Unravelling the Mechanistic Links Between Pro-Arrhythmia and Mechanical Function

Hannah J Smith*, Francesca Margara, Blanca Rodriguez

Department of Computer Science, University of Oxford
Oxford, UK

Sudden cardiac death (SCD) from ventricular arrhythmias is a leading cause of mortality worldwide. Accurate arrhythmic risk stratification is vital for diagnosis and preventative clinical interventions. Ejection fraction (EF) is currently the primary metric for arrhythmic risk stratification, but its accuracy is under debate, with a majority of patients experiencing SCD having a preserved EF. Thus, identifying clear mechanistic links between EF and arrhythmic risk is critical.

As a first step towards this goal, here, we investigate the ionic processes determining cellular pro-arrhythmic mechanisms and their relationship with active tension amplitude (a fundamental contributor to EF). A population of 2500 human ventricular electromechanical cellular models was created, with variations in key ionic current expressions, building on the new coupled electrophysiology ToR-ORD model and the contractile Land-Niederer model. Several pacing frequencies and ionic block were applied in order to stimulate pro-arrhythmic behaviour. We quantified the susceptibility of each model to develop early afterdepolarizations (EADs) and action potential duration (APD) shortening, a risk factor for re-entry arrhythmias.

Tension decreases were seen with both high and low EAD susceptibility. Models displaying the lowest risk for EADs had significantly reduced median tension amplitude - 12kPa (normal pacing) and 6.8kPa (slow pacing) compared with 15kPa for the entire population. APD shortening, however, has a weak positive correlation with active tension amplitude with $\rho = 0.10$ (normal pacing) and $\rho = 0.20$ (fast pacing). The nature of the relationship between both arrhythmic markers and tension amplitude is highly dependent on ionic mechanism, with increased EAD susceptibility being associated with increased active tension when caused by high L-type calcium current, but decreased active tension when caused by reduced SERCA expression. Variability in L-type calcium current was the primary determinant of active tension ($\rho = 0.77$) and had a significant effect on both EAD susceptibility and APD, with contributions also made by SERCA and hERG expression. Preserved tension amplitude did not exclude increased arrhythmic risk for either marker, though particularly for EADs.