Cardiac Electrophysiology I

1735-Pos

Action Potential Duration Adaptation and Reverse-Rate Dependency in Human Ventricular Myocytes: Insights from a Computer Model

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We recently developed and validated a novel mathematical model for Ca handling and ionic currents in human ventricular myocytes that is more robust than previous models in recapitulating relative contributions of various repolarizing K currents, and in describing Ca cycling processes (Biophys J. 2009;96(3) S1:664a-665a). Here, we present intriguing results on some emergent properties of this model. With increasing pacing frequency, AP shortening and parallel increases in intracellular [Ca] and [Na] are predicted. Remarkably, accumulation of $[Na]_i$ at fast rates predominates in the AP shortening (e.g. vs. K current changes), due to outward shifts in Na-pump (I_{NaK}) and Na-Ca exchange (I_{NaCa}) currents. Indeed, when clamping $[Na]_i$ to prevent Na accumulation, APD does not change with heart rate. No APD adaptation occurs when we prevent only I_{NaK} and I_{NaCa} from sensing the $[Na]_i$ rise (i.e. neither fast nor background Na currents contribute), and simulations indicate that I_{NaK} is dominant over I_{NaCa} in this effect. Moreover, acute Na-pump blockade is expected to causes gradual AP shortening as seen experimentally, that is secondary to gradual Na accumulation (after instantaneous APD prolongation due to block of outward I_{NaK}). We speculate that the increased $[Na]_i$ seen in heart failure may limit the AP prolongation that is caused by reduced K currents and increased late Na current. Our model (uniquely among human AP models) recapitulates reverse-rate dependence of APD upon I_{Kr} block, e.g. drug-induced AP prolongation is larger at slow stimulation rates. Simulation indicates that this is not due to frequency dependent properties of repolarizing currents (e.g. I_{Ks}), but is ''intrinsic'' to the system. That is, when AP repolarization is slower (at lower frequency with smaller net repolarizing current) any given current change (I_{Kr} block) causes a larger APD change.

1736-Pos

Effects of Stochastic Channel Gating and Stochastic Channel Distribution on the Cardiac Action Potential

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Cardiac ion channels exhibit stochastic conformational changes that determine their open-close gating behavior, leading ultimately to the action potential (AP). However, in computational models of conduction, ion currents are usually represented deterministically. Moreover, the natural intercellular variability of the number of membrane and gap junctional channels is never considered. Our aim was to quantify the effects of stochastic current fluctuations and channel distributions on AP duration (APD) and intercellular conduction delays (ICDs) using a ventricular cell model (Rudy et al.) with Markovian formulations of the principal ion currents (I_{Na}, $I_{Ca,L}$, I_{Kr}, I_{Ks} and I_{K1}). Stochastic channel transitions were simulated explicitly and channel counts were drawn randomly from Poisson distributions.

In single cells paced at 1 Hz, stochastic channel gating generated APD variability (APD = 143 ± 1.8 ms) with a coefficient of variation (CVar) of 1.3%. APD variability decreased at higher pacing frequencies. I_{Ks} fluctuations contributed most (85%) to APD variance, followed by those of $I_{Ca,L}$ and I_{Kr} (12% and 2%, respectively). Poissonian channel distribution induced APD variability with a CVar of 0.65%. In cell strands, the CVar of APD was strongly decreased by intercellular coupling. During conduction, stochastic channel gating generated ICD variability with a CVar of 0.25%. Reduction of I_{Na} or gap junctional coupling slowed conduction, but did not increase the CVar of ICDs above 1%. Poisson distribution of membrane channels exerted a similar small effect. However, during strong gap junctional uncoupling (60-200 channels/junction, conduction velocity <1 cm/s), Poisson distribution of gap junction channels resulted in a large ICD variability (>20%), highly heterogeneous conduction patterns and conduction blocks.

Therefore, the variability of the number of channels in different gap junctions contributes to the heterogeneity of conduction patterns observed previously in experiments in cardiac tissue with altered intercellular coupling.

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Comparison of the Effects of the Transient Outward Potassium Channel Activator NS5806 on Canine Atrial and Ventricular Cardiomyocytes

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Objective: NS5806 activates the transient outward potassium current (Ito) in canine ventricular cells. We compared the effects of NS5806 on canine ventricular versus atrial tissues and myocytes. Methods: NS5806 (10 μM) was evaluated in arterially-perfused canine right atrial and left ventricular wedges. Atrial and ventricular epi- and endocardial cells were isolated by enzymatic dissociation. Current and voltage-clamp recordings were made in the absence and presence of NS5806. Results: In ventricular wedges NS5806 increased phase 1 repolarization in epi- and midmyocardial cells. A minor effect on conduction and upstroke velocity also was observed. In contrast, application of NS5806 to atrial preparations slowed upstroke velocity and reduced excitability, consistent with sodium channel block. In ventricular myocytes, NS5806 increased the magnitude of Ito by 80% and 16% in epi and endo, respectively (at +40 mV). In atrial myocytes, NS5806 increased peak Ito by 25% and had no effect on the sustained pedestal current, IKur. INa density in atrial myocytes was nearly 100% greater than in endocardial myocytes. NS5806 caused a negative shift in steady-state mid-inactivation (V1/2) for both cell types (73.9 ± 0.27 to −77.3 ± 0.21mV for endocardial and −82.6 ± 0.12 to −85.1 ± 0.11mV for atrial cells). The shift in V1/2 resulted in a reduction of INa in both cell types. However, the more negative V1/2 in atrial cells suggests that atrial cells lose excitability at more depolarized voltages than endocardial cells which may explain the greater reduction of excitability in atrial vs ventricular wedges by NS5806. Conclusion: NS5806 produces a prominent augmentation of Ito with little effect on INa in the ventricles, but a potent inhibition of INa with little augmentation of Ito in atria.

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Intracellular Zn^{2+} Release Modulates Cardiac Ryanodine Receptor Function and Cellular Activity

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Several Ca^{2+}-binding proteins bind also Zn^{2+}, suggesting that Zn^{2+} can modulate the structure and function of many proteins involved in heart function. We first investigated intracellular Zn^{2+} homeostasis and its possible role in cardiac excitation-contraction (EC)-coupling by using confocal microscopy in adult rat cardiomyocytes loaded with either Zn^{2+}- or Ca^{2+}-specific dye, Fluo-Zin-3 or Fluo-3, respectively. The local ionic releases (sparks) recorded in FluoZin-3 loaded cells were significantly smaller, shorter and less frequent than those of the Fluo-3 loaded cells under control resting conditions. Following 1-μM zinc-pyrithione exposure, the amplitude of the FluoZin-3 sparks increased by 35% leaving Ca^{2+}-sparks unaffected, and a 10-mV leftward shift was observed in the L-type Ca^{2+}-current (I_{Ca})-voltage relation without significant effect on maximal I_{Ca} density. Applications of either caffeine or ryanodine, and either a mitochondrial (MT) protonophore or a MT complex I inhibitor suggested that both sarcoplasmic reticulum and mitochondria are intracellular Zn^{2+} pools. Our western-blot data further showed that there are correlations between the intracellular Zn^{2+} level and the hyperphosphorylation levels of RyR2 and CAMKII as well as with total PKC activity. Additionally, hyperphosphorylation levels of both ERK-1 and NF-κB also showed a strong dependency on internal Zn^{2+}-level. In conclusion, intracellular Zn^{2+} might have an important role in the regulation of heart function including transcription and gene expression, implying that intracellular Zn^{2+} not only has a role in EC-coupling but it is also a major intracellular second messenger in cardiomyocytes.

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Uneven Expression Patterns of KCNQ1 and KCNE Subunits in the Heart Impact on the Function of Slow Delayed Rectifier (I_{Ks}) Channels

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Background: I_{Ks} has 2 major components: pore-forming (KCN)Q1 channel & regulatory (KCN)E1 subunits. Human heart expresses other members of the KCNE family (E2 - E5) that can all associate with Q1 & confer distinctly different channel phenotypes. The expression patterns of Q1 & different KCNE subunits in the heart, and their relation to the I_{Ks} channel function, is not clear. **Methods:** We use immunoblotting to quantify the protein levels of Q1 & E1 - E3 in different regions of the heart, and use patch clamp to quantify I_{Ks} current density and gating kinetics in left atrial (LA) and ventricular (LV) myocytes. We use the guinea pig model because of the robust cardiac I_{Ks}. **Results**: Immunoblot data: (1) Q1 protein is more abundant in atria (A) than in ventricles (V) (immunoblot densitometry ratio of A:V ~ 1:0.4), (2) E1 & E2 proteins are more