The Role of the Transient Outward Current in Action Potential Repolarization: A Simulation Study

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The time-course of action potential (AP) repolarization, and thus AP duration (APD), is the result of a delicate balance of currents during the AP plateau. As the potassium transient outward current (Ito) is active only during the early plateau, its role in governing APD is controversial. Recently, Virág et al experimentally showed that blocking Ito significantly lengthens APD in canine epicardium, something that could be key in arrhythmogenesis. In this work, we have combined electrophysiological experiments with simulations to study and explain the contribution of Ito to repolarization.

After isolating myocytes from dog ventricular epicardium, whole-cell patch-clamp experiments were performed to characterize the kinetic properties of Ito. An overlap region was found between the steady-state activation and inactivation curves, suggesting the potential existence of a window current in the range of -20mV to -40mV. Also, Ito inactivation was found to follow a two-exponential time course, with a slow component of tau=24ms at 20mV.

These data was used to formulate a new mathematical model for Ito, which was then inserted in the Decker (2009) model for canine epicardial AP. Simulations in control conditions yielded an APD of 202ms. Blocking IKs, only a slight prolongation of APD was observed (209ms). When an additional block of Ito was simulated, APD increased to 221ms, which is consistent with the experimental findings by Virág et al. Further IKr blocking produced EADs even at 1Hz stimulation frequency, something which could lead to lethal arrhythmias in vivo.

Inspection of ionic currents suggested that Ito reactivation (96nA/uF) due to the activation-inactivation overlap, and indirect changes exerted by Ito blockade on ICaL (110nA/uF increase during the plateau) and IKr (42nA/uF) are responsible for this paradoxical increase in APD. These novel findings emphasize the importance of Ito in repolarization and suggest a potential role of Ito blockade in arrhythmogenesis.