Cardiac Bioelectricity and Arrhythmia Center (CBAC)

Calcium and Action Potential Alternans in Cardiac Cells: Role of CaMKII and repolarising currents

Leonid Livshitz and Yoram Rudy

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 Ca^{2+} transient (CaT). Because of experimental difficulty in independently controlling the 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 the AP duration (APD) and CaT amplitude. **(II)** 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). **(III)** CaT alternans results from refractoriness of the SR release system; alternation of the L-type calcium current ($I_{Ca(L)}$) has a negligible effect; **(IV)** In canine. CaT-AP coupling during late AP occurs through the sodium-calcium exchanger (I_{NaCa}) and underlies APD alternans; **(V)** Increased Ca^{2+}/calmodulin-dependent protein kinase II (known to modulate its activity in response to the frequency, amplitude and duration of CaT) activity extends the range of CaT and APD alternans to slower frequencies and increases alternans magnitude; its decrease suppresses CaT and APD alternans, exerting an antiarrhythmic effect; **(VI).** In canine. increase of the rapid delayed rectifier (I_{Kr}) also suppresses APD alternans, but 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.

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

Methods

Ventricular Myocyte Model

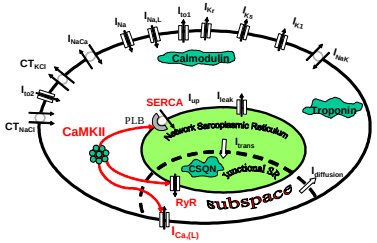

Fig.1. The model cell structure. Models of the guinea pig [2] and canine [3] ventricular myocytes. The canine model incorporates the CaMKII regulatory pathway (red line) that regulates that targets $I_{Ca(L)}$, RyR, and the SERCA/PLB complex [3]. Numerical integration was performed using Matlab.

Results

Frequency-dependence of CaMKII activity

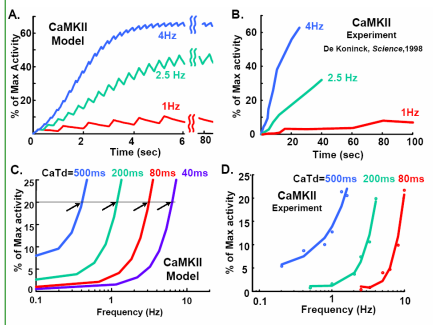

Fig.2. (A) Simulated and **(B)** experimental [4] time course of CaMKII activity. The Ca^{2+} transient (CaT) duration and amplitude are held constant at 20 ms and 2 mmol/L, respectively. Different time scales reflect different isoforms in model and experiment. (**C**) Simulated and (**D**) measured [4] frequency dependence of CaMKII activity for indicated CaT durations (CaTd).

CaMKII and Cardiac Function

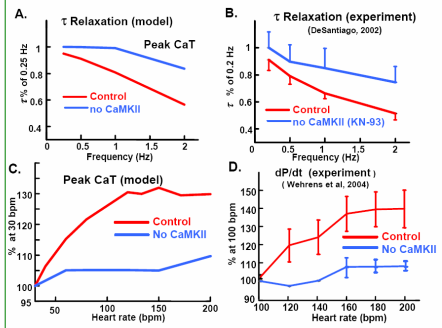

Fig.3. (**A**) Simulated and (**B**) measured [5] effect of CaMKII inhibition (by KN-93) on rate of CaT decline and mechanical relaxation. (**C**) Simulated effect of CaMKII inhibition on force-frequency (CaT-frequency) relation. (**D**) Corresponding experimental data [6]. Total CaMKII inhibition (as by KN-93) greatly suppresses this rate dependence.

APD and CaT Alternans

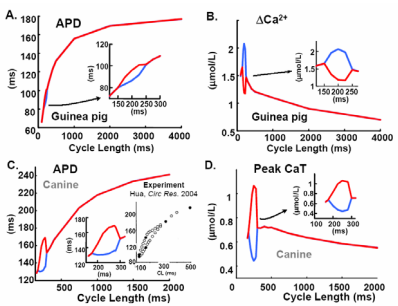

Fig.4. APD and CaT rate-adaptation curves. Insets show bifurcation portions on enlarged scale. **(A)** and (B) guinea-pig model, (**C**) and (**D**) canine model. Inset in panel (**C**) shows experimental data (canine) [8].

APD and CaT Clamp

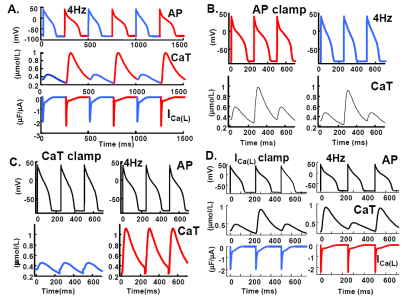

Fig.5. AP and CaT clamp protocols. Simulated results confirm that Ca^{2+} cycling subsystem is driving the AP alternans

APD and CaT Coupling

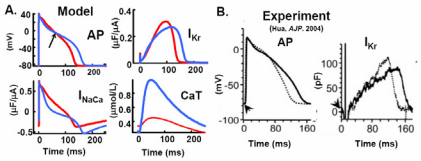

Fig. 6. (A) Superimposed AP, CaT, I_{NaCa} and I_{Kr} of consecutive beats during alternans at CL=250 ms. **(B)** experiment (canine) [9]. I_{NaCa} provides the coupling between CaT and AP alternans.

CaMKII and IKr Modulate AP Alternans

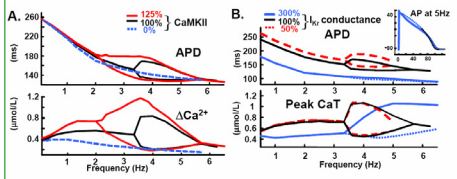

Fig.7. (A) Steady -state APD and CaT as a function of frequency at different levels of basal CaMKII activity. An increase of the CaMKII activity shifts the onset of CaT and AP alternans to slower frequencies and increases its magnitude, while decrease of CaMKII suppresses both alternans. (**B**) Effect of IKr on APD and CaT alternans. APD (**top**) and CaT (**bottom**) adaptation curves for three different levels of IKr conductance. Inset: superimposed consecutive APs at 5 Hz for IKr increase of 300%. Note that increase of IKr suppresses APD alternans, without suppressing CaT alternans

Conclusions

I. In the guinea pig, APD-CaT alternans are discordant (large CaT accompanied by short APD) while in the canine alternans are concordant (large CaT accompanied by long APD).

II. Increased CaMKII activity extends the range of CaT and APD alternans to slower frequencies and increases alternans magnitude; its decrease suppresses CaT and APD alternans, exerting an antiarrhythmic effect;

III. In canine, increase of the IKr also suppresses APD alternans, but without suppressing CaT alternans. Thus, CaMKII inhibition eliminates APD alternans by eliminating its cause (CaT alternans), while IKr enhancement does so by weakening CaT-APD coupling. The simulations identify combined CaMKII inhibition and IKr enhancement as a possible antiarrhythmic intervention.

Acknowledgements

We gratefully acknowledge the valuable help of members of the Rudy's lab: K. Decker, G. Faber, T. O'Hara, T. Hund, J. Silva, A. Nekouzadeh, N. Gaur, and Li Li.

References

1. Livshitz LM and Y. Rudy.. AJP., in press, (2007).
2. Luo C.H., Rudy Y. Circ Res. 74:1071-96,(1994)
3. Hund, T.J. and Y. Rudy, Circulation. 110:3168-3174,(2004)
4. Koninck and Shulman, Science, 279, 227-230, (1998)
5. DeSantiago et al., J Mol Cell Cardiol. 34, 975-84 (2002)
6. Wehrens et al., Circ Res. 94:61-70, (2004)
7. Hua and Gilmour, *Circ Res*. 94: 810-819 (2004)
8. Hua et al *Am J Physiol*. 286:H2342-H2352 (2004)

Washington University in St.Louis

This work has been supported by Washington University in St. Louis Cardiac Bioelectricity and Arrhythmia Center and the NIH-NHLBI Grants R37-HL33343 and RO1-HL49054.

http://rudylab.wustl.edu