Rate Dependence and Regulation of Action Potential and Calcium Transient in a Canine Cardiac Ventricular Cell Model

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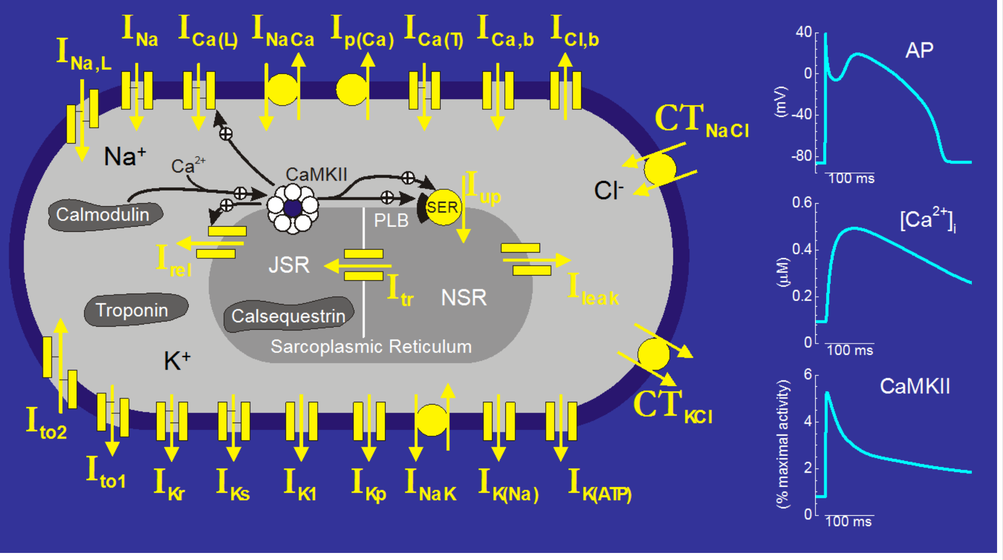
Abstract: Computational biology is a powerful tool for elucidating arrhythmogenic mechanisms at the cellular level, where complex interactions between ionic processes determine behavior. A novel theoretical model of the canine ventricular epicardial action potential and calcium cycling was developed and used to investigate ionic mechanisms underlying Ca^{2+} transient (CaT) and action potential duration (APD) rate dependence. The Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) regulatory pathway was integrated into the model, which included a novel Ca^{2+}-release formulation, Ca^{2+} subspace, dynamic chloride handling, and formulations for major ion currents based on canine ventricular data. CaMKII is an important determinant of the rate dependence of CaT but not of APD, which depends on ion-channel kinetics. The model of CaMKII regulation may serve as a paradigm for modeling effects of other regulatory pathways on cell function.

HRd model of the canine ventricular myocyte

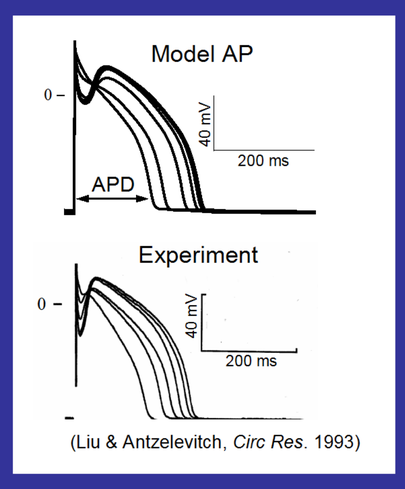


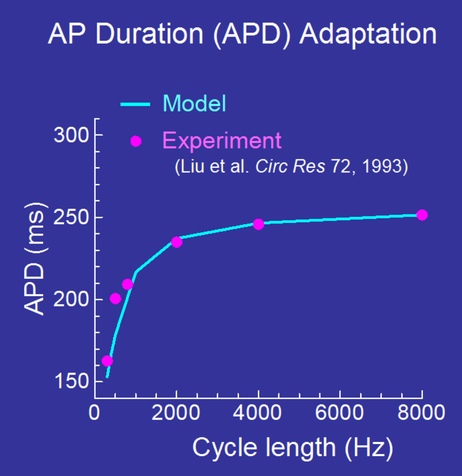
Introduction

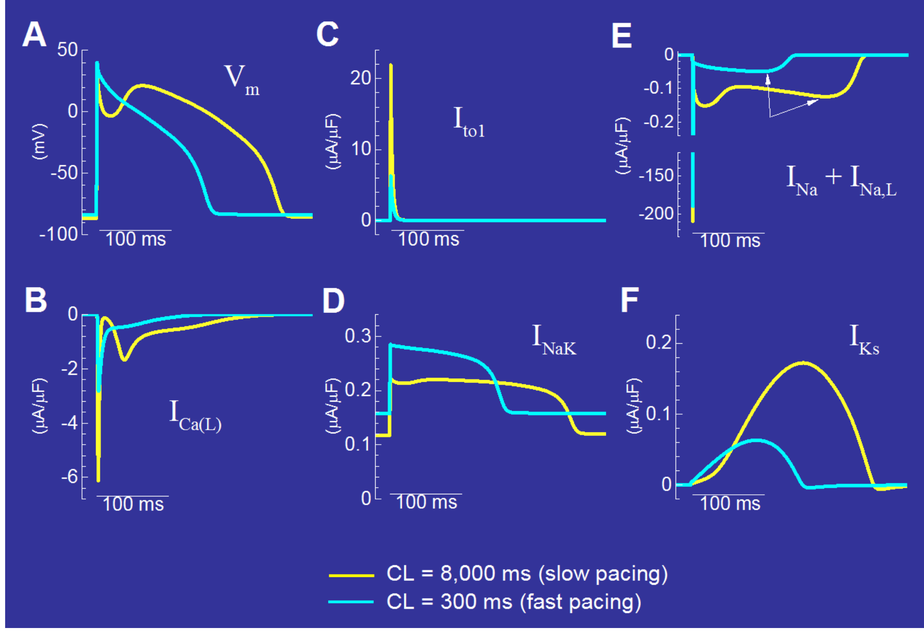
- In cardiomyocytes, CaMKII substrates include L-type Ca^{2+} channels, ryanodine receptor Ca^{2+}-release channels, sarcoplasmic reticulum (SR) Ca^{2+}-ATPase and phospholamban (PLB).
- We used the model to gain new insights into ionic processes underlying APD and CaT rate dependence and how CaMKII regulates these processes.

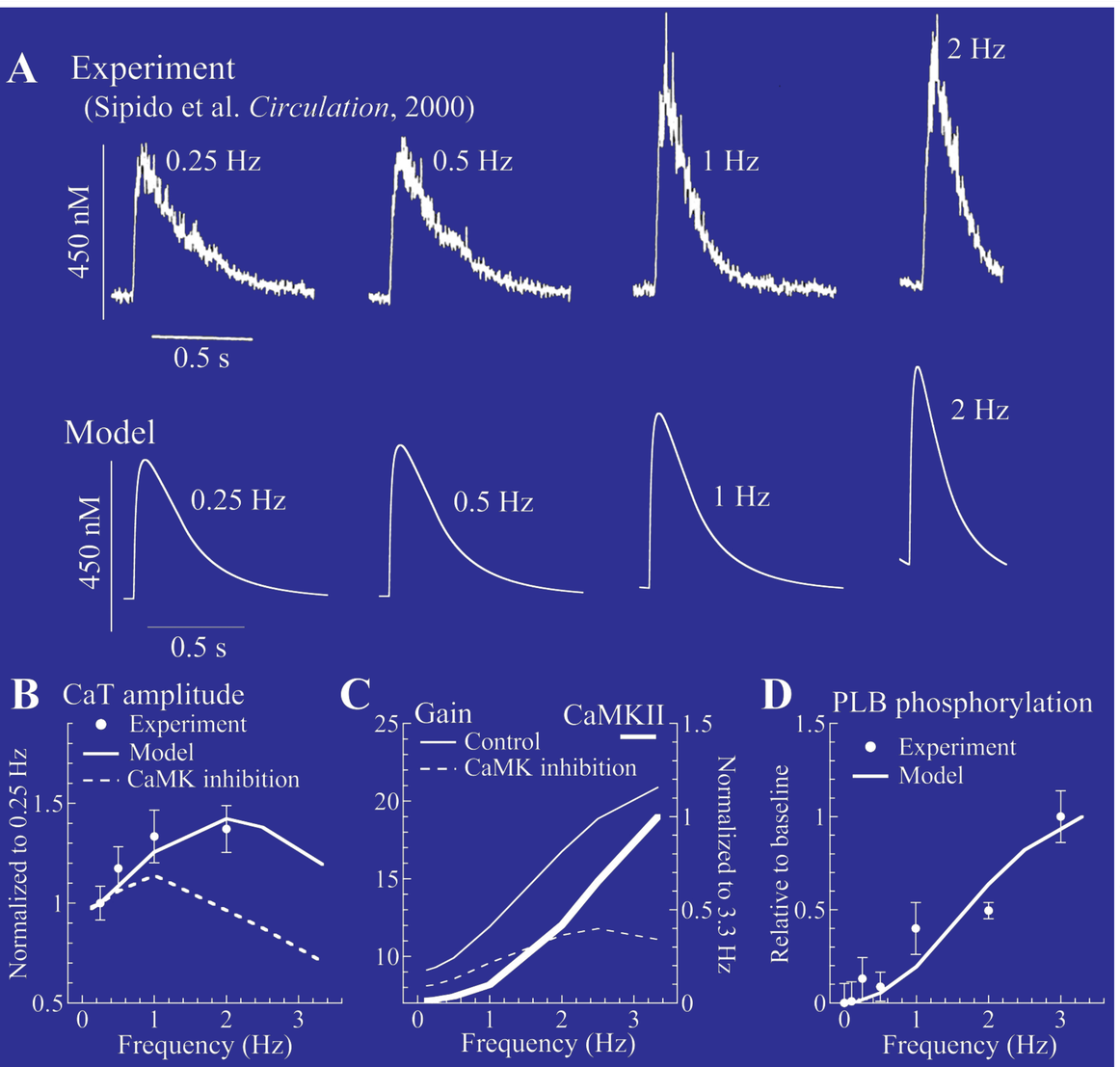
- Model AP morphology and APD agree with canine epicardial recordings.
- Most important for APD rate adaptation is $I_{Ca(L)}$ (**B**) although I_{to1} (**C**) also plays a significant role.
- I_{NaK} (**D**) and $I_{Na,L}$ (**E**) play secondary roles in APD rate adaptation.
- Canine I_{Ks} is small and does not accumulate between beats (**F**) marginalizing its role in APD rate adaptation in the absence of β-adrenergic stimulation.
- CaMKII had very little effect on APD adaptation.
- Interestingly, a decrease in I_{to1} (**C**) facilitates APD shortening.

Action potential (AP) rate dependence: Model and experiment









- Consistent with experiment, the model diastolic $[Ca^{2+}]_i$ and CaT_{amp} increased as pacing frequency increased (**A,B**).
- CaMKII inhibition produces a negative CaT_{amp}-frequency relation (**B**) and flattened the gain-frequency relation (**C**).
- CaMKII inhibition reduced CaT_{amp} by decreasing I_{up}, which reduced SR Ca^{2+} load, by decreasing peak $I_{Ca(L)}$, which reduced trigger for SR release, and by reducing I_{rel} directly.

Conclusions

- $I_{Ca(L)}$ is primarily responsible for APD adaptation in the normal canine ventricular myocyte.
- Transient outward K^+ current plays a secondary but significant role in adaptation.
- CaMKII is capable of detecting pacing rate in cardiac myocytes.
- Through its regulation of I_{up}, I_{rel}, and $I_{Ca(L)}$, CaMKII mediates rate-dependent changes in CaT_{amp}.