Modelling of Intracellular Ca2+ Alternans and Ca2+-Voltage Coupling in Cardiac Myocytes

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In cardiac tissue, Ca2+ cycling plays the most important role in regulating mechanical contraction and the membrane potential (voltage). Intracellular Ca2+ transient alternans may produce not only mechanical contraction alternans, but also action potential duration (APD) alternans via Ca2+-Voltage coupling, which is pro-arrhythmic. The aim of this study was to investigate the interaction between Ca2+ and APD alternans by using computer simulations.

The mathematical model of canine ventricular action potential developed by Shiferaw et al. was used in the study. In the model, a cell was divided into 75 sarcomeres elements, which were coupled together via Ca2+ diffusion. In each element, ionic channels were modelled by equations of Fox et al.. At the cellular level, Ca2+ and APD alternans were produced either by rapid pacing (3.57 Hz), or by slow pacing (2.5 Hz) with an increased stiffness of the relationship between SR Ca2+ content and cytoplasimc Ca2+ concentration, which were consistent with experimental observations. In the spatially extended (75 elements) cell model, spatially discordant Ca2+ alternans was observed under the condition of strong Ca2+-induced L-type Ca2+ channel inactivation, while Ca2+ alternans tended to be concordant for weak Ca2+ induced inactivation. APD alternans with concordant Ca2+ alternans is more significant than that with spatially discordant and fragmented Ca2+ alternans, which leads to approximately identical total L-type Ca2+ current of the whole cell during successive stimulations and thus suppressing APD alternans.

This study indicates that Ca2+ alternans can be induced under both rapid and relatively slow pacing rates via different mechanisms, each of which may produce concordant or discordant Ca2+ alternans. The coupling between Ca2+-Voltage may reduce the amplitude of APD alternans, though Ca2+ distribution is spatially heterogeneous in the cell.