Insights into the mechanisms of calcium wave propagation failure from a computational model of the rabbit atrial cardiomyocyte

In atrial cardiomyocytes without a well-developed T-tubule system calcium diffuses from the periphery towards the center via centripetal calcium waves. Under altered diffusion conditions, for example due to atrial remodelling, centripetal calcium-wave propagation can fail to propagate (‘‘calcium silencing’). This has been observed in a rabbit model of rapid atrial pacing and in patients with atrial fibrillation, but the underlying mechanisms remain incompletely understood. In this study, we developed a novel computational model of the rabbit atrial cardiomyocyte that incorporates detailed compartmentalization of intracellular calcium dynamics. This model was used to investigate the mechanisms underlying calcium silencing.

We incorporated ion-current formulations reflecting rabbit electrophysiology into a previously published human atrial cardiomyocyte model. The model was matched to a varied source of experimental data, and it is able to reproduce normal electrophysiological properties of rabbit atrial cardiomyocytes. We then assessed the effect of varying parameters related to the rate of calcium diffusion between the calcium-release-unit space and the cytosol ($\tau diff_{cyt}$), and within the calcium-release space ($\tau diff_{SRS}$) on calcium-wave propagation. $Tdiff_{cyt}$ and $Tdiff_{SRS}$ modulate calcium availability to activate neighboring calcium release sites.

Simulation results showed that calcium-wave propagation was highly sensitive to τdiffcyt during pacing at 2 Hz. We observed impaired calcium-wave propagation for a range of values of $\tau diff_{cyt}$. Calcium silencing occurred for values of $Tdiff_{cyt}$ above 12.7 ms and below 5 ms, suggesting different mechanisms leading to calcium-wave propagation failure. We also observed intermittent calcium waves for intermediate values of $Tdiff_{cyt}$, and for low values of $Tdiff_{SRS}$.

This study provided new insight into the mechanisms of calcium-wave propagation failure in rabbit atrial cardiomyocytes and motivates further investigation of the effects of altered calcium diffusion on wave-propagation abnormalities. Moreover, the newly developed model will be a useful tool for studying conditions which permit restoration of normal calcium wave propagation.