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and reduces If currents, which increases the application of hiPSC-CMs in disease modeling.

1607-Pos

Investigational Treatments for COVID-19 May Increase Ventricular Arrhythmia Risk through Drug Interactions

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Several drugs proposed for the treatment of COVID-19 have reported cases of cardiac adverse events such as ventricular arrhythmias. To properly weigh risks against potential benefits in a timely manner, mathematical modeling of drug disposition and drug action can be useful for predicting patient response. Here we explored the potential effects on cardiac electrophysiology of 4 COVID-19 proposed treatments: lopinavir, ritonavir, chloroquine, and azithromycin, including combination therapy involving these drugs. To address this, we combined simulations of pharmacokinetics (PK) with mechanistic mathematical modeling of human ventricular myocytes to predict adverse events caused by these treatments. We utilized a mechanistic model to construct heterogenous populations of 4 patient groups (healthy male, healthy female, diseased male, and diseased female) each with 1000 members, and studied the varied responses of drugs and combinations on each population. To determine appropriate drug concentrations for recommended COVID-19 regimen, we implemented PK models for each drug and incorporated these values into the mechanistic model. We found that: (1) drug combinations can lead to greater cellular action potential (AP) prolongation, analogous to QT prolongation, compared with drugs given in isolation; (2) simulations of chloroquine with azithromycin caused a significantly greater increase in AP duration ($\Delta APD \approx 190$ ms) compared to lopinavir with ritonavir ($\Delta APD \approx 6$ ms); (3) drug effects on different patient populations revealed that females with pre-existing heart disease are more susceptible to drug-induced arrhythmias as 85 members formed arrhythmias, and less than 20 in each of the other three; and (4) logistic regression analysis performed on the population showed that higher levels of the sodium-calcium exchanger may predispose certain females with heart failure to drug-induced arrhythmias. Overall, these results illustrate how PK and mechanistic modeling can be combined to precisely predict cardiac arrhythmia susceptibility of COVID-19 therapies.

1608-Pos

Effects of Mechanical Stimulus on Beat Sequence of Cardiomyocytes with Feedback Control

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Not only electrical stimulus but also direct mechanical stimulus induces beating of cardiac cells, particularly where the deformation by the stimulus is resemble to that created by beating neighboring cardiac cells. As primary cardiac cells forming aggregation become synchronized their beating while incubated more than 24 h, periodic stimulus artificially deforming cell aggregation like beat contraction by a probe may induce beating as pacemaker cell does. We fabricated an instrumentation to apply such periodic stimulus by a tungsten probe to a cardiac cell aggregate on a plastic Petri dish or on a PDMS substrate. We continuously observed the beat sequence of a cell aggregation under such a periodic stimulus longer than 24 h inside an incubator. Typically, cardiac cell aggregates beat spontaneously under culture conditions before applying an external stimulus. After the stimulus, the beat variability increased significantly, and then mostly stopped beating. Evidently, the beat by cell aggregates were sensitive to the phase difference between their intrinsic beat and the periodic mechanical stimulus. To control such phase difference, we also added a function to apply mechanical stimulus with a real-time feedback using fast image processing using LabVIEW. This real-time feedback system allows us to apply a probe stimulus synchronized with the intrinsic beat of a cardiac cell aggregate with variable phase differences. In this presentation, we will discuss the beat rate and variability of a cardiac cell aggregate under phase controlled mechanical stimulus.

1609-Pos

Effects of Estrogens on the Actions of hERG

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Regulation of cardiac ion channels by sex hormones accounts for gender-differences in susceptibility of Torsades de Pointes (TdP) arrhythmias associated with QT prolongation, that is: women are more prone to develop drug-induced arrhythmias which can lead cardiac sudden death. We previously found that β-estradiol (E2) directly interacts with a drug-binding site, F656 of the hERG channel, and alters the effect of a selective hERG blocker. Although these actions were observed for other estrogens, the effect of estrogen on other drugs has been unknown. In this study, to reveal impacts of the actions of estrogens on hERG currents, we compared the hERG screen data in the absence and the presence of estrogens using manual and automated patch-clamp experiments. HEK293 cells stably-expressing the hERG channels were seeded into 384-well plates, and were cultured in a steroid-free condition. Whole-cell hERG currents were recorded by the patch-clamp technique with SyncroPatch 384i (Nanion). Effects of 22 compounds were assessed by percentage changes of hERG peak tail currents with or without estrogens (E2, estrone sulfate; E1S, and ethynylestradiol; EE2) and by molecular docking simulations. Our hERG screening depicted that some estrogens showed distinct effects on respective blockers. Estrogens did not change the degree of hERG block by most of compounds. However, we have newly found that inhibitory action of one drug was increased by E2, and that of another drug was decreased by EE2. This means that specific combinations of an estrogen and a hERG blocker can alter the hERG blockade significantly. Indeed, some combinations resulted in larger hERG currents. This study suggests potential risks using estrogen therapy/medication and the necessity of taking sex hormonal differences into consideration for more accurate prediction of QT prolongation proclivity of drug candidates.

1610-Pos

Cardiac L-Type Channel Modulation by LRRC10 Proteins

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L-type calcium channels (LTCC) play a central role in cardiac physiology by conveying Ca^{2+} influx that initiates cardiac muscle contraction following membrane depolarization. LTCC activity is fine-tuned by diverse regulatory subunits, and alterations in channel regulation cause debilitating cardiac diseases. Importantly, leucine-rich repeat containing protein 10 (LRRC10) was recently identified as a novel regulatory subunit of cardiac LTCC (Woon et al (2018) JAHA 7:e006528). Mutations in LRRC10 have been identified in patients with dilated cardiomyopathy (DCM) and sudden unexplained nocturnal death syndrome (SUNDS). Here, using single-channel and whole-cell electrophysiology, we show that LRRC10 markedly upregulates LTCC activity, diminishes the voltage-threshold for channel activation, and enhances Ca^{2+}-dependent inactivation. Using flow-cytometry based FRET 2-hybrid assay we show that these effects stem from LRRC10 interaction with binding sites within the channel amino- and carboxy-termini. Further, analysis of SUNDS versus DCM linked LRRC10 variants show differential effect on channel inactivation and variable reduction in peak channel activity. These results highlight the rich and sophisticated mechanisms of Ca^{2+} channel regulation by modulatory subunits in the heart, as well as reveal new insights into the pathophysiological mechanisms underlying SUNDS and DCM.

1611-Pos

Post-Translational Modifications in Human Beta Myosin Heavy Chain

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Post translational modifications (PTM) modulate cell signaling and protein function and have been shown to fine-tune myocardial contractility. Acetylation plays a vital role in histone protein regulation in many cell types, including cardiomyocytes, but was subsequently found as a protein modification outside of the nucleus. Our interest is to further characterize the K-acetylation and S-, T-, and Y-phosphorylation found on the beta-myosin heavy chain (beta-MHC) protein in donor, ischemic, and non-ischemic human heart samples with the long-term goal of understanding the potential role of PTMs on cardiac function. Using bottom-up proteomics and label-free quantification, we identified seven