Sinoatrial Node Cell Response to Isoprenalin Stimulation and Hypocalcemia

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Introduction: The purpose of this study is to assess the effects of autonomic modulation and hypocalcemia on the peacemaking rate of sinoatrial node (SAN) cells. The clinical relevance is to bring a better understanding of the increased risk of sudden cardiac death in chronic kidney disease patients who regularly undergo hemodialysis, which has been reported to be 14 times higher than in patients with cardiovascular disease and normal kidney function.

Methods: The Fabbri et al. (2017) SAN model was used to study the gradual response on isoprenalin between 0 and 1.5 uM with the extracellular calcium concentrations ([Ca]o) in the range from 1.2 to 2.2 mM. Simulations were performed until a limit cycle was reached. The pacemaking capacity of the cells was evaluated by assessing the spontaneous activation frequency in beats per minute (BPM).

Results: Lower extracellular calcium concentrations led to decreased beating rates: at 1.4 mM [Ca]o, the cycle length without any autonomous modulation was only 50 BPM compared to 74 BPM at the physiological [Ca]o of 1.8 mM. This effect can be counteracted by autonomous stimulation. The amount of isoprenaline necessary to restore the reference beating rate was 0.5 uM and 1 uM when [Ca]o was reduced to 1.6 mM and 1.4 mM, respectively.

Conclusion: Isoprenalin stimulation can conserve the pacemaking capacity during hypocalcemia in an in silico model of human SAN cells. The model accurately reflects the qualitative response observed in experiments but the extreme isoprenalin concentrations may lead to saturation and a non-linear response, which is not accounted for in the model currently. To improve the accuracy of the model, further work should integrate more signaling pathways to account more precisely for physiological control of excitation.