enhancing the mitochondrial ROS production with either antimycin or rotenone. Oscillations of IKATP could be either initiated or potentiated upon rapid, but not slow, transition to near-anoxia and they were closely paralleled by depolarization of delta Psi, indicative of a transient inability of the F1F0-ATPase to keep delta Psi. At elevated oxidative stress, rapid transition to near-anoxia caused a burst of H2DCF oxidation which correlated with an increased rate of IKATP activation. These results show that metabolic oscillations occur in cardiomyocytes at near-anoxia and that these oscillations are controlled by mitochondria through the rate of ATP hydrolysis which in turn depends on ROS production.

2736-Pos

A New Mathematical Cardiac Cell Model for the Elucidation of the Mechanisms of Reperfusion Arrhythmogenesis

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Reperfusion arrhythmias result from pathologies of cardiac myocyte physiology that develop when previously ischemic myocardium experiences a restoration of normal perfusion. The mechanisms of reperfusion arrhythmogenesis, which involve many components of a highly coupled nonlinear system, have been under investigation for many years. Despite these efforts, an effective therapy for the prevention of reperfusion arrhythmias has yet to be translated into routine clinical practice. Because of the highly complex nature of the problem, we have developed a cardiac cellular mathematical model tailored to the study of reperfusion arrhythmogenesis. This model allows more realistic simulations of ischemia and reperfusion than have been conducted previously, because it includes coupled intra- and extracellular pH regulation systems, as well as modification of the activity of ionic channels and exchangers secondary to changes in pH and the concentrations of ATP, ADP and other associated metabolites. We show that the model more closely reproduces experimental ischemia data than other existing models. Because of this, the model has strong promise for elucidating mechanisms of reperfusion arrhythmogenesis.

2737-Pos

Understanding Pro-Arrhythmic Effects of Drugs using Computational Models and Parameter Sensitivity Analysis

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Increased risk of ventricular arrhythmia is a dangerous side effect of many pharmacological agents. Often, drugs block the K^+ channel responsible for rapid delayed rectifier current (I_{Kr}), leading to delayed repolarization of action potentials, prolongation of the QT interval, and increased arrhythmia risk. Some drugs, however, block I_{Kr} potently but are nonetheless safe. In addition, the effects of a drug on action potential morphology depend not just on the channel that is blocked, but also on the other channels present in the cell, a concept known as "repolarization reserve." We have gained new insight into both phenomena through analysis of ventricular myocyte computational models with parameter randomization and multivariable regression. The most likely targets of a non-specific drug can be deduced from the relationship between action potential duration and drug concentration, if the data are compared to the parameter sensitivity analysis of an appropriate electrophysiological model. Simulations also provide insight into how the electrophysiological substrate of a ventricular myocyte affects the response of the cell to a drug that blocks I_{Kr}. Such a drug always prolongs action potential duration, but the effects can be either exacerbated or attenuated, depending on the characteristics of the other ion channels present. Specifically, simulations with a common human ventricular myocyte model suggest that the most important factors influencing the response to an I_{Kr}-blocking drug are: 1) the underlying density of I_{Kr}; 2) the density of slow delayed rectifier current I_{Ks}; 3) the voltage-dependence of I_{Kr} inactivation; 4) the density of L-type Ca^{2+} current, and 5) the kinetics of I_{Ks} activation. These simulations provide for a quantification of the important concept of repolarization reserve, and demonstrate how analysis of computational models can provide insight into the factors that influence adverse drug reactions.

2738-Pos

Properties of Time Domain Vs. Frequency Domain Methods used in Atrial Fibrillation

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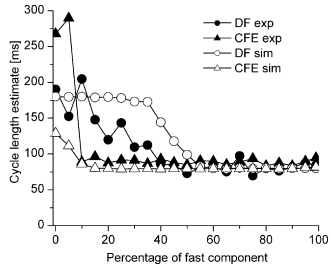
Complex Fractionated Electrogram (CFE) and Dominant Frequency (DF) are two methods commonly used to guide radio frequency ablation for treatment of atrial fibrillation (AF). CFE is based on the time domain and DF on the frequency domain.

We generated electrograms, composed of two components representing near- and far-field effects, with varying amplitude and white noise. Cycle lengths (CL) ranged from 80 to 180 ms. The electrograms were analyzed using time domain (CFE), and frequency domain (DF) methods, both in computer simulations and using the NavX system, routinely used in clinical practice to locate fast (<120ms) AF sources.

In computer simulations, DF approach estimated accurately CL of the fast (80 ms) and the slow (180 ms) signal and yielded 96 ms for equally combined signal. CFE method estimated CL of 129, 80 and 80 ms, respectively. When signals were fed into the NavX system via its hardware interface, DF yielded values of 190, 84 and 73 ms, respectively. CFE yielded 268, 85 and 95 ms, respectively.



The DF approach was more robust, since CFE tended to overdetect short CLs (see figure), thus unnecessarily prompting ablation more often than DF.

2739-Pos

Gender and Regional Differences in I_{cal} Distribution in Adult Rabbit Right Ventricle Influence Action Potential Duration and the Propensity for Eads in a Model of Long QT Syndrome Type 2

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Sex and apex-base differences in cardiac L-type calcium current (I_{CaL}) levels have been found to modulate vulnerability to arrhythmogenic early afterdepolarizations (EADs) in a drug-induced model of Long QT Syndrome Type 2 (LQTS2) in adult rabbit heart left ventricular epicardial myocytes. However, it is unknown whether similar gender and regional differences in I_{CaL} exist in the right ventricle. To further investigate the role of I_{CaL} as a determinant of EAD genesis, the apex-base distribution and biophysical properties of the calcium current in adult male and female right ventricles were assessed by the patch clamp technique and a modified Luo Rudy dynamic model of the cardiac action potential (AP). We found that I_{CaL} density measured at 0 mV was 48.2% higher in female (7.3 ± 1.2 pA/pF, n=6) compared to male base myocytes (3.8 ± 0.5, n=9, $p<0.008$). Analysis of regional differences in I_{CaL} in female right ventricle revealed 38.1% higher current density at the base (7.3 ± 1.2 pA/pF, n=6) compared to female apex myocytes (4.5 ± 0.5 pA/pF, n=8, $p<0.04$). There were no significant sex differences in I_{CaL} density in apex myocytes and no significant gender or regional differences in I_{CaL} activation and inactivation. Incorporation of I_{CaL} differences into the model showed that suppression of the rapid delayed rectifier potassium current to mimic LQTS2 resulted in increased AP duration and enhanced propensity for EADs in simulated female base myocytes. Taken together, these data demonstrate that sex and apex-base differences in right ventricle I_{CaL} correlate with the LQTS2-arrhythmia phenotype found in adult rabbit left ventricular epicardium and support the hypothesis that higher I_{CaL} underlies the propensity for EAD genesis.

2740-Pos

The Inter-Dependency of Local Myocardial Metabolism and Epicardial Electrical Activity during Acute Ischemia and Reperfusion

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Metabolic changes caused by the lack of adequate coronary flow lead to short and long term disturbances in local activation sequences. Our goal has been to study short term disturbances using parallel fluorescence imaging of epicardial NADH (fNADH) and transmembrane potential (TMP). METHODS: Experiments were conducted using Langendorff-perfused rat hearts while controlling the rate of flow to the left anterior descending coronary artery (LAD). Acute regional ischemia was induced by stopping flow to the LAD, followed by a period of low-flow reperfusion with subsequent full-flow reperfusion. Changes in local epicardial conduction velocities, as well as the incidence and dispersion of epicardial breakthroughs, were analyzed with the corresponding local changes of fNADH. With this approach, conduction velocities and reentrant activity could be correlated with changes in fNADH. RESULTS: Regional ischemia led to a reduction in Purkinje fiber activity within the ischemic zone. Approx 4 minutes after the initiation of ischemia, conduction velocities increased within regions with elevated fNADH. Afterward, conduction velocities in the ischemic zone declined and were lowest in the center, eventually falling to values below 20 cm/sec. Reductions in conduction velocity lagged behind