Potential Pharmacological Therapies for Atrial Fibrillation: A Computational Study

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Persistent atrial fibrillation (AF) is mainly sustained by reentrant wavelets which propagate through excitable tissue, but its underlying ionic mechanisms are still unclear. In this study we: 1) quantify the sensitivity of properties related with arrhythmic risk to changes in human atrial ion channel properties; 2) investigate alternative methods to prevent AF from propagating. Simulations are performed using the Maleckar action potential (AP) model and its extension to tissue, and validated using experimental data from the literature. The sensitivity analysis shows that IK1 inhibition by 30% results in an anti-arrhythmic increase in action potential duration (APD) (from 197 ms under control conditions to 318.2 ms) and Vrest (from -73.75 mV to -64.7 mV). Regarding APD rate adaptation, overexpression of either ICaL or INaK causes at least a 1.5-fold anti-arrhythmic decrease of the time constants associated with both fast and slow adaptation phases. Overexpression of IK1 or inhibition of INaK implies shallower APD restitution slopes that favor reentry stability but prevent wave-breaks from happening. Tissue simulations show that 30% block of INa leads to a significant slowing of conduction velocity (CV) (from 48.5 cm/s to 36.38 cm/s). Besides, 30% block of IK1 and INaK lead to anti-arrhythmic increases in both effective refractory period (ERP) (from 223 ms to 287 ms and 272 ms, respectively) and wavelength (WL=ERP*CV) (from 10.82 cm to 14.28 cm and 13.45 cm, respectively). Simulations are also conducted to evaluate the role of electrical remodeling caused by sustained AF, resulting in lower ERP (151 ms), CV (45.95 cm/s) and WL (6.94 cm), and higher reentrant dominant frequency (from 4.39 Hz under control to 6.84 Hz). Sensitivity of parameters related to both reentry stability and reentrant properties to changes in ion channel electrophysiology as provided here can help in the design and screening of new multi-channel action anti-AF drugs.