Abstract

Alternans of cardiac repolarization is associated with arrhythmias and sudden death. At the cellular level, alternans involves beat-to-beat oscillation of the action potential (AP) and possibly Ca²⁺ transient (CaT). Because of experimental difficulty in independently controlling the AP and electrical subsystems, mathematical modeling provides additional insights into mechanisms and causality. Pacing protocols were conducted in guinea pig and canine ventricular myocyte models with the following results:

(I) both models produce sustained alternation of both AP duration (APD) and CaT amplitude. In the guinea pig, alternans are discordant (large CaT accompanied by short APD) while in the canine alternans are concordant (large CaT accompanied by long APD).

(II) alternation of the L-type calcium current (I_{Ca,L}) effect; different levels of basal CaMKII activity. An increase of the CaMKII through the sodium-calcium exchanger (INaCa) and underlies activity shifts the onset of CaT and AP alternans to slower APD alternans; increased Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) frequency and increases its magnitude, while decrease of CaMKII suppresses both alternans. (III) increase of IKr suppresses APD alternans, without suppressing CaT alternans. Thus, CaMKII inhibition eliminates APD alternans by eliminating its cause (CaT alternans), while enhancement does so by weakening CaT-APD coupling. The simulations identify combined CaMKII inhibition and enhancement as a possible antiarrhythmic intervention.

Methods

Ventricular Myocyte Model

![Cell model structure](image)

This work is the subject of a recent publication [1].

Results

Frequency-dependence of CaMKII activity

APD and CaT Alternans

![APD and CaT alternation curves](image)

![Simulated and experimental frequency dependence of CaMKII activity](image)

![APD and CaT rate-adaptation curves](image)

APD and CaT Clamp

![APD and CaT clamp protocols](image)

CaMKII and IKr Modulate AP Alternans

![Steady state APD and CaT as a function of frequency at different levels of basal CaMKII activity](image)

Conclusions

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References


http://rudylab.wustl.edu