Incremental Pacing Induces Sustained Reentry in a Computational Model of Brugada Syndrome

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**Background**: Brugada Syndrome (BrS) is a form of idiopathic ventricular fibrillation, which most frequently occurs during sleep or at rest. To date, there is no definitive theory about how ventricular fibrillation is initiated, or a consensus on its substrate. Currently, two major hypotheses are considered for the pathological mechanism of BrS, the repolarization hypothesis, and the depolarization hypothesis. The repolarization disorder theory attributes the arrhythmic behavior to nonuniform alteration of the epicardial right ventricular action potential duration, whereas the depolarization disorder theory explains the pathological phenotype with slow and discontinuous conduction.

**Methods**: We developed a computational model of Brugada Syndrome, including both structural and electrophysiological abnormalities in a slab of transmurally heterogeneous cardiac tissue (3x3x0.7 cm). The ionic current was described with the ten Tusscher et al model with a modified $I_{to}$ formulation with a fast ($I_{to}^f$) and slow ($I_{to}^s$) recovery component. To simulate electrophysiological alterations of BrS, we introduced linear endo-epi gradient in $I_{to}$ density and reduced the maximum sodium conductance in the epicardium. Additionally, we introduced diffuse fibrosis in the epicardial layer. We studied the effect of incremental pacing (i.e., with increasing pacing cycle length) on the generation of reentrant activity. We employed a pacing protocol consisting of a fixed basic cycle length (BCL) prepacing followed by an extrastimulus after a long interval.

**Results**: We observed that for each BCL, a vulnerable window exists wherein an extrastimulus induced sustained arrhythmia. For lower BCLs, the width of the vulnerable window was larger and sustained arrhythmia occurred for lower extrastimulus intervals.

**Conclusion**: Our results confirmed reentry near the percolation threshold as a putative mechanism of BrS-related arrhythmias, and highlighted a rate-dependent behavior that is explained by the dynamics of $I_{to}^s$. Indeed, our model suggests that incremental pacing can unmask the arrhythmic substrate of BrS.