In Silico Assessment of Arrhythmic Risk in Infarcted Ventricles Engrafted with Engineered Heart Tissues

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Engineered heart tissues (EHTs) from human induced pluripotent stem cell-derived cardiomyocytes represent novel alternatives to repair damaged cardiac tissue after myocardial infarction (MI). However, their slow conduction and prolonged action potential (AP) duration (APD) can favor arrhythmicity. Here, in silico modeling and simulation was used to assess the proarrhythmic potential of EHTs as a function of their electrical conductivity (EHTc) and degree of attachment (EHTa) to the host myocardium.

A computational porcine-specific biventricular (BiV) electrophysiological model was generated and coupled with a realistic EHT representation. The BiV model included an MI region and was defined from magnetic resonance imaging. The EHT model was constructed, deformed to follow the epicardium surface and subsequently coupled to the BiV model. Rule-based fiber orientations, electrical conductivities and cellular AP models were assigned to the BiV-EHT model. An endocardial conduction system (CS) was implemented for realistic stimulation and the monodomain equation was solved to simulate electrical propagation. EHTc values of $10\,\%$, $50\,\%$ and $90\,\%$ of that in healthy myocardium were evaluated. Null, partial and complete EHTa were tested.

Results showed that EHTa, even if minimal, inhibited EHT automaticity. The activation time (AT) and APD in the EHT were driven by the engrafted myocardium. Higher EHTa and EHTc led to lower repolarization gradients (RTGs), considered as indicative of arrhythmic risk. For the minimum EHTc of $10\,\%$, maximum RTG was reduced by $52.3\,\mathrm{ms/mm}$ from minimum to complete EHTa. For the minimum EHTa of $25\,\%$, the maximum RTG was decreased by $98.8\,\mathrm{ms/mm}$ when EHTc increased from $10\,\%$ to $90\,\%$.

Proarrhythmicity in cardiac tissue engineering highly depends on the EHT conductivity and degree of engraftment on the host myocardium.

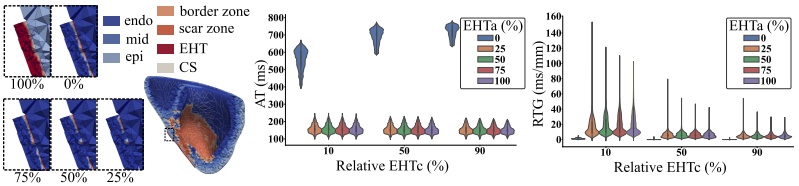

Figure: BiV-EHT model and EHTa (left). EHT AT (middle) and RTG (right).