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EDITORIAL COMMENT

Anger Management May Save Your Life

New Insights Into Emotional Precipitants of Ventricular Arrhythmias*

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Sudden cardiac arrest is a leading cause of mortality, accounting for over 400,000 deaths annually in the U.S. alone (1). Most sudden cardiac arrests are due to ventricular tachycardia or ventricular fibrillation (1). Given the dismal survival statistics for out-of-hospital sudden cardiac arrest, substantial efforts have focused on identifying high-risk individuals who may benefit from prophylactic placement of an implantable cardioverter-defibrillator (ICD). This "primary prevention" strategy was validated in the landmark MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) (2) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (3) studies and incorporated into current treatment guidelines (4). In both of these studies, the major selection criterion for inclusion was left ventricular dysfunction without additional invasive or noninvasive

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risk stratification. Although prophylactic ICD placement is cost-effective in comparison to other established cardiovascular therapies (5), the majority of the patients studied in the SCD-HeFT and MADIT-II trials did not receive appropriate therapies for ventricular arrhythmias. Although it is anticipated that the incidence of appropriate shocks will rise with longer follow-up, these patients receive no initial benefit and incur the large upfront costs of prophylactic ICD implantation. In addition, they are exposed to surgical complications, inappropriate shocks, and potential failures of the implanted defibrillation lead or pulse generator (6). These considerations have likely contributed to the reluctance of some cardiologists to prescribe prophylactic ICD implantation for patients who meet current treatment guidelines. As a result, there has been great interest in developing accurate noninvasive risk stratification tests that can reliably identify low-risk SCD-HeFT patients who may not require an ICD.

Microvolt T-wave alternans (TWA) measures beat-to-beat alternation in the amplitude, shape, or timing of the T-wave. T-wave alternans can arise from differences in action potential duration in adjacent myocardial regions (spatial dispersion of repolarization) or from alternation in action potential duration over time within a given segment of myocardium (temporal dispersion of repolarization) (7). In several animal models, stimuli such as ischemia, ventricular extrasystoles, and progressive increases in heart rate produced phenomena such as "discordant alternans" and higher-order T-wave oscillations, which create large spatial gradients of repolarization (8,9). The presence of spatial dispersion of repolarization favors the occurrence of unidirectional block, re-entrant propagation, and the initiation of ventricular fibrillation (8). These experimental findings suggested that TWA is mechanistically linked to the pathogenesis of ventricular fibrillation and sudden cardiac arrest. Recent clinical studies have also documented that surges of TWA occur immediately before episodes of sustained ventricular tachycardia on Holter monitoring (10) and before spontaneous ventricular arrhythmias requiring treatment in ICD patients (11).

Most clinical trials of TWA have been conducted using the commercially available spectral method. In numerous studies conducted using this methodology, TWA has been associated with an increased risk of spontaneous and inducible ventricular arrhythmias (12–15). The major focus of recent clinical investigations of TWA has been to assess the negative predictive value (NPV) of the test in patients who are currently candidates for primary prevention ICDs. If the NPV is sufficiently high (i.e., >95%), ICD implantation could be safely deferred in patients with a negative TWA test. Initial results were favorable in some (14,15) but not all (16,17) studies. Potential reasons for this discrepancy include differing risk profiles of the populations studied, which directly influences the NPV, and lack of standardization of ICD programming, which can influence end point event detection. These limitations were overcome in 2 recent large TWA trials that required standardized ICD programming: MASTER (Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial (18) and the SCD-HeFT TWA substudy (19). Remarkably, TWA did not predict arrhythmic events in either trial. Although it is well recognized that ventricular arrhythmias detected by ICDs can overestimate the risk of sudden cardiac arrest, as some of these arrhythmias may have abated spontaneously (20), these data have substantially dampened enthusiasm for using TWA as a screening test to withhold ICDs from patients who meet current primary prevention criteria. The high rate of "indeterminate" TWA tests in the SCD-HeFT TWA substudy (41%) is also of interest (19). The spectral method of TWA

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measurement requires elevation of the heart rate to 105 beats/min or greater using treadmill exercise. Indeterminate tests occur when patients are deconditioned or when frequent ventricular ectopy is present; noisy recordings that reflect technical rather than patient factors are no longer considered indeterminate (21). Recent evidence indicates that indeterminate TWA tests carry an adverse prognosis similar to that of a positive TWA test, which has led to the classification of TWA results as "negative" and "non-negative" (21). Many of the favorable reports of TWA had very low rates of indeterminate tests (~10% to 20%) (14,15), which likely reflect selection of lower-risk patients who are able to complete the exercise protocol and who lack ambient ventricular ectopy. If the SCD-HeFT results truly represent the "real world" of spectral TWA measurement, other methodologies to measure TWA may be needed if TWA is to be useful clinically. The available data regarding physiological influences on TWA provide important guidance for future research directions in this area.

T-wave alternans is critically dependent on heart rate (22). Early studies of TWA used atrial pacing during electrophysiological studies to elevate the heart rate (12). Subsequently, protocols were developed using bicycle ergometer and treadmill exercise that allowed TWA testing to be performed noninvasively (13,14). Exercise TWA testing has greater prognostic value than TWA testing using pacing (23). The most likely explanation for this finding is that the sympathetic activation and vagal withdrawal induced by physical exercise more closely approximates the autonomic milieu that provokes spontaneous ventricular arrhythmias. Similarly, acute beta blockade markedly reduces the magnitude of TWA and the prevalence of positive TWA tests independent of heart rate effects (24). Adrenergic activation can be induced by anger and the strong emotions that may be experienced after natural disasters. Sudden cardiac arrest increases after earthquakes (25), and ICD patients experienced a greater incidence of appropriate ICD therapies following September 11, 2001 (26). Other investigators have documented that an anger-like behavioral state induces TWA in canines (27), and mental stress (anger recall and mental arithmetic) can elicit TWA in humans (28,29).

In this issue of the *Journal*, Lampert et al. (30) present new data regarding the prognostic value of anger-induced TWA in patients with ICDs. They studied 62 patients with ICDs during a mental stress protocol using ambulatory electrocardiograms. T-wave alternans was measured using 2 time-domain techniques: the intrabeat average and modified moving average analyses. Time-domain techniques offer the potential advantage of expanding the pool of patients eligible for risk stratification if sufficient information can be obtained from ambulatory electrocardiogram recordings without exercise testing. The investigators provide the first evidence that patients with higher levels of anger-induced TWA during provocative testing are at greater risk for ventricular arrhythmias detected by ICDs during follow-up. Important limitations of this study include the small sample size, the highly selected nature of this small cohort enrolled over nearly 4 years, the low event rate, and the impact of lack of standardization of ICD programming on the primary end point. Although time-domain techniques offer the potential advantage of greater applicability to larger numbers of patients who need risk stratification, several issues must still be resolved including the lack of validated cut points, uncertainty regarding the need for exercise testing to detect sufficient levels of TWA, and the comparability of time-domain TWA results to the spectral method. Future studies should investigate whether provocative testing for anger-induced TWA improves the NPV of TWA testing conducted using the spectral and time-domain methods and whether this new methodology could facilitate the identification of susceptible patients with less severe left ventricular dysfunction, who comprise the greatest proportion of those who experience sudden cardiac arrest events (31).

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