

Anti-arrhythmic Effects of Atrial Specific Ultra Rapid Potassium Current Block: A Modelling Study

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Introduction: The atrial specific ultra rapid potassium current (I_{Kur}) provides an attractive target in the management of AF.

In this study we investigate *in silico* the anti-arrhythmic effects of pharmacological blocking of I_{Kur} under sinus rhythm (SR) and atrial fibrillation (AF) conditions.

Methods: Reduction of I_{Kur} by 80% based on experimental data was incorporated into a computer model of human atrial action potential (AP) developed by Courtemanche *et al.* under normal (*i.e.* sinus rhythm) and AF conditions, that considered the AF-induced ion channel remodelling in human atrial cells. The effects of I_{Kur} block on atrial AP were quantified by changes in the characteristics of

APs that include the AP duration (APD), APD restitution (APDr), effective refractory period (ERP) and ERP restitution (ERPr). Using 1D strand models, intra-atrial conduction velocity (CV), CV restitution (CVr) and temporal vulnerability window (VW) of tissue to genesis of uni-directional conduction block by an extra-stimulus were computed. Re-entrant wave behaviour in idealized 2D sheets and realistic 3D anatomical model was simulated.

Results: As shown in the figure, under SR conditions, I_{Kur} block prolonged the AP plateau phase, but marginally shortened APD (by 4.8%) and ERP (by 2.5%). In the AF-remodeled tissue, I_{Kur} block increased APD (by 16.2%) and ERP (by 15.4%). I_{Kur} block did not affect CV at low pacing rates (0.27 mm/ms under SR, 0.25 mm/ms under AF), but modulated tissue's ability to support excitation wave conduction at high pacing rate. The cut off pacing cycle length (PCL) (*i.e.* the maximal PCL at which the tissue can sustain propagation) was reduced from 320 ms to 313 ms in the normal tissue, but was increased from 198 ms to 217 ms in the AF-remodeled tissue. I_{Kur} block augmented tissue's VW by 7.5% in the normal tissue, but reduced it by 19.2% in the AF-remodeled tissue. In 2D idealized sheets and in the 3D simulations, blocking I_{Kur} did not affect re-entrant wave or scroll wave dynamics.

Conclusions: Simulation data shows the pro-arrhythmicity of block I_{Kur} under SR, but anti-arrhythmic effects in the AF case. Since I_{Kur} is atrial specific, it is an attractive potential target for AF drug therapy treatment.

