Modeling Arrhythmia Vulnerability due to Perivascular Excitation Tunneling in Ischemia-Reperfusion

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**Aims:** This study aims to evaluate arrhythmia vulnerability due to perivascular excitation tunneling (PVET) during ischemia-reperfusion (I/R). PVET is a novel investigated potential re-entry mechanism based on faster electrical recovery along the main artery trunk during reperfusion that may give rise to an excitable tunnel within the still-inexcitable ischemic zone.

**Methods:** A truncated ellipsoidal surface representing the ventricles of a rabbit heart was generated in combination with a circular area on the ventricular wall that could either be hyperkalemic (HiK$^+$), hypoxic (LoO$_2$), acidic (HiH$^+$), or ischemic (combination of all three). Reperfusion from the aforementioned conditions was reproduced by implementing a partially recovered canal across the affected area. An S1-S2 pacing protocol was used to evaluate the arrhythmogenic risk of PVET across the parameter-space of the affected area, involving (1) remodeled condition, (2) affected area size, (3) width of the partially-recovered canal, and (4) recovery level within the canal. To reduce the computational cost, a re-entry search algorithm based on the root-finding bisection method was devised.

Panoramic optical mapping of Langendorf-perfused rabbit hearts was performed. Local cannulation of the anterior branch of the left circumflex artery allowed controlled regional perfusion of solutions mimicking any of the three aspects of ischemia, or ischemia itself, and subsequent reperfusion.

**Results:** Simulations and experiments resulted in HiK$^+$ being the most reliably able to cause PVET due to its effects in effective refractory period prolongation and conduction hindering. HiK$^+$-reperfusion, and a larger affected area led to a higher prevalence to arrhythmias, while LoO$_2$ and HiH$^+$ showed to have a protective effect against PVET during reperfusion.

**Conclusion:** Computational simulations and isolated rabbit heart experiments support the hypothesis of PVET as a potential re-entry mechanism during I/R, highlighting HiK$^+$ as the key component. This study suggests that targeting HiK$^+$ during reperfusion may be a successful anti-arrhythmia strategy.