N2091S Mutation Promotes Action Potential Alternans in Middle Cells of Human Ventricle: A Simulation Study

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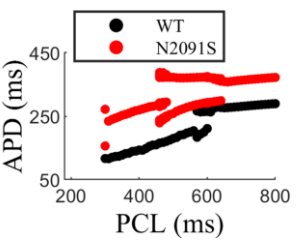
Background: CACNA1C-N2091S mutation, localized in L-type calcium channel (LTCC), increases risk for arrhythmia that may manifest as sudden cardiac death (SCD). Action potential (AP) alternans is closely related to ventricular arrhythmia and SCD. However, the contribution of N2091S mutation on AP alternans is unidentified.

Objective: This study aimed to investigate the effects of N2091S mutation on AP alternans of ventricular myocytes.

Method: The previously proposed models of human ventricular myocyte and CaMKII regulation were used in this study. Based on the experimental data and N2091S mutant ventricular myocyte model developed by Bai, LTCC was altered under the N2091S mutation condition. The dynamic pacing protocol was used to induce alternans.

Result: Comparing with wild type (WT), N2091S mutation apparently increased L-type calcium current (I_{CaL}), which further prolonged action potential duration (APD) and increased Ca^{2+} concentration. APD rate dependence curves in middle cell (MCELL) showed that N2091S mutation caused a decrease in threshold of stimulation frequency for AP alternans and wider alternans vulnerable window (pacing cycle length ranging 570 ms to 600 ms in WT versus 460 ms to 640 ms in N2091S mutation). Further analysis demonstrated that AP alternans was induced only when increasing maximal I_{CaL} conductance (G_{CaL}) exceeded a critical value (156.98% larger than that in WT), via a mechanism of the prolongation of AP plateau phase that led to the inhibition of inward I_{NCX} and the increase of sarcoplasmic reticulum (SR) Ca^{2+} loading, which produced incomplete recovery of I_{CaL} promoting inward I_{NCX} and consequently decreased SR Ca^{2+} loading, facilitating the genesis of Ca^{2+} cycling and AP alternans.



Conclusion: This study demonstrates that N2091S mutation makes MCELL more prone to arrhythmia and the increase of G_{CaL} is the main factor for inducing alternans. The findings of study provide new insights into arrhythmic mechanism with N2091S mutation.