The Frustrating Search for Arrhythmia Risk Stratifiers in Heart Failure Due to Nonischemic Cardiomyopathy

Does T-Wave Alternans Testing Help?*

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Identification of heart failure patients who are at risk for life-threatening arrhythmias due to cardiomyopathy has been challenging, particularly for those without underlying coronary artery disease. The inherent complexity of risk stratification in this group is probably attributable to multifactorial changes in myocardial substrate and disruption in autonomic function. Risk identification in patients with this diagnosis is a pressing problem, because this condition accounts for 10% of adult sudden cardiac deaths (SCDs) and is associated with an annual mortality rate of 10%. The utility of electrophysiologic testing in these patients has proved to be limited, but signal-averaged electrocardiograms (ECGs) and depressed heart rate variability are potentially useful. Guiding therapy, including use of potentially life-saving implantable cardioverter-defibrillators (ICDs), is an important goal that must be performed reliably, because the devices carry risk with respect to infection, lead complications, and inappropriate delivery of therapy.

T-wave alternans (TWA) testing has been shown increasing to be useful in diverse patient populations using both the traditional spectral method (1) and the time-domain modified moving average approach, which can be implemented during routine exercise testing (2). With respect to nonischemic cardiomyopathy, the TWA literature is less extensive and the results have been mixed (3–6).

The Current Study

In this issue of the Journal, Salerno-Uriarte et al. (7) present the results of the ALPHA (T-Wave ALternans in Patients With Heart fAilure) study. The main objective of this multicenter, prospective, observational study was to assess the predictive utility of TWA in patients with New York Heart Association (NYHA) functional class II and III heart failure of nonischemic etiology with left ventricular ejection fraction (LVEF) ≤40%. The study enrolled 446 consecutive unselected patients, the majority of whom had a diagnosis of idiopathic dilated cardiomyopathy. T-wave alternans was analyzed during exercise stress testing using the spectral method, and patients were followed for a median of 19 months.

This study adds importantly to our current understanding of TWA testing, because it is 1 of the largest studies in patients with nonischemic cardiomyopathy. Patient follow-up was excellent. A large majority (~80%) of patients were receiving a contemporary heart failure medication regimen, which consisted of beta-blockade, angiotensin-converting enzyme inhibition, and diuretics, and one third were taking aldosterone antagonists as well. These medications were continued at the time of testing, unlike in some TWA studies (3), in which beta-blockade was withheld before testing. The ALPHA study demonstrated that patients with abnormal (non-negative) TWA test results had an adjusted hazard ratio (HR) of 3.2 for the combined primary end point of cardiac death and life-threatening arrhythmias. This yielded a negative predictive value (NPV) of 97.3% at 18 months but a positive predictive value of only 9%.

A potential limitation is the relatively low event rate, with 1-year all-cause mortality of 4.2%, compared with 6.2% in the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial (8). The authors argue that this difference is attributable to inclusion of patients with higher LVEF (mean 29.5% vs. 21.4%) and exclusion of patients with atrial fibrillation and ambient ventricular arrhythmia. They suggest that if these proven risk factors are considered, the event rate of the ALPHA study would be comparable to that of existing studies in patients with nonischemic cardiomyopathy.

Controversy has been raised regarding the prognostic capacity of TWA in patients with left bundle branch block. In the ALPHA study, where 42.6% of patients had left bundle branch block, QRS duration had a minimal effect on the NPV of TWA testing. Similarly, the adjusted HR remained significant at 3.91 with an NPV of 96.8% at 18 months, even when only patients with LVEF ≤35% were analyzed. This subgroup analysis is instructive, because even in patients with a presumed higher arrhythmic risk, the NPV of TWA remains persuasive.

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Evidence conflicting with the results of the ALPHA study has been reported from a substudy of the SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial) (5), which investigated TWA in 490 patients with LVEF ≤35% and NYHA functional class II and III symptoms. The SCD-HEFT substudy failed to demonstrate the capacity of TWA testing to predict the composite primary end point of SCD, sustained ventricular arrhythmia, or appropriate ICD discharge. Some key differences between these 2 studies include a 41% indeterminate rate (compared with 20.6% in the ALPHA study), the inclusion of ischemic cardiomyopathy, and an LVEF cutoff of ≤35%. A more thorough comparison awaits the full-length publication.

Notwithstanding a number of positive observational studies, a critical piece of evidence will be the demonstration in a randomized clinical trial that TWA contributes to guiding ICD implantation. The results of the ABCD (Alternans Before Cardioverter Defibrillator) trial, which was designed for this purpose, await publication (9).

Conclusions
The sizable ALPHA study represents a significant step forward in arrhythmia risk stratification of patients with heart failure due to nonischemic cardiomyopathy. The results are encouraging with respect to identifying patients who are unlikely to benefit from an ICD. There is a need to improve the positive predictive value of TWA test results, which, in the 9% range, was relatively low.

An attractive strategy is to depart from the current binary approach of classifying test results either as “abnormal” or “normal/negative” and to reconsider the potential value of quantitative assessment of TWA. Klingenheben et al. (4) demonstrated that patients with heart failure due to dilated versus ischemic cardiomyopathy and those with ventricular tachyarrhythmias exhibited higher TWA levels. They proposed that quantitative TWA assessment may provide additional pathophysiologic insights and prognostic information over qualitative binary TWA test classification. This approach is consistent with recommendations from our group (10).

Also, because this diagnosis includes multiple pathologies with derangements in myocardial substrate and varying degrees of altered autonomic function, a multiparameter approach including LVEF could prove useful. Ambulatory ECG analysis offers the intrinsic advantage of TWA testing (11,12) in combination with autonomic function by heart rate turbulence (13). This surmise could be tested in the ALPHA study, because 24-h ambulatory ECG monitor-

ing was part of the protocol. These new tools offer considerable promise in dealing with the intrinsic complexities of nonischemic cardiomyopathy. Although considerable progress has been made by the present and earlier studies, a major missing element remains, namely, randomized clinical trials evaluating the utility of TWA in guiding therapy.

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