Electrophysiology

A combined anatomic and electrophysiologic substrate based approach for sudden cardiac death risk stratification

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Background Although left ventricular ejection fraction (LVEF) is the primary determinant for sudden cardiac death (SCD) risk stratification, in isolation, LVEF is a sub-optimal risk stratifier. We assessed whether a multi-marker strategy would provide more robust SCD risk stratification than LVEF alone.

Methods We collected patient-level data (n = 3355) from 6 studies assessing the prognostic utility of microvolt T-wave alternans (MTWA) testing. Two thirds of the group was used for derivation (n = 2242) and one-third for validation (n = 1113). The discriminative capacity of the multivariable model was assessed using the area under the receiver-operating characteristic curve (c-index). The primary endpoint was SCD at 24 months.

Results In the derivation cohort, 59 patients experienced SCD by 24 months. Stepwise selection suggested that a model based on 3 parameters (LVEF, coronary artery disease and MTWA status) provided optimal SCD risk prediction. In the derivation cohort, the c-index of the model was 0.817, which was significantly better than LVEF used as a single variable (0.637, $P < .001$). In the validation cohort, 36 patients experienced SCD by 24 months. The c-index of the model for predicting the primary endpoint was again significantly better than LVEF alone (0.774 vs 0.671, $P = .020$).

Conclusions A multivariable model based on presence of coronary artery disease, LVEF and MTWA status provides significantly more robust SCD risk prediction than LVEF as a single risk marker. These findings suggest that multi-marker strategies based on different aspects of the electro-anatomic substrate may be capable of improving primary prevention implantable cardioverter-defibrillator treatment algorithms. (Am Heart J 2013;166:744-52.)

Although improved pharmacologic therapies for coronary artery disease (CAD) and congestive heart failure have a favorable impact on the incidence of sudden cardiac death (SCD), the implantable cardioverter-defibrillator (ICD) has emerged as a mainstay of SCD prevention and seminal clinical trials have demonstrated significant reduction in all-cause mortality among patients at heightened risk for SCD but without a history of ventricular arrhythmias (ie, "primary prevention" ICDs).[1,2]

Currently both New York Heart Association class and left ventricular ejection fraction (LVEF) are recommended in guiding ICD implantation for primary prevention.[3] Unfortunately, given the dynamic nature of New York Heart Association class and the notorious limitations of its subjective assessment,[4] LVEF has emerged as the primary determinant of eligibility for primary prevention ICD therapy.[3] However, as highlighted in the recent National Heart, Lung and Blood Institute and Heart Rhythm Society report on SCD prediction and prevention,[5] there is widespread recognition that LVEF reflects only one aspect of the complex electro-anatomic substrate that gives rise to ventricular arrhythmias and in isolation, LVEF is a sub-optimal risk stratification tool.

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Specifically, among patients who are currently candidates for primary prevention ICD therapy (ie, LVEF ≤35%), only a small percentage of patients (~2%-5% per year) will suffer a ventricular arrhythmia resulting in SCD,[5,6] demonstrating that the positive predictive value and specificity of low LVEF for predicting SCD is quite limited. Conversely, the majority of SCD events occur in patients with only mildly impaired or even preserved LV systolic function,[7,8] thus highlighting the limited negative predictive value and low sensitivity of impaired LVEF for determining SCD risk.

At least part of the limitation of using LVEF cut points for SCD risk stratification is that although patients with impaired LVEF are at heightened risk for SCD, they are also at increased risk for other causes of death, such as progressive heart failure,[6] in which case ICD therapy is not expected to be beneficial. In order to optimize ICD utilization and reduce the burden of SCD, more robust risk stratification tools are necessary which better reflect the complex electro-anatomic substrate that gives rise to malignant arrhythmias and sudden death. Although numerous invasive and non-invasive markers have been tested for ventricular arrhythmia and SCD risk prediction,[5] currently available metrics remain suboptimal for determining which patients are most or least likely to benefit from ICD therapy.

In order to test the hypothesis that a multi-marker strategy reflecting different aspects of the electro-anatomic substrate is capable of providing better SCD risk prediction than LVEF alone, we have developed and validated a model based on 3 easily accessible clinical parameters to predict the risk of SCD across a wide range of LVEF.

Methods

Derivation and validation cohorts

We performed a PubMed literature search for all studies with "alternans" in the title published between 1998 and 2010. We chose 1998 as the beginning for the literature search because the first version of the MTWA-specific exercise protocol with the Cambridge Heart testing system was released in September 2000. However, certain studies were performed using the new protocol prior to its official release and in an effort to capture all studies performed with the MTWA-specific protocol, we extended the search back to 1998. We identified prospective clinical trials involving at least 100 patients in which MTWA testing using the spectral analytic method was used to predict the risk of SCD with at least 12 month follow-up. In order to minimize the impact of ICD therapy on study endpoints, we excluded studies where ≥15% of the patients had ICDs implanted at baseline or ≥15% of the total arrhythmic outcome events were due to "appropriate" ICD therapy.[9] Additionally, in order to further minimize the impact of ICD therapy, patients with ICDs from the included studies were excluded from the final pooled cohort analysis. We also excluded studies where MTWA testing was performed soon after (ie, ≤4 weeks) acute myocardial infarction.

The initial search identified 17 studies of >100 patients in which MTWA was used to predict SCD. Seven studies were excluded because ≥15% of the patients had ICDs or ≥15% of the arrhythmic outcome events were due to "appropriate" ICD therapy[10-16] and 2 studies were excluded because they used an older version of the Cambridge Heart system which did not include MTWA-specific exercise protocols and did not require sub-maximal exercise.[17,18] One study was excluded because MTWA testing was performed early after myocardial infarction (mean 8.1 ± 2.4 days).[19] Two studies did not include a SCD endpoint in the original publication.[20,21] The authors of both studies were contacted to find out if data on SCD was available: one study was excluded because data on SCD was not available[20] whereas the authors of the other study were able to provide data on SCD and therefore, that study was included in our cohort.[21] Ultimately, 6 studies met the inclusion criteria and were included in the final cohort.[21-26] Of note, although there were a significant number of patients with ICDs reported in the paper by Chan et al,[22] the ICD and non-ICD cohorts were prospectively followed and described separately and therefore, we included the non-ICD cohort in the pooled analysis.

To minimize heterogeneity across studies, we obtained patient level data from the authors of the 6 studies included in this pooled cohort. After exclusion of 556 patients with ICDs, the final study cohort included 3355 patients. The baseline characteristics of the 6 studies included in our cohort have been published previously and are summarized in Table I. Two-thirds of the patients from each of the 6 studies were randomly selected and merged to form the derivation cohort (n = 2242) and the remaining one-third of patients from each of the 6 studies was merged to form the validation cohort (n = 1113).

Microvolt T-wave alternans testing

All 6 of the pooled studies utilized microvolt T-wave alternans (MTWA) testing with the spectral method[27] (CH 2000 system; Cambridge Heart, Bedford, MA) and the results of each MTWA test (positive, negative or indeterminate) were classified by the investigators within each study based on established criteria.[28] In brief, MTWA studies were classified as positive if there was sustained alternans >1.9 μV for at least 1 minute with an alternans ratio (*k* score) >3.0 with an onset heart rate <110 beats/min. Studies were classified as negative if criteria for positive were not met in an artifact-free period of data collection with a heart rate of at least 105 beat/min for at least 1 minute. All remaining studies not meeting criteria for either positive or negative were classified as indeterminate.

Statistical analysis

The primary end point for this study was SCD/arrhythmic mortality at 24 months. All arrhythmic events and mortality endpoints were adjudicated by the study investigators based on the specific definitions used within each study protocol.[21-26] Clinical covariates available for all patients included age, gender, LVEF, presence of CAD, beta adrenergic blocker use at the time of study enrollment and MTWA status. Logistic regression models were used to identify univariate and multivariate predictors of the primary end point.

A parsimonious set of covariates was selected with the use of stepwise selection to define a multivariable model to predict the risk of SCD at 24 months. Three main effects were selected for