of SR Ca^{2+} stores in the normal and diseased heart is not well described. Our data shows that STIM1 is present at low levels in adult normal cardiac myocytes, but expression levels increase after cardiac injury. Because STIM1 is involved in regulating intracellular Ca^{2+} homeostasis, we hypothesize that increased STIM1 expression after cardiac injury may be involved in the disturbed Ca^{2+} cycling within diseased cardiomyocytes. Using cultured adult ventricular feline myocytes, we found that adenoviral vector mediated overexpression of STIM1 induces cell death in 80% of myocytes versus only 5% in uninfected controls. We also showed that rested state contractions were minimally increased in unpaced STIM1 overexpressing myocytes, compared with control myocytes (3 fold increase), suggesting that STIM increases SR Ca^{2+} stores under conditions in which SR Ca^{2+} stores are usually depleted. STIM1 overexpressing myocytes had increased Ca^{2+} transient peaks (measured with fluo-4) as well as increased contractions. We are currently exploring how STIM1 modifies SR load and mechanisms by which STIM1 alters excitation-contraction coupling. Our findings show that STIM1 can increase SR Ca^{2+} loading and this could have effects on contractility and arrhythmias in disease.

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Regional Heterogeniety of the Inwardly Rectifying Potassium Current in the Canine Heart

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Background: The inward rectifier potassium current, IK1, regulates the terminal phase of repolarization of the action potential, as well as the resting membrane potential. Regional variation in IK1 has been noted in the canine heart, but the biophysical properties have not been directly compared. We examined the properties and functional contribution of IK1 in isolated myocytes from ventricular, atrial and Purkinje tissue.

Methods and Results: Action potentials (AP) were recorded from canine left ventricular midmyocardium, left atrial and Purkinje tissue. The terminal rate of repolarization of the AP (as assessed by the minimum dV/dt) in ventricle, but not in Purkinje, depended on changes in external K+ ([K+]o). Isolated ventricular myocytes had the greatest density of IK1 while atrial myocytes had the lowest. Furthermore, the outward component of IK1 showed that ventricular cells exhibited a prominent outward component and steep negative slope conductance, which was also enhanced in 10 mM [K+]o. In contrast, both Purkinje and atrial cells exhibited little outward IK1, even in the presence of 10 mM [K+]o, and both cell types showed more persistent current at positive potentials. Expression of Kir2.1 in the ventricle was 76.9-fold higher than that of atria and 5.8-fold higher than that of Purkinje, whereas the expression of Kir2.2 and Kir2.3 subunits was more evenly distributed in Purkinje and atria.

Conclusions: IK1 and Kir2 subunit expression vary dramatically in regions of the canine heart, these variations in IK1 properties could potentially explain the differences in the AP rate of repolarization between heart regions in response to [K+]o changes.

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Transient Outward K^+ Current Underlies Heterogeneity of Action Potential Duration and Early Afterdepolarization from Right Ventricle in Transgenic Rabbit Model of Long QT Type 1

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Introduction: Long QT syndrome type 1 (LQT1) is a congenital disease lacking slowly activating K^+ channel (IKs), associated with polymorphic VT (pVT) and sudden cardiac death. Tissue heterogeneity has been proposed as an important factor to trigger and maintain pVT. We investigated ionic mechanisms that underlie regional differences in the formation of early afterdepolarization (EAD) using transgenic rabbit model of LQT1.

Methods: The initiation of pVT under isoproterenol was mapped using optical mapping and myocytes isolated from RV and septum were studied using voltage clamp and confocal calcium imaging.

Results: Optical mapping of LQT1 hearts showed pVT preferentially originating from right ventricle (RV) (16 of 18 pVTs), which was changed after perfusing transient outward K channel (Ito) blocker, 0.5 mM 4-aminopyridine (only 1 of 5 pVTs from RV, n=5 hearts). Myocytes isolated from RV demonstrated higher incidence of EADs under 50 nM isoproterenol (8 of 12 cells from RV vs. 2 of 11 cells from septum). Voltage clamp study highlighted regional differences of Ito (4.7 ± 0.5 in RV vs. 2.9 ± 0.7 pA/pF in septum at 0 mV) but other currents such as ICaL, IKr and RyR-mediated Ca^{2+} leak and SERCA-mediated Ca^{2+} uptake were same between RV and septum. Computer modeling study of rabbit action potential lacking IKs exhibit frequent EADs but reduction of Ito prevented EAD formation, verifying that Ito plays a major role in EAD formation by providing repolarizing currents during the plateau phase to maintain the membrane potential lower enough to re-activate ICa window current to form EADs.

Conclusion: Regional differences of Ito in LQT1 rabbits underlie frequent pVTs originating mostly from RV myocytes with high incidence of EADs.

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Action Potential Repolarization in Equine Hearts

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The heart rate in horses can vary between 30 and 250 beats per minute. This suggests an important role for a dynamic regulation of the repolarizing potassium currents.

Methods and Results: Kv7.1 and KCNE1 that underlie the slow delayed rectifying current (IKs) as well as Kv11.1 and KCNE2 that underlie the rapid delayed rectifying current (IKr) were cloned from equine hearts. All subunits exhibit a high degree of homology with their human variants. Co-expression of equine Kv7.1 and KCNE1 in Xenopus laevis oocytes revealed a current with overall properties similar to the human Kv7.1/KCNE1 complex, however, the voltage dependence of activation was significantly right shifted (V1/2 , equine=51.7 mV and V1/2, human=26.4 mV) and the deactivation was slower (Tauequine=1288 and Tauhuman=613 ms). Equine Kv11.1 and KCNE2 current kinetics were similar to those of the human variants and the channel complex was susceptible to pharmacological block by terfenadine. To address the functional role of IKr and IKs in equine hearts, we recorded action potentials from arterially-perfused wedge preparations from the right ventricular wall at different pacing rates. In the presence of 10 μM terfenadine a marked prolongation of the action potential duration (from 420 ms to 495 ms at 90% of repolarization (APD90) at a basic cycle length of 2000 ms) was observed.

Conclusions: The expression of Kv7.1 and Kv11.1 in equine hearts suggests as in humans they are important for cardiac repolarization and we have demonstrated a functional role for IKr in equine hearts. The slower activation of equine IK7.1/KCNE1 may be an adaption to long action potential duration at rest and the slower deactivation may lead to current accumulation during fast rates and thus be important for decreasing action potential duration at faster heart rates.

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Overexpression of Adenylyl Cyclase 8 (AC8) in Mice Increases Intrinsic Heart Rate (IHR) and Reduces Heart Rate Variability (HRV), and Detaches HR and HRV from Autonomic Modulation

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While changes in HRV have been ascribed to changes in neural autonomic input to the heart, recent studies have shown that beating rate variability also exists in isolated sinoatrial (SA) node tissue and SA node cells (SANC). Adenylate cyclases are constitutively expressed in SANC, where they ensure a high basal level of phosphorylation of pacemaking proteins even in the absence of autonomic receptor stimulation. AC8 is a Ca^{+2}/calmodulin-activated AC which, when overexpressed in mice, leads to an increased rate and amount of Ca^{+2} cycling from the sarcoplasmic reticulum. We hypothesized that AC8 overexpression would affect IHR and HRV *in vivo*.

ECGs were recorded from wild type (WT) C57 and transgenic AC8 mice under light anesthesia before and after dual autonomic blockade with atropine and propranolol. Time- and frequency-domain parameters of HRV were measured. AC8 mice displayed significantly higher basal and intrinsic HRs, and significantly lower basal and intrinsic measures of HRV (total power 13% of WT basal; 21% of WT intrinsic). Dual autonomic blockade caused reductions in most HRV parameters in WT mice, but had no effect in AC8 mice. A shift in β coefficients from log-log plots of FFT-derived power spectra (basal: −1.82 in WT to −1.17 in AC8; intrinsic: −1.62 to −1.10) indicated more fractal-like behavior in the HR of AC8 mice.

In summary, genetic manipulation of a cAMP-generating mechanism intrinsic to SANC alters not only basal and intrinsic HR and HRV, but also dissociates HR and HRV from autonomic control. Thus mechanisms of intrinsic SANC automaticity, in isolation of and in concert with autonomic neural impulses, can regulate HR and HRV *in vivo*.