Published in final edited form as:

Heart Rhythm. 2009 March ; 6(3 Suppl): S15–S21. doi:10.1016/j.hrthm.2008.10.006.

Sudden Cardiac Arrest in Patients with Preserved Left Ventricular Systolic Function: A Clinical Dilemma

Navinder Sawhney, MD and Sanjiv M. Narayan, MD, FHRS

University of California, San Diego, CA

Abstract

Stratifying the risk for sudden cardiac arrest (SCA) in individuals with preserved systolic function remains a pressing public health problem. Current guidelines for the implantation of cardiac defibrillators largely ignore patients with preserved systolic function, even though they account for the majority of cases. However, risk stratification for such individuals is increasingly feasible. Notably, most individuals who experience SCA have structural heart disease, even if undiagnosed. Thus, clinical risk scores have been developed to identify high risk. Moreover, there are now promising data that T-Wave Alternans (TWA), alone and in combination with other indices, effectively predicts SCA in this population. This article presents our current understanding of SCA due to ventricular arrhythmias in patients with preserved LV systolic function, and attempts to build a framework to predict risk in this population.

Keywords

Sudden Cardiac Arrest; T-wave Alternans; Preserved Systolic Function; Coronary Disease; Risk Stratification

Introduction

Sudden cardiac arrest (SCA) is generally defined as death due to cardiac causes occurring within one hour of the onset of symptoms (1). Randomized trials have shown that patients with depressed left ventricular (LV) systolic function are at high risk for SCA from arrhythmias, for which implantation of a cardioverter defibrillator (ICD) improves survival compared to medical therapy (1). However, this strategy may have only modest impact on the incidence of SCA, because most cases occur in individuals with preserved LV systolic function. Thus, there is an urgent need to stratify risk for SCA in this population.

Sudden cardiac arrest is a heterogeneous condition that likely results from the interaction of acute myocardial ischemia, cardiac structural disease, a pro-arrhythmic neurohumoral milieu and other triggers in the context of genetic susceptibility. Despite this complexity, however,

Correspondence: Sanjiv M. Narayan, MB, MD, Associate Professor of Medicine, University of California, San Diego, Cardiology/111A, 3350 La Jolla Village Drive, San Diego, CA 92161 Voice: 858/642 – 1108 Fax: 858/552 – 7490, E-mail: snarayan@ucsd.edu.

Disclosures.

Dr. Narayan has received speaking honoraria and consulting fees from Cambridge Heart, St. Jude Medical, Boston Scientific and Medtronic Corporations. Dr. Sawhney has no direct disclosures. The University of California, San Diego receives fellowship support from St. Jude Medical, Boston Scientific and Medtronic Corporations.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

recent studies have uncovered genetic, clinical and electrophysiological indices that provide the beginnings of a framework to stratify risk for SCA in the wider population.

Sudden Cardiac Arrest and Heart Disease

Cardiovascular disease is the most common cause of natural death in developed nations, and SCA may account for 50% of all deaths from cardiovascular causes (1). It is estimated that 350,000 deaths due to SCA occur in the United States per annum. Most cases occur in the setting of coronary disease, whether diagnosed or undiagnosed, followed by dilated cardiomyopathies, valvular disease, infiltrative disorders, primary electrophysiology disorders, congenital heart disease, and genetic ion channelopathies (1).

Sudden Cardiac Arrest and the “Normal” Heart

Although SCA in the general population often occurs in individuals without a known cardiac history, structural abnormalities can be identified in the majority (2). In a retrospective study of 270 cases of SCA in patients without apparent heart disease, aged 42 ± 14 years, careful pathologic examination revealed structural disease in 95% of individuals (3). Two thirds had specific pathology, including coronary disease (two-thirds of this group), congenital abnormalities, myocarditis and cardiomyopathy. In the third of patients without specific pathology, two thirds had left ventricular hypertrophy, while others had mitral valve prolapse and interstitial fibrosis. These results confirm earlier findings in patients with SCA aged > 45 years (4).

Thus, the clinical dilemma is to determine under what conditions these structural heart abnormalities, that are highly prevalent, contribute to ventricular arrhythmias and SCA in a small minority of individuals.

Arrhythmias at the Time of Sudden Cardiac Arrest

Fatal arrhythmias typically involve the cascade of ventricular tachycardia (VT), leading to ventricular fibrillation (VF) then asystole (4). In a series of 157 patients whose SCA was captured by 24 hour Holter monitoring: 62% had VT/VF, 8% had primary VF, 13% had polymorphic VT or torsades de pointes, and 16% had predominantly bradycardic events (5). Interestingly, most episodes were preceded by premature ventricular contractions (PVCs).

Although defined as ‘sudden’, many victims of SCA actually experience cardiac and other symptoms for many hours preceding their event, re-emphasizing that early symptom recognition may avert some episodes (2). Bradyarrhythmias may also be the primary electrical event at the time of sudden death, although this is more common in patients with advanced heart disease (4). Polymorphic VT or torsades de pointes may be the initial arrhythmia in patients with genetic or acquired structural heart disease, and it is well recognized that ventricular fibrillation may arise in patients with ventricular pre-excitation.

The Genetic Framework

Prospective cohort studies reveal a clear inheritable component to SCA in the population-at-large. The Paris Prospective Study found that a family history of parental sudden death was the single most important independent risk factor for SCA in 7746 unselected middle aged male civil servants followed for > 20 years (6). Other studies show that primary VF (SCA at the time of acute coronary syndrome), clusters in certain families (1). This was recently reaffirmed in a case-control study of patients with acute coronary syndrome with and without primary VF, none of whom had prior structural disease. In these patients, family history of

SCA was the single biggest difference between patients with and without primary VF (adjusted odds ratio 2.7) (7).

Nevertheless, the use of genetic screening to risk-stratify for SCA is in its early stages. Certainly, great strides have been made in identifying genetic mutations responsible for rare conditions associated with increased SCA risk such as the long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, hypertrophic cardiomyopathy and arrhythmogenic RV cardiomyopathy (8). However, even in these syndromes, disease penetrance varies greatly between probands and mutation carriers, emphasizing the likely importance of additional genetic or environmental factors.

In the wider population, it remains a major challenge to identify genetic indices of risk for SCA. While candidate gene studies suggest that plausible mutations in cardiac ion channel genes for potassium, sodium and calcium may increase risk for ventricular arrhythmias (8), recent postmortem analyses have not found potassium (HERG) (9), sodium (10) or other channel mutations in SCA victims. For this reason, interest has recently turned to genome-wide analyses, based on the rationale of identifying genetic risk markers for SCA without limiting analysis to currently identified mechanisms (8).

Risk Stratification

For many reasons, risk stratification for SCA is far less clear in patients with preserved LV systolic function (LVEF > 40%) than in traditional high-risk populations.

There are many important areas of uncertainty surrounding SCA in this population. For instance, the mechanisms for human ventricular arrhythmias may be focal or reentrant, from elegant intraoperative mapping studies (in human explanted hearts) (11). In addition, triggers may play a particularly central role in individuals with preserved LVEF and “less extensive” substrate. Therefore, risk stratification methods used in patients with systolic dysfunction may not be directly transferable to this population, may require different cutpoints or operate via different mechanisms.

Clinical Risk Scores for SCA

The Framingham study has shown that simple bedside clinical information may help to identify SCA risk in individuals with preserved LV systolic function. Compiling a risk score based upon data such as age, the presence of ECG abnormalities, elevated systolic blood pressure, cholesterol, weight and heart rate, the investigators found that 40% of SCA cases occurred in patients in the top decile of risk (12). Women were found to have a lower overall incidence of SCA than men, yet experience a higher portion of sudden deaths in the absence of diagnosed coronary disease.

A recent post-hoc evaluation of 8290 patients in the PEACE study, with stable coronary disease and relatively preserved LVEF (> 40%), confirmed that clinical factors can identify SCA risk (13). Independent ‘predictors’ of SCA in this study included age, current angina, EF 41–50 % (as opposed to > 50%), diuretic and digoxin use. Predictors of lower risk included prior coronary revascularization, female gender or Caucasian race (13). A risk score based on these characteristics identified a subpopulation with significant SCA risk over a 4.8 year period (10.4%, or 2.2%/year) even though the overall risk of SCA in this population was low.

Electrocardiogram

The routine 12-lead ECG is central to identifying several important conditions associated with SCA (1). Some well-recognized abnormalities include long QT and short QT syndromes, right

ventricular dysplasia (via an epsilon wave), hypertrophic cardiomyopathy, and Brugada syndrome. Recently, it has been shown that fragmented QRS complexes (notched QRS complexes unrelated to bundle-branch block) predict cardiovascular events in patients with prior myocardial infarction (14). In addition, early repolarization (defined as an elevation of the QRS-ST junction of at least 0.1 mV from baseline in inferior or lateral leads) has recently been linked with SCA in individuals with preserved systolic function (15). (Figure 1)

T Wave Alternans and Human Ventricular Arrhythmias

T-Wave Alternans (TWA) indicates beat-to-beat oscillations in the shape, timing or amplitude of the ECG T wave, and reflects a temporal dispersion in intracardiac repolarization that may contribute to reentrant arrhythmias (16). Indeed, many clinical studies have shown that TWA predicts fatal arrhythmias and SCA on long-term follow-up in numerous patient populations (16). Although the predictive value of TWA was recently questioned in patients with LV systolic dysfunction (in the MASTER and TWA substudy of the Sudden Cardiac Death in Heart Failure Trials), formal publication of those studies is awaited to determine if this reflects technical issues, vagaries in endpoint determination, or other factors.

Nevertheless, this controversy emphasizes the need to precisely define mechanisms for TWA (and all risk factors) in individuals with preserved, as well as reduced, LVEF. Unfortunately, the mechanisms for TWA are poorly understood in humans. In normal animal hearts and simulations, action potential duration (APD) alternans may arise at rapid rates due to spatial dispersion of repolarization (17), APD rate-response (restitution) slope > 1 (enabling self-amplifying APD oscillations at rapid rates, culminating in wavebreak and reentry) (18) or impaired myocyte calcium handling (19). Under appropriate conditions, such alternans may precipitate arrhythmias (18).

However, these mechanisms arise at rapid rates, often immediately preceding ventricular arrhythmias. Conversely, TWA is only of clinical utility if present at < 90 – 109 beats/min (16). Because human APD restitution is flat at such heart rates in patients with or without systolic dysfunction (20), APD restitution slope > 1 likely does not explain APD oscillations or TWA. Since oscillations in ventricular activation time are also unlikely at slow rates (20), they likely do not explain TWA.

We recently tested the hypothesis that patients at risk for SCA may exhibit evidence for myocardial calcium oscillations at relatively slow rates, as opposed to the rapid rates at which they arise in normal hearts (19). Theoretically, this could cause oscillations in action potential plateau voltage, and provide a mechanistic link with VT or VF (18,19). Indeed, in patients with systolic dysfunction, we found beat-to-beat oscillations in action potential plateau amplitude (not duration; figure 2) that predicted arrhythmic outcome and correlated with TWA (20). Furthermore, we used computational modeling to confirm that such oscillations in action potential plateau were best explained by impaired sarcoplasmic reticulum calcium uptake (23). This mechanism may also explain recent human studies linking alternans in unipolar electrograms with TWA (21,22).

To optimally apply TWA in patients with preserved systolic function, it is essential that studies are performed to understand the mechanisms that may link it with lethal arrhythmias in this population. This approach will also enable TWA testing to be combined most effectively with other modalities.

Clinical Utility of TWA in patients with Preserved Systolic Function

TWA has traditionally been applied to patients with reduced systolic function (24), yet several recent studies suggest that TWA also predicts SCA and total mortality in patients with relatively preserved LVEF.

In a Japanese study of 1041 patients with LVEF > 40 % after myocardial infarction, TWA measured 48±66 days post-MI was recently shown to predict SCA or life-threatening arrhythmias (25). Despite the low event rate in this population (1.8% after 32±14 months), abnormal TWA provided a multivariate hazard ratio for events of 19.7, with sensitivity 83 %, specificity 83 %, and negative predictive value (NPV) 99.6 % (figure 3). TWA provided higher predictive accuracy than the signal averaged ECG and other indices. However, the positive predictive value (PPV) of TWA, of central importance when screening a relatively healthy population, was only 9 %. It may thus be necessary to combine TWA with additional markers to improve PPV. Mechanistically, it remains to be shown whether TWA reflects scar-related dispersion of repolarization in this population. Interestingly, most events in this population occurred in the first year (figure 3), so that TWA provided a 1-year predictive value akin to that seen in high-risk populations (25). It is unclear if this reflects the fact that only 21 % of these post-MI patients received beta-blockers, and 7 % received class-I anti-arrhythmic agents. Therefore, it is important to validate these results in a wider cohort receiving traditional post-MI therapy.

TWA was recently applied to a very broad population of 1037 patients during clinically indicated exercise stress test, most of whom had normal LVEF. During 44±7 months' follow-up, there were 59 deaths, of which 34 were cardiovascular and 20 were attributed to SCA. In multivariate analysis, abnormal TWA conferred a relative risk of 7.4 for SCA and 6.0 for cardiovascular mortality (26). Although TWA was measured using the less-validated modified moving average approach, positive TWA gave a sensitivity of 35%, specificity of 92%, NPV of 98.6 % and PPV 8 % for SCA. However, because TWA was not compared to results from exercise testing, and because the presence of diabetes mellitus and hypertension did not predict events, it is unclear whether TWA reflected mechanisms related to coronary disease in this study.

In 322 post-MI patients with LVEF < 50 % (median LVEF 47 % at 8 weeks), the Risk Estimation Following Infarction - Noninvasive Evaluation (REFINE) trial (27) showed that TWA and other indices were predictive when used 10–14 weeks post MI and less effective when used in the first month. Abnormal TWA measured 10–14 weeks post-MI provided a hazard ratio of 2.75 for cardiac death or resuscitated SCA. Although this was associated with modest predictive value (area under receiver operating characteristic, ROC, curve = 0.62), predictive value was far superior when combined with measures of autonomic function (abnormal heart rate turbulence) and LVEF < 50 %. This combination provided an area under the ROC curve of 0.74, with with sensitivity 55%, specificity 86 %, NPV 96 % and an impressive PPV of 27 %.

These data highlight the need to better define the mechanisms for TWA in patients with preserved systolic function, that will provide a rationale for combining risk indices, and to validate its clinical utility in populations with and without prior MI and for various ranges of systolic function. Currently, the AHA/ACC/ESC guidelines provide a Class IIa recommendation for the use of TWA to stratify risk for ventricular arrhythmias, and do not distinguish between its use in patients with and without systolic dysfunction (1).

Other Indices of Exaggerated Repolarization Dispersion

The QT variability index (QTVI) is another index of repolarization dispersion, which evaluates exaggerated beat-to-beat QT interval variability independent of changes related to rate. QTVI can predict arrhythmic risk in patients with systolic dysfunction with and without coronary artery disease (28), although its ability to predict events in patients with preserved EF has not been documented.

Evidence for Myocardial Scar: Signal Averaged Electrocardiogram (SAECG) and Notched/Fragmented QRS Complexes

The signal averaged ECG (SAECG) measures slow conduction as 'late potentials' at the QRS terminus (11). Late potentials are low-amplitude, high frequency signals caused by slow and fragmented conduction due to infarction and conditions including arrhythmogenic right ventricular dysplasia. Although slow conduction regions causing late potentials may not always participate actively in VT circuits, late potentials are present in 70–92 % of patients with coronary disease and ventricular tachycardia. In an important substudy of the Multicenter UnSustained Tachycardia Trial (in post-MI patients with LVEF $\leq$ 40%), late potentials predicted arrhythmic outcome more effectively than did programmed ventricular stimulation (29).

Late potentials were recently shown to predict events in post-MI patients with relatively preserved LVEF [Ikeda, 2006 #2683; Exner, 2007 #2790], yet were less predictive than TWA. The SAECG also generally has a low PPV (11), although this is improved in combination with other indices.

It has recently been reported that fragmented QRS complexes (14), describing notches and slurring during the ECG QRS complex unrelated to bundle branch block, accurately represents prior myocardial infarction. Although its pathophysiology requires definition, this ECG phenotype may reflect conduction through scar. Importantly, fQRS may predict major adverse cardiac events and total mortality independently of LVEF and other clinical indices (14).

Measures of Autonomic Function: Heart Rate Variability, Heart Rate Turbulence and Baroreflex Sensitivity

The autonomic nervous system likely plays an important mechanistic role for ventricular arrhythmogenesis, and may be central in individuals with preserved systolic function and less extensive substrate.

Heart rate variability (HRV) quantifies R-R interval fluctuations during sinus rhythm, and reflects the balance of parasympathetic and sympathetic inputs to the sinus node. In post MI patients with relatively preserved LV systolic function, reduced HRV (standard deviation of sinus R-R intervals) indicates sympathetic over parasympathetic activity and provides specificity 80–90% and sensitivity of 30–40% for subsequent VT or VF (30). The strength of HRV lies in its NPV, although combining HRV with other indices raises the PPV.

Two other indices of autonomic function may also predict VT/VF. Baroreflex sensitivity measures heart rate slowing in response to elevated blood pressure, typically from phenylephrine, and a blunted response predicts ventricular arrhythmias (31). Heart rate turbulence may indicate similar pathophysiology, by quantifying heart rate slowing after a premature beat. Abnormal heart rate turbulence independently predicts mortality in patients with preserved systolic function (32) (figure 4).

In post-MI patients with relatively preserved LVEF (27), each of these autonomic indices measured 10–14 weeks post-MI predicted cardiac death or resuscitated SCA with hazards ratios of 2–3. The predictive value of HRT, in particular, was increased when used in combination with TWA (27). Future studies should test these observations prospectively in larger community populations. Current guidelines for the management of patients at risk for SCA provide a class IIb indication for the use of HRT, HRV and baroreceptor sensitivity to stratify risk for VT or VF (1).

Characterization of Scar by Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) holds promise for the risk stratification for SCA associated with cardiac structural disease. First, the volume and surface area of myocardial scar measured with CMR correlates with inducible ventricular arrhythmias on programmed stimulation in patients with ischemic and non ischemic cardiomyopathy (33). Second, a larger scar border zone on CMR, that may indicate tissue heterogeneity and arrhythmogenic substrate (figure 5), was recently shown to predict all-cause and cardiovascular mortality independent of age or systolic function (34). Further studies are thus required to define the pathophysiologic and prognostic significance of scar and border zone quantification in patients with preserved systolic function, alone and in combination with electrical and autonomic indices.

Conclusions

Risk stratification for SCA in individuals with preserved systolic function remains a major public health problem. Because of limited data, current guidelines for implanting cardiac defibrillators largely exclude such individuals. However, pathologic studies convincingly show that SCA in the general population often occurs in individuals with coronary and structural heart disease, even if undiagnosed. As a result, carefully constructed clinical risk scores are now available for the bedside risk stratification of SCA. Moreover, exciting data show that T-wave alternans predicts SCA and overall mortality in patients with preserved systolic function post-myocardial infarction, and potentially those referred for exercise stress testing. Further studies are needed to define the mechanisms by which TWA predicts arrhythmias in such patients. The positive predictive value of TWA may be increased in combination with indices of pro-arrhythmic autonomic activity, of slow conduction and of scar border zone.

These exciting preliminary data provide a rational framework to stratify risk for SCA in the community. It is imperative that we build momentum to design clinical studies that will test these hypotheses prospectively, and translate these findings into tangible public health benefits.

Acknowledgements

Supported, in part, by grants from the National Heart, Lung and Blood Institute (70528, 83359) and Doris Duke Charitable Foundation to SMN.

References

1. Zipes D, Camm A, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: 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): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e385–484. [PubMed: 16935995]
2. Müller D, Agarwal R, Arntz H-R. How sudden is sudden cardiac death? *Circulation* 2006;114:1146–50. [PubMed: 16952983]

3. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. *Circulation* 2000;102:649–54. [PubMed: 10931805]
4. Zipes DP, Wellens HJJ. Sudden Cardiac Death. *Circulation* 1998;98:2334–2351. [PubMed: 9826323]
5. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;117:151–159. [PubMed: 2911968]
6. Jouven X, Desnos M, Guerot C, et al. Predicting sudden death in the population: the Paris Prospective Study. *Circulation* 1999;99:1978–83. [PubMed: 10209001]
7. Dekker L, Bezzina C, Henriques J, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* 2006;114:1140–5. [PubMed: 16940195]
8. Arking DE, Chugh SS, Chakravarti A, et al. Genomics in sudden cardiac death. *Circ Res* 2004;94:712–23. [PubMed: 15059941]
9. Chugh SS, Senashova O, Watts A, et al. Postmortem molecular screening in unexplained sudden death. *J Am Coll Cardiol* 2004;43:1625–9. [PubMed: 15120823]
10. Stecker EC, Sono M, Wallace E, et al. Allelic variants of SCN5A and risk of sudden cardiac arrest in patients with coronary artery disease. *Heart Rhythm* 2006;3:697–700. [PubMed: 16731473]
11. Pogwizd SM, Qi M, Yuan W, et al. Upregulation of Na⁺/Ca²⁺ Exchanger Expression and Function in an Arrhythmogenic Rabbit Model of Heart Failure. *Circ Res* 1999;85:1009–1019. [PubMed: 10571531]
12. Kannel W, Wolf P, Benjamin EJ, et al. Prevalence, Incidence, Prognosis and Predisposing Conditions for Atrial Fibrillation. Population-Based Estimates. *Am J Cardiol* 1998;82:2N–9N.
13. Hsia J, Jablonski KA, Rice MM, et al. Sudden cardiac death in patients with stable coronary artery disease and preserved left ventricular systolic function. *Am J Cardiol* 2008;101:457–61. [PubMed: 18312757]
14. Das MK, Saha C, El Masry H, et al. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm* 2007;4:1385–92. [PubMed: 17954396]
15. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016–23. [PubMed: 18463377]
16. 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]
17. Pastore JM, Rosenbaum DS. Role of Structural Barriers in the Mechanism of Alternans-Induced Reentry. *Circulation Research* 2000;87:1157–1163. [PubMed: 11110773]
18. Weiss JN, Karma A, Shiferaw Y, et al. From Pulsus to Pulseless: The Saga of Cardiac Alternans (Review). *Circ Res* 2006;98:1244. [PubMed: 16728670]
19. Pruvot EJ, Katra RP, Rosenbaum DS, et al. Role of Calcium Cycling Versus Restitution in the Mechanism of Repolarization Alternans. *Circ Res* 2004;94:1083–1090. [PubMed: 15016735]
20. Narayan SM, Franz MR, Kim J, et al. T-wave Alternans, Restitution of Ventricular Action Potential Duration and Outcome. *J Am Coll Cardiol* 2007f;50:2385–2392. [PubMed: 18154963]
21. Selvaraj RJ, Picton P, Nanthakumar K, et al. 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;49:338–46. [PubMed: 17239715]
22. Sandhu RK, Costantini O, Cummings JE, et al. Intracardiac alternans compared to surface T-wave alternans as a predictor of ventricular arrhythmias in humans. *Heart Rhythm* 2008;5:1003–8. [PubMed: 18598955]
23. Narayan SM, Bayer J, Lalani G, Trayanova NA. Action Potential Dynamics Explain Arrhythmic Vulnerability in Human Heart Failure. *J Am Coll Cardiol* 2008d;52in press
24. Hohnloser SH, Ikeda T, Bloomfield DM, et al. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *The Lancet* 2003b;362:125–126.
25. 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]
26. 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;28:2332–7. [PubMed: 17652105]
 27. Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive risk assessment early after a myocardial infarction the REFINE study. *J Am Coll Cardiol* 2007;50:2275–84. [PubMed: 18068035]
 28. Haigney MC, Zareba W, Gentlesk PJ, et al. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *Journal of the American College of Cardiology* 2004;44:1481–1487. [PubMed: 15464332]
 29. Gomes JA, Cain ME, Buxton AE, et al. Prediction of Long-Term Outcomes by Signal-Averaged Electrocardiography in Patients With Unsustained Ventricular Tachycardia, Coronary Artery Disease, and Left Ventricular Dysfunction. *Circulation* 2001;104:436–441. [PubMed: 11468206]
 30. Copie X, Hnatkova K, Staunton A, et al. Predictive Power Of Increased Heart Rate versus Depressed Left Ventricular Ejection Fraction and Heart Rate Variability for Risk Stratification After Myocardial Infarction. *Journal of the American College of Cardiology* 1996;27:270–6. [PubMed: 8557893]
 31. La Rovere MT, Jr JTB, Marcus FI, Mortara A, Schwartz PJ, et al. A Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators [see comments]. *Lancet* 1998;351:478–84. [PubMed: 9482439]
 32. Makikallio TH, Barthel P, Schneider R, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J* 2005;26:762–9. [PubMed: 15778204]
 33. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation* 2005;112:2821–5. [PubMed: 16267255]
 34. Yan A, Shayne A, Brown K, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation* 2006;114:32–9. [PubMed: 16801462]

Figure 1. ECG Indices of SCA Risk in Patients with Preserved LVEF

(A) Early Repolarization. Each panel shows the first QRS complex recorded at baseline (left) and subsequent complexes recorded before an arrhythmic event (right). The arrows show clear accentuation of early repolarization compared with baseline. Panel B shows a premature ventricular complex. A similar beat triggered VF a few hours later on ECG monitoring. Panel C shows the onset of VF. Adapted, with permission, from (15).

(B) Fragmented QRS. This panel shows various morphologies of fragmented QRS (fQRS) in patients with prior myocardial infarction. The definition of fQRS *excludes* complete or incomplete right bundle branch block, and is focused on RSR patterns observed in the midprecordial or inferior leads. Such ECG findings have recently been shown to predict cardiac and overall mortality (14).

Figure 2. T-Wave Alternans in Humans May Represent Oscillations in Action Potential Amplitude In a 59 year old man with ischemic cardiomyopathy and LVEF 20% (A) during pacing at 109 beats/min pacing; (B) Action potential duration shows minimal oscillations over time. However, when 64 consecutive beats were superimposed, (C) action potential (AP) amplitude shows marked alternans, shown by the separation of even (blue) and odd (red) beats. (D) AP amplitude alternans is depicted on this spectrum across beats, as peak magnitude at 0.5 cycles/beat. (E) Notably, TWA is simultaneously positive (gray areas in X, Y and vector magnitude Vm leads) with low levels of bad beats, noise and no confounding respiratory, heart rate (HR) or RR interval alternans. Computational modeling showed that impaired sarcoplasmic reticulum calcium uptake best explained these results. Adapted, with permission, from (20).

Figure 3. T-wave Alternans predicts ventricular arrhythmias in Patients with Preserved Systolic Function

In 1,041 post-MI patients with $LVEF \geq 40\%$, this figure shows Kaplan-Meier event-free curves for serious arrhythmic events (i.e., sudden cardiac death, cardiac arrest, and resuscitated ventricular fibrillation) based on positive or negative microvolt T-wave alternans test. Reproduced, with permission, from (25).

Figure 4. Abnormal Heart Rate Turbulence Predicts SCA in Patients with Preserved LVEF

In 2130 patients after myocardial infarction, Kaplan–Meier survival curves for SCA show that (A) in patients with preserved LVEF, abnormal post ectopic turbulence slope (TS) identified those at high risk for SCA. (B) In all 2130 patients, depressed LV systolic function predicted only a slightly higher risk for SCA than abnormal heart rate turbulence in patients with preserved LVEF. Reproduced, with permission, from (32).

Figure 5. Substantial Peri-Infarct Zone Characterized by Cardiac MRI Predicts Mortality

This figure shows an example of cardiac MRI in a 64 year old man with an inferior myocardial infarction (white arrows), preserved LV systolic function (LVEF, 61%), and normal LV systolic volume index (54 mL/m²). The infarct of this patient was characterized by a substantial peri-infarct zone (yellow region). The patient died 11 months after undergoing this examination. Adapted with permission from (34).

Table 1**Measures of Risk for SCA in Patients with Preserved Systolic Function**

Pathophysiologic Substrate	Index
Comorbid Conditions	Clinical Risk Score (12,13)
Repolarization Dispersion	T-Wave Alternans (22) QT Variability Index (12) ECG-defined syndromes, such as long/short QT syndromes, Brugada syndrome and early repolarization (15).
Slow Conduction	Fragmented QRS complexes (14) Signal Averaged ECG (11)
Pro-arrhythmic balance in the autonomic nervous system	Heart Rate Variability (30) Baroreceptor Sensitivity (31) Heart Rate Turbulence (32)
Myocardial Scar and Tissue Heterogeneity	Cardiac MRI imaging (33,34) Fragmented QRS complexes (14) Signal Averaged ECG (11)