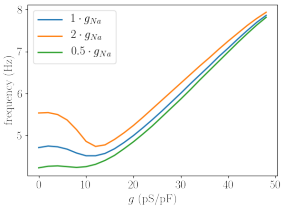
Computational Mechanistic Investigation of Chronotropic Effects on Murine Sinus Node Cells

Benjamin Winkelmann, Eike M. Wülfers, Callum M. Zgierski-Johnston, Peter Kohl, Jens Timmer, Gunnar Seemann

Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg · Bad Krozingen and Physics Institute, University of Freiburg, Freiburg, Germany

A chronotropic response in beating rate to constant illumination was observed in sinus nodes (SN) of mice with genetically expressed light activated cation non-selective channels (CNSC). At low intensities, the response was 10%-30% positive. The positive response decreased with higher intensity and eventually became up to 50% negative. A similar negative chronotropic response of murine SN has been described in response to stretch. Contrarily, rabbit SN have exhibited a positive chronotropic response to stretch. Stretch-activated CNSC have been hypothesized to be the cause of these effects.

We investigated possible underlying mechanisms using mathematical models. We modelled CNSC by adding a continuous Ohmic current to a mathematical model of murine sinus node cells by Kharche et al. We varied the channel conductance and quantified the resulting change in beating rate. For low channel conductance, the beating rate increased marginally (0.8%). With increasing conductance, chronotropic response became up to 4% negative before monotonously increasing up to 100% positive.



The non-selective current pulls the transmembrane voltage towards the reversal potential of the channel, here 0 mV, thereby decreasing the maximum diastolic potential. On the one hand, the additional depolarising current via the non-selective channel and the smaller potential difference between maximum diastolic potential and threshold decrease the cycle length. On the other hand, the shift of the maximum diastolic potential leads to decreased depolarising currents, e.g. by inactivating voltage gated sodium channels.

The chronotropic responses observed in the computational model do not match experimental observations in magnitude or order (positive to negative), but we have identified two competing chronotropic effects. In future studies, we are aiming to investigate model and model parameter dependencies as well as tissue effects on the chronotropic response.