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T-wave Alternans Testing: Can it Predict Arrhythmogenesis?

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Sudden cardiac death (SCD) resulting from ventricular arrhythmias causes almost 300,000 deaths in the US annually.¹ The disappointing performance of antiarrhythmic drugs has meant that the implantable cardioverter defibrillator has emerged as the primary therapy for preventing SCD.² However, a major challenge that needs to be addressed is the identification of patients at the highest risk of SCD, since implantation of ICDs is expensive, and a majority of these devices never deliver shocks.³ Several strategies, either invasive (electrophysiology study, EPS), or non-invasive measurements such as left ventricular ejection fraction (LVEF), heart rate variability (HRV), signal averaged electrocardiogram (SAECG), QT dispersion, magnetic resonance imaging, and T wave alternans (TWA) are now under investigation for better stratification of patients at risk for arrhythmogenesis.^{4,5}

In the last two decades, TWA testing has emerged as a potentially useful tool to predict susceptibility to arrhythmias.⁶⁻⁸ TWA is defined as the alteration of the T wave amplitude and/or shape on the ECG from beat to beat, and is primarily observed at high heart rates.⁶ Studies using animal models have underlined the link between gradients of repolarization on the surface of the heart, alternans in the action potential duration (APD) in time and space, and inducibility of ventricular fibrillation (VF).⁹ The underlying mechanisms are quite complex, and have been linked to steeper restitution of the APD and/or conduction velocity, calcium cycling, intrinsic or functional heterogeneities in refractoriness, or the effects of memory in the myocardium.^{6,10-12}

Despite its early promise,¹³ the clinical utility of TWA testing remains controversial. A recent prospective sub-study of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) concluded that TWA testing did not predict arrhythmia events or mortality, and was therefore not a useful marker in identifying patients for ICD implantation.¹⁴ In contrast, investigators from the recent ABCD (Alternans Before Cardioverter Defibrillator) trial compared the utility of EPS versus TWA testing in patients with ischemic cardiomyopathy and having a LVEF < 0.4.¹⁵ Their results led them to conclude that the identification of patients with higher risk was comparable between the EPS and the TWA tests.¹⁵

The article by Amit et al in this issue of *Heart Rhythm*¹⁶ is in part a continuation of the analyses of the results from the ABCD trial. The authors hypothesized that TWA and EPS tests would predict distinct arrhythmia outcomes. To this end, they divided the observed arrhythmias into two major groups: (1.) Stable Monomorphic Ventricular Tachyarrhythmic Events (S-VTE) (2.) Unstable Ventricular Tachyarrhythmic Events (U-VTE), consisting of polymorphic ventricular tachycardia and VF. Their results indicated that the TWA test was more predictive of U-VTEs, whereas the EPS test was more predictive of S-VTEs.

Furthermore, the TWA test predicted events better than EPS when LVEF ≤ 0.3 , whereas for LVEF > 0.3 , the reverse was true.

The results from the study of Amit et al¹⁶ are interesting because they confirm what one might reasonably postulate based on the basic design of the study; i.e. since the EPS test induces arrhythmia via premature stimuli, whereas the TWA test relies on a graded exercise protocol, the nature of the induced arrhythmias might be different as well. It also raises the intriguing question as to why a stable arrhythmia is almost always the outcome in an EPS test, whereas the TWA test leads to unstable arrhythmias in these patients with ischemic cardiomyopathy. These questions can be best answered by further experiments in relevant animal models of arrhythmia in the ischemic heart, which carefully attempt to understand the link between the arrhythmia mechanism and the method of induction (the trigger). This does not rule out the fact that the underlying substrate might have been very different in these patients. In view of the different results obtained for EPS versus TWA predictive ability when classified based on LVEF, it might also be interesting to explore the possible relationship between LVEF, related electrical substrate remodeling and its interactions with different triggers that initiate arrhythmias.

However, many caveats exist. The biggest limitation of the study by Amit et al¹⁶ pertains to the extremely small number of events (for example it was 2.7% in which the TWA test was predictive of the so-called U-VTEs). In addition, the duration of their follow-up time was only one year. The authors acknowledge such limitations. It is also clear from the ABCD trial (see Table 2¹⁵) that some events were predictable by both the TWA test and the EPS test, while some events were not predictable by either approach. This suggests that the arrhythmia classification as attempted in the study by Amit et al may not always be possible, and further that these tests (TWA and EPS), alone or in combination will also fail to identify all the patients at risk. Furthermore, the ABCD trial also did not include patients with unstable coronary artery disease, or those who had permanent atrial fibrillation. Thus it is unclear whether the TWA test can be a universal marker. Lastly, the reasons for the vastly different outcomes for TWA testing in the ABCD trial, and patients in the SCD-HeFT study remain unclear.

In summary, the results thus far suggest that clinical trials with a larger cohort of patients, and carried out for a longer duration of time, will be necessary in order to assess whether the TWA test might be able to increase our ability to identify patients at risk for arrhythmogenesis, and distinguish between varied arrhythmogenic substrates. In the meanwhile, additional basic research is warranted into these fascinating, yet unresolved, questions regarding TWA.

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