T-Wave Alternans in the Sudden Cardiac Death in Heart Failure Trial Population: Signal or Noise?

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Editorial

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Signal or Noise?

David S. Rosenbaum, MD

Although the cardiovascular death rate has fallen in recent years, the proportion of cardiovascular deaths attributed to sudden cardiac death (SCD) is on the rise. SCD is usually caused by ventricular tachyarrhythmias resulting from complex electroanatomic changes that follow myocardial injury, most often associated with coronary artery disease. Ventricular tachyarrhythmia episodes and the factors responsible for triggering them are poorly understood, usually occur without warning or provocation, and result almost invariably in death. Therefore, efforts aimed at predicting and preventing SCD have emerged as the major paradigm for addressing this significant unresolved public health dilemma.

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Two major randomized clinical trials demonstrated that implantable cardioverter defibrillators (ICDs) reduce mortality in patients selected for primary prevention of SCD on the basis of reduced left ventricular ejection fraction (LVEF) alone.[1,2] However, recent studies have questioned whether LVEF used in isolation from other disease markers is sufficient to guide SCD prevention.[3] Although ICDs are highly effective in aborting SCD from ventricular fibrillation, only ≈1 of 15 patients satisfying current guidelines for prophylactic ICDs on the basis of an LVEF <0.35 benefit from ICDs. Moreover, current guidelines fail to address the largest source of SCD victims (ie, patients with LVEF >0.35). Also, we have yet to ascertain how to incorporate estimates of competitive risk from nonarrhythmic and noncardiac mortality into the decision to implant ICDs. Finally, current paradigms that focus on assessing risk at 1 time point do not account for dynamic time-varying modulation of SCD substrates that occur in response to intervening cardiac events.

Because LVEF only measures contractile but not electrophysiological dysfunction, it does not provide any direct assessment of functional electrophysiological substrates responsible for triggering SCD episodes. Therefore, it should not be surprising that most patients with markedly impaired LVEF do not benefit from ICDs, while it remains uncertain how to identify which of those patients with relatively preserved LVEF might benefit from ICDs. There is no question that risk stratification using invasive electrophysiological testing to directly probe electrophysiological substrates can identify enriched subsets of patients who are more likely to benefit from ICD therapy.[4] However, electrophysiological testing is invasive, expensive, and impractical as a broadly applied screening tool. Herein lies the rationale for noninvasive risk markers to directly probe arrhythmia substrates, potentially allowing clinicians to better predict which patients are likely to manifest a SCD phenotype.

Microvolt-level T-wave alternans (TWA) was first established as a marker of arrhythmia risk in humans[5] when it was discovered that with carefully controlled elevation of heart rate, patients at risk for SCD exhibit TWA at significantly reduced heart rates compared with controls. Several subsequent observational studies suggested that TWA is a marker of risk in relevant primary prevention populations[6–9] whereas some other studies have not.[10] TWA is attractive in that it is closely linked to cellular arrhythmia mechanisms[11]; unlike many other risk markers it appears to track arrhythmia susceptibility independent of progression of heart failure and is comparably predictive of events in patients with both ischemic and nonischemic cardiomyopathy.

Is Microvolt T-Wave Alternans a Marker of Risk in the SCD Heart Failure Trial Population?

The study by Gold et al[12] in the current issue of the Journal not only assesses TWA as a risk marker for SCD in a clinically relevant population, but it also provides the unique and unprecedented opportunity for tracking and comparing the "TWA signal" with the emergence of the "SCD phenotype" in the same population. In previous observational trials investigating TWA, it was not possible to determine if or when the TWA marker actually coincided with the emergence of a SCD phenotype in the population under study. Because the SCD Heart Failure Trial (SCD-HeFT) randomized ICD therapy, ICD implantation was distributed equally regardless of TWA classification. Because ICDs can only diminish mortality by reducing the SCD rate, the time point when the ICD-treated group manifested improved mortality over the placebo group can be taken as the time when the SCD phenotype emerged in the SCD-HeFT population.[2] Hence, one would predict that a marker which specifically tracks SCD rather than non-SCD risks would, in fact, reveal

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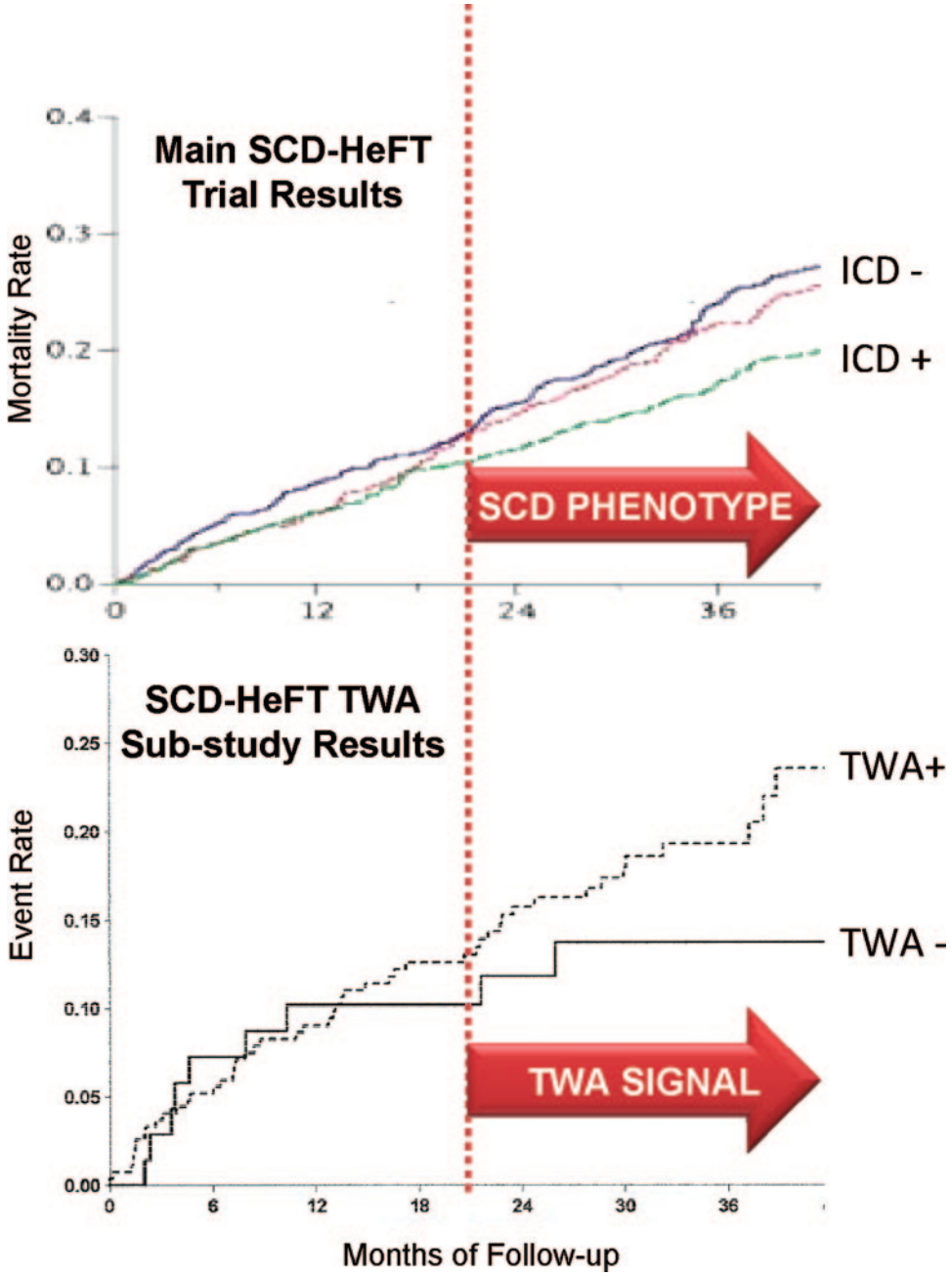

Figure. Top, Mortality rate from the original SCD-HeFT trial. The plot illustrates the time course when mortality among patients randomized to ICD therapy (ICD+) begins to deviate from mortality in patients not randomized (ICD−) to ICDs (either placebo or amiodarone). The beneficial impact of ICDs on survival did not achieve statistical significance until after 36 months of follow up, but an apparent benefit begins to emerge between 18 and 24 months (depicted approximately by the hatched vertical line). Because ICDs can only reduce SCD mortality, the data suggest that this population was characterized by a late-appearing (>24 mos) "SCD phenotype." Reprinted from Bardy et al[2] with permission from the publisher. Copyright © 2005 Massachusetts Medical Society. All rights reserved. Bottom, Event rates in patients with negative TWA tests (TWA−) compared with patients with nonnegative TWA tests (TWA+).[12] The time base is scaled to match the survival curves from the main SCD-HeFT trial (top), permitting comparison of the time course of an apparent prognostic TWA signal (separation of TWA+ and TWA− curves) and the emergence of a detectable SCD phenotype in the same population. The data suggest a strong correspondence between the TWA signal and SCD phenotype. The time-dependent nature of the SCD phenotype and other factors (see text) may have precluded detection of statistically significant event rates between TWA− and TWA+ patients when analyzed over the entire follow-up period.

no signal of risk during time periods when the SCD events were relatively quiescent but, conversely, would begin to signal the higher-risk group at a time when the SCD phenotype becomes apparent. The TWA SCD-HeFT Substudy report included 19% of the total SCD-HeFT population, and survival rates of TWA+ versus TWA− patients only began to differ after 14 to 28 months of follow up (Figure 1A and 1B in Gold et al[12]) depending on the particular definition of TWA positivity used. This was precisely the time period when the SCD phenotype emerged in the SCD-HeFT population (Figure). The results suggest that a TWA signal of risk closely corresponded with emergence of the SCD phenotype in this population (Figure).

Therefore, the authors' conclusion that TWA did not predict outcomes in this population, though correct when only considering events in aggregate throughout the entire follow-up period, does not account for the dichotomous and time-dependent risk patterns evident in the population. In addition to the time-dependent nature of the SCD phenotype, other factors may have precluded detection of statistically significant event rates analyzed over the entire follow-up period between TWA− and TWA+ patients. The TWA SCD-HeFT substudy notably had unusually large proportions (41%) of indeterminate TWA studies, inclusion of amiodarone-treated patients, which obscures interpretation of TWA (30% of study population), and lower-than-expected duration of follow up (ie, the minimum follow-up duration target achieved in only half of the patients), all serving to limit statistical power. Although not designed to address this question specifically, the TWA SCD-HeFT Substudy raises an interesting and heretofore underappreciated aspect of risk stratification for SCD. Competitive mortality risks, both cardiac and noncardiac, exist, which can emerge over distinct periods of time, that need to be taken into account when trying to correlate 1 particular risk (eg, SCD) with any particular risk marker (eg, LVEF or TWA). The time-dependent nature of risk needs to be factored into future assessment of a marker's capability of predicting that risk.

The Confounding Influences of the "Appropriate ICD Shock" as a Surrogate End Point for SCD

A large proportion of end points achieved in the TWA SCD-HeFT substudy included ICD therapies adjudicated as "appropriate" shocks and therefore assumed to be a surrogate for SCD. If one excludes amiodarone-treated patients, 52% of patients in Gold et al[12] were randomized to ICD therapy, and 38% of end points were derived from what was classified as "appropriate" shocks delivered from ICDs. Even though ICDs were uniformly programmed with prolonged detection intervals to reduce detection of arrhythmias more likely to self-terminate and not lead to SCD, it is well recognized that the correlation between ICD-detected events and SCD is limited.[13] A recent analysis of the 269 SCD-HeFT patients[14] who received ICD shocks revealed that most (52%) of these patients received inappropriate shocks (ie, for reasons unrelated to SCD). Even when ICD shocks are deemed "appropriate," their occurrence is not tantamount to a life saved. ICD shocks may simply represent a progression of underlying disease with an inevitable malignant course irrespective of therapy. In the SCD-HeFT population, appropriate shocks were associated with a 5.7-fold increased mortality over patients who did not experience appropriate shocks.[14] Similarly, in the II Multicenter Automated Defibrillator Implantation Trial (MADIT II) population, after appropriate shocks for ventricular fibrillation, the 3-year mortality rate was as high as 75%.[15] A recent review by Tung et al[16] highlighted the poor correlation between ICD events and SCD rate, with ICD events consistently overestimating actual risk for SCD. This poor correlation raises the question whether the absence of a "statistically significant relationship" between TWA and events in the TWA SCD-HeFT population may be attributable to limitations of the ICD end point rather than the predictive accuracy of TWA.

This question was examined recently by Hohnloser et al[17] in a meta-analysis of 14 clinical trials in relevant patient populations where TWA was measured during exercise by the spectral method (as in the TWA SCD-HeFT Substudy). The trials that utilized ICD-related end points (>15% of end points associated with ICD shocks) involving 2234 patients demonstrated relatively weak correlation between TWA and events (average Hazard Ratio of 1.6). In contrast, trials that utilized clinical end points such as total or SCD mortality with minimal reliance on ICD end points demonstrated very strong correspondence between TWA positivity and events (average hazard ratio 16.6). Moreover, the annualized event rate in TWA-negative patients who were ostensibly not treated with ICDs was only 0.3%/y, which is substantially lower than the event rate of SCD-HeFT patients who received ICD therapy. Taken together, these observations suggest that TWA can provide a signal for relevant cardiac events that more closely corresponds to SCD than to ICD-related events.

The Need for Simple and Practical Risk Assessment Tools

The ideal risk marker would be one that provides detailed and reliable prognostic information with sufficient sensitivity and specificity to compel specific therapies that improve outcomes. It is also highly desirable for a marker to be inexpensive, simple to interpret, safe to obtain, and readily accessible in a broad range of healthcare environments, including primary care. An implicit tradeoff exists between simplicity of testing and the extent to which the test can reflect the actual complexities that underlie electro-anatomic substrates for arrhythmias. For example, despite its limited prognostic accuracy and inability to probe electrophysiological substrate, noninvasive measurement of LVEF is an attractive risk marker because it is easy to measure and adds no risk to patients. Conversely, despite the fact that invasive electrophysiological testing directly probes functional electrophysiological properties of the heart and provides useful prognostic information about SCD risk, it is expensive, invasive, and requires specialized healthcare resources. Ongoing efforts to assess arrhythmia risk from measurements of infarct mass by cardiac magnetic resonance imaging represent another exciting opportunity, but they will also need to be evaluated in terms of its use of resources. Herein lies the rationale for developing noninvasive markers such as TWA, which can potentially probe arrhythmia substrates in a manner that is practical to implement clinically.

The rate of indeterminate TWA tests (41%) reported in the TWA SCD-HeFT Substudy[12] is 2- to 4-fold greater than the indeterminacy rate of TWA demonstrated in other trials in similar populations and highlights an important current limitation of noninvasive TWA testing. To their credit, these investigators attempted to simulate real-life clinical conditions by permitting broad entry criteria for inclusion in the TWA substudy and somewhat relaxed requirements for the exercise protocol used to induce TWA. One of the important limitations of TWA testing is that it requires controlled elevation of heart rate into a diagnostic range that elicits

TWA in high-risk subjects but does not elicit alternans in normal subjects. This is because TWA is rarely detectable at rest but can be elicited in normal subjects if heart rate is elevated uncontrollably. Therefore, the TWA test requires careful attention to a number of methodological details including meticulous preparation of ECG leads to minimize noise, and very carefully graded heart rate elevation by exercise. Unfortunately, attempts to simplify the acquisition of data by circumventing exercise using ambulatory Holter recordings will further reduce the ability to control heart rate in a manner required to measure TWA. Therefore, further refinements are required to allow clinicians to more broadly apply TWA testing and interpretation without the need for extraordinary technical expertise.

The Final Word

The need for risk stratification tools to better identify patients at risk for SCD is compelling. The current guidelines, which rely almost exclusively on assessment of LVEF, fail to account for at-risk patients with preserved LVEF and lack sufficient specificity to assure that most patients with low LVEF will manifest a SCD phenotype rather than a clinical phenotype of progressive heart failure. Noninvasive TWA testing is an attractive tool for risk stratification because clinical and experimental evidence suggest that it is a marker of arrhythmia substrate rather than progressive left ventricular contractile dysfunction. The TWA SCD-HeFT substudy highlights the need for further simplification of the TWA test so it is more broadly applicable to clinical practice. Despite several technical limitations associated with the TWA measurement in the TWA SCD-HeFT substudy, the trial results suggest that TWA does indeed track susceptibility to SCD in a population where primary prevention strategies are highly relevant. The trial also illustrates the importance of ascertaining the time-dependent nature of SCD risk in a population when determining when and if a marker exhibits a signal for SCD risk in the population. Future advances in risk stratification will also require trials where therapy is randomized on the basis of risk markers that reflect electrophysiological substrates for SCD and clinically relevant end points are used that do not include ICD-related events.

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