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Learning for Prevention of Sudden Cardiac Death

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Sudden cardiac death (SCD) is a devastating event and a significant healthcare burden. While coronary artery disease and overall cardiovascular deaths have declined significantly over the last decades[1], a disproportionately high contribution to mortality results from SCD, with the majority of events due to ventricular arrhythmias, VA (ventricular tachycardia, VT or ventricular fibrillation, VF). The development of new methodologies and the enhancement of existing ones for prediction and prevention of SCD is critical to addressing this healthcare need. Accurate SCD risk stratification is an area of active investigation, and it has been recognized early on that success will require integration of multi-disciplinary efforts from the molecular level to the bedside, and conducting studies in the general population[2].

Currently, assessment of left ventricular (LV) ejection fraction (LVEF) is the clinical standard in identifying patients at high risk of SCD and is used to guide primary prevention of SCD[3] by the deployment of a cardioverter-defibrillator (ICD). LVEF, however, does not adequately represent the underlying myocardial structural and electrophysiological remodeling in heart disease predisposing to VAs and SCD, and is thus insensitive and nonspecific[4]. Accordingly, considerable effort has been extended in establishing biomarkers that reflect arrhythmia substrates more directly and developing invasive and noninvasive techniques to identify patients at risk for SCD. Invasive electrophysiological testing using programmed cardiac stimulation has been shown to add specificity in identifying patients with ischemic heart disease at risk for VAs, however, the approach does not confer sufficient sensitivity to deem patients with a negative test at a low risk of SCD. Comorbidities, structural remodeling parameters identified in clinical imaging scans such as contrast-enhanced (i.e late gadolinium enhanced, LGE) cardiac magnetic resonance (CMR), and alterations in ECG parameters are the three main groups of biomarkers that have been investigated in the effort to better stratify patients for SCD risk. Presence of atrial fibrillation, interim heart failure hospitalization, and worse NYHA class have been associated with higher VT/VF risk. Chronic ventricular dilation and remodeling of cardiac structure, and particularly the extend of disease-induced scar and fibrosis, predispose to VA[5]. Electrophysiological remodeling, manifested as prolonged QRS interval, and particularly, changes in restitution properties, reflected as oscillations in the T-wave[6] have been linked to VT/VF occurrence. Personalized computational modeling has also made advances in predicting risk of VAs[7], integrating both structural and electrophysiological remodeling in

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post-infarction patients, and setting the stage for the utilization of new computational and engineering technologies in SCD patient risk stratification.

Among the new technological advancements, machine learning (ML) is making quick strides in entering clinical practice. ML applications have also seen a rapid growth and popularity in arrhythmia research. A number of studies have employed ML in SCD risk stratification. Texture analysis of LGE-CMR has identified imaging features predictive of elevated VA risk. In hypertrophic cardiomyopathy, ML achieved diagnostic accuracy ranging from 82.8% to 94.1% in a small cohort of 64 patients[8]. ML has been employed to construct patient-specific complexity scores based on the analysis of LGE-MRI scans of 122 ischemic cardiomyopathy patients[9]. In a hyperthrophic cardiomyopathy cohort, VA risk has been assessed from electronic health records[10], identifying 10 new variables as well as 12 known variables, as VA risk predictors. While the above studies offer a static risk score, a few studies have also attempted to predict SCD risk dynamically. A probabilistic neural network was used to predict[11], from intensive care unit signals (ECGs, non-invasive continuous blood pressure and arterial oxygen saturation) the occurrence of VF 5 min before the event with an accuracy of 82.5%. A recent study[12] used random forest ML model to predict survival outcomes with baseline and time-varying predictors, achieving area under the receiver operating curve (AUC) of 0.88 on a training set of 382 ischemic cardiomyopathy patients; predictive variables included heart failure hospitalization, LV scar, LV and left atrial volumes, left atrial function, and interleukin-6 levels. These studies demonstrate significant interest and underscore the initial successes in utilizing a number of ML approaches to advance SCD prediction.

The study by Rogers et al[13] in the current issue of this journal presents the latest research employing ML approaches to predict risk of VT/VF in ischemic cardiomyopathy. The study focused on the contribution of cell electrophysiology to VA risk. The authors hypothesized that the morphology of the action potential may predict VA risk and long-term outcome. To record in-vivo action potentials in these patients, a monophasic action potential (MAP) catheter was used, shown previously to accurately reflect transmembrane action potentials in patients8. Measurements consisted of 5706 ventricular MAPs acquired during right ventricular apex steady-state pacing from 42 patients with LVEF ≤40%. Each MAP beat was analyzed as a voltage-time series in a time window that encompassed the longest MAP.

The patients were randomly split into a 70% cohort for training and a 30% cohort for testing, and a K-fold cross-validation (K=10) was performed to increase generalizability (i.e. the ability to predict outcome on an unseen patient); each iteration providing one training set and one test set not used in training. The methodology to predict patient outcomes from MAP beats consisted of two steps. First, a supervised ML algorithm (support vector machine or a convolutional neural network) was trained to predict the endpoint of sustained VT/VF (with an additional endpoint of mortality at 3 years) using as input all MAP beats across patients; the support vector machine model provided a superior performance. Second, the proportion of each patient’s beats classified by the ML model to be predictive of the clinical outcome was calculated, thus constructing a MAP score for that patient. The AUC for the MAP score was 0.90 (95% CI = 0.76–1.00) in predicting VT/VF outcome; the optimal MAP score cut-point yielded an accuracy of 85.7%. For the mortality endpoint, AUC was 0.91

(95% CI: 0.83–1.00), with the MAP score optimal cut-point point having accuracy of 81.0%. In this patient cohort, neither testing for induction of VT/VF, nor the presence of ICD within 14 days of testing, nor coronary artery disease distributions from angiography predicted VT/VF – in the multivariate model, the MAP score was the only predominant predictor of VT/VF. There results demonstrate that alterations in action potential shape in ischemic cardiomyopathy patients are predictive of clinical outcome.

The authors also compared the average MAP shapes that were predictive of sustained VT/VF versus those that were not. MAP waveforms that predicted VT/VF had higher plateau (i.e. phase II of the action potential) voltage and longer phase II duration compared to MAPs that did not. Simulations with a human ventricular action potential model revealed that, not surprisingly, increased I_{CaL} or enhanced NCX current (potentially due to increased intracellular Ca resulting from elevated I_{CaL}) could lead to elevated voltage and prolonged plateau during phase II. Increased I_{CaL} is known to promote VAs in heart failure[14] and in patients with certain channelopathies[15] and the results by Rogers et al indicate that it could potentially also increase VA propensity in ischemic cardiomyopathy. Future studies will need to address the question whether elevated I_{CaL} is indeed a biomarker of increased vulnerability to VT/VF in ischemic cardiomyopathy. The study by Rogers et al presents a clear example of how ML methods can improve VA risk prediction and even suggest mechanistic interpretation.

The MAPs analyzed in this study were from the right ventricular apex. As the ischemic insult in these patients is typically in the LV, it would be important to understand whether changes in action potential such as those documented by the MAP recordings here are a global or a regional hallmark of elevated propensity to VT/VF. Would similar differences in action potential morphology between patients with different outcomes exists in other regions of the heart? Should these changes be regional, would such heterogeneity confer additional arrhythmogenic propensity, on top of the potential changes in I_{CaL}?

Alterations in action potential morphology (and potentially in the underlying Ca cycling) in ischemic cardiomyopathy patients with VT/VF outcome, whether regional or global, represent one important aspect of the arrhythmogenic substrate in this disease. Presence of scar and infarct border zone and their 3D extents have been strongly associated with VT risk and the mechanisms by which structural remodeling sets up the stage for reentrant VTs in these patients have been previously explored. Thus, a generalizable VT/VF ML risk model in this population would likely need to use as inputs both electrophysiological and structural remodeling data as well as other potential covariates. Of particular value would be if such risk predictors are dynamic, allowing for an update in prediction when new data becomes available, which requires that the model learns from non-invasive measurements. Furthermore, assessing survival outcome rather than outcome at a single point of time would enhance the clinical value of the prediction. With careful choices and realistic expectations, ML appears well poised to address this healthcare need.

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