

other models and can be extended to study memory effect in conduction velocity and other quantities.

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Studies of reentrant arrhythmias in a detailed model of human ventricular tissue

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We study wave propagation in a model of human ventricular tissue. Our model is based on recent experimental data on the major ionic currents for human ventricular cells: the fast sodium, L-type calcium, transient outward, rapid and slow delayed rectifier, and inward rectifier current. The model includes intracellular sodium, potassium and calcium dynamics, allowing for the realistic modeling of calcium transients, frequency dependence of the intracellular sodium concentration, and the positive contraction staircase typical for human ventricular myocardium. The model describes the three main types of cells, epicardial, endocardial and M cells. We study wave propagation both in 2D tissue sheets and in a 3D detailed anatomical model of the human ventricles that incorporates muscle fiber direction and anisotropy. We show that in 2D we have a complex meandering pattern with a 'Z-shape' core and a period of 265ms. We vary parameters of the model and study their effect on spiral wave meandering and spiral wave stability. In the anatomical model of the human ventricles we simulate tachycardias driven by a single reentrant source at different locations in the heart and ventricular fibrillation (VF) organized by multiple wavelets, which occur as a result of spiral wave breakup. We show that ECG patterns resemble those recorded in patients. We demonstrate that surface excitation patterns during VF in our human heart model have a simpler spatial organization than those observed in experiments in the canine heart and in heart models using FitzHugh-Nagumo (FHN) equations for cardiac tissue. We count the number of excitation sources and conclude that VF in the human heart may be organized by a smaller number of sources than were previously predicted from FHN models and a canine heart geometry.

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Heterogeneous conduction in pulmonary veins: A model of atrial fibrillation due to slow reentrant circuits appearing as local activity

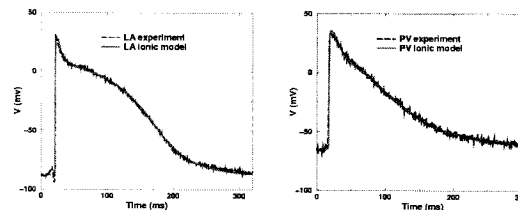
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Introduction: Focal activity originating from the pulmonary veins (PV) has been implicated as a cause of atrial fibrillation (AF). However, it has been unclear how such focal activity can be produced since PV cardiomyocytes often do not show spontaneous activity under physiological conditions. It has been hypothesized that heterogeneous propagation within the PVs may be involved in triggering AF.

Methods and Results: Using action potential (AP) data obtained experimentally, including AP rate of rise, morphology, resting membrane potential, and rate adaptation, we developed separate mathematical models of canine PV and LA cardiomyocyte APs (see figure) and incorporated them into an atrial structure model. Along with slower PV conduction due to slower rate of rise (259 V/s in LA vs. 98 V/s in PV), heterogeneities in propagation were introduced within the PV region by randomly removing specified fractions of cell-to-cell connections in the longitudinal (f_l) and transverse (f_t) directions to simulate uncoupling due to highly heterogeneous fiber orientation. We found that while large values of f_l and f_t (i.e., large reductions in coupling) completely blocked PV propagation and small values allowed normal PV activation, certain combinations produced a slow reentrant circuit within a single PV that re-excited the atria at a

faster rate than normal sinus rhythm. For sustained reentry ($f_l \sim 0.25-0.3$, $f_t \sim 0.7-0.75$), it was necessary to have $f_t > f_l$ so that propagation could progress far enough along the vein to form the reentrant circuit. Non-sustained reentry could occur for smaller degrees of uncoupling with either $f_l > f_t$ or $f_l > f_t$.

Conclusions: Our results indicate that activity emanating from the PVs may appear as focal activation when it is in fact due to a slow reentrant circuit propagating heterogeneously around the vein and driving the LA.



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The role of intracellular Ca^{2+} handling in determining stability of a genetically engineered pacemaker

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Background: Miake et al (2002) have devised a genetic technique to create a biological pacemaker as an alternative to the implantable electronic pacemaker. Suppression of the Kir2.1 channel reduces the inward-rectifier potassium current (I_{K1}) and converts ventricular myocytes to pacemaker cells with spontaneous and rhythmic action potentials (AP). In this study we investigated the factors affecting stability of this pacemaker rhythm.

Methods: A single cell model of human ventricular myocytes was used to investigate the ionic mechanisms underlying pacemaker activity when I_{K1} is depressed. Long time courses (over 10 s) of APs, individual ionic channel currents, total net ionic current and intracellular Ca^{2+} concentration during APs were recorded. The role of $[Ca^{2+}]_i$ on stability was investigated by buffering $[Ca^{2+}]_i$ to 250 nM.

Results: Decreasing I_{K1} results in a net inward current during the diastolic phase, which depolarises the cell and leads the Na^+ and subsequently the Ca^{2+} channels to open, generating AP. A 85% decrease in I_{K1} can produce rhythmic and spontaneous APs. However, repetitive firing generates an updrift in $[Ca^{2+}]_i$ similar to that observed in ventricular myocytes subjected to a series of stimuli, which inactivates the L-type Ca^{2+} channel resulting in a damping of i_{CaL} . As a consequence, the pacemaker activity is unstable and terminates at 9 s. However, when $[Ca^{2+}]_i$ is buffered to 250 nM a stable rhythmic pacemaker activity is established.

Conclusion: Depressing I_{K1} generates a net inward current in the diastolic phase which is responsible for the transient spontaneous electrical activity in the genetically engineered pacemaker cells. Pacemaker stability is dramatically increased by buffering Ca^{2+} .

ABSTRACT SESSION 45: CLINICAL ELECTROPHYSIOLOGY V: Genetics of Arrhythmias

Saturday, May 22, 2004
11:30 a.m.–1:00 p.m.

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Spectrum and prevalence of cardiac sodium channel variants among 829 healthy Black, White, Asian, and Hispanic individuals: Implications for long QT syndrome and Brugada syndrome genetic testing

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