Pacemaker-induced reentrant waves in engineered cardiac cell culture and model

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Rotating waves generated by the interaction of pacemakers are investigated using optical imaging of engineered cardiac cell cultures and nonlinear reaction-diffusion equations. Embryonic chick ventricular cells are cultured to exhibit dominant central pacemaker waves. Side pacemaker waves are induced by the potassium channel-blocker, E-4031. The side pacemaker waves break over the central pacemaker to form reentrant waves. Controlling side pacemaker period in the modified FitzHugh-Nagumo equations induces comparable transitions in dynamics. These studies may contribute to our understanding of the role of pacemakers in generating reentrant waves in the heart.

***Keywords* — pacemakers, excitable media, reentrant waves, cardiac monolayer, cardiac arrhythmia**

I. Introduction

THE typical rhythm of the healthy heart consists of the sinus node pacemaker periodically emitting waves of depolarization that entrain secondary pacemakers. However, this dominant pacemaker dynamic may, under pathological conditions, transition to reentrant waves associated with cardiac arrhythmias [4].

Culturing cardiac cells on 2-D surfaces [1,2,6] enables investigation of the role of pacemakers in reentrant wave generation in simplified and controlled conditions. We engineer a novel cardiac cell culture configuration that can switch from central pacemaker waves to reentrant waves under hERG potassium channel block with E-4031. This is interesting inasmuch as impaired hERG function is known to be pro-arrhythmic in human heart [5].

Theoretical studies of reentrant wave patterns in excitable tissue have been carried out using several reaction-diffusion models [1,3,6]. We develop a simple FitzHugh-Nagumo model to investigate how the interaction of pacemaker waves can generate the types of wave patterns seen (and not seen) in the cell culture experiments.

II. Results

A. *Dominant pacemakers and reentry in cell culture*

Ventricular cells from seven to eight-day-old embryonic chick are plated as a 9 mm disk with a higher density in a 2 mm central disk. Macroscopic intercellular calcium imaging is used to detect sustained periodic focal waves emitted from the central pacemaker in 8/12 preparations.

Transition from central pacemaker to reentry is induced with 0.75 μM E-4031 (Sigma-Aldrich). This leads to the emergence of side pacemakers in 6/7 cases, with interbeat intervals at side pacemakers shorter than the previously dominant central pacemaker. Side pacemaker waves break over the central pacemaker to form reentrant waves.

B. *Pacemaker entrainment and reentry in model*

The wave dynamics in the cell cultures are modeled using modified FitzHugh-Nagumo equations [3] of excitable media with a central and side pacemaker.

Decreasing intrinsic period the side pacemaker induces transitions: 1) from dominant central pacemaker to dominant side pacemaker, when the side pacemaker period is shorter than the central pacemaker period and 2) from side pacemaker to reentry, when side pacemaker period is shorter one-to-one entrainment limit of the central pacemaker.

Reentrant waves are generated through side pacemaker wave break over the central pacemaker. The core of the reentrant wave forms on the side of the central pacemaker that is farthest from the side pacemaker. This allows for coexistence of rotating and side pacemaker waves.

III. Conclusion

Simple experimental and mathematical models of cardiac wave propagation are used to demonstrate how pacemaker interactions can guide transitions to reentrant wave patterns. This may be relevant to the sunderstanding and control of pacemaker-induced arrhythmias in the heart.

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