

# Phase-2 Reentry Without Heterogeneity in Brugada Syndrome: Insights from Human Heart Experiments

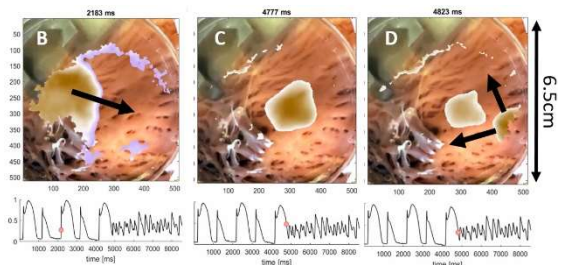
I Uzelac, F Fenton

Virginia Commonwealth University, Richmond, VA, USA

**Introduction:** Induction of ventricular fibrillation (VF) in Brugada syndrome is commonly attributed to phase-2 reentry, and it is thought to arise from mismatched durations of action potentials (AP) across different cardiac regions. While this has been shown numerically and experimentally with electrical mapping, it is widely believed that spatial heterogeneity in the expression of  $I_{to}$  current is necessary for reentry induction in Brugada Syndrome.

**Methods:** A rejected human donor heart with elevated lactic acid levels was coronary perfused, stained with the voltage-sensitive dye JPW-6003, and the endocardial side of the right ventricle was imaged using high-resolution optical mapping (256x256 pixels, at 500 Hz, over an area of 6x6 cm<sup>2</sup>). No drugs were used, other than the contraction decoupler (-)-Blebbistatin. A restitution pacing protocol was initiated to study the heart's electrophysiology. The obtained experimental data were fitted to a simplified ionic model.

**Results:** Pacing at an 800 ms period resulted in the formation of discordant alternans, characterized by large spatial gradients of repolarization, leading to phase-2 reentry and



subsequent VF. The figure illustrates wavefront propagation into a region of prolonged AP, as evident by the bottom AP signal. Due to an extensive repolarization time (middle), a phase-2 reentry is formed with a wavefront traveling from the right. An ionic model, fitted with experimental data, demonstrated that completely isotropic tissue under the conditions typical of Brugada syndrome can give rise to large depolarization regions and phase-2 reentry.

**Conclusion:** Experimental observations, supported by an ionic model, show that irregular anatomical regions, as commonly thought, are not required for phase-2 reentry in Brugada syndrome. Instead, these can develop dynamically through the formation of alternans, leading to phase-2 reentry and subsequent VF.