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EDITORIAL COMMENT

T-Wave Alternans and Serious Ventricular Arrhythmias: A Tale of Two T-Waves*

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Sudden cardiac death (SCD) is one of the most important public health problems in the world today and is the leading cause of mortality in developing countries. Serious ventricular arrhythmias are the most common mechanism responsible for SCD. Thus, in order to prevent SCD, it is crucial to have effective diagnostic tools to identify patients at risk for these arrhythmias. Unfortunately, despite multiple trials in acute myocardial infarction (AMI) and congestive heart failure, our understanding of how to identify those patients at highest risk for SCD and how to best prevent this devastating occurrence remains incomplete.

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To date, various noninvasive tests such as the left ventricular ejection fraction (LVEF) (1,2), signal-averaged electrocardiography (SAECG) (3,4), ventricular ectopy determined by Holter monitoring, autonomic tone as measured by heart rate variability and baroreflex sensitivity (5–7) and abnormalities of ventricular repolarization as reflected by QT dispersion (8) have been proposed as modalities to identify patients at high risk for developing ventricular arrhythmias. However, the predictive value of each of these tests is low, with the majority of patients with a positive test never developing a life-threatening arrhythmia. Furthermore, with recent studies confirming the benefit of implantable cardioverter-defibrillators (ICDs) in preventing SCD (9,10), and the high cost associated with this therapy, our need for a diagnostic test or set of tests to identify those patients who will most likely benefit from ICD therapy is essential.

While beat-to-beat alterations in the electrical amplitude of the electrocardiogram (ECG) have been appreciated for almost a century (11), it has only been in the last 25 years that this phenomenon has been linked to SCD. By examining the specific fluctuations in the morphology of the T wave during alternating beats, numerous investigators have demonstrated that T-wave or repolarization alternans is associated with the development of ventricular arrhythmias in animal models. These findings, coupled with the observations that T-wave alternans (TWA) precedes the development of ventricular arrhythmias in patients undergoing coronary angioplasty (12), with Printzmetal's angina (13), long QT syndrome (14,15), AMI and electrolyte derangements (16), have prompted several investigators to explore whether TWA could be used as a clinical tool to identify patients at high risk for developing SCD. In the pursuit of this goal, Smith et al. (17) and others (18) developed sophisticated signal-processing techniques and found that subtle alterations in T-wave morphology, which are not apparent on the surface ECG, are reflective of physiologically important abnormalities in repolarization.

This technique, referred to as microvolt-level electrical alternans of the T wave or microscopic TWA, has been the focus of several clinical studies. The original studies required the use of atrial pacing to unmask the microvolt alternans signal. Using this method, Rosenbaum et al. (19) examined 83 patients referred for diagnostic electrophysiologic testing and found that TWA was a significant and independent predictor of inducible arrhythmias on electrophysiologic testing (sensitivity 81%, specificity 84%; RR = 5.2). Of the 66 patients followed up to 20 months, TWA was essentially as useful as electrophysiologic testing in predicting arrhythmia-free survival. Hohnloser et al. (20) and Estes et al. (21) subsequently found that the assessment of microvolt TWA could be simplified by substituting atrial pacing with exercise to accelerate the heart rate to the optimal level. With this advance, TWA could be assessed completely noninvasively. Using this noninvasive approach, Ikeda et al. (22) prospectively assessed TWA, SAECG and LVEF in 102 patients after AMI. The sensitivity and negative predictive value of TWA was very high (93% and 98%, respectively), suggesting that such a test could be used as a screening test. However, the positive predictive value was only 28%, suggesting that TWA had many of the limitations of the previously identified risk stratification tests. Importantly though, patients with a positive study on both TWA and SAECG had a 50% event rate, suggesting that by combining these two tests one could identify a very high risk group.

The present study by Gold et al. (23) included 313 patients, making it the largest prospective study of patients scheduled to undergo electrophysiologic testing. The primary end point of the study was the occurrence of ventricular tachyarrhythmic events, as defined prospectively by SCD, sustained ventricular tachycardia, ventricular fibrillation or appropriate implantable defibrillator therapy for ventricular tachycardia or cardiac arrest. Overall, the test performed very well, and in a multivariate analysis in which 11 clinical parameters were examined, only TWA and electrophysiologic testing were independent predictors of these events. Although it was not stated in the article, the

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sensitivity and specificity for this outcome were 88% and 64%, respectively (personal communication, Dr. Gold), suggesting again that TWA may be an ideal screening test. However, the probability of experiencing an event at 400 days in patients with a positive TWA test was 19%, versus only 2% in patients with a negative TWA test. In other words, 81% of the TWA-positive patients remained event-free. Patients with both a positive TWA and SAECG had an event rate of 32.3%, versus <3% for all other patients with a determinant test. Thus, TWA appears to be a very useful noninvasive tool to identify patients at risk for ventricular tachyarrhythmic events (high sensitivity and high negative predictive value), and the combination of SAECG and TWA can be used to identify patients at high risk for these events.

Some issues and limitations of this study should be highlighted. First, while the combination of SAECG and TWA appears to be a reasonable way of identifying high risk patients, it is important to point out that of the 313 patients in the study, only 155 patients had a determinant SAECG and TWA. Of these 155 patients, only 10 experienced a ventricular tachyarrhythmic event. The authors state that overall there were 27 patients who experienced a ventricular tachyarrythmic event. Thus, of the 158 patients with an indeterminate test result on either TWA or SAECG (and thus who were not apparently included in the analysis), 17 experienced an adverse event. This suggests that the majority of patients who experienced a ventricular tachyarrhythmic event did not have a determinate SAECG or TWA, limiting the utility of this combined testing approach. Further, it appears that those patients with an indeterminate test might have actually been relatively high risk as well. This may not be surprising, because the main reason for having an indeterminate TWA was inability to exercise to a target heart rate of 100 or the presence of frequent ventricular ectopy, both of which might be expected to be associated with increased risk of SVE and death. Similarly, the most common reason for having an indeterminate SAECG was the presence of a wide QRS complex, which is also known to be associated with a worse prognosis. Thus, it would be interesting to explore whether patients with an indeterminate test are actually at increased risk compared with patients who have a negative test and whether this information could be incorporated into the testing algorithm to enable TWA testing to be applicable to more patients.

Another limitation of this study is that there was no mention of concomitant medications during the follow-up period. It is possible that this could have affected the results of the study. Beta-blockers are clearly very effective antiarrhythmic agents and prevent the development of SCD (24), but despite this, they are significantly underutilized (25). It is unfortunate that most studies investigating the utility of risk stratification tests fail to have the majority of eligible study patients on beta-blocker therapy. Whether TWA would have been as useful a test had all eligible patients received beta-blocker therapy is unknown. If the beneficial effect of beta-blocker therapy is in part related to its effect on reducing repolarization heterogeneity, then one might hypothesize that such an interaction might exist. It is important to explore this issue further in future studies.

Finally, the study by Gold et al. (23) examined only the SAECG, TWA, LVEF and an electrophysiology study. Recent studies have suggested that baroreflex sensitivity testing and heart rate variability are two very important risk stratification techniques and may have a role in identifying patients at risk for SCD. Whether the combination of TWA and autonomic tone testing would have been substantially superior to TWA and SAECG is yet to be determined and could be the focus of future studies.

Despite these caveats, the article by Gold et al. (23) provides an important contribution to the literature and adds to our understanding of TWA. As always, several important questions remain unanswered. The most important question is: How should these noninvasive tests be used clinically? It is tempting to propose that TWA and SAECG could replace invasive testing to identify patients at high risk for SCD who might benefit from ICD therapy. This should be the focus of future clinical research, but we simply do not have enough data today to support this approach. It is important to remember that the Antiarrhythmic Versus Implantable Defibrillator trial (9) and Multicenter Automatic Defibrillator Implantation Trial (10), which demonstrated superiority of automatic implanted cardiac defibrillator therapy over antiarrhythmic drug therapy, required spontaneous sustained ventricular arrhythmias and inducible ventricular arrhythmias, respectively, for inclusion into the trial. The Coronary Artery Bypass Graft-Patch trial (26), which did not show a benefit of ICD therapy, used SAECG to identify high risk patients. Thus, it is possible that not all patients at high risk for death from SCD will benefit from ICD therapy and that the modality chosen to identify high risk is very important.

In the year 2000, it is clear that we have effective devices to decrease SCD, but unfortunately no ideal test to identify those patients who need them. Charles Dickens might have described this ironic situation with the following words, "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness . . . we had everything before us, we had nothing before us . . . " Hopefully, the Tale of Two T Waves will evolve, and the continued pursuit for the perfect test or tests to identify patients at risk for a ventricular tachyarrhythmic event will be fruitful. Through such endeavors, I am confident that we will someday be able to treat more effectively the most devastating clinical problem in cardiology today—sudden cardiac death.

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