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 hEKG-transfected HEK-293/CHO-cells (hEKG 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 pattern 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 Poincare’ plotting; 2) spatial dispersion of cells causing spatial 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 setup and possible application of this system for drug discovery and toxicology using spatiotemporal Poincare’ plotting measurement.

2353-Pos Board B339 
Supernormal Excitability Causes Alternans, Block, Wavebreak and Reentry in Cardiac Tissue

**Enno de Lange, Jan P. Kucera, Zhihui 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 by 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 the 1D cable, while conduction in the upper half remained stable. This even-tually 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 Monox-ime (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 electro-physiology 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 $\times$ 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 rabbit heart, and is associated with a 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.