Human Atrial Cell Models to Analyse the Effect of Extracellular Calcium on Action Potential Duration

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Regulation of cardiac electrical and mechanical activities are highly dependent on L-type calcium current (ICaL). Moreover, the phenomena of ICaL inactivation plays a crucial role in adjusting action potential (AP) repolarization. The relationship between extracellular calcium concentration [Ca+2]o and action potential (AP) has been investigated. The phenomena of calcium-dependent inactivation (CDI) of ICaL has also been analyzed to quantify its dependence on [Ca+2]o.

The paper aims to 1) study the response of [Ca+2]o changes on APD, 2) quantify the i) CDI dependence on [Ca+2]O and its impact on ICaL and INCX (sodium-calcium exchange current) by using AP-clamp technique ii) the dependence of driving force (DF) on [Ca+2]o. For this purpose, we have analyzed three human atrial cell models (Courtemanche et al. (CRN), Koivumaki et al. (KM), and Ellinwood et al (EM)) by testing benchmarks like AP, ICaL, and INCX with the variation of [Ca+2]o. Similarly, the role of CDI was assessed by the application of the AP-clamp technique followed by running the baseline model 1) under normal CDI mechanism and 2) without the CDI mechanism. In CRN and KM model the $[Ca^{+2}]_o$ modulation of DF is not acting, indeed the I_{CaL} formulations of these models has a DF not dependent at all on $[Ca^{+2}]_o$. So the right behavior of CRN and KM is actually relying on an incorrect assumption. The EM model behaves completely the opposite of real cells and our in silico analysis pointed out the reasons: the DF produces a large direct dependence of the current from [Ca+2]o compare to the CDI. The I_{NCX} contribution further exacerbates this. The comparison of three hAMs shows that besides the contribution of CDI, driving force (DF), and INCX current should also be considered while studying the relationship between AP duration (APD) and [Ca+2]O.