

## **ACETECHOLINE EFFECT ON HYPOKALEMIC SINOATRIAL NODE CELLS – SIMULATION STUDY**

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Acetylcholine, a neurotransmitter liberated by vagal stimulation, acts on cardiac muscarinic receptors on the membrane of sinoatrial node (SAN) cells to decrease heart rate by modulating the activity of pacemaker membrane currents. Hypokalemia is a common electrolyte disturbance, characterized by an abnormally small concentration of potassium in the circulating blood. Several clinical, electrophysiological, and theoretical studies using cardiac myocytes have shown that low extracellular potassium concentration is a risk factor alongside bradycardia for the development of atypical polymorphic ventricular tachycardia known as Torsade de Pointes leading to sudden cardiac death. It is well established that the pacing rate in intact rabbit hypokalemic SAN tissue exhibits little or no dependence on changes in extracellular potassium. Surprisingly, however, the efficacy of vagal nerve stimulation of these cells significantly increases with decreasing extracellular potassium. To obtain insights into ionic mechanism governing acetylcholine effect on hypokalemic cardiac sinoatrial node computer simulations were performed based on a computer model of electrical activity of SAN cells. One cell was described by nonlinear first-order differential equations that describe the time course of transmembrane potential difference, ionic concentrations, and states of the voltage gated ionic channels. The equations were solved based on the Runge-Kutta fourth-order method, which includes an automatic step-size adjustment. The purpose of this study is to explain the ionic basis for the changes in the cycle length of hypokalemic SAN cells elicited by vagal stimulation. The model predicts the changes in cycle length elicited by changes in extracellular potassium and by vagal stimulation in single SAN cells.