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♡ **A novel trigger-substrate mechanism based on clinically concealed repolarization abnormalities underlies idiopathic ventricular fibrillation**

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🎤 Speaker: **Matthijs Cluitmans (Maastricht, Netherlands (The))**
⚑ Session title: **New Insights into Arrhythmogenesis**
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Abstract

Citation: N/A

Background
Sudden cardiac arrest (SCA) is most often due to ventricular fibrillation (VF). When no cause is found during diagnostic follow-up, fibrillation is classified as idiopathic (iVF). We hypothesize that a critical functional substrate-trigger interaction underlies iVF.

Purpose

To study electrophysiological triggers and substrate for iVF in a clinical cohort; and seek mechanistic explanations in explanted pig hearts and computer models mimicking trigger-substrate interactions.

Methods

Repolarization time (RT) isochrones on the epicardium were studied with electrocardiographic imaging (ECGI) in patients with iVF, patients with frequent monomorphic premature ventricular complexes (fmPVC) but no structural disease or SCA, and controls without cardiovascular disease.

RT gradients were created in explanted, Langendorff-perfused pig hearts by local infusion of dofetilide ('dof', 250 nM, delaying RT) and pinacidil ('pin', 30 μM, shortening RT) in adjacent regions of the heart. Arrhythmia inducibility was tested by programmed stimulation (8 atrial stimuli [S1] followed by one ventricular stimulus [S2] paced at regions of early or late RT).

A computational ventricular monodomain model was used to study the location-dependency of trigger-substrate interaction; RT gradients were created by local changes in potassium channel conductance.

Results

Although QTc values were similar, iVF survivors (n=11) displayed significantly steeper RT gradients than controls (n=10) or fmPVC individuals (n=7): 269±111 vs 179±40 vs 171±76 ms/cm respectively (panel A). Unipolar electrograms (EGMs) at the gradients displayed a change in polarity of the local T wave (B). In iVF, PVCs originated more often from regions with early RT than in fmPVC individuals (yellow circles in A; 64% vs 14%).

In the explanted hearts (C), drug infusion resulted in similar RT gradients and polarity changes of EGM T waves (D-E). VF inducibility by pacing of the early RT region (D) increased significantly with steeper RT gradients (baseline: 3/6 hearts inducible, dof+pin: 3/3). Pacing of late RT regions (E) did not induce arrhythmias in baseline (0/6) nor with RT gradients (0/3). For similar pacing intervals at the early RT region, the 12-lead ECG R-on-T morphology was similar but VF only occurred in the presence of RT gradients (F).

In the computer model, the number of inducible pacing intervals critically depended on the stimulus location (G).

Conclusion

Combined, these results demonstrate that R-on-T superposition per se is insufficient to explain arrhythmogenesis. Rather, not only the temporal coupling interval but also the spatial origin of PVCs in relationship to the degree of local repolarization abnormalities are critical elements. In iVF, a substrate of RT gradients (panel H1) with triggers from early RT regions (H2) precipitate reentry (H3). Noninvasive ECGI can uncover these substrate and trigger characteristics in (at least a subset of) iVF survivors.
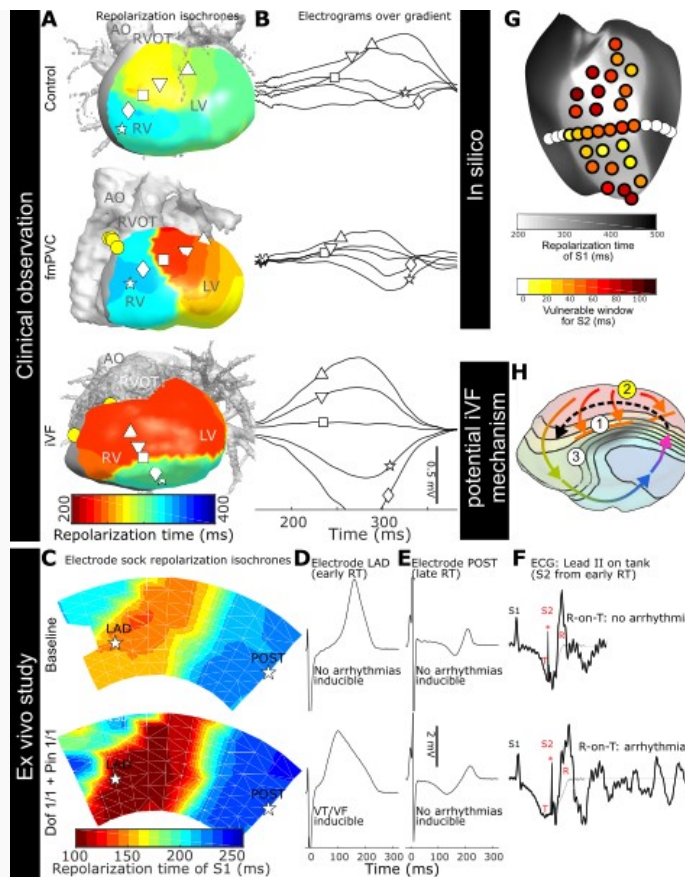
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