Arrhythmogenicity of Genetic Mutations on a 3D Human Atrial Model

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Background

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia and it has been related to the presence of genetic defects in genes encoding potassium channel protein structures in otherwise healthy patients. The arrhythmogenicity of three genetic mutations - KNCH2 T436M, KCNH2 T895M and KCNE3-V17M - has been previously studied at the cellular and tissue levels.

Objective

The aim of this study is to investigate the pro-arrhythmogenic effects of such mutations by modeling and simulating its electrical activities on a 3D atrial geometry.

Methods

The 3D hexahedral mesh, representing the human atrial model, is characterized by 21 regions and 56 subregions to account for heterogeneous histological properties and fiber orientation, and by a spatial resolution of 300 μm. The cellular electrical activity was modelled using a modified version of the Courtemanche-Ramirez-Nattel model, which includes both the formulation of the acetylcholine-activated potassium current and the parameters reproducing the genetic mutations' effects. Nine ionic models were implemented by tuning several ionic conductances to account for regional electrical properties. Longitudinal conductivities and anisotropy ratios were also tuned in each region to reproduce tissue heterogeneities and activation sequences. The electrical models were stabilized by applying 10 continuous beats to the sinoatrial node (SAN) with a 1000 ms basic cycle length (BCL). To get re-entrant activity, a train of 5 stimuli was applied to the coronary sinus (CS) region with a BCL of 160 ms for the mutation KCNH2 T436M, of 170 ms for KCNH2 T895M, and of 90 ms for the mutation KCNE3-V17M. During the CS pacing, the SAN was simultaneously stimulated by a 5-pulse train with BCL of 1000 ms. Temporal vulnerability to re-entrant activity for each mutation was computed as the width of the window when a train of stimuli in the CS would elicit a re-entry.

Results

The presence of the mutations increased the vulnerability of the atria to reentry and different types of arrhythmic behavior were observed. The KCNH2 T436M mutation presented a vulnerable window (VW) of 10 ms, and macro-reentries perpetuated for a minimum of 3.8 s and for a maximum of 5 s. In the presence of the mutation KCNH2 T895M, the VW has a 7 ms-width, and was characterized by the appearance of mostly macro-reentries and rotors, generated in the right atrium (RA) and perpetuating until the end of the simulations (5s). Finally, the VW for the KCNE3-V17M mutation was 24 ms-wide. In this case, all the rotors appeared in the CS area, moved around the RA walls and were sustained for the remaining simulation time. Collisions of multiple waves led to the formations of several instable rotors in both right and left atrium, wave breaks and to an overall more complex arrhythmogenic pattern.

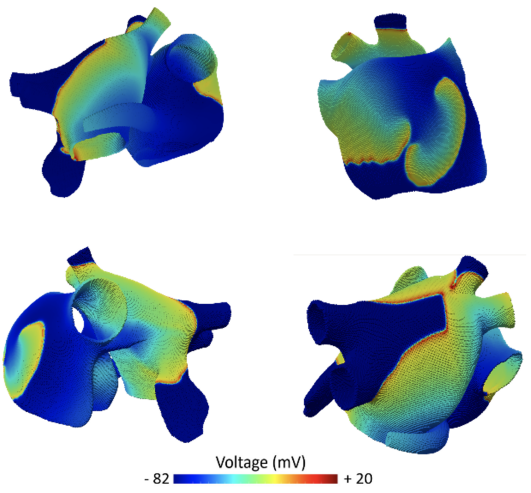

Figure 1: Simulation of complex spiral waves in 3D human atria in presence of the KCNE3-V17M mutation.

Discussion

This preliminary study supports that the presence of the genetic mutations in 3D human atrial model resulted in a more arrhythmogenic substrate, leading to mutation-dependent forms of arrhythmias.