QUANTITATIVE & SYSTEMS BIOLOGY SEMINAR: Thermodynamic Analysis of the Intracellular Ca2+ Dynamics Using (FLOM) Reveals the Molecular Mechanisms of T-Wave Alternans in the Heart

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Date:
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Time:
2:30 PM-3:45 PM

Location:
COB2 140

Abstract:

Myoplasmic Ca2+ alternans commonly occur during conditions such as tachycardia, ischemia, or hypothermia. This is a serious condition that can lead to sudden cardiac death. Myoplasmic Ca2+ alternans are alternating beat-to-beat changes in the amplitude of the Ca2+ transient. They typically arise from a variation in the amount of Ca2+ released from the sarcoplasmic reticulum (SR) between two consecutive heartbeats. This variability in the release of Ca2+ has previously been attributed to a delay in the recovery of the ryanodine receptor (RyR2), an incomplete Ca2+ refilling of the SR, or a change in the duration of the action potential. In each case, the RyR2 will mobilize Ca2+ from the SR in an alternating manner, thus generating Ca2+ alternans. To investigate the myoplasmic Ca2+ alternans in more depth, we utilized a novel experimental approach, Fluorescence Local Field Optical Mapping (FLOM), to record at the epicardial layer of an intact heart with subcellular resolution. These recordings were collected in conjunction with a local cold finger, where a temperature gradient was locally imposed on the tissue. In the colder regions, Ca2+ alternans were larger and occurred without changes in the duration of the action potential duration. Upon analyzing changes in the Q10 of several kinetic processes defining the intracellular Ca2+ dynamics, we found the imposed temperature gradient to have a significant effect on the relaxation of intracellular Ca2+ transients. The precipitous temperature dependency of Ca2+ alternans observed suggests they arise from an insufficient Ca2+ uptake into the SR by the ATPase of SR (SERCA2a). Interestingly, we found Ca2+ alternans to be heavily dependent on the SR Ca2+ and could be fostered with increased heart rate, which decreased the time for SERCA2a reuptake into SR beat to beat. Similarly, the partial pharmacological inhibition of SERCA2a with Thapsigargin increased the amplitude of myoplasmic Ca2+ alternans. Finally, the FLOM experimental approach is a valuable technique that can shed light on how arrhythmogenesis correlates with the spatial distribution of metabolically impaired myocytes along the myocardium.

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