**EDITORIAL COMMENT**

**T-Wave Alternans and Human Ventricular Arrhythmias**

What Is the Link?*

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Sudden cardiac arrest (SCA) from ventricular arrhythmias affects over 400,000 individuals/year in the U.S. alone and has a dismal survival rate (1). Although reduced left ventricular systolic function (i.e., left ventricular ejection fraction) (2) and symptomatic heart failure (i.e., congestive heart failure) (3) are the major predictors of risk for SCA, they are more sensitive than they are specific. Thus, their primacy in guidelines for implantable cardioverter-defibrillators (ICDs) might lead to potentially unnecessary implantations (1). This motivates the identification of markers for the pathophysiology of ventricular arrhythmias that can improve indices for ICD insertion.

Several candidates exist. Inducing sustained ventricular arrhythmias at electrophysiologic study (EPS) was historically the gold standard but has become tarnished of late. Certainly, SCA is more frequent in ischemic cardiomyopathy patients with positive EPS, yet those with negative EPS still have a substantial arrhythmic risk (4,5). The precise reasons why the initiation of ventricular arrhythmias at EPS suboptimally predicts outcome or why EPS is less useful in non-ischemic cardiomyopathy are unclear (1). Therefore, attention has turned to indices of slow conduction and exaggerated dispersion of repolarization that are central to reentrant arrhythmogenesis. Evidence for slowed conduction after myocardial infarction, assessed indirectly by the signal averaged electrocardiogram (ECG) (6), successfully predicted SCA in the MUSTT (Multicenter Unsustained Tachycardia Trial) (7). Elevated sympathetic nervous activity increases the dispersion of repolarization and—when detected by cardiac nuclear imaging (8), reduced heart rate variability (9), or heart rate turbulence (10)—predicts events after myocardial infarction. Ventricular stretch slows conduction and exaggerates repolarization dispersion (11), and accordingly, elevated serum levels of B-type natriuretic peptide predict SCA in cardiomyopathy patients (12).

T-wave alternans (TWA) is a promising ECG risk factor that indicates alternate-beat changes in T-wave shape or amplitude and reflects repolarization dispersion (13). In a decade of contemporary clinical use (14), TWA has shown a negative predictive accuracy for SCA above 90% in a cumulative population of thousands of cardiomyopathy patients, both ischemic and non-ischemic (15,16). Accordingly, Markov models suggest that TWA should improve the economics of ICD insertion (17).

So, then, is TWA a fully developed risk stratifier? To be elevated in status above that of a mere epiphenomenon, an ideal risk stratifier must be plausible, predictive, and pathophysiologic. Certainly, TWA meets the first 2 criteria. However, a divide exists between animal studies—where TWA has been linked with repolarization dispersion and arrhythmias, albeit under extreme conditions of acute ischemia, hypothermia, very rapid pacing, or drug proarrhythmia (13,18–20)—and the dearth of clinical studies linking TWA with arrhythmogenesis under the conditions that might precede SCA.

In this issue of the *Journal*, Selvaraj et al. (21) provide important data to bridge this divide. In a small population of patients with ischemic and nonischemic cardiomyopathy, the authors compared ECG TWA with intracardiac repolarization alternans (RPA), using multipole catheters in the right ventricular endocardium and, via the anterior interventricular vein, the left ventricular epicardium. The spatial and temporal concordances that they describe strengthen the pathophysiologic basis of TWA and suggest ways in which it could be further refined as a clinical tool.

Selvaraj et al. (21) report that RPA was seen at more intracardiac sites in patients with than without TWA, consistent with the step-down in alternans magnitude seen from the heart to the T-wave in isolated rabbit (22) and guinea pig (20) hearts. This poses the question of what RPA magnitude contributes to lethal ventricular arrhythmias. Addressing this question requires studies of RPA in control subjects without left ventricular dysfunction, which might help explain "false-positive" tests that diminish the positive predictive value of TWA for SCA (13). It also requires comparison against arrhythmic outcome that was not reported by Selvaraj et al. (21) but could be used to define receiver-operating characteristics of RPA for SCA in a larger cohort.

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Selvaraj et al. (21) also report that RPA was spatially non-uniform and more prevalent in left ventricular epicardial than right ventricular endocardial sites. Normal rabbit hearts also show maximal RPA in the left ventricular free wall (22). Although sites of maximal RPA might vary dynamically (20), one might hypothesize that RPA in ischemic cardiomyopathy is maximal near scar and that patient-tailored spatial analysis could optimize the utility of TWA. Indeed, the TWA vector was recently shown to reflect echocardiographic scar in patients with ischemic cardiomyopathy (23), and cardiomyopathy patients with more extensive TWA (i.e., in more ECG leads) have more arrhythmic events (24). Selvaraj et al. (21) also suggest a transmural gradient in RPA, yet their recordings did not span the same myocardial region, so this needs further validation.

Notably, spatial non-uniformity in RPA suggests a mechanism by which unfortunately timed beats might encounter regional block to initiate re-entry. In animals, spatially non-uniform RPA after premature beats, rapid pacing (20), or acute ischemia (18) might lead to discordant alternans, where juxtaposed myocardial regions alternate with opposite phase, leading to unidirectional block, re-entry, and ventricular fibrillation (18,20). The “discordance” noted in patients by Selvaraj et al. (21) is likely different, not just because no patient imminently developed ventricular arrhythmias but also because of the integrative effects of unipolar recordings and their T waves. First, by averaging a wide field, unipolar recordings might not reflect homogeneous region whose cells all alternate with 1 phase so that the line of block needed to initiate reentry might not form (20). Second, unipolar “T waves” integrate many action potentials and have arbitrary polarity, unlike action potentials. Discordant RPA could thus reflect differences in baseline T-wave polarity between sites rather than discordant cellular alternans. Nevertheless, it is important to study arrhythmic outcome in patients with discordant RPA or an ECG TWA surrogate. We recently reported that premature beats, which produced discordant RPA in some patients reported by Selvaraj et al. (21), might reverse the phase of ECG TWA in cardiomyopathy patients. Such patients went on to suffer a markedly worse outcome than those with TWA but without phase reversal (25). Studies are needed to verify whether TWA phase reversal or another index reflects a particularly pro-arrhythmic intracardiac dispersion of repolarization.

Selvaraj et al. (21) should be commended on their novel and important study that begins to link TWA with dispersion of ventricular repolarization and arrhythmogenesis in humans. Future work should relate RPA to regional structural abnormalities and to the rate-dynamics of action potential duration (26). In particular, it is important to define the routes leading to spatial non-uniformity and their relation to arrhythmic outcome. Such studies might help define TWA indices of dynamic arrhythmic susceptibility and, in parallel, shed valuable insights into human ventricular arrhythmogenesis.

REFERENCES


