**1375-Pos Board B326**

**A Guinea Pig Model for Heart Failure-Associated Sudden Cardiac Death**

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Sudden cardiac death (SCD) is the leading cause of mortality in patients with heart failure (HF). However, the mechanisms underlying SCD are incompletely understood. In the present study, we developed a guinea pig model for HF-associated SCD. Male adult guinea pigs underwent ascending aortic constriction (AC) in addition to isoproterenol (iso) challenge by daily i.p. injection of iso at 1 mg/kg in week 1 and 2 mg/kg after week 1. Isoproterenol was given in excess of doses for 3 weeks had no significant effects on cardiac function and geometry in sham control, however, iso treatment worsened cardiac function in AC hearts. Animal with AC and iso challenge (ACi) displayed earlier depolarization term and higher incidence of SCD (100%) compared to 60% of ACi animals died without overt symptom of HF within 4 weeks. Electrocardiography (ECG) indicated QT prolongation and high incidence of premature ventricular beat (PVB) and ventricular fibrillation (VF) in ACi animals. Electrophysiological study, performed in isolated ventricular myocytes from ACi and sham hearts in week 4, revealed prolonged action potential (AP) (APD90: 279±19 ms vs 203±17 ms in sham) and reduced potassium currents (IK1 at −150 mV was −28±4 pA/pF vs 0.8 in ACi vs −47±6 pA/pF ≥2.3 in sham; Tail current of IK1 and IKs at +50 mV were 0.28±0.03 pA/pF in ACi and 0.30±0.03 in ACi vs 0.55±0.02 and 0.54±0.02 in sham, respectively) in ACi animals. Our results demonstrated that the combination of AC and iso challenge produces high incidence of arrhythmia and SCD in guinea pig with features of prolonged QT and reduced repolarization reserve, thus providing a novel model for HF-associated arrhythmia and SCD.

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**Iron Overload Promotes Arrhythmias via ROS Production and Mitochondrial Membrane Potential Depolarization**

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Genetic disorders or frequent blood transfusions often cause iron overload which can lead to arrhythmias. However, the underlying mechanism is not well known. In the present study, we assess the hypothesis that iron overload promotes arrhythmias via reactive oxygen species (ROS) production and mitochondrial membrane potential (ΔΨm) depolarization, opening the mitochondrial permeability transition pore (mPTP) and promoting Ca waves. ROS levels were measured by DCF fluorescence. Perfusion with FeCl3 (1–10 mM) significantly increased relative ROS levels. For example, 1 mM FeCl3 raised ROS levels 465 ± 14% compared to the control (p < 0.01). TMRRM fluorescence decrease was used as an index of ΔΨm depolarization. FeCl3 significantly decreased TMRRM fluorescence (1 mM: 81.2 ± 2.3%, 10 mM: 94.8 ± 2.9%), compared to the baseline in myocytes, indicating ΔΨm depolarization by FeCl3. Intracellular Ca2+ was imaged with Fluo-4 AM. Spontaneous Ca waves were induced in high external Ca2+ (4 mM). Furthermore, FeCl3 significantly increased the rate of Ca waves: 1 mM FeCl3 significantly increased the rate from 23.9 ± 5.2 Hz in sham to 72.3 ± 7.6 Hz (p < 0.05). FeCl3-promoted Ca waves were significantly reduced by the mPTP inhibitor cyclosporine A (CSA; 1 μM). ECGs were recorded from Langedorff-perfused hearts. Arrhythmia induction testing was conducted through programmed S1–S3 stimulation. Hearts treated with Fe3+ (1 mM) alone significantly increased arrhythmia scores compared to hearts pretreated with CSA prior to Fe3+ (p < 0.05), indicating mPTP inhibition can ameliorate the proarrhythmic effects of iron-overload. These observation were confirmed in the cyclophosphamide mouse (Crp), a model of chronic iron-overload induced by using transgenic rabbit model of Long QT Type 1 (LQT1) lacking ICaL. LQT1 and littersmate control (LMC) rabbits underwent MI procedures and optical mapping was performed to record Vm and Ca2+ simultaneously from the 3 week post-MI hearts (n=9 LQT1-MI, 4 LQT-MI Sham, 10 LMC-MI, 9 LMC-Sham hearts).

Results: The dispersion of APD was enhanced in LQT1-MI compared to LQT1-Sham and LMC-MI (APDmax-min = 28 ± 4 ms vs 20 ± 3 ms and 27 ± 6 ms). APD alternans was more pronounced in LQT1-MI, accompanied with large amplitude Ca2+ alternans, and often spatially discordant (see traces and restitution curves in panel A&B). Spatially discordant alternans in LQT1-MI was highly dynamic, preceded by sudden appearance of Ca2+ nodal lines near the MI border zone (panel C; dark lines), associated with high VF induction (n=9 LQT1-MI vs. 1/4 LQT1-sham and 7/10 LMC-MI).

Conclusion: Our results demonstrate the importance of ICaL as a repolarization reserve in MI and that significant downregulation of ICaL may promote spatially discordant Ca2+ and APD alternans and VF induction.

**1374-Pos Board B325**

**Modulation of Action Potential Alternans by IKs in Myocardial Infarction**

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Background: Patients with post myocardial infarction (MI) have increased incidence of ventricular arrhythmias. The slowly activating K channels (IKs) has been reported to be downregulated consistently but in different degrees in the post-MI hearts. The role of downregulation of IKs in arrhythmogenesis in post MI remains to be defined.

Hypothesis: We hypothesize that significant suppression of IKs in post MI impairs the rate-dependent and Ca2+-dependent augmentation of repolarization reserve resulting in increased alternans and thereby arrhythmias. Methods: The effect of downregulation of IKs by using transgenic rabbit model of Long QT Type 1 (LQT1) lacking ICaL and littersmate control (LMC) rabbits underwent MI procedures and optical mapping was performed to record Vm and Ca2+ simultaneously from the 3 week post-MI hearts (n=9 LQT1-MI, 4 LQT-MI Sham, 10 LMC-MI, 9 LMC-Sham hearts).

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Conclusion: Our results demonstrate the importance of IKs as a repolarization reserve in MI and that significant downregulation of IKs may promote spatially discordant Ca2+ and APD alternans and VF induction.

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