Design of engineered heart tissues to minimize arrhythmic risk after implantation in infarcted hearts

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Remuscularization of infarcted hearts with engineered heart tissues (EHTs) built from human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) represents a promising therapy to restore cardiac function after myocardial infarction (MI). Nevertheless, EHT implantation may entail high arrhythmic risk due to the poor maturation of hiPSC-CMs in these constructs, leading to slow conduction and prolonged action potential duration (APD). We in silico assessed the arrhythmic potential of EHT engraftment as a function of its electrical conductivity (EHTc) and the alignment of its hiPSC-CMs (EHTal) with respect to the native epicardial tissue.

We used our previously developed porcine-specific biventricular (BiV) electrophysiological model with representation of MI in the left apical region. The anatomy and tissue properties were defined based on magnetic resonance image processing. The fiber field was computed from a rule-based model. An endocardial conduction system (CS) was built by interconnecting landmarks with geodesic paths and a fractal tree algorithm. Next, we engrafted an EHT model covering the MI region. We tested EHTc values of $10\,\%$, $50\,\%$ and $90\,\%$ of that in healthy myocardium and random, parallel and perpendicular EHTal.

Results showed that APD values in the EHT were driven by the surrounding myocardium, with this effect being enhanced for increasing EHTc. Importantly, EHTal did not play a role in repolarization time gradients (RTGs), while higher EHTc led to lower RTGs, thus implying lower repolarization dispersion and decreased arrhythmic risk. For all EHTal cases, the maximum RTG was reduced by $70\,\mathrm{ms/mm}$ when EHTc increased from $10\,\%$ to $90\,\%$.

As a conclusion, proarrhythmicity after EHT implantation in MI hearts mainly depends on EHTc while hiPSC-CMs alignment seems to play a secondary role in the electrophysiological alterations induced by EHT therapy.

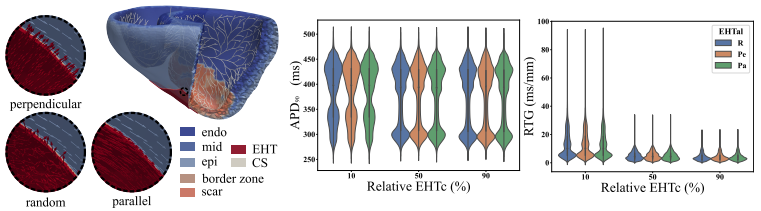

Figure: BiV-EHT model and examples of EHTal cases (left). APD (middle) and RTG (right) values for the different EHTc and EHTal tested cases.