**1338-Pos Board B182**

**Optical Mapping Of VF In Isolated Swine Hearts With Scars**

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Ventricular fibrillation (VF) is the main cause of sudden cardiac death. We hypothesized that VF induced by large scars in an isolated porcine heart model could aid the understanding of VF in human hearts associated with structural disease. The explanted hearts were perfused with blood and Tyrode solution at 37C, and optically imaged with a voltage-sensitive fluorescence dye (di4-ANEPPS excited at 530nm with 150W halogen lamp). The emitted signal was filtered (610nm) and recorded with high speed cameras (MiCAM02, BrainVison, Jp) at 0.7mm spatial resolution. No optical signals could be recorded from the core of chronic infarcts or RF lesions. A total of 10 hearts were used: 4 controls, 3 with lesions generated via RF ablation and 3 with chronic infarcts. We observed the propagation of the depolarization waves and analyzed the VF waveforms at the border zone (BZ) and normal myocardium. We analyzed the VF waves in the frequency domain by calculating the dominant frequency (DF) on select regions of interest using Matlab (Mathworks, Ca). Our results showed that DF is smaller at the BZ compared to healthy tissue. Referenced to the average DF in the control hearts (10.07+/-0.54 Hz), the DF was slightly smaller in healthy myocardium of infarct hearts (i.e., 8.9+/-0.71Hz) and significantly smaller at the border zone (i.e., 6.03 +/- 0.86Hz). In ablated hearts, mean DF in normal myocardium was 9.16+/-0.7Hz and 7.24+/-0.66Hz at BZ, respectively. We suggest that these differences are related to the heterogeneous restitution properties as well as the changes in tissue structure at the BZ. The BZ of chronic scars is comprised of a mixture of viable and necrotic fibers; whereas in the acute settings of RF lesions, inflammation and edema are present at the BZ without alteration of fiber directions.

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**Negative Regulation of LQT2-Associated Kv11.1 Mutant Channels by Alpha(1A)-Adrenoceptors in Mammalian Cell Line**

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Mutations in KCNH2 gene underlie type 2 of the congenital long-QT syndrome (LQT2), in which rapid component of $I_K$ ($I_{Kr}$) is malfunctional and startled auditory stimuli are specific symptomatic trigger. The latter suggests fast arrhythmogenic mechanism. Therefore, we investigated acute alpha$_{(1A)}$- and cAMP-related beta-adrenergic modulation of $I_{Kr}$ in HL-1 cardiomyocytes, wild type (wt-) and two LQT2-associated mutant Kv11.1 channels (Kv11.1-Y43D and Kv11.1-K595E) reconstituted in Chinese Hamster Ovary (CHO) cell line.

$I_{Kr}$ and Kv11.1 currents were recorded through whole-cell patch-clamp technique and confocal microscopy of HL-1 cardiomyocytes transfected with GFP-tagged pleckstrin homology domain of phospholipase C-delta$_{(1)}$, visualized the fluctuations of membrane $PIP_2$ content.

In HL-1 cardiomyocytes expressing human alpha$_{(1A)}$-adrenoceptor, superfusion with 30 micromol/l phenylephrine significantly reduced $I_{Kr}$ amplitude, shifted current activation to more positive potentials and accelerated kinetics of deactivation. Confocal images demonstrated decline of $PIP_2$ concentration during phenylephrine exposure. Stimulation of beta$_{(1)}$- and beta$_{(2)}$-adrenoceptor downstream enzyme adenylyl cyclase by 5 micromol/l forskolin shifted $I_{Kr}$ activation to more negative potentials but did not significantly altered tail current amplitude. In parallel, alpha$_{(1A)}$-adrenoceptor activation downregulated reconstituted wt-Kv11.1 channels but forskolin (5 micromol/l) produced little effects. Expressed alone, Y43D-Kv11.1 or K595E-Kv11.1 channel had no measurable function. However, co-expression of wt-Kv11.1 and each mutant protein evoked currents with loss-of-function alterations but identical to wt-Kv11.1 alpha$_{(1A)}$- and forskolin-induced regulation.

Acute adrenergic regulation of at least two Kv11.1 mutant channels is preserved as in wt-Kv11.1 and native $I_{Kr}$ and could have arrhythmogenic potential in some LQT2 cases.

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**The Role Of Mineralocorticoid Receptors In The Adaptation Of Cardiac Myocytes To Pregnancy**

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**Aim:** Pregnancy is characterized by a hypertrophic remodeling of the heart, but little is known about the role of hormonal regulation in this cardiac modification. Mineralocorticoid receptors (MRs) have been shown to mediate structural and functional remodeling of the heart in pathological conditions. Also, its agonists, glucocorticoids and mineralocorticoids, are significantly enhanced in pregnancy. Our aim is therefore to examine the possible role of MRs in cardiomyocyte adaptation during rat pregnancy. **Methods:** Pregnant rats were studied one day before parturition. One group of pregnant rats (Pcan) was treated with potassium canrenoate (20 mg/kg/day), a MRs antagonist, for the last seven days of pregnancy, and compared to normal pregnant rats (P). These groups were also compared to non-pregnant rats, treated (NPcan) or not treated (NP). M-mode echocardiography was performed for the whole heart study. Rapid video-imaging was used to record cell contractility at 0.5 Hz. Patch clamp technique was applied to study L-type calcium currents (ICa-L). **Results:** MR antagonism in Pcan induced a decrease of the systolic and diastolic dimensions of the heart, when compared to P. This result was corroborated by a lower cell volume in Pcan. Cell contractility was not modified in all groups, when glucose was the only energetic substrate. However, our results uncovered a modified responsiveness to energetic substrates lactate and pyruvate, naturally increased in the blood of P. Indeed, while cell contractility was raised in P in the presence of these substrates, this effect was not observed in Pcan. Interestingly, in Pcan, ICa-L tend to increase in the same energetic condition when compared to ICa-L with glucose only. **Conclusions:** Our data indicate that MRs are involved in the adaptation of cardiac myocytes to pregnancy at the structural, metabolic, as well as functional level.

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**The Sialyltransferase, ST3Gal-IV, Modulates Cardiac Action Potential Waveforms And $I_K$**

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Atrial arrhythmias can be caused by changes in atrial action potential (AP) waveform or conduction. The regulated activity of ion channels, including voltage-gated potassium ($K_v$) channel isoforms, is crucial to normal AP waveform. Each $K_v$ channel isoform is uniquely glycosylated; glycans are typically terminated by sialic acid residues. Reports have shown sialic acids can modulate $K_v$ channel gating through isoform-specific mechanisms. Here, we questioned whether regulated sialylation alters AP waveforms and voltage-gated $K^+$ currents ($I_K$) produced in the atrium. AP waveform parameters and two types of $I_K$, the transient outward, $I_{to}$, and the slowly inactivating, $I_{K,slow}$, were compared in atrial myocytes isolated from neonatal control versus ST3Gal-IV knockout animals. ST3Gal-IV is a sialyltransferase expressed at uniform levels throughout the heart and adds sialic acid residues to N- and O-linked glycans through $\alpha$2-3 linkages. ECG recordings suggest that cardiac conduction/rhythm are altered in ST3Gal-IV$^{(-/-)}$ animals. AP duration (APD) was prolonged significantly in ST3Gal-IV$^{(-/-)}$ atrial myocytes compared to control APD. $APD_{10}$, $APD_{50}$, and $APD_{90}$ values for ST3Gal-IV$^{(-/-)}$ myocytes were ~50-80% greater than control values ($p<0.004$). A reduction in $K_v$ channel activity is one mechanism by which AP repolarization can be prolonged. To determine whether $K_v$ channel activity is modulated by ST3Gal-IV expression, whole cell $I_K$ from control versus ST3Gal-IV$^{(-/-)}$ atrial myocytes were measured and compared. The voltages of half-activation for $I_{to}$ and $I_{K,slow}$ were shifted significantly by >10 mV to more depolarized potentials in ST3Gal-IV$^{(-/-)}$ myocytes compared to control ($p < 0.001$); a depolarizing shift in activation voltage will lead to fewer $K_v$ channels active at a membrane potential, effectively reducing $K_v$ channel activity. These data suggest that the regulated expression of a single sialyltransferase, ST3Gal-IV, can alter $I_K$, thus modulating the rate of atrial repolarization and potentially leading to arrhythmias.

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**Ion Channel Toolbox for Cardiac Safety Evaluation**

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The cardiac action potential is comprised of multiple ion channel currents acting in concert and these ion channels are important in cardiac safety liability assessment of potential drug candidates. Currently, hERG current screening is a critical part of the preclinical assessment of a drug candidate and is required before first in human (FIH) clinical studies. Through our ongoing efforts to provide efficient cardiac safety evaluation, while reducing animal usage, we have incorporated the use of several cellular ion channel whole-cell voltage clamp screens using heterologously expressed and native cardiac ion channels. With heterologously expressing cell lines, the use of planar patch technology (PatchXpress and QPatch) allows for moderate throughput by providing automated, simultaneous whole-cell voltage clamp recordings. In this study we highlight five cardiac ion channels; 3 heterologously expressed cardiac potassium channels (hERG [$I_{Kr}$], Kir2.1 [$I_{K1}$], KvLQT1/minK [$I_{Ks}$]) that contribute to the repolarization phase of the action potential and two additional cardiac ion