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“Data mining” to improved detection of arrhythmogenic T wave alternans

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One of the major unresolved challenges in our field is to develop and apply clinical paradigms that allow better prediction and prevention of sudden cardiac death (SCD)¹. Microvolt-level T wave alternans (MTWA) continues to have considerable appeal as a SCD risk marker because it is a reflection of arrhythmia substrate rather than overall progression of disease.^{2,3} This is key to the clinical application of risk markers because treatment directed against ventricular fibrillation, as with implantable defibrillators, will only mitigate SCD risks, and can actually amplify risk for non-SCD risk such as progression of heart failure.⁴ Moreover, MTWA was shown to possess greater predictive accuracy when compared head to head to other risk markers. While several methodological approaches have been proposed for measuring MTWA, the so called “spectral method” applied during controlled heart-rate based exercise testing is the only method that has been rigorously standardized with consistent exercise protocols, standard rules for ECG lead sets, and cut-points for test-positivity applied prospectively and repeatedly in numerous clinical trials.⁵ However, the current standards for MTWA testing with the spectral method produce either a positive or negative or indeterminate test result. Other methods have been applied inconsistently, measuring MTWA during exercise testing without controlled heart rate elevation (i.e. workload versus heart rate based exercise), during recovery from exercise, or without any exercise provocation at all, and using various cut-points for MTWA positivity typically applied retrospectively to the study population at hand. Consequently, there are relatively little systematic data available to determine whether the relative MTWA magnitude evaluated as a continuous rather than a dichotomous variable might provide greater predictive accuracy for the MTWA test.

In this issue of the Journal, Leino et al⁶ present a retrospective analysis of MTWA recorded from a large population of patients undergoing exercise stress testing for a variety of clinical indications. While no specific hypothesis is put forward, their goal was to systematically determine whether the magnitude of MTWA assessed as a continuous variable would be correlated with greater risk, and whether selective evaluation of particular ECG lead sets would further enhance the prediction of events. This is an important question that not only has practical implications to MTWA testing, but is mechanistically sound as the magnitude of cellular alternans was found previously to increase progressively prior to initiation of

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ventricular fibrillation in experimental models.³ Moreover, prior clinical studies have already suggested that patients at risk for arrhythmic events exhibited higher MTWA voltages (10.8 versus 7.4 microvolts) occurring in a greater number of ECG leads (7.6 versus 6.4 leads).⁷ In their analysis derived from the Finnish Cardiovascular Study, Leino et al analyzed 3,598 stress tests where MTWA was measured by the modified moving average method. Importantly, stress testing was performed for common clinical indications (e.g. evaluation of ischemic heart disease) and not necessarily because there was a priori concern or risk for SCD. Consequently, subjects were generally at low risk for cardiovascular and arrhythmic events with mean age 55 years and the large majority (71%) with class 1 heart failure. Endpoints of total, cardiovascular, and SCD mortality were ascertained from death certificates during a 55 month follow up period. The overall mortality rate was 6.4% (1.4%/yr) with 2.7% cardiovascular mortality (0.3%/yr), reaffirming the relatively low-risk nature of the population. Based on a statistical comparison of MTWA magnitude between precordial leads, the authors conclude that MTWA measured in lead V5 was superior to all other single leads or combination of leads in predicting outcomes. Also, based on a 64% increase in hazard ratio for cardiovascular mortality for a 20 microvolt rise in MTWA, it is concluded that the magnitude of MTWA may contain prognostic information that is missed when restricting analysis to a dichotomous assignment of MTWA positivity versus negativity.

These data merit very careful consideration as this is an unprecedented study in terms of the sample size of systematically analyzed MTWA data. While the richness of the data set provided a wonderful opportunity for data mining, the retrospective nature of the work and lack of pre-hoc hypothesis greatly limits extrapolation of the findings to other patient populations, but does provide helpful insights for future study. Therefore, it must be emphasized that the results of this study require prospective evaluation in an independent population to ultimately assess the applicability of these results.

The authors' conclusion that MTWA measured in ECG lead V5 was most predictive of outcomes, while statistically valid, may have limited clinical relevance because the effect size is so small. It is evident, for example, in figure 2 that while the differences in MTWA magnitude between survivors and non-survivors was greatest in lead V5, the differences are extremely small and the variability (error bars) are relatively large. It is possible that the attribution of statistical significance to the detection of such small differences was explained by the very large sample size of the study (i.e., beta error). It should also be emphasized that there may be serious risk in restricting analysis of MTWA to limited lead sets since the projection of cellular action potential alternans onto the surface ECG is likely to vary as a function of extent and etiology of cardiac disease. A similar argument can be made in relation to the authors' contention that the magnitude of MTWA predicts outcomes. There was no obvious trend between MTWA magnitude and SCD or cardiovascular mortality, and only a small apparent relation to total mortality. Even so, the differences in annualized total mortality rate between pts with "9 to 13 microvolts" and "< 25 microvolts" of alternans was only 0.4% deaths/yr. This rather small effect is unlikely to have much import to prognostication in individual patients. Therefore, one could legitimately argue that the results of this study suggest the opposite conclusions; i.e. there is a threshold MTWA level, above which risk increases over the general population.

The nature of the patient population and end-point selection also merit some discussion. It is well established that the performance of any diagnostic test is strongly dependent on the population in which the test is applied. In this case, MTWA is most notable for its negative predictive value (i.e. high sensitivity compared to specificity), hence it has greater value in a population where there is elevated a priori risk for SCD. Therefore, negatively risk stratifying a patient by MTWA testing who would otherwise be assumed to be at high risk

has considerable clinical value. Conversely, a negative MTWA test in a patient who is already known to be at low risk has comparatively little value. Leino et al⁶ evaluated a low risk population in whom risk assessment for SCD is not normally a consideration. Therefore, the practical relevance of the findings is diminished. Also, the use of death certificates to adjudicate cause of death is known to be fraught with hazards, making evaluations of anything other than total mortality rather precarious.

Finally, there are concerns regarding selection of methodology use to measure MTWA in this study. The selection of the modified moving average (MMA) analytical method with uncontrolled exercise may be suboptimal, particularly in a low risk population where sensitive detection of low-level MTWA that is distinguishable from noise is best accomplished by the spectral method. Also, the lack of deployment of exercise with controlled heart rate greatly hampers the detection of the alternans-heart rate relationship, and the heart rate threshold for MTWA which is key to distinguishing significant MTWA from MTWA that occurs at more rapid rates irrespective of patients arrhythmia risk status. Instead of assessing the magnitude of MTWA in reference to heart rate, Leino et al⁶ selected maximum MTWA during the test. This obviously makes the result susceptible to greater variability, data outliers, and whatever heart rate the patient happened to achieve during the exercise test.

In summary, the work of , Leino et al⁶ represents an important effort to systematically improved approaches for using MTWA to assess risk. The study suggests, but does not prove the hypothesis that MTWA alternans magnitude may vary importantly between ECG leads, and the different leads showing MTWA may convey different prognostic information. The study also suggests that future studies are required to evaluate MTWA as a continuum of risk rather than the more restrictive dichotomization of MTWA results as either positive or negative test.

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