Investigation of the Extracellular Calcium Effects on Action Potential using the Most Recent Human Ventricular Cell Models

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The present work aims to answer the following question: what are the quantitative contributions of the mechanisms involved in the relationship between extracellular calcium concentration [Ca2+]o and the action potential (AP)? In this context, human-based modeling and simulations could provide useful support to investigate this phenomenon. However, [Ca2+]o dependence on AP duration, which is opposite, is not reproduced correctly by most of the commonly used human AP models.
Four of the most recent human ventricular AP models (Grandi-Bers (GB), O'Hara-Rudy (ORd), Tomek et al. (TorORd), and Bartolucci et al. (BPS)) have been tested by simulating different extracellular calcium concentrations during an AP-clamp protocol.

From earlier studies, it is well known that the L-type Ca2+ current (ICaL) is the ionic current mainly affected by [Ca2+]o changes. In particular, calcium-dependent inactivation (CDI) seems to play the most significant role. For this reason, we simulated two different conditions: with the basal models and with the models in which the CDI has been turned off during AP-clamp simulations.

The result of our analysis was three ventricular models (ORd, GB, and TorORd) responded with APD prolongation to $[Ca^{2+}]_o$ increase, a behavior which is in contrast to the APD shortening observed *in vitro* and *in vivo* when extracellular, or plasma calcium concentration, is increased. Instead, the BPS model correctly reproduced this dependence. The effects of CDI on I_{CaL} in the ORd, and TorORd models are underestimating; in the GB model, this behavior is less evident, but still, the APD-$[Ca^{2+}]_o$ dependence was not correctly simulated. Therefore in the BPS model strong CDI, enables simulating APD prolongation at decreasing $[Ca^{2+}]_o$. To better understand the GB behaviour we analyzed the other currents affected by $[Ca^{2+}]_o$ variations and this investigation pointed out the contribution of I_{NaCa}.