endocardium covered by APA alternans increased significantly from $14.15\pm6.5\%$ at 1Hz to $32.97\pm7.3\%$ at 5Hz (Fig.1E).

**Conclusion:** TWA can serve as a biomarker of dynamic changes in ischemic substrates and localized APA and APD alternans underlie arrhythmogenesis in chronic MI ovine hearts.

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**PO-645-06**

**EPICARDIAL ELECTRICAL HETEROGENEITY AFTER AMIODARONE TREATMENT INCREASES VULNERABILITY TO VENTRICULAR ARRHYTHMIAS IN A SWINE MODEL UNDER THERAPEUTIC HYPOTHERMIA**

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**Background:** Amiodarone is commonly used during therapeutic hypothermia (TH) following cardiac arrest due to ventricular arrhythmias.

**Objective:** Electrophysiological changes and proarrhythmic risk after amiodarone treatment have not yet been explored in TH.

**Methods:** Epicardial high-density bi-ventricular mapping was performed in pigs under baseline temperature (BT), TH (32-34°C), and amiodarone treatment during TH. The total activation time (TAT), conduction velocity (CV), local electrogram (LE) duration, and wavefront propagation from pre-specified segments were analyzed during sinus rhythm (SR) or right ventricular (RV) pacing (RVP), along with tissue expression of connexin 43. The vulnerability to ventricular arrhythmias was assessed.

**Results:** Compared to BT, TH increased the global TAT, decreased the CV, and generated heterogeneous electrical substrate during SR and RVP. During TH, the CV reduction and LE duration prolongation were greater in the anterior mid RV than in the other areas, which changed the wavefront propagation in all animals. Compared to TH alone, amiodarone treatment during TH further increased the QTc/ Tpeak-Tend, TAT and LE duration and decreased the CV in both the global heart and regional areas during SR and RVP. Heterogeneous conduction was partially attenuated after amiodarone treatment. After TH and amiodarone treatment, the connexin 43 expression in the anterior mid RV was lower than that in the other areas, compatible with the heterogeneous CV reduction. The animals under TH and amiodarone treatment had a higher incidence of inducible ventricular arrhythmias than those under BT or TH.

**Conclusion:** Electrical heterogeneity during amiodarone treatment and TH was associated with vulnerability to ventricular arrhythmias.

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**PO-645-07**

**SLEEP-RELATED CHANGES IN CARDIOVASCULAR AUTONOMIC REGULATION IN APOE KNOCKOUT RATS: NEURAL MECHANISM FACILITATING ARRHYTHMIA IN HYPERCHOLESTEREMIA**

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**Background:** The plasma levels of total cholesterol and low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease. Several reports suggest that elevated plasma cholesterol also leads to fetal arrhythmias.

**Objective:** We aimed to evaluate the LDL cholesterol and its relationship to cardiac autonomic activity, especially its relationship to sleep cycle.

**Methods:** Wireless transmission of polysomnographic recording was performed in wild type (n=5) and ApoE knockout (hypercholesteremia with elevated LDL-C, n=4) rats during 24 hours. Spectral analyses of the electroencephalogram (EEG) and electromyogram (EMG) were evaluated to define active waking (AW), quiet and paradoxical sleeps (QS, PS). Cardiac autonomic activities were measured by analyzing the power spectrum of heart rate variability (HRV).

**Results:** In the HRV analysis, we found that the LF/HF ratio and LF significantly increased in ApoE knockout rats during QS stage compared to that in normal rats (Fig A and C). The decreased QS times were noted in ApoE knockout rats compared to the normal rats (Fig E). Cardiac autonomic activities were measured by analyzing the power spectrum of heart rate variability (HRV).

**Conclusion:** We found that sympathetic hyperactivity developed in ApoE knockout rats, especially at QS stages. Those findings suggest that autonomic dysfunction is a possible mechanism for impairment of sleep quality and increased sudden cardiac death risk during QS stage in hypercholesteremia.
The goal of this study is to develop a model to understand fibrosis development in the context of persistent atrial fibrillation (AF). The combination of dilated atria, thinner walls and fibrosis contributes to structural remodelling resembling changes seen in mechanical overload on atrial slices derived from tissue biopsies to tissue mechanical overload. We hypothesize that application of combined IN VITRO STIMULATION will help to better understand fibrosis development and to find potential targets to control progressive remodelling.

Methods: Atrial slices, 400 μm thick and 3-5 mm long and wide, were kept in biomimetic chambers for up to 5 days. Optimal pacing frequency was investigated and chronic preload was applied throughout the culture period. Tissue quality was assessed via monitoring of (i) systolic and diastolic forces; (ii) responses to mechanical stimuli (Frank-Starling mechanism, slow force response); (iii) responses to changes in stimulation (force-frequency relationship, post-rest potentiation). Collagen and cell membranes were stained to analyse tissue remodelling.

Results: Our results show that slice contractility was well maintained over the observation period, as were key mechanosensitive responses. Expected effects to well-known modulators of cardiomyocyte contractility such as isoproterenol were also observed. In the intervention group, tissue was mechanically challenged by the application of a constant preload of 2 mN over 3 days, to mimic the overload in patients. This mechanical stimulation resulted in collagen remodelling, which was analysed in comparison to control tissue data, using a tailor-made automated image analysis method.

Conclusion: Atrial tissue can be maintained in culture for up to 5 days with preserved functionality, making this model suitable for medium-term investigations of mechanical load effects on atrial functional and structural remodelling. Application of mechanical load over 3 days leads to fibrosis induction. It will be interesting to explore to what extent stretch-induced collagen production contributes to protecting cardiomyocytes (and nonmyocytes) from excess diastolic strain. We envision that the biomimetic system will facilitate target identification and drug testing to reduce, slow, or reverse fibrosis.

POSTER PO-646:
Posters: Basic Science at Pod 3
Saturday, April 30, 2022
10:00 AM - 12:00 PM

PO-646-01
HIGHLY REACTIVE ISOLEVUGLANDINS MEDIATE CYTOKINE-INDUCED ELECTRICAL REMODELING TO PROMOTE ATRIAL FIBRILLATION
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Background: Proinflammatory cytokines have been shown to induce oxidative stress and electrical remodeling. Mice lacking the lymphocyte adaptor protein (Lnk−/−), a negative regulator of cytokine signaling, display systemic and atrial inflammation, oxidative stress, and atrial fibration (AF) susceptibility in the absence of structural abnormalities. Previously, we found highly reactive products of lipid peroxidation, isolevuglandins (IsoLGs), to be key mediators of AF susceptibility in Lnk−/− mice. Objective: To test the hypothesis that IsoLGs mediate cytokine-induced atrial electrical remodeling to promote the AF substrate.

Methods: At weaning, Lnk−/− or wild-type littermate (WT) mice received either vehicle or an IsoLG scavenger (2-hydroxybenzylamine; 2-HOBA). At 14 wks, ECG was obtained, and atria processed for electrophysiologic/cytokine studies. The effect of cytokines on IsoLG-modified proteins and electrical remodeling was studied in mouse atrial (HL-1) cells.

Results: Lnk−/− mice demonstrated significant increases in P wave (+22%), QRS (+17%), and QT (+9%) duration compared to WT controls, and 2-HOBA prevented P wave prolongation compared to WT (+7%). Action potential duration (at 90% repolarization; APD90) was prolonged in Lnk−/− atrial myocytes (90.2±3.8 vs 63.1±2.4ms in WT, [mean±SEM; n=36, 24; P<0.01]), an effect prevented by 2-HOBA (62.1±3.6ms; n=18; P<0.01). Lnk−/− atrial myocytes also displayed reduced maximum phase 0 upstroke velocity compared to WT (26.1±0.6 vs 32.5±0.6mVs/nm; n=36, 24; P<0.01) that was partially restored by 2-HOBA (29.3±0.3mVs/nm; n=18; P<0.01 vs Lnk−/−). Lnk−/− atrial myocytes displayed increased late INa (61%) and ICa,L (+51%) and a reduction in TCa (−20%), as well as reduced peak INa (−26%), to account for AP changes, and 2-HOBA prevented this electrical remodeling. Lnk−/− mice displayed significant increases in plasma TNFα and IL-1β in atrial tissue. In HL-1 cells, 24h incubation with TNFα or IL-1β increased IsoLG-adducted proteins by immunofluorescence and both cytokines prolonged APD90 with acute and 24h exposure.

Conclusion: These data indicate that TNFα and IL-1β promote IsoLG formation and atrial myocyte electrical remodeling to promote an AF-prone substrate.