T-Wave Alternans for Arrhythmia Risk Stratification in Patients With Idiopathic Dilated Cardiomyopathy*

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Identification of individuals at risk for life-threatening arrhythmias has proved to be challenging in patients with nonischemic heart disease in general and in those with idiopathic dilated cardiomyopathy (DCM) in particular. This is an important clinical problem, as DCM accounts for approximately 10% of all adult sudden cardiac deaths and has a one-year mortality of 10% to 50% (1,2). Most of the patients affected by this condition have no definable etiology for the cardiomyopathic process that underlies their complex, highly arrhythmogenic myocardial substrate. The mainstay for arrhythmia risk evaluation, electrophysiologic testing, has proved to be of limited utility (1,3–5). Other investigators have determined that depressed heart rate variability (HRV) and late potentials on signal-averaged electrocardiogram (SAECG) are potentially useful in evaluating arrhythmia risk in patients with DCM (6,7), but QT dispersion has not proved to be reliable.

In this issue of the Journal, Hohnloser et al. (8) evaluate the utility of microvolt T-wave alternans (MTWA), a parameter that is routinely measured during exercise testing with bicycle ergometry or treadmill. Additional determinations included a battery of contemporary risk stratifiers, namely left ventricular ejection fraction, baroreflex sensitivity (BRS), mean heart rate, HRV, presence of nonsustained ventricular tachycardia, SAECG, and presence of intraventricular conduction defect, in predicting ventricular tachyarrhythmic events in patients with DCM. Only MTWA and BRS were found to be significant univariate predictors of events. Hohnloser et al. focused on MTWA because of a growing body of experimental and clinical evidence supporting the potential utility of this end point in assessing cardiac electrical instability, particularly in patients with underlying ischemic heart disease (9–11). The present study population consisted of a mixture of 100 patients who were evaluated for primary prevention, as well as 37 patients who had already suffered a clinical event and undergone implantation of an implantable cardioverter/defibrillator (ICD). In those with determinate tests, MTWA by Kaplan-Meier analysis was found to be a potent predictor of ventricular tachyarrhythmic events and arrhythmia-free survival (p < 0.035) during an average of 14 months of follow-up. Thus, the present prospective observational study enrolling a sizeable number of individuals with a nonischemic substrate represents an important contribution.

Two central caveats remain. The first is that the relatively high indeterminacy rate is a limitation of the test. In this study, 27% of patients had indeterminate results even after exclusion of patients with atrial fibrillation. This is consistent with previous studies that have reported indeterminate rates from 20% to 40% (12). Almost half (18/37 or 49%) of patients with indeterminate test results were unable to achieve a heart rate of 105 beats/min with exercise. Three of the patients with events in follow-up had indeterminate tests and were not included in Kaplan-Meier analysis. The second main limitation is that the study population of 137 patients included 37 who already had ICD implantation based on overt manifestation of their high-risk status. Their inclusion introduces a selection bias, as the likelihood both of an event and an MTWA positive test was inherently greater in these patients. Although inclusion of this group of patients to achieve an adequate event rate appears justifiable, it nonetheless limits the inferences that can be drawn from the study. Because the reported odds ratio for events in non-ICD patients was relatively low, 1.93 ± 2.2, further studies will be required to assess whether MTWA might have a role in the identification of DCM patients without previous clinical events who are at risk for life-threatening arrhythmias.

It is important to consider that MTWA values are usually obtained during exercise. This fact raises the possibility that provocative testing of the myocardial substrate may contribute to its capacity to stratify risk. This feature of MTWA testing may hold intrinsic advantages over other measures such as QT dispersion and SAECG, which are typically made at rest. Although no MTWA results are reported in patients at rest in the current study, the general experience with this parameter in patients with ischemic heart disease is that prognostic power is superior during exercise testing (11,12). The stimulus of exercise incorporates a number of potential proarhythmic influences in addition to elevation in heart rate, notably an increase in plasma catecholamine levels (13), which may be important in inducing T-wave alternans (TWA) as a marker of electrical instability.

The electrophysiologic basis for arrhythmogenesis in patients with DCM is unknown. This deficiency relates in part to the complexities of derangements in the myocardial...
substrate of these patients. Koumi et al. (14) demonstrated that ventricular myocytes from DCM patients had a longer action potential duration and slower repolarization phase 3 of the action potential than those from ischemic hearts and suggested differences in the rectifying K⁺ channel. Kawara et al. (15) provided histological evidence that the architecture of fibrosis in DCM contributes to activation delay. Hsia and Marchlinski (16) provided evidence that abnormal tissue either from scar or fatty tissue infiltration may lead to abnormal conduction and subsequent heterogeneity of repolarization in patients with DCM. Major disturbances in calcium handling (17–19) and enhanced adrenergic stimulation (20,21) have been implicated in both DCM and hypertrophic cardiomyopathy. The role of conduction abnormalities in heterogeneity of recovery of excitability needs further evaluation. Although unproven, it is likely that the vulnerable substrate of patients with nonischemic disease may be susceptible to transient factors such as alterations in neural activity and electrolyte imbalance in the initiation of disturbances in cardiac repolarization and ventricular arrhythmogenesis (2).

Several of these arrhythmogenic characteristics of DCM have been shown experimentally to increase TWA, supporting the rationale for investigating TWA as a potential marker of risk in DCM. Specifically, TWA provides a quantitative measure of temporal and spatial unevenness of repolarization (9,11,22), which is likely to be present in the irregular fibrotic substrate in DCM patients (16). A link between disturbed calcium handling and TWA is supported in experimental models by the fact that repolarization alternans occurs in concert with oscillations in calcium fluorescence (23–25) and during intracellular calcium overload (26,27). Conversely, TWA can be prevented by calcium antagonists (28) and by ryanodine, an inhibitor of sarcoplasmic reticulum calcium reuptake (29,30). The capacity of TWA to detect the influences of adrenergic activity is suggested by the facts that TWA magnitude is increased by sympathetic nerve stimulation and behavioral stress in both humans and animals (31–33) and blunted by beta-adrenergic blockade (34,35).

In summary, Hohnloser et al. (8) have provided promising results regarding the value of MTWA in risk stratifying patients with DCM. Their findings also underscore the potential value of physiologically provocative testing to uncover latent electrical instability in these patients. In the future, dynamic evaluation may not be restricted to exercise testing, because methodological developments have been made that permit assessment of TWA during ambulatory monitoring (36).

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