to anesthesia and TS mice showed increased sensitivity to anesthetic (ketamine) with much lower QT prolongation and arrhythmias such as premature beats and apparent AV block.

3437-Pos Board B484
Ranolazine Antagonizes The Effects Of Anemone Toxin-II On Intracellular Ca2+ Cycling In Whole Heart
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The late sodium current (INa,L) is pathologically enhanced in several cardiac disease states, including ischemia, causing increased intracellular Na+ and Ca2+ loading and cellular dysfunction. Ranolazine (RAN) is a blocker of INa,L and this mechanism is thought to underlie its effectiveness at reversing many of the cellular effects of ischemia. The goal of this study was to determine if RAN antagonizes the effect of anemone toxin II (ATX-II), an INa,L enhancer known to increase Na+ influx, to alter intracellular Ca2+ cycling in individuals myocytes of intact heart. Langendorff-perfused rat hearts were loaded with fluo-4AM (15µM) and placed in a chamber on the stage of a confocal microscope (contractions abolished with cytochalasin-D and blebbistatin). ATX-II (1nM) prolonged the early phase[1] of basal Ca2+ transients (CaTs) in cells of hearts paced at a rate of 2 Hz[2]. ATX-II slowed the rate of recovery of cellular CaTs (i.e., restitution) and promoted the development of CaT alternans at slower pacing rates. RAN (10µM) partially reversed the effects of ATX on restitution and alternans, shifting both to shorter interbeat intervals[3]. In addition, pre-treatment with RAN reduced the effects of subsequent exposure to ATX-II on both restitution and alternans development and blunted the ATX-induced changes in basal CaTs. These effects are consistent with an action of RAN to block INa,L, reducing Na+ influx and resulting intracellular Ca2+ accumulation, and therefore suggest RAN treatment may reverse the effects of Ca2+ accumulation that occur in response to disease states in which INa,L is enhanced (such as ischemia). Consequently, RAN may also reduce the arrhythmias that might result from repolarization gradients established by Ca2+ alternans and the resulting action potential duration alternans.

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NS5806 Activates the Transient Outward Potassium Current in the Canine Ventricle and Provides a New Model of the Brugada Syndrome
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Background: The Brugada syndrome (BrS) is characterized by elevated ST segments in the right precordial leads, ventricular tachycardia and sudden death. The syndrome has been linked to loss-of-function of sodium and calcium channels, however the transient outward potassium current (Ito) is thought to be central in the pathogenesis of BrS. We assessed the effects of Ito augmentation in a mammalian model using a novel activator of Ito, NS5806. Methods and Results: Voltage-clamp experiments were performed on midmyocardial cells isolated from the canine left ventricular wall. At 40mV NS5806 (10 µM) increased peak Ito by 79 ± 4 % and the time-course of inactivation was slowed (from Tau=12.6 ± 3.2 ms to 20.3 ± 2.9 ms). We next assessed the effect of increased Ito in the development of BrS phenotype using canine ventricular wedge preparations. NS5806 increased the epicardial action potential (AP) phase 1 magnitude, whereas the APs of endocardial cells were largely unaffected. The accentuated epicardial notch was associated with an accentuated J-wave on the ECG. RAN reduced the effects of subsequent exposure to ATX-II on both restitution and alternans development and blunted the ATX-induced changes in basal CaTs. These effects are consistent with an action of RAN to block INa,L, reducing Na+ influx and resulting intracellular Ca2+ accumulation, and therefore suggest RAN treatment may reverse the effects of Ca2+ accumulation that occur in response to disease states in which INa,L is enhanced (such as ischemia). Consequently, RAN may also reduce the arrhythmias that might result from repolarization gradients established by Ca2+ alternans and the resulting action potential duration alternans.

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Assembling And Imaging Long Cables Of Live Cardiomyocytes For Validation Of Cable Theory Relationships
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Theoretical work on excitable tissue (heart, brain, muscle) often employs concepts from cable theory and resorts to one-dimensional models of wave propagation to capture the essential functional properties. We offer an experimental technique to spatially pack, image and computationally unpack quasi-one dimensional long cables (>10cm) of live excitable cells within the imaging field of view. This is achieved by micropatterning neonatal rat cardiomyocytes into Archimedean spiral topologies and imaging the whole cable at ultra-high resolution. We validate the method’s applicability to studies of wave propagation assessing distortions due to curvature effects. Some preliminary demonstrations of the utility of the proposed method include experimental verification of the eikonal relationship linking the velocity of a wave in a homogenous cardiac tissue and the radius of curvature seen by the wavefront. This is achieved by patterning thin cables with well defined linearly varying curvature. Furthermore, the technique is applied to validation of theoretical predictions regarding spatially discordant alternans based on spatially varying activation patterns during H2O2-induced EADs and PVT showing a mixture of focal activity and reentry, consistent with this chaos synchronization mechanism. Chaos synchronization is a novel mechanism for cardiac arrhythmogenesis which may account for lethal arrhythmias appearing suddenly during bradycardia.