig. 3, right) (29). Action potential duration alternans may follow accelerated pacing in human atria (36) ventricles (37), and

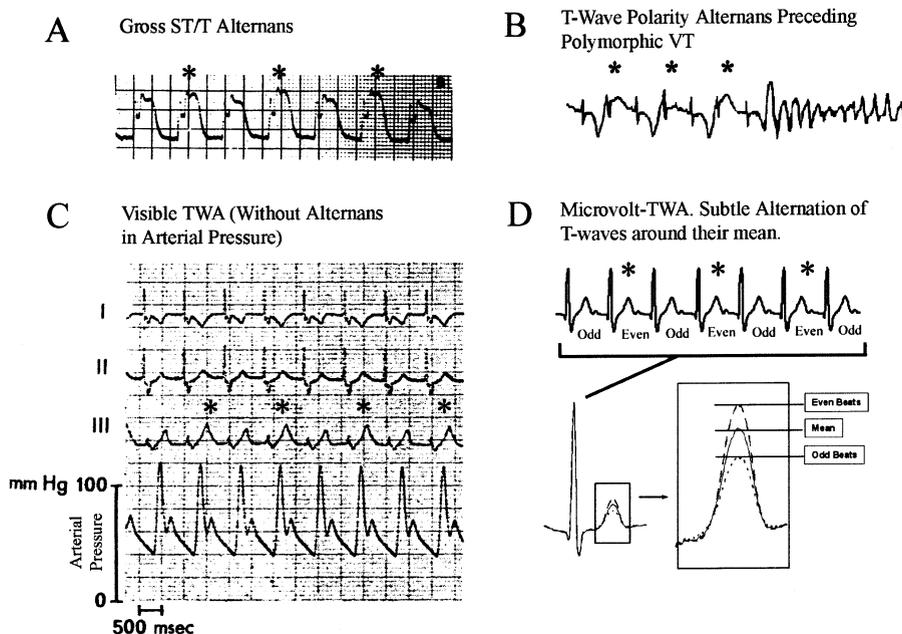


Figure 1. T-wave alternans (TWA) of increasing subtlety detected through the years. (A) *Gross alternans* of elevated ST/T-segments in a patient with angina pectoris preceding ventricular tachycardia (VT); (B) *Visible alternans* of T-wave polarity in a woman without angina, heralding polymorphic VT; (C) *Subtle but visible TWA* after tachycardia termination, without arterial pressure alternans (bottom); (D) *Visually inapparent microvolt-level TWA*, uncovered by digital signal processing (8,23). *The more positive T-wave of each alternating pair. Panel A was reprinted with permission from reference 11. Panel B was reprinted with permission from reference 22, Copyright ©2006 Massachusetts Medical Society. Panel C was reprinted with permission from reference 21.

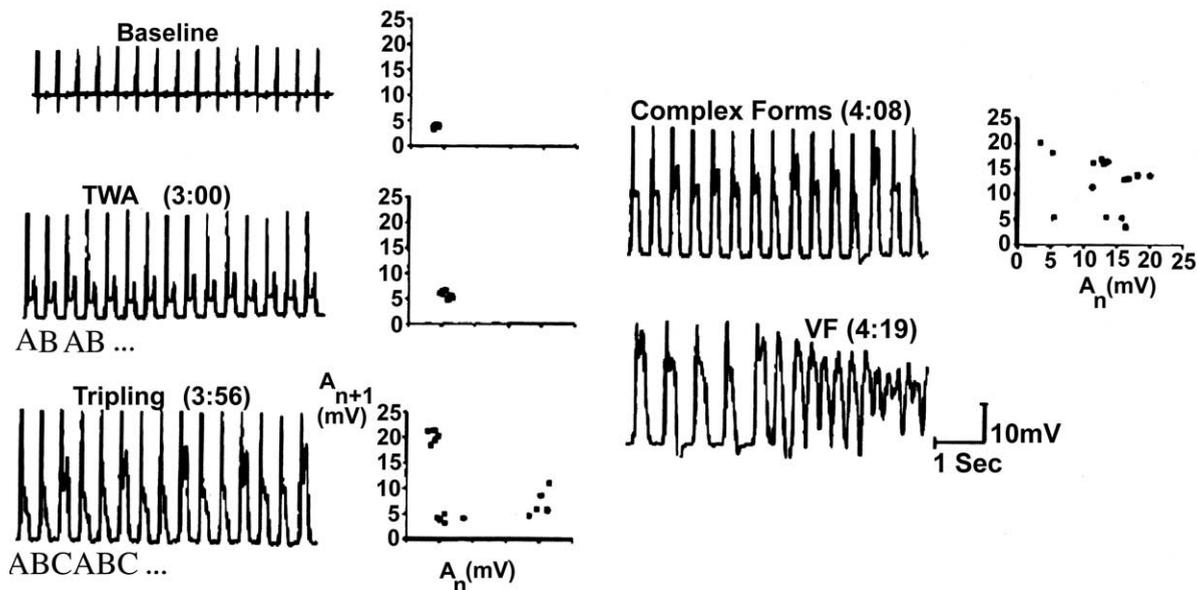


Figure 2. “Orderly transition” from stable rhythm, via T-wave alternans (TWA), to ventricular fibrillation (VF). Electrocardiograms (ECGs) of canine hearts after the onset of ischemia (times in min:s) show period doubling to TWA, i.e., two clusters in the Poincaré plot (T-wave amplitude of each beat against its successor). Further multippling causes higher-order oscillations, complex forms, and then VF. Reprinted with permission from reference 28.

Langendorff-perfused ventricles (14), and, under certain conditions, may lead to conduction block and fibrillation.

Action potential duration alternans is facilitated by the mechanism of *steep restitution*. Action potential duration restitution expresses the relationship between the APD of one beat and the diastolic interval (DI) interval separating it upstroke from the preceding action potential (37) (Fig. 3,

bottom right). If APD restitution is steep (maximum slope >1 ; Fig. 3, bottom right), small changes in DI from a slightly early beat, for example, cause large APD fluctuations that facilitate alternans (38). Under certain conditions (39), this may lead to wavefront fractionation and VF (25). Recent data suggest that steep restitution in conduction velocity (32,33), reflecting analogous rate-related behavior

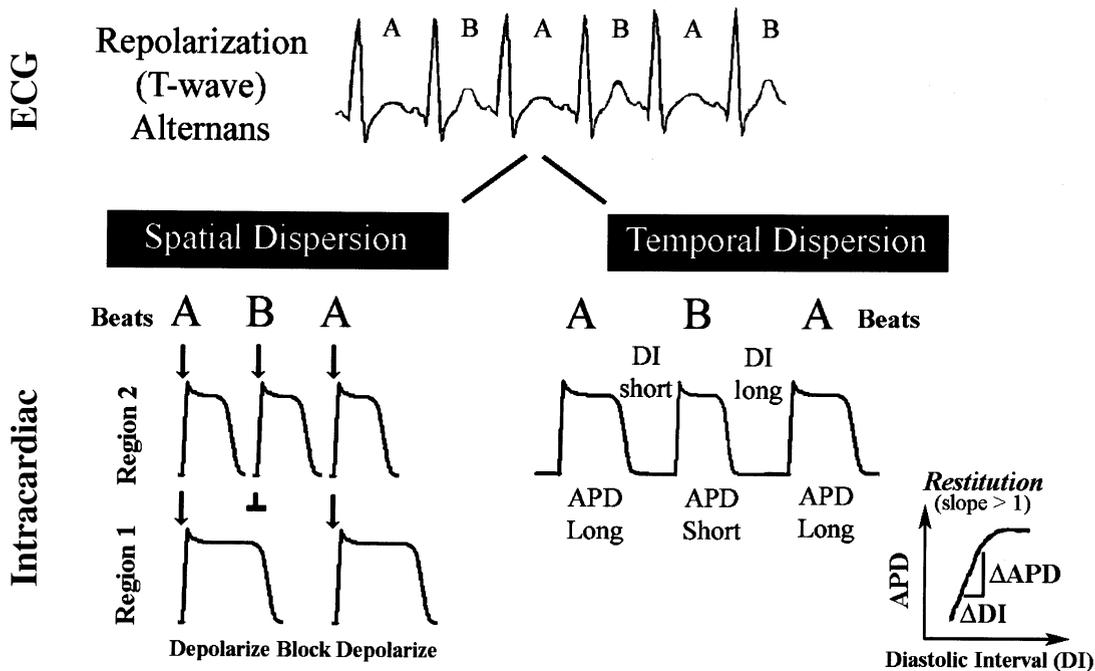


Figure 3. Mechanisms underlying T-wave alternans (TWA). (Left) spatial dispersion of repolarization. Compared to region 2, region 1 has longer action potential duration (APD) and depolarizes every other cycle (beats 1 and 3). (Right) Temporal dispersion of repolarization. Action potential duration alternates between cycles, either from alternans of cytosolic calcium (not shown) or steep APD restitution. Action potential duration restitution (inset) is the relationship of APD to diastolic interval (DI), the interval separating the current action potential from the prior one. If restitution is steep (slope >1), DI shortening abruptly shortens APD, which abruptly lengthens the next DI and APD, leading to APD alternans.

in conduction, and effects from several prior DI (32,39) also contribute to APD alternans and arrhythmias.

Alternans of cytosolic calcium (40,41) may underlie APD alternans at an ionic level (42). Normally, calcium enters the myocyte via voltage-gated L-type Ca^{2+} channels and activates ryanodine receptors to trigger calcium release, from sarcoplasmic reticulum, and contraction. A recirculating fraction of this calcium is sequestered by Ca^{2+} -ATPase, and the remainder is extruded by the Na^{+} - Ca^{2+} exchanger. Rapid heart rates may overload this homeostatic capacity to cause alternans of calcium cycling (40,43) and APD, via effects on membrane currents (42,44). Calcium accumulation may explain hysteresis in repolarization alternans (45) and TWA (10), such that alternans is larger in magnitude following deceleration from a rapid heart rate. Impaired calcium cycling may facilitate APD alternans in heart failure (46). Calcium cycling also links electrical with mechanical alternans (35,41) and explains why, in some preparations, mechanical alternans precedes electrical alternans (43).

Finally, APD alternans during ischemia may also follow transmural differences in potassium channel (K_{ATP}) activity (47), reduced ATP availability (48), or cellular uncoupling (49).

CLINICAL MEASUREMENT OF TWA FROM THE ECG

Several methods exist to measure TWA. Spectral analysis during controlled heart rate acceleration has been the most widely applied to date (50), yet alternative methods of analysis (51) during ambulatory activity (23) may eventually broaden the scope of TWA testing.

Heart rate and other conditions for TWA measurement.

T-wave alternans occurs at elevated heart rates, although at a lower threshold in patients at risk for SCA than in normal individuals (10). Typically, therefore, TWA is measured at heart rates above rest but below rates likely to cause false positives. Exercise (12,52) and pacing (9,53) (indicated by the † symbol in Table 1) have both been used to accelerate heart rate for TWA analysis, and both have merits. Exercise is convenient and was superior in some studies (52), yet pacing has recently been shown to reduce indeterminate TWA tests (54), and prevents rate fluctuations that may artifactually elevate TWA (10,45). Important recent work reveals TWA at times of higher heart rate in ambulatory ECGs (23) that, hypothetically, may reflect the diurnal milieu predisposing to SCA.

It is generally felt that beta-blocking medications should be continued while assessing TWA (55), although interactions with the autonomic nervous system are unclear. On one hand, beta-blockade (56) and sotalol (55) attenuate TWA, reflecting antiarrhythmic effects and improved systolic function (57). On the other, beta-stimulation does not always augment TWA (58). Procainamide (59), amiodarone (60), and calcium-channel antagonists (61) also attenuate

TWA, with unclear impact on its diagnostic accuracy. The effects of digoxin on TWA are unclear.

Measuring TWA spectrally. Spectral analysis (8,15) treats TWA as a signal superimposed upon every other T-wave. For the consecutive ECG beats aligned in Figure 4A, alternans at any time point within the T-wave (arrows) results in oscillations (“up-down-up”) between beats. Fast Fourier transformation represents these oscillations as the spectral peak at 0.5 cycles/beat. Spectra from all T-wave points are then summated. In the summated spectrum, the peak at 0.5 cycles/beat defines the magnitude of alternans (ΣT), distinct from respiratory modulation (“Resp.”) and adjacent spectral noise. T-wave alternans is then quantified as the (a) voltage of alternation (V_{alt}) equal to (ΣT -spectral noise)/T-wave duration; and (b) *k*-score, equal to ΣT /noise standard deviation.

Interpretation of spectral TWA test results. Criteria for interpreting TWA from the most widely used commercial system (Cambridge Heart, Bedford, Massachusetts) are well-described (62), yet are rather detailed. It is therefore helpful if TWA is interpreted by an experienced practitioner. *Positive TWA* (Fig. 4B) is defined as TWA sustained for ≥ 1 min with $V_{\text{alt}} \geq 1.9 \mu\text{V}$ and *k*-score > 3.0 , in any vector (X, Y, Z), or two precordial ECG leads, if onset heart rate < 110 beats/min. Positive TWA must also have $< 10\%$ bad beats and $< 2 \mu\text{V}$ spectral noise *without* artifactual alternans from breathing or relative risk (RR) alternans. *Negative TWA* is the absence of positive TWA as long as a heart rate > 105 beats/min was achieved (“maximum negative heart rate”), whereas *indeterminate TWA* classifies other results. Of many additional criteria (62), recent studies in patients with left ventricular (LV) dysfunction following a myocardial infarction (MI) (labeled with the ‡ symbol in Table 1) used the simple approach of identifying negative TWA, then grouping all other tests (positive and indeterminate) as “abnormal” TWA. This is helpful because indeterminate results occur in 9% to 47% of tests, but seem appropriate only if indeterminacy reflects ectopy, which predicts adverse outcome, rather than ECG noise (62).

Time-domain analyses of TWA. Time-domain analysis of TWA involves subtracting T-waves of “even” versus “odd” beats (Fig. 1D), as in the commercially available Modified Moving Average (MMA) method (23) (GE Systems, Milwaukee, Wisconsin). Time-domain analysis can theoretically measure shorter-duration TWA than spectral analysis and, in preliminary studies, TWA measured over ≥ 15 s stratified SCA risk from ambulatory ECGs in patients after MI (23).

However, the promise of MMA for ambulatory TWA testing is currently limited by the absence of established diagnostic criteria. Furthermore, its sensitivity is unclear because TWA detected by MMA (25 to 100 μV) was an order of magnitude greater than detected spectrally (23). Prospective studies are required to compare the predictive accuracy of TWA using MMA and spectral methods.

Table 1. Studies Linking TWA With Ventricular Arrhythmias in Patients With Post-MI LV Dysfunction

Authors (Reference)	No. of Patients	LVEF, %	CAD, %	CHF Class	End Point	No. End Points	Follow-Up	% Ind TWA	Sens	Spec	PPV	NPV	RR
Predicting inducible VT/VF at EPS													
Smith et al. (8)†	19	—	84	—	VT, VF	13	—	—	92	50	71	83	—
Estes et al. (91)	27	51 ± 14	41	—	VT, VF	10	—	47	89	75	67	92	8.7
Narayan and Smith (10)†	60	41	83	—	VT, VF	36	—	—	88	65	79	78	—
Predicting spontaneous SCA													
Rosenbaum et al. (9)†	66 follow-up (83 total)	—	64	—	VT, VF	13	20 months	—	—	—	—	—	4.5
Hohnloser et al. (74)†	95	36 ± 14	75	—	ICD Rx	41	442 ± 210 days	18	78	61	67	73	2.5
	71 (CAD)		100						85	68	73	81	3.9
Gold et al. (12)	215 (high-risk subgroup)	39 ± 18	55	—	SCA, ICD Rx, mortality	15	195 ± 126 days	24	—	—	—	—	8.0
Verrier et al. (23)	44	42	100	—	SCA, VT, VF	14	21 ± 8 months	N/A	—	—	—	—	7.9
Rashba et al. (68)	144	28 ± 7	100	2.1	VT, VF, ICD Rx	50	509 ± 387 days	25	82	43	40	84	2.2
Narayan et al. (53)†	59	39	100	—	VT, VF mortality	25	36 ± 12 months	—	96	32	55	90	—
Predicting mortality (post-MI, LVEF ≤30%)													
Hohnloser et al. (65)‡	129	26 ± 5	100	—	SCA, VT, VF	20	17 ± 8 months	13	—	—	—	—	5.5
Bloomfield et al. (13)‡	177	23 ± 6	100	1.8	All-cause mortality	23	20 ± 6 months	41	—	—	14*	96*	3.55

*From meta-analysis (50). †TWA elicited by pacing in some/all patients. ‡Indeterminate TWA was grouped with positive TWA.

CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; EPS = electrophysiologic study; ICD Rx = implantable cardioverter-defibrillator therapy for ventricular arrhythmias; Ind = indeterminate TWA test; LV = left ventricle; MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value; RR = relative risk; SCA = sudden cardiac arrest; TWA = T-wave alternans; VF = ventricular fibrillation; VT = ventricular tachycardia; — = data not available.

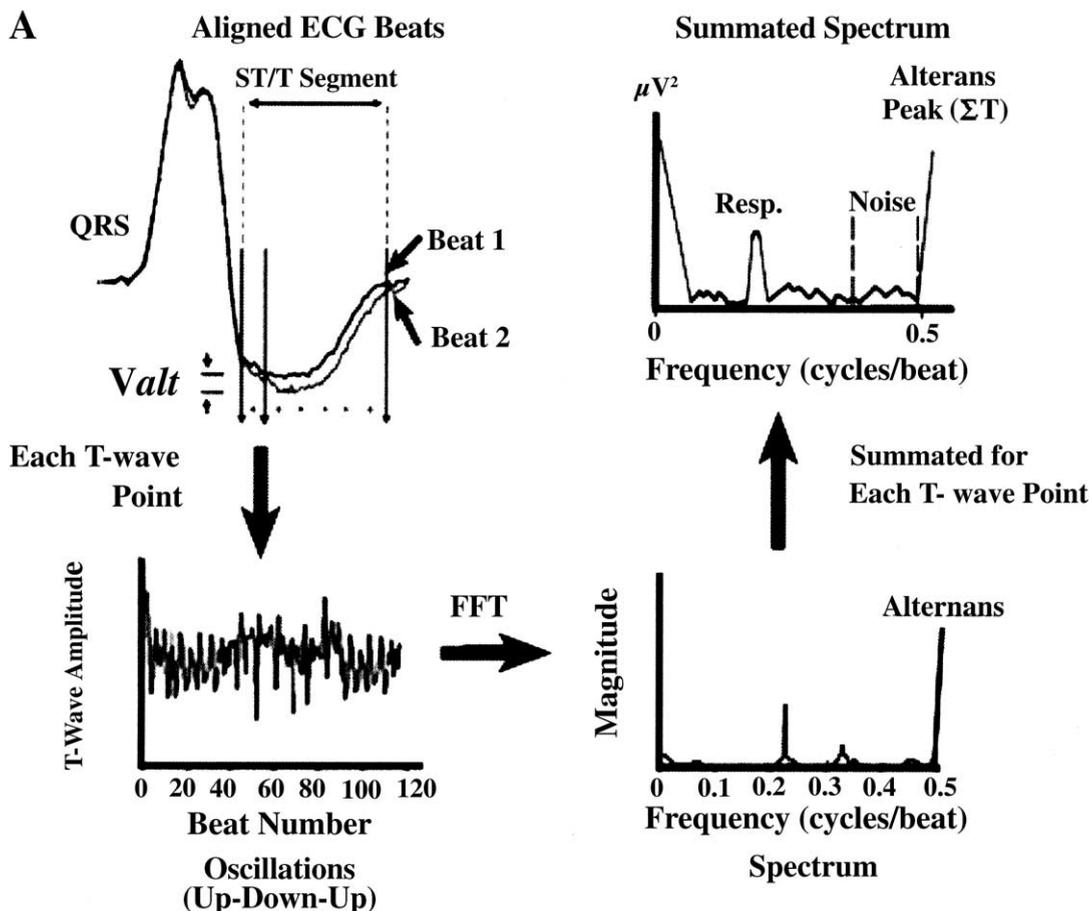


Figure 4. (A) Spectral computation of T-wave alternans (TWA). In the original aligned ECG beats, alternans at each time point within the T-wave (vertical arrows) results in down-up-down oscillations. Fast Fourier transformation (FFT) yields a spectrum, in which the alternating component of these oscillations causes the 0.5 cycles/beat peak (ΣT). In the final spectrum (summed for all time points), ΣT is related to spectral noise to compute V_{alt} and k -score (see panel B).

INCORPORATING TWA INTO CLINICAL RISK STRATIFICATION ALGORITHMS

T-wave alternans is best established for stratifying susceptibility to SCA in high-risk patients (50) with reduced left ventricular ejection fraction (LVEF) and coronary disease (2–4) or heart failure (5). The excellent negative predictive value of TWA in these populations identifies individuals with a very low event rate (Tables 1 and 2), and TWA has therefore been suggested as a component of the proposed national outcomes database for primary ICD therapy (63). Although TWA also stratifies risk in SCA survivors (50), their risk is already well-established, and TWA is less validated in other populations. Scenarios where TWA enhances risk stratification for primary SCA are illustrated in Figure 5, summarized in Tables 1 and 2, and discussed in detail in the following text.

TWA in patients with coronary disease and LVEF $\leq 30\%$. The second Multicenter Automatic Defibrillator Trial (MADIT-2) showed that patients with coronary disease and LVEF $\leq 30\%$ benefit from empiric ICD implantation (4); this is likely most beneficial for patients whose MI occurred at least 40 days previously (64). Potentially,

negatively TWA may identify individuals in this population with a low arrhythmic event rate (7).

In 177 patients of the MADIT-2 type studied by Bloomfield et al. (13), negative TWA predicted improved survival over 20 ± 6 months' follow-up compared with abnormal TWA, providing a negative predictive value of 96% (50) (Table 1). Therefore, although 18 ICD implants were required to save one life in MADIT-2 (4), by also requiring abnormal TWA this number needed to treat falls to seven (13). In a retrospective study by Hohnloser et al. (65) of 129 similar patients, those with negative TWA had no arrhythmic mortality after 24 months, versus 15.6% in those with abnormal TWA (Table 1).

Therefore, in patients of the MADIT-2 type, the addition of negative TWA identifies a very low-risk population. Combining LVEF and TWA as primary and secondary indices is likely more powerful than using either alone (50), and additional combinations should be studied. The just-completed Microvolt T-wave Alternans Testing for Risk Stratification of post-MI patients (MASTERS) study may further clarify these issues by prospectively testing the

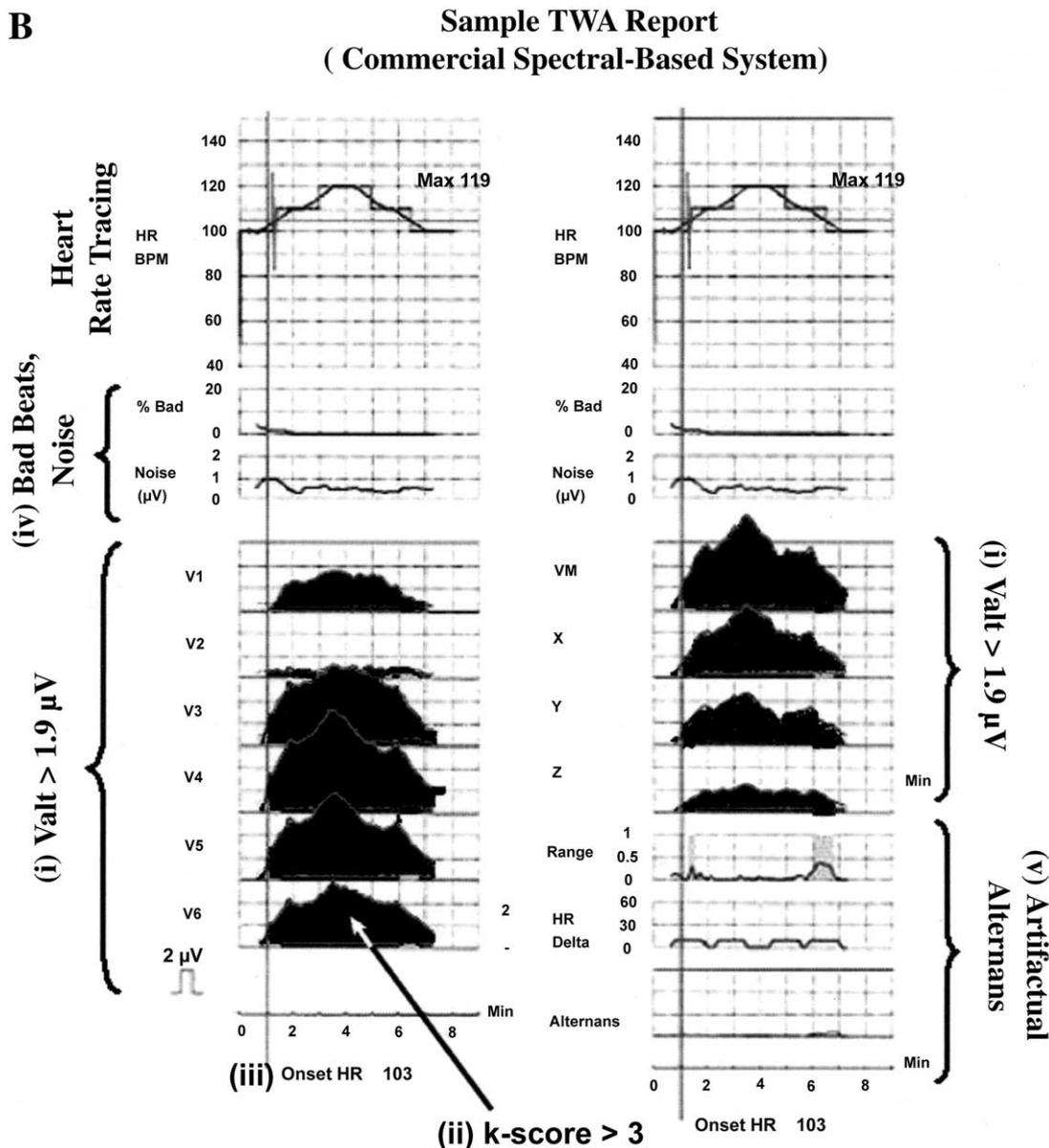


Figure 4 Continued. (B) Positive TWA (from commercial system) shows (i) $V_{alt} \geq 1.9 \mu V$ in two precordial or one vector lead (here $V_{alt} \approx 4$ to $6 \mu V$ in V_3 to V_6) with (ii) $k\text{-score} \geq 3$ (gray shading) for >1 min (here ≈ 5 min), at (iii) onset rate <110 beats/min (here 100 beats/min), with (iv) $<10\%$ bad beats and $<2 \mu V$ noise, without (v) artifactual alternans (see text). Black horizontal bars indicate periods when conditions for positive TWA are met.

predictive value of TWA for arrhythmic events and mortality in 600 MADIT-2 type patients and 1,200 registry patients with LVEF 31% to 40%.

TWA in patients with coronary disease and LVEF 31% to 40%. Risk stratification for SCA is less defined in this population, since individuals with lower LVEF ($\leq 30\%$) were also included in the Multicenter Unsustained Tachycardia Trial (MUSTT) study (required LVEF $\leq 40\%$; mean LVEF 30% [3]) and the first MADIT study (required LVEF $\leq 35\%$; mean LVEF 26% [2]). However, in MUSTT patients with LVEF 31% to 40%, lower risk was identified by the absence of inducible arrhythmias at electrophysiologic study (EPS). However, the fact that EPS-

negative individuals still suffer substantial arrhythmic risk (66) motivates the need for alternative indices.

In the TWA Labeling Study, Gold et al. (12) showed that TWA predicted arrhythmic and overall mortality better than EPS. Their population was mixed, yet in 215 patients at high SCA risk (LVEF $39 \pm 18\%$, 55% with coronary disease; Table 1) negative TWA predicted one-year arrhythmic mortality $<10\%$, while positive TWA had RR for VT/VF of 8.0, versus 3.0 for EPS. In another study of 248 patients, TWA predicted VT, VF, and all-cause mortality in 123 patients with varying structural heart diseases (67). Therefore, one caveat of these studies is their enrollment of heterogeneous patient populations.

Table 2. Studies Linking TWA with Ventricular Arrhythmias in Patients With Heart Failure, or After MI

Authors (Reference)	No. of Patients	LVEF, %	CAD, %	CHF Class	End Point	End Points	Follow-Up	% Ind TWA	Sens	Spec	PPV	NPV	RR
Predicting SCA (patients with CHF, NICM)													
Adachi et al. (92)	58	FS 19%	—	1.6 ± 0.8	VT	16	No F/U Prior VT	17	88	72	—	—	Acc = 77 %
Hennersdorf et al. (93)	60	≈57.5	0	1.63	VT, VF	16	6 months	9	65	98	<30*	100*	>4.45*
Klingenheben et al. (76)	107	28 ± 7	65	>2	VT, VF	13	14.6 months	21	—	—	21*	100*	Infinity
Kitamura et al. (70)	104	41 ± 13	0	1.7 ± 0.7	VT, VF	12	21 ± 14 months	20	92	51	24	97	8.8
Hohnloser et al. (69)	137	29 ± 11	0	—	SCA, VT, VF, ICD Rx	18	14 ± 6 mo	27	87	38	22	94	3.44
Grimm, MACAS et al. (71)	263	30 ± 10	0	2.1	VT, VF, mortality Transpl	38	52 ± 21 months	21	—	—	13*	90*	NP (1.3)
Predicting SCA (after MI)													
Ikeda et al. (78)	834	51% (in 149, LVEF <40)	100	—	SCA or VF	25	25 ± 13 months	12	92	99	7*	100*	11.4
Ikeda et al. (73)	119	28 with LVEF <40	100	—	VT, VF	15	13 ± 6 months	—	93	59	28	98	16.8
Tapanainen et al. (77)	379	45 ± 9.6	100	1.5	Mortality	26	14 ± 8 months	14	—	—	0*	99*	NP; for Ind, RR = 15
Schwab et al. (79)	140	56 ± 14	100	—	Mortality VT/VF	3	451 ± 210 days	26	—	—	4*	99*	NP

*From meta-analysis (50).

Acc = diagnostic accuracy; FS = fractional shortening; MACAS = Marburg cardiomyopathy study; NICM = non-ischemic cardiomyopathy; NP = non-predictive; Transpl = heart transplant; — = data not available; other abbreviations as in Table 1.

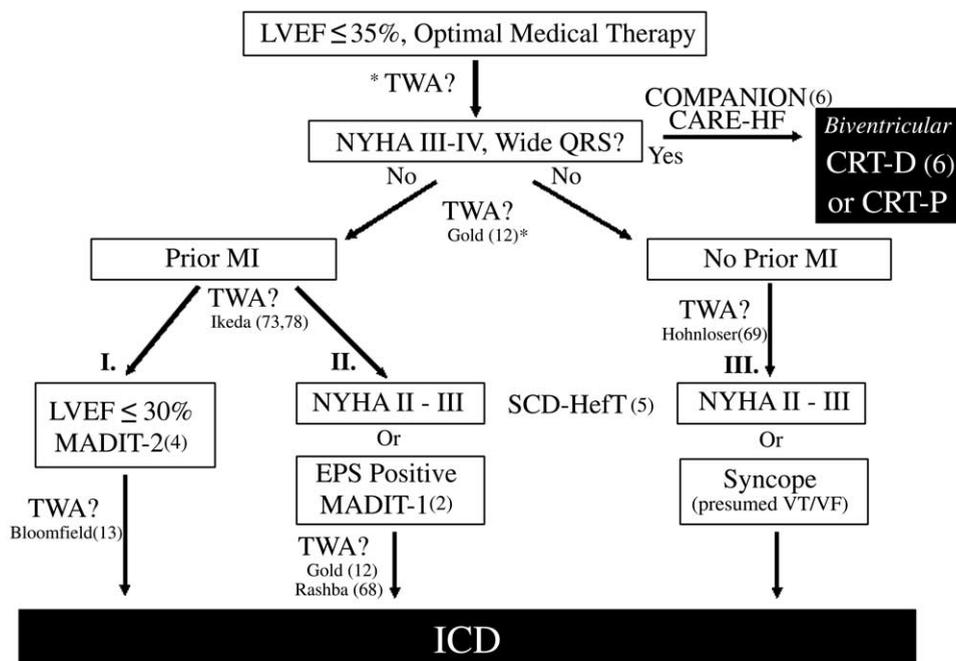


Figure 5. Evidence-based flow chart for primary prevention of sudden cardiac arrest (SCA) including T-wave alternans (TWA). Scenarios where TWA has been validated are referenced, and labels I to III are keys to these sections of the text. *High-risk subgroup of (12) with left ventricular ejection fraction (LVEF) slightly higher than 35%, at $39 \pm 18\%$. See Tables 1 and 2.

In a homogeneous population of 59 patients with coronary disease and mild to moderate LV dysfunction (LVEF $38 \pm 15\%$) without prior VT or VF, Narayan et al. (53) confirmed that TWA better predicted VT, VF, and total mortality than results from EPS or LV mass over 36 ± 12 months, and negative TWA predicted one-year survival $>90\%$. In an important study by Rashba et al. (68) in 144 patients with coronary disease (39% with prior VT or VF), TWA predicted this same end point over 509 ± 387 days' follow-up in patients with LVEF 30% to 40% (Table 1). Notably, EPS added to the predictive value of negative and indeterminate TWA.

Thus, in patients with coronary disease and moderately reduced LVEF, negative TWA identifies patients in whom empiric ICD implantation may be less beneficial. The optimal approach will likely combine TWA with results from EPS or other indices (50). Results from the Alternans Before Cardioverter Defibrillator study, of patients with coronary disease and LVEF $\leq 40\%$ who received ICDs for positive EPS or TWA, may, with the MASTERS study registry, clarify these issues.

TWA in patients with non-ischemic cardiomyopathy (NICM) The Sudden Cardiac Death in Heart Failure trial showed that patients with NICM, LVEF $\leq 35\%$, and heart failure in New York Heart Association functional classes II and III enjoy improved survival with empiric ICD implantation over 5 years' follow-up (5). Recent studies suggest that TWA may improve risk stratification in this population (50).

In 137 patients with NICM (LVEF $29 \pm 11\%$), Hohnloser et al. (69) showed that negative TWA indicated a low

rate of arrhythmic events (Table 2). This was confirmed by Kitamura et al. (70) in 104 NICM patients (LVEF $37 \pm 13\%$), in whom TWA onset ≤ 100 beats/min (not 110 beats/min) gave excellent negative predictive value for arrhythmic events (Table 2).

However, the utility of TWA in NICM has also been questioned. In the Marburg Cardiomyopathy study (MACAS) (Table 2) (71), neither TWA nor other noninvasive tests predicted arrhythmic or transplant-free survival, although LVEF and lack of beta-blocker use did. Notably, beta-blockers were withheld for TWA testing and, although indeterminate TWA was a univariate predictor of arrhythmic mortality, the causes of indeterminacy were not reported. Results from the "TWA in CHF" and "ALPHA" studies may further clarify the role of TWA in this population.

TWA and other non-invasive stratifiers of SCA risk. Many studies have compared TWA to the signal-averaged electrocardiogram (SAECG). Abnormal SAECG reflects slow conduction through scarred myocardium, was shown to predict arrhythmic events in the MUSTT study (72), and, therefore, may complement the repolarization index of TWA. Indeed, in 102 post-MI patients studied by Ikeda et al. (73) (Table 2), abnormal SAECG provided higher positive predictive value for arrhythmic events than TWA, while TWA provided higher negative predictive value and sensitivity. However, when studied by Gold et al. (12), the SAECG (RR = 3.4 for arrhythmic events) was inferior to TWA (RR = 6.1) in a population of whom 55% had coronary disease. In studies by Hohnloser et al. (74), Armoundas et al. (75), and Klingenheben et al. (76), some of which included only patients with NICM (76), the

SAECG was non-predictive of arrhythmias, whereas TWA gave an RR of 2.5, 6.8, and infinity, respectively (Tables 1 and 2). Clearly, the utility of combining SAECG with TWA depends upon the population studied, and still requires definitive clarification in post-MI patients.

Whether other indices add to the predictive value of TWA for SCA is less clear (50). T-wave alternans is more predictive for SCA than widened QRS duration (13), abnormal baroreceptor sensitivity (74,76), heart rate variability (76), or non-sustained VT (74,76). However, in a few studies in which TWA was non-predictive, studies disagree on whether indices such as baroreceptor sensitivity were (77) or were not (71) predictive. Further studies are needed to define optimal combinations of risk stratifiers for different at-risk populations.

TWA immediately after acute myocardial infarction. Risk stratification for SCA after MI remains difficult. The DINAMIT study (64) showed that ICD implantation within 6 to 40 days of most recent MI did *not* reduce mortality in patients with LVEF $\leq 35\%$ (and elevated heart rate or reduced heart rate variability).

T-wave alternans may predict outcome if measured >30 days after MI, although post-MI risk stratification is itself difficult in populations with preserved systolic function and correspondingly low event rates (Table 2). In 834 patients, Ikeda et al. (78) showed that positive TWA measured 2.7 ± 5.4 months post-MI predicted SCA or resuscitated VF. However, when TWA was measured earlier (eight days) after MI by Tapanainen et al. (77), it failed to predict mortality. A similar result was reported by Schwab et al. (79) for TWA measured 15 ± 6 days after MI. The Alternans Cardiac Electrical Stability Study (80) examined 448 patients with LVEF $48 \pm 11\%$ after MI, and reported that TWA evolves from early (5 to 21 days) to later (28 to 56 days) measurements, with 67% concordance. The Risk Estimation Following Infarction-Noninvasive Evaluation study may definitively clarify the evolution of structural disease and TWA after MI.

TWA in other populations. Most cases of SCA occur in the large healthy population of individuals who escape current definitions of “high-risk” (7). Although TWA may stratify SCA risk in subgroups of this population, such as in athletes without structural heart disease (81), it is still most established in patients with some form of heart disease.

TWA IN HYPERTROPHIC CARDIOMYOPATHY (HCM). T-wave alternans may predict outcomes in patients with HCM, in whom indices such as EPS are less useful. In a small recent study (82), TWA was more likely to be positive in patients with HCM than LVH with similar LV mass, and reflected the extent of disarray on biopsy. T-wave alternans may also identify HCM patients at high risk for ventricular arrhythmias (83).

TWA AND QRS WIDENING. Left-bundle branch block predicts mortality in patients with LV dysfunction (84). Notably, TWA was more predictive of mortality than widened

QRS duration (13) in MADIT-2 type patients, although its predictive value in the 32% of patients with QRS duration >120 ms was not reported. In addition, TWA elicited by ventricular pacing predicts inducible (10) and spontaneous (53) ventricular arrhythmias. However, in 108 patients with coronary disease and LVEF $\leq 40\%$, TWA did not predict events if QRS duration >120 ms (85). Thus, the utility of TWA in the presence of QRS widening still requires definitive clarification.

TWA IN THE LQTS. The utility of TWA in patients with LQTS is unclear. Visible TWA (86) is a component of the LQTS point-scoring system and reflects transmural gradients of repolarization (29). Microvolt TWA has also been reported in LQTS 1 to 3, yet its predictive value for arrhythmias has been questioned (87).

TWA IN THE BRUGADA SYNDROME. The utility of TWA in Brugada syndrome also needs further study. In 62 patients with the Brugada ECG pattern, macroscopic TWA (and VT) were induced more often by the sodium channel blocker pilsicainide in patients with than without symptoms (88). Interestingly, exercise-induced TWA may not identify symptomatic patients (89), possibly because exercise is known to attenuate the Brugada phenotype.

TWA AND THE DYNAMIC RISK FOR VENTRICULAR ARRHYTHMIAS. Recent data intriguingly suggest that TWA may identify dynamic arrhythmic triggers. First, TWA rises in patients during anger recall or mental arithmetic (90), likely reflecting heightened sympathetic tone. Second, ventricular extrasystoles abruptly reverse TWA phase in patients at risk for SCA (17), which independently predicts spontaneous arrhythmias (53). Ongoing studies may clarify the link between dynamic perturbations, myocardial electrical stability, and SCA.

Limitations of TWA. There are several clinical and technical limitations on the use of TWA. First, the role of TWA is unclear in patients with atrial fibrillation. The absence of gradual heart-rate increases with exercise has typically precluded its analysis (91), whereas irregular R-R (and hence QT) intervals question the validity of interpreting alternans. Although preliminary studies used ventricular pacing to study TWA in patients with atrial fibrillation (53,54), further validation is needed. Second, the role of TWA is also less clear in patients with non-ischemic cardiomyopathy and mild to moderately reduced LVEF (69,92,93), as well as in the aforementioned patients.

From a technical standpoint, the interpretation of indeterminate TWA must be standardized, since at present some studies considered indeterminate TWA as “abnormal” (labeled with the ‡ symbol in Table 1), whereas others did not. Attempts to reduce indeterminacy, such as measuring TWA in pacing (54), should also be explored further. One final limitation is that TWA analysis is currently performed at a single point in time. Analysis of TWA over extended time periods, such as from ambulatory heart-rate records

(23), may extend its future utility and promote repeated measurements.

CONCLUSIONS

T-wave (repolarization) alternans is a promising ECG index of sudden cardiac arrest that has been linked with dispersion of repolarization and ventricular arrhythmias. Clinically, TWA has excellent negative predictive value for ventricular arrhythmias in patients with reduced systolic function, in whom negative TWA identifies individuals who may benefit less from empiric ICD therapy. However, the value of TWA in other populations, the optimum time and conditions for its measurement, and the value of combining it with additional risk markers need further definition. Future studies may establish TWA as an integral part of risk stratification for SCA and define its role in patients with QRS widening, atrial fibrillation, and diverse etiologies for cardiac disease.

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