Published in final edited form as:

Prog Cardiovasc Dis. 2008 ; 51(2): 118–127. doi:10.1016/j.pcad.2007.11.001.

T-Wave Alternans Testing For Ventricular Arrhythmias

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Keywords

T-wave Alternans; Repolarization Alternans; Calcium overload; Heart Failure; Sudden Cardiac Death; Sudden Cardiac Arrest

Introduction

Sudden cardiac arrest (SCA) from ventricular arrhythmias is the largest cause of death in industrialized countries and claims over 300,000 lives in the U.S. per year (1). Unfortunately, identifying individuals at risk of this fate remains challenging, as does the task of optimally identifying potential recipients of the implantable cardioverter-defibrillator (ICD). Although reduced systolic function (2) and heart failure (3) identify risk, they lack specificity.

T-wave Alternans (TWA) is a promising ECG index of arrhythmic susceptibility, that has been shown to provide a high negative predictive value for ventricular arrhythmias (4) and thus identify individuals who may not benefit from ICD implantation (5). T-wave alternans measures beat-to-beat fluctuations in the timing or shape of the ECG T-wave, and was first observed nearly a century ago (6,7). Visible TWA has since been linked with arrhythmias in the long QT syndrome (8), electrolyte abnormalities (9) and ischemia (10) and, over time, has been detected at increasingly subtle levels (fig. 1). Contemporary TWA testing uses ECG signal processing to detect oscillations on the order of microvolts that are invisible to the unaided eye yet related mechanistically to visible TWA (4).

Pathophysiology of TWA

A wealth of bench-to-bedside studies show that alternans of intracardiac repolarization (action potential duration, APD) may directly initiate ventricular arrhythmias in animals (11,12), and may be linked with human microvolt-level TWA (13,14). These mechanistic studies provide unique scientific validation to TWA as a risk stratifier, although some details on the link between TWA and human arrhythmias remain unclear (13,14).

TWA and Spatial Repolarization Dispersion

The left panel of figure 2 shows spatial repolarization dispersion between regions 1 and 2. APD is longer in region 1 than 2 and so, at fast heart rates, region 1 may still be repolarizing and fail to depolarize every-other-beat (15). Regions of long APD may also be sites of block where

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reentry initiates (16). Ischemia or extrasystoles may exaggerate spatial dispersion in animals (17) and amplify human TWA (18). Under critical conditions, such factors may reverse the phase of cellular Alternans so that juxtaposed regions alternate out-of-phase. The interface (nodal lines) between such *discordant* regions can be sites of unidirectional block that lead to reentry (11,12).

TWA and Action Potential Alternans

Alternatively, the right panel of figure 2 shows that APD may alternate at a single site (temporal dispersion). Indeed, APD alternans has been shown in human ventricles (19) (and human atria (20)) at very fast rates > 200 beats/min and, if it disorganizes, may lead to fibrillation. *Steep APD restitution* (11,12) may facilitate this. Restitution relates APD to the diastolic interval (DI) separating the current beat from the last beat. As in the figure 2 inset (bottom right), steep restitution (slope > 1) enables a premature beat (with short DI) to lead to amplified oscillations in APD and DI that may lead to wave break; this is facilitated by slow conduction or a premature beat (12,21).

Recent data show that alternans may reflect oscillations in cytosolic calcium (22), potentially explaining the link between TWA, heart failure (23) and volume load (24). Thus, steep restitution is less implicated in TWA that is clinically apparent at < 109 beats/min (25). At such rates, APD restitution is flat even if maximum slope (at short DI) is steep (fig. 3) (14).

Measuring TWA

Practical Considerations When Measuring TWA

TWA is a rate-related phenomenon that is typically measured during gradual rate rises. TWA develops < 110 beats/min in patients at risk for SCA, but also arises in controls at faster rates. Thus, measurement at < 109 beats/min minimizes false positives (25). Thus, TWA is not tested during atrial fibrillation, because RR irregularities influence repolarization and prevent controlled heart rate elevations.

Heart rate is preferably accelerated by exercise (26). Since some patients cannot easily exercise, pacing has also been used (27,28) although such TWA may be less clinically useful (26). Finally, small studies have used atropine and dobutamine (29) to accelerate heart rate, yet these methods likely modulate TWA directly (30) and are not validated or recommended.

Recent studies confirm that β -blocking medications can be continued while measuring TWA (31). Anti-arrhythmic drugs such as procainamide and amiodarone may attenuate TWA, with unclear effects on its clinical utility (4).

Interpretation of Spectrally Measured TWA

TWA is most commonly extracted using spectral analysis, that considers TWA as a periodic signal superimposed on T-waves at a frequency of half the heart rate (18). Criteria for positive spectral TWA are well-described for the most widely used system (Cambridge Heart, Bedford, MA) (25). However, clinicians are now recommended to use the automated Alternans Report Classifier *without* over-reading (23,32), that greatly simplifies interpretation and minimizes reproducibility issues that may have caused recent discrepant results (33,34).

It is recommended that indeterminate tests are immediately repeated, that may reduce the indeterminacy rate (35). Once a test has been classified (positive, negative or indeterminate), tests are grouped as 'abnormal' any tests that are positive *and* indeterminate due to physiologic causes (e.g. failure to achieve sufficient heart rate) *but not noise* (36). Grouping positive and indeterminate TWA from causes *including* noise (5) is now considered suboptimal.

Alternative Methods of Extracting TWA, and their interpretation

Alternative mathematical approaches for TWA are becoming available, although they are less well validated. One example computes a modified moving average (MMA) of even versus odd beats, and subtracts them to identify TWA (37) (GE Medical Systems, Milwaukee, WI).

TWA detected via MMA was recently used to predict mortality in a large Finnish population undergoing routine exercise testing (38). These patients were at low risk for adverse outcomes (most had normal systolic function). Our group recently compared MMA-TWA to spectral TWA in patients with systolic dysfunction, and found that MMA significantly amplified TWA and was less specific for SCA than spectral TWA (39). At present, therefore, few clinical data support the use of TWA extracted by the MMA method to stratify risk for arrhythmic events.

Incorporating TWA into Risk Stratification Schemes for SCA

The major issue in using TWA is to incorporate TWA test results into practice guidelines. TWA recently received a class IIa indication in guidelines by the American College of Cardiology, American Heart Association and European Society of Cardiology (40), because its high negative predictive value (NPV) in many populations implies that individuals who test TWA negative may not require an ICD (5). Nevertheless, TWA has yet to be formally integrated into ICD implantation guidelines. This section (and the table) summarizes the utility of TWA in specific populations, and figure 4 provides a suggested practice flowchart incorporating the results from TWA testing.

I. TWA in Patients with Moderately Reduced Systolic Function (LVEF $\leq$ 40 %) and Coronary Disease

The use of TWA is best supported in this population. As summarized in the table, the Alternans Before Cardioverter Defibrillator (ABCD) study examined 566 patients (age 65 ± 10 years, 84 % male) with prior MI and LVEF ≤ 40 % in NYHA classes I-III. Although the final publication is awaited, TWA provided 95 % NPV for sustained arrhythmias and positive TWA gave a hazard ratio of 2.1. TWA complemented electrophysiologic testing (EPS), with a combined NPV of 98% (32). These results support the original 'TWA Labeling Study' that, in 215 pre-specified 'high-risk' patients (LVEF 39 ± 18 %, 55 % with coronary disease) showed that TWA provided NPV > 90 % for 1-year arrhythmic mortality. The relative risk of positive TWA for VT/VF was 8.0 (versus 3.0 for EPS) (41). Our group also confirmed this result in 59 patients with coronary disease and LVEF 38 ± 15 % (42).

One important caveat is that TWA may be less effective in patients with baseline QRS widening (43,44) (table). It is unclear if this reflects worse outcome associated with intraventricular conduction delay (2) or the impact of secondary T-wave abnormalities on TWA (45).

II. TWA in Patients with Severely Depressed Systolic Function (LVEF $\leq 30\%$) and Coronary Disease

It is less clear whether TWA is useful in this population. In the important study by Rashba et al. in 144 patients with coronary disease and LVEF 28 ± 7 %, TWA predicted arrhythmic mortality after 509 ± 387 days in patients with moderate systolic dysfunction (LVEF 31–40 %), but *not* those with LVEF $< 30\%$ (46). TWA was also less effective in patients with LVEF ≤ 30 % versus those with LVEF 31–40 % in the ABCD study (32).

Nevertheless, conflicting data exist that TWA *does* stratify risk in such patients. In $n=177$ patients, Bloomfield et al. (47) showed that TWA predicted higher survival over 20 ± 6 months than abnormal TWA, and that abnormal TWA provided a hazard ratio for total mortality of 4.8. Retrospective studies also support this result (48). If confirmed, results from Bloomfield

et al. suggest that the number needed to treat to save one arrhythmic death in patients enrolled in the second Multicenter Automated Defibrillator Trial (MADIT-2) (2) would fall from 18 to 7 (47).

Further studies are needed to establish if TWA provides high NPV in patients with severe systolic dysfunction (figure 4). Indeed, TWA may be more effective in subsets of this population, such as those with narrow QRS duration (2,44) and better NYHA functional class. Clarification may come from subset analysis of the ABCD trial, and from the Microvolt T-wave Alternans Testing for Risk stratification of post-MI patients (MASTER) study, that prospectively tested the predictive value of TWA for arrhythmic events in 600 MADIT-2 type patients.

III. TWA in Patients with Non-Ischemic Systolic Dysfunction and Symptoms

Many studies support the use of TWA in this population, particularly in patients with better preserved systolic function. The recently presented ALPHA study examined 446 patients (age 59 ± 13 years, 78 % male) with $LVEF \leq 40$ % and NYHA functional classes II-III (35). Although the final publication is awaited, the hazard ratio of abnormal TWA for arrhythmic events was 3.2 with NPV 98 % at 21 months. The trial was well performed in that all TWA was elicited by exercise, consistency was ensured by the Alternans Report Classifier, and indeterminate TWA tests were repeated. This may explain the low 21 % rate of indeterminacy. These data are supported by the TWA in CHF trial (547 patients with $LVEF \leq 40$ %), of whom 358 were in NYHA class II-III. In the non-ischemic cohort, TWA provided a 2-year NPV for arrhythmic events of 97.1 %, and patients with abnormal TWA showed a 17.7 % event rate (23).

However, negative studies exist. Most notably, 490 patients in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) were tested for TWA (34). Although the final publication is awaited, TWA did not predict arrhythmic events. One potential confounder was the high 41 % rate of indeterminate TWA, versus 21–35 % in prior trials (5,23,33). It is unclear how many indeterminate TWA tests were noisy and should ideally have been excluded (36), and how often TWA was elicited by pacing (e.g. from ICDs), that is less diagnostic than exercise-induced TWA (26). The Marburg Cardiomyopathy study (MACAS) in 343 patients also found that TWA (and other non-invasive tests) did not predict arrhythmic or transplant-free survival after 52 ± 21 months (33). Limitations of that study are that the causes of indeterminate TWA tests were not elaborated, and β -blockers were withheld during TWA testing.

Thus, TWA may stratify risk for SCA in patients with non-ischemic cardiomyopathy in NYHA functional classes II-III, and may be more effective in patients with better preserved systolic function ($LVEF$ 31–40%). Differences in measurement practice may also explain discrepancies between trial results, and should be minimized in future work.

IV. TWA in Patients with Minimal Systolic Dysfunction Post-Myocardial Infarction

Most individuals in this population do not meet current indications for ICD implantation (40). Although their SCA risk is higher than in individuals without structural disease, event rates are sufficiently low that a risk stratifier must show a high positive predictive value (PPV).

In 1041 post-infarction patients with $LVEF > 40$ %, TWA measured 48 ± 66 days post-MI predicted arrhythmic events with a hazard ratio (of an abnormal TWA) for arrhythmic events of 19.7 and NPV of 99.6 % at 32 ± 14 months (49). Unfortunately, the important PPV measure was disappointing (9 %). Importantly, TWA is likely not effective if measured acutely in the peri-infarct period (<30 days) (4), and this likely explains the negative results in some studies and hence in a recent meta-analysis (50).

Thus, exciting preliminary data suggest that TWA may help to stratify arrhythmic risk in patients with minimal systolic dysfunction > 30 days post-MI. Future work may improve the positive predictive value in this population by incorporating TWA into a risk scoring system with other clinical features (51). Results from the awaited Risk Estimation Following Infarction - Noninvasive Evaluation (REFINE) trial may better clarify the effectiveness of combining TWA with other risk factors in post-MI patients.

Limitations

TWA is not validated during atrial fibrillation. Although TWA during ventricular pacing could potentially be used during AF and in patients with AV block, and has been reported by several groups (45,52,53), it requires validation in larger populations. TWA interpretation is now simplified by recommendations to use the Alternans Report Classifier *without* manual over-reading (23,32). Although indeterminate results remain a limitation, if indeterminate tests due to noise are excluded (< 10 % of all tests) then the remainder can be combined with positive TWA as 'abnormal' TWA (36).

Many limitations of TWA may be obviated, in part, by its inclusion in a risk score (51). In particular, TWA be more valuable if combined with clinical features such as QRS widening (2,44), imaging for post-MI de-innervation (54), invasive electrophysiologic testing (32,46) and the signal-averaged ECG (55) discussed elsewhere in this volume. Ongoing studies are evaluating this concept.

Conclusions

T-wave alternans is an ECG index that has been linked mechanistically with ventricular arrhythmias in numerous bench-to-bedside studies. Prospective studies now confirm that TWA has a one-year negative predictive value for ventricular arrhythmias near 95 % in populations with mild, moderate and potentially even severely reduced systolic function. Consensus from the clinical community is now required to integrate TWA into clinical management flowcharts, as suggested in this work. Future improvements in predictive value may involve the combination of TWA with QRS widening and other clinical features of high-risk.

Acknowledgments

This work was supported by grants from the National Heart, Lung and Blood Institute (HL 70529, 83359), and Doris Duke Clinical Foundation to SMN.

References

1. Zheng Z-J, Croft JB, Giles WH, Mensah GA. Sudden Cardiac Death in the United States, 1989 to 1998. *Circulation* 2001;104:2158–2163. [PubMed: 11684624]
2. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *N Engl J Med* 2002a;346:877–883. [PubMed: 11907286]
3. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. *New Engl J Med* 2005;352:225–237. [PubMed: 15659722]
4. Narayan SM. T-Wave Alternans and The Susceptibility to Ventricular Arrhythmias: State of the Art Paper. *J Am Coll Cardiol* 2006a;47:269–281. [PubMed: 16412847]
5. Chow T, Kereiakes D, Bartone C, et al. Microvolt T-wave alternans identifies patients with ischemic cardiomyopathy who benefit from implantable cardioverter-defibrillator therapy. *J Am Coll Cardiol* 2007;49:50–58. [PubMed: 17207722]
6. Hering H. Experimentelle Studien an Säugetieren über das Electrocardiogram. *Z. Exper Med* 1909;7:363.

7. Lewis T. Notes upon alternation of the heart. Q. J. Med 1910;4:141–144.
8. Roden DM, Lazzara R, Rosen M, Schwartz PJ, Towbin J, Vincent GM. LQTS tSFTFo. Multiple Mechanisms in the Long-QT Syndrome: Current Knowledge, Gaps, And Future Directions. Circulation 1996;94:1996–2012. [PubMed: 8873679]
9. Reddy CVR, Kiok JP, Khan RG, et al. Repolarization alternans associated with alcoholism and hypomagnesemia. Am J Cardiol 1984;53:390–391. [PubMed: 6695758]
10. Roselle HA, Crampton RS, Case RB. Alternans of the depressed ST segment during coronary insufficiency. American Journal of Cardiology 1966;18
11. Walker ML, Rosenbaum DS. Cellular alternans as mechanism of cardiac arrhythmogenesis. Heart Rhythm 2005;2:1383–1386. [PubMed: 16360097]
12. Weiss JN, Karma A, Shiferaw Y, Chen P-S, Garfinkel A, Qu Z. From Pulsus to Pulseless: The Saga of Cardiac Alternans (Review). Circ Res 2006;98:1244. [PubMed: 16728670]
13. Selvaraj RJ, Picton P, Nanthakumar K, Mak S, Chauhan VS. Endocardial and Epicardial Repolarization Alternans in Human Cardiomyopathy: Evidence for Spatiotemporal Heterogeneity and Correlation with Body Surface T wave Alternans. J. Am. Coll. Cardiol 2007;49:338–346. [PubMed: 17239715]
14. Narayan SM, Franz MR, Kim J, Lalani G, Sastry A. T-wave Alternans, Restitution of Ventricular Action Potential Duration and Outcome. J Am Coll Cardiol. 2007;in press
15. Chinushi M, Restivo M, Caref EB, El-Sherif N. Electrophysiological Basis of Arrhythmogenicity of QT/T Alternans in the Long QT Syndrome: Tridimensional Analysis of the Kinetics of Cardiac Repolarization. Circulation Research 1998a;83:614–628. [PubMed: 9742057]
16. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism Linking T-wave alternans to the Genesis of Cardiac Fibrillation. Circulation 1999;99:1385–1394. [PubMed: 10077525]
17. Hashimoto H, Suzuki K, Nakashima M. Effects of the ventricular premature beat on the alternation of the repolarization phase in ischemic myocardium during acute coronary occlusion in dogs. J. Electrocardiol 1984a;17:229–238. [PubMed: 6207256]
18. Narayan SM, Lindsay BD, Smith JM. Demonstrating the Pro-arrhythmic Preconditioning of Single Premature Extrastimuli Using the Magnitude, Phase and Temporal Distribution of Repolarization Alternans. Circulation 1999d;100:1887–1893. [PubMed: 10545433]
19. Koller ML, Maier SKG, Gelzer AR, Bauer WR, Meesmann M, Gilmour RF Jr. Altered Dynamics of Action Potential Restitution and Alternans in Humans With Structural Heart Disease. Circulation 2005;112:1542–1548. [PubMed: 16157783]
20. Narayan SM, Bode F, Karasik PL, Franz MR. Alternans Of Atrial Action Potentials As A Precursor Of Atrial Fibrillation. Circulation 2002b;106:1968–1973. [PubMed: 12370221]
21. Banville I, Gray RA. Effect of Action Potential Duration and Conduction Velocity Restitution and Their Spatial Dispersion on Alternans and the Stability of Arrhythmias. J Cardiovasc Electrophysiol 2002;13:1141–1149. [PubMed: 12475106]
22. Pruvot EJ, Katra RP, Rosenbaum DS, Laurita KR. Role of Calcium Cycling Versus Restitution in the Mechanism of Repolarization Alternans. Circ Res 2004;94:1083–1090. [PubMed: 15016735]
23. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-Wave Alternans and the Risk of Death or Sustained Ventricular Arrhythmias in Patients With Left Ventricular Dysfunction. Journal of the American College of Cardiology 2006;47:456–463. [PubMed: 16412877]
24. Narayan SM, Drinan DD, Lackey RP, Edman CF. Acute Volume Overload Elevates T-Wave Alternans Magnitude. J Appl Physiol 2007b;102:1462–1468. [PubMed: 17158246]
25. Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and Classification of Microvolt T-Wave Alternans Tests. J. Cardiovasc Electrophysiol 2002;13:502–512. [PubMed: 12030535]
26. Rashba EJ, Osman AF, MacMurdy K, et al. Exercise is superior to Pacing for the Measurement of T-Wave Alternans. J Cardiovasc Electrophysiol 2002;13:845–850. [PubMed: 12380918]
27. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330:235–241. [PubMed: 8272084]
28. Narayan SM, Smith JM, Lindsay BD, Cain ME, Davila-Roman VG. Relation of T-Wave Alternans to Regional Left Ventricular Dysfunction and Eccentric Hypertrophy Secondary To Coronary Artery Disease. Am. J. Cardiol 2006b;97:775–780. [PubMed: 16516574]

29. Ritvo BS, Magnano AR, Bloomfield DM. Comparison of exercise and pharmacologic methods of measuring T wave alternans [abstract]. *Pacing and Clinical Electrophysiology* 2000;23:688.
30. Rashba EJ, Cooklin M, MacMurdy K, et al. Effects of Selective Autonomic Blockade on T-Wave Alternans in Humans. *Circulation* 2002a;837–842.
31. Zacks E, Morin D, Ageno S, et al. Effect of oral beta-blocker therapy on microvolt T-wave alternans and electrophysiology testing in patients with ischemic cardiomyopathy. *Am Heart J* 2007;153:392–397. [PubMed: 17307418]
32. Costantini O, Rosenbaum DS, Hohnloser SH, et al. The Alternans Before Cardioverter Defibrillator (ABCD) Trial: A Noninvasive Strategy for Primary Prevention of Sudden Cardiac Death Using T Wave Alternans (abstract). *Late Breaking Clinical Trials III. Circulation* 2006;114:2426.
33. Grimm W, Christ M, Bach J, Muller H-H, Maisch B. Noninvasive Arrhythmia Risk Stratification in Idiopathic Dilated Cardiomyopathy: Results of the Marburg Cardiomyopathy Study. *Circulation* 2003b;108:2883–2891. [PubMed: 14623812]
34. Gold MR, Chilson D, Ip JH, et al. T-Wave Alternans SCD HeFT Study: Primary Endpoint Analysis (Abstract). *Circulation* 2006;114:2113. [PubMed: 17088465]
35. De Ferrari G, Klersy C, Ferrero P, et al. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. *Eur J Heart Failure* 2007;9:502–509.
36. Kaufman E, Bloomfield D, Steinman R, Namerow P, Costantini O, Cohen R, Bigger JJ. "Indeterminate" microvolt T-wave alternans tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;48:1399–1404. [PubMed: 17010802]
37. Nearing BD, Verrier RL. Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. *J Appl Physiol* 2002a;92:541–549. [PubMed: 11796662]
38. Nieminen T, Lehtimäki T, Viik J, et al. T-wave alternans predicts mortality in a population undergoing a clinically indicated exercise test. *Eur Heart J* 2007;28:2332–2337. [PubMed: 17652105]
39. Cox VL, Patel M, Kim J, Liu T, Sivaraman G, Narayan SM. Predicting Arrhythmia-Free Survival Using Spectral and Modified-Moving Average Analyses of T-Wave Alternans. *Pacing & Clinical Electrophysiology* 2007;30:352–358. [PubMed: 17367354]
40. ACC/AHA/ESC. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death—Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:1064–1108.
41. Gold MR, Bloomfield DM, Anderson KP, et al. A Comparison of T Wave Alternans, Signal Averaged Electrocardiography and Programmed Ventricular Stimulation for Arrhythmia Risk Stratification. *J. Am. Coll. Cardiol* 2000a;36:2247–2253. [PubMed: 11127468]
42. Narayan SM, Smith JM, Schechtman KB, Lindsay BD, Cain ME. T-wave alternans phase following ventricular extrasystoles predicts arrhythmia-free survival. *Heart Rhythm* 2005a;2:234–241. [PubMed: 15851310]
43. Rashba EJ, Osman AF, MacMurdy K, et al. Influence of QRS duration on the prognostic value of T wave alternans. *J. Cardiovascular Electrophysiol* 2002f;13:770–775.
44. Morin DP, Zacks ES, Mauer AC, et al. Effect of Bundle Branch Block on Microvolt T-Wave Alternans and Electrophysiologic Testing in Patients with Ischemic Cardiomyopathy. *Heart Rhythm* 2007;4:904–912. [PubMed: 17599676]
45. Shalaby A, Voigt A, El-Saed A, Mains M, Shusterman V. Microvolt T-wave alternans during atrial and ventricular pacing. *Pacing & Clinical Electrophysiology* 2007;30:S178–S182. [PubMed: 17302700]
46. Rashba EJ, Osman AF, MacMurdy K, et al. Enhanced Detection of Arrhythmia Vulnerability Using T Wave Alternans, Left Ventricular Ejection Fraction, and Programmed Ventricular Stimulation: A Prospective Study in Subjects with Chronic Ischemic Heart Disease. *J Cardiovasc Electrophysiol* 2004;15:170–176. [PubMed: 15028046]

47. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-Wave Alternans Distinguishes Between Patients Likely and Patients Not Likely to Benefit From Implanted Cardiac Defibrillator Therapy: A Solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Conundrum. *Circulation* 2004b;110:1885–1889. [PubMed: 15451804]
48. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *The Lancet* 2003b;362:125–126.
49. Ikeda T, Yoshino H, Sugi K, et al. Predictive Value of Microvolt T-Wave Alternans for Sudden Cardiac Death in Patients With Preserved Cardiac Function After Acute Myocardial Infarction; Results of a Collaborative Cohort Study. *J Am Coll Cardiol* 2006;48:2268–2274. [PubMed: 17161258]
50. Gehi AK, Stein RH, Metz LD, Gomes JA. Microvolt T-wave alternans for risk stratification of ventricular tachyarrhythmic events: a meta-analysis. *J Am Coll Cardiol* 2005;46:75–82. [PubMed: 15992639]
51. Buxton AE, Lee KL, Hafley GE, et al. Limitations of Ejection Fraction for Prediction of Sudden Death Risk in Patients With Coronary Artery Disease: Lessons From the MUSTT Study. *J. Am. Coll. Cardiol* 2007;50:1150–1157. [PubMed: 17868806]
52. Narayan SM, Smith JM. Exploiting Rate Hysteresis in Repolarization Alternans to Optimize the Sensitivity and Specificity for Ventricular Tachycardia. *J. Am. Coll. Cardiol* 2000c;35:1485–1492. [PubMed: 10807451]
53. Raatikainen M, Jokinen V, Virtanen V, Hartikainen J, Hedman A, Huikuri H. Investigators. C. Microvolt T-wave alternans during exercise and pacing in patients with acute myocardial infarction. *PACE* 2005;28:S193–S197. [PubMed: 15683495]
54. Harada M, Shimizu A, Murata M, et al. Relation between microvolt-level T-wave alternans and cardiac sympathetic nervous system abnormality using iodine-123 metaiodobenzylguanidine imaging in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 2003;92:998–1001. [PubMed: 14556884]
55. Ikeda T, Sakata T, Takami M, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. *J Am Coll Cardiol* 2000b;35:722–730. [PubMed: 10716476]
56. Kleinfeld MJ, Rozanski JJ. Alternans of the ST segment in Prinzmetal's angina. *Circulation* 1977;55:574–577. [PubMed: 837498]
57. Raeder EA, Rosenbaum DS, Bhasin R, Cohen RJ. Alternans of Electrocardiographic T-wave May Predict Life-Threatening Ventricular Arrhythmias. *New Engl J Med* 1992:271–272. [PubMed: 1727982]
58. Wellens HJJ. Isolated electrical alternans of the T-wave. *Chest* 1972a;62:319–321. [PubMed: 5056591]
59. Smith JM, Clancy E, Valeri C, Ruskin J, Cohen R. Electrical Alternans and cardiac electrical instability. *Circulation* 1988a;77:110–121. [PubMed: 3335062]

Figure 1. Historical Evolution: Detecting T-Wave Alternans of Increasing Subtlety

(A) *Extreme alternans* of elevated ST/T segments in a patient with angina pectoris preceding VT (56); (B) *Visible alternans* of T-wave polarity, preceding VF (57); (C) *Subtle but visible TWA* following tachycardia termination, without arterial pressure alternans (bottom) (58); (D) *Visually-inapparent microvolt-level TWA*, extracted by signal processing (59). (*) indicates the more positive T-wave of each alternating pair. (Panels A–C with permission).

Figure 2. Mechanisms Underlying TWA. Left. Spatial Dispersion of Repolarization

Compared to region 2, region 1 has longer APD and depolarizes every-other-cycle (beats 1 and 3) at this rate, producing alternans. **Right. Temporal Dispersion of Repolarization.** APD alternates between cycles. In the restitution plots (inset: of APD against diastolic interval, DI), the early beat 'a' (at short DI) abruptly shortens APD, that lengthens the next DI and hence APD, and so on. If APD restitution has slope < 1 (upper graph), alternans converges. If APD restitution has slope > 1 (lower graph), alternans is amplified to facilitate wave break and fibrillation.

TWA Positive and APD Alternans Positive in a Study Patient

Figure 3. Positive TWA in a patients with systolic dysfunction, despite non-steep APD Restitution (maximum slope < 1)

Diastolic intervals lie on the flat portion of the APD restitution curve, at rates < 109 beats/min where TWA is utilized. Thus, APD restitution likely does not explain alternans at this rate. This result has also been confirmed in patients with steep maximum APD restitution at short diastolic intervals (14).

Figure 4.

Proposed Integration of TWA Into Management Flowchart For The Primary Prevention of SCA, referenced to studies that have validated TWA in each clinical population. *High-risk subgroup of (41) with LVEF=39±18 %.

Table
In Defined Populations, Negative Predictive Value of TWA for Clinical Endpoints

Study and Reference	Sample Size	LVEF %	NYHA Class	Endpoint	1Y	NPV	2Y
Severe Systolic Dysfunction (LVEF ≤ 30 %), Post-MI							
<i>Rashba et al. substudy</i> [†]	(46)	68	—	<i>Death/VT/VF</i>	≈67		≈62
TWA in CHF substudy	(47)	177	23±6	Death	98		96
MASTER (awaited)							
Moderate Systolic Dysfunction (LVEF ≤ 40%), Post-MI							
ABCD (presented data)	(32)	566	28±7	I-III	95		—
Morin et al., QRSd<120 ms	(44)	277	30±8	—	≈90		84
<i>QRSd≥120 ms</i> [‡]		109	26±8	—	≈80		68
Ohio/Michigan	(5)	768	27±5	—	—		≈95
TWA in CHF [†]	(23)	267	≈25±6	I-III	—		95
TWA Labeling Study [†]	(41)	215	39±18	in 45%	≈97		—
Moderate Systolic Dysfunction (LVEF ≤ 40 %), NYHA Class II-III, No CAD							
ALPHA (presented data)	(35)	446	30±7	II-III	100		≈98*
TWA in CHF [†]	(23)	282	≈25±6	I-III	—		100
<i>TWA in SCD-HeT^{††}</i> (presented data)	(34)	490	25	II-III	90		88
<i>MACAS</i> [‡]	(33)	263	30±10	2.I	≈95		≈93
Preserved/Minimally Reduced Systolic Function (LVEF ≥ 40%), Post-MI							
Ikeda et al.	(49)	1041	55±10	—	≈99		≈97
REFINE (awaited)							

* **Key:** At 21 months

[†] study included similar numbers of patients with and without coronary disease. CAD – coronary artery disease; NPV – negative predictive value; SCA – sudden cardiac arrest; VT/VF – sustained ventricular arrhythmias

[‡] TWA was non-predictive (similar event rates for normal and abnormal TWA) also denoted in *italics*.