Fibroblasts Induce Calcium Alternans When Coupled to Cardiomyocytes: a Simulation Study

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Cardiac alternans have been related to reentrant arrhythmias due to the temporal and spatial gradients they generate. In many cases, because of the bidirectional coupling between membrane potential and Ca^{2+} transients (CaT), action potential alternans are concomitant to CaT alternans (Ca-alt). Although cardiac alternans mainly occur at rapid pacing, many factors can reduce the threshold for heart rate alternans, including interaction with fibroblasts. It has been observed that the effects of myocyte-fibroblast coupling lead to action potential duration (APD) shortening and depressed CaT in cardiomyocytes, and these altered CaTs might increase the occurrence of Ca-alt in these cells.

The aim of the present work is to investigate the role of fibroblasts in the generation of arrhythmogenic Ca-alt. Beat-to-beat variations of APD and systolic $[Ca^{2+}]_i$ were evaluated in simulated myocyte-fibroblast pairs and also in uncoupled myocytes at different pacing rates to determine the threshold for alternans. The ionic mechanisms responsible for this alternating behavior were analyzed with populations of models at a cycle length of 300 ms. Populations were generated by varying parameters with scaling factors that followed a normal distribution (mean = 1, standard deviation = 0.15). Then, the resulting models were classified in alternans or non-alternans groups.

Our results show that myocytes coupled to fibroblasts were more prone to alternans than isolated myocytes. At equal pacing rates, 47% of the models from the heterocellular population presented Ca-alt, as compared to 33% from the other. However, the ionic mechanisms that promoted these alternations were similar in both cases. We observed significant differences between groups, highlighting higher NCX, I_{NaK}, J_{rel} and lower SERCA in models developing Ca-alt as ionic transport pathways that contribute to intracellular Ca^{2+} reduction. These results suggest that myocyte-fibroblast coupling impairs CaT, making myocytes more susceptible to alternans.