Conclusions: Both alterations in ion channels and FRP shortening are necessary to explain APDR slopes > 1 in the left atria of persistent AF patients. Future studies should determine the mechanisms by which FRP is altered in AF patients and whether strategies for lengthening FRP would be effective for managing AF during increased Beta-adrenergic stimulation.

2352-Pos Board B338

Spatiotemporal Poincare Plotting for Torsades De Pointes Prediction *In Vitro* Drug-Screening System Exploiting Human iPS Cells and Other Pluripotent Stem Cells

Fumimasa Nomura, Tomoyuki Kaneko, Kenji Yasuda.

QT prolongation is still a major safety concern for selecting and developing candidate compounds. The current integrated assay systems using hERG-transfected HEK-293/CHO-cells (hERG assay), isolated animal tissues (APD or MAP assay) and conscious and/or anesthetized whole animals (QT or Map assay) may identify QT prolongation, but cannot fully predict the potential lethal arrhythmias such as Torsades de Pointes (TdP) or ventricular fibrillation (VF) by drug candidates.

Understanding the importance of spatial and temporal regulation of cellular orientation, community size and shape, variety and interactions are keys to resolving mechanisms of epigenetic processes in highly complex cellular systems like tissues and organs. To investigate the meaning of the spatial distribution of cells, an on-chip cell network cultivation system has been developed, and extra-cellular signals (field potentials: FP) of human embryonic cardiomyocytes in geometrically patterning chambers have been recorded with an on-chip multi-electrode array (MEA) system.

A proposed strategy for an on-chip assay for providing further insight into the extrapolation of preclinical data to human clinical settings or for expanding or replacing existing in vitro and in vivo cardio- toxicity models includes the following: 1) abnormal triggering (temporal dispersion) causing lethal arrhythmias is estimated by analyzing the time course field potential dispersion of single cells in loop network using Poincaré plotting; 2) spatial dispersion of cells causing spiral re-entry is modeled by using a wider width of cell network loop which can choose different propagation pathways of cells among neighboring circulations; and 3) human ES/iPS cell-based cardiomyocytes are used for cell network formation. In this presentation, we present the system set-up and possible application of this system for drug discovery and toxicology using spatiotemporal Poincaré plotting measurement.

2353-Pos Board B339

Supernormal Excitability Causes Alternans, Block, Wavebreak and Reentry in Cardiac Tissue

Enno de Lange, Jan P. Kucera, Zhilin Qu.

It is well known that alternans can lead to cardiac arrhythmias. Alternans typically occurs in single cells due to voltage or calcium cycling instabilities. We showed in a previous study that alternans can also result from an instability caused by supernormal excitability (negative slope of the conduction velocity (CV) restitution curve), in the absence of voltage or calcium cycling instabilities. In this study, we used computer simulations of cables and two-dimensional domains of Luo-Rudy phase 1 model cells in which supernormal conduction was induced by decreasing the extracellular potassium concentration ($[K^+]_o$, 2.0 mmol/L) to explore arrhythmogenesis in the presence of supernormal excitability.

Conduction was stable in a homogeneous cable (10 cm long) paced at one end at a basic cycle length (BCL) of 290 ms. However, when a slightly premature stimulus was applied and pacing at BCL was resumed, alternans developed gradually towards the end of the cable. This alternans was caused by supernormal CV restitution. The amplitude of alternans progressively increased until conduction block occurred at approximately 2/3 of the length of the cable.

Conduction was also stable in a homogeneous two-dimensional domain (10x10 cm) paced on the left border at BCL=280 ms. However, when a premature pulse was applied at the lower half of the left border and pacing at BCL was resumed, alternans developed in the lower half of the domain via the same mechanism as in the 1D cable, while conduction in the upper half remained stable. This eventually led to conduction block and wavebreak formation in the lower half of the domain, which initiated spiral wave reentry.

In conclusion, supernormal excitability represents a novel mechanism of alternans, which can lead to conduction block, wavebreak formation and reentry in cardiac tissue.

2354-Pos Board B340

Panoramic Imaging Reveals Mechanisms of Resistance to Ventricular Arrhythmias Under Blebbistatin as Compared to 2,3-Butanedione Monoxime (BDM)

Qing Lou, Wenwen Li, Vadim V. Fedorov, Igor R. Efimov.

Unlike other excitation-contraction uncouplers (such as BDM), blebbistatin does not have apparent side effects, and is increasingly used in cardiac electrophysiology studies using optical mapping. However, the effects of blebbistatin on restitution and ventricular arrhythmia remain unknown. Determining these effects is important for the use of blebbistatin and a better understanding of the mechanisms of arrhythmia.

Monophasic action potentials at various cycle lengths were measured before and after the application of blebbistatin in Langendorff-perfused rabbit hearts (n=5). Optical mapping experiments were conducted in rabbit hearts (n=7) which were sequentially perfused with BDM and blebbistatin. Action potential duration (APD) restitution, conduction velocity (CV) restitution, and vulnerability to shock-induced arrhythmia were measured. Panoramic imaging system was used to optically record the action potentials and the reentry circuits from the entire ventricular epicardium.

Application of blebbistatin did not change the APD restitution. In contrast, BDM significantly decreased the APD and flattened the APD restitution. BDM also significantly decreased the CV at both longitudinal and transverse directions, and thus decreased the wavelength (APD × CV). Vulnerability to shock-induced arrhythmia was much higher under BDM compared with that under blebbistatin (inducibility of sustained arrhythmia: 23/99 vs. 2/123). Stable reentry was responsible for the sustained arrhythmia under BDM, while wave breaks and wave extinctions were frequent and facilitated the self-termination of shock-induced arrhythmia under blebbistatin.

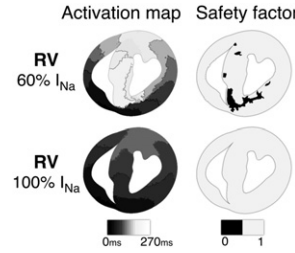
In conclusion, blebbistatin has no significant effect on the APD restitution in the normal rabbit heart, and is associated with low sustainability of shock-induced arrhythmias. Low dynamic instability under BDM facilitates the maintenance of stable reentrant arrhythmia, while the combination of relatively high dynamic instability and long wave length under blebbistatin facilitates the self-termination of reentrant arrhythmia and thus explains the resistance to arrhythmia.

2355-Pos Board B341

Arrhythmogenesis in Brugada Syndrome: Role of Ventricular Structure

Carolyn J. Park, Hermenegild J. Arevalo, Natalia A. Trayanova.

Brugada syndrome is a genetic disorder that results in decreased expression of cardiac Na^+ channels, leading to abnormal electrical activity with onset in the right ventricle (RV). Given that I_{Na} is reduced globally, it remains unclear why the RV is more susceptible to arrhythmogenesis. This study tests the hypothesis that differences in geometry between left ventricle (LV) and RV promote altered conduction patterns under reduced I_{Na}. Using a 3D rabbit ventricular model that incorporates realistic geometry, simulations were performed where I_{Na} maximal conductance was varied from 60 to 100% of the normal level. Reentry was induced via diastolic stimulation of the LV or RV epicardium. Sustained reentry developed only at the 60% I_{Na} level for RV stimulation, while no reentry was induced for the LV regardless of I_{Na} levels. Activation map (figure) for the 60% I_{Na} model shows conduction block at the RV insertion region, where the safety factor (the ratio of total intracellular current vs. current needed to excite the cell) was zero. Propagation from the thin RV has insufficient current to excite tissue in the septum/LV, resulting in source-sink mismatch and block, thus predisposing the RV to arrhythmogenesis under reduced I_{Na}.



2356-Pos Board B342

Regional Mitochondrial Depolarization Causes Spontaneous Ventricular Arrhythmia in Cardiac Tissue

Lufang Zhou, Soroosh Solhjoo, Gernot Plank, Roselle Abraham, Sonia Cortassa, Natalia Trayanova, Brian O'Rourke.

Sudden cardiac death (SCD) resulting from ventricular arrhythmia remains a leading cause of death in the USA. The underlying molecular and structural mechanisms of arrhythmic SCD, however, are still unclear. We have recently reported that oxidative stress can trigger the abrupt collapse of mitochondrial inner membrane potential ($\Delta\Psi m$), reverse of ATP synthase and decrease of ATP concentration. This could activate the sarcolemmal ATP sensitive potassium channel (KATP), affecting cellular electrical excitability and electrical wave propagation in the cardiac tissue. To test this hypothesis, we investigated the effect of regional mitochondrial depolarization on electrical wave propagation using combined optical mapping and computer simulations. The regional mitochondrial depolarization was induced in the center of cardiac cell monolayer by oxidative stress or mitochondrial uncoupler. The results show a coupling between $\Delta\Psi m$ depolarization, activation of KATP current and shortening of action potentials. When this effect is amplified, regional mitochondrial depolarization could form a metabolic current sink, preventing