**POSTER PO-614: FACTORS IMPACTING FOLLOW-UP VENTRICULAR PACING PERCENTAGE (VP%) BURDEN AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) FOR PATIENTS RECEIVING PROPHYLACTIC PERMANENT PACEMAKER (PPM) IMPLANT**

**Background:** Heart block is a known complication of transcatheter aortic valve implantation (TAVI) due to implant proximity to conduction system (panel A), and high risk patients may receive prophylactic implant of a permanent pacemaker (PPM) prior to TAVI. The long term ventricular pacing percentage (VP%) burden for these prophylactic PPM patients is not well characterized.

**Objective:** To assess factors associated with VP% burden after TAVI for patients receiving prophylactic PPM.

**Methods:** We assessed our institution’s TAVI database to identify and obtain data for all TAVI patients who received prophylactic PPM implanted up to 100 days prior to TAVI. Additionally, we sought pacing follow up data for each patient through until Dec 31st 2021.

**Results:** 47 patients (37 male, 83±6 years at TAVI) were identified who had prophylactic PPM implanted 31 days (IQR 15 - 67) pre TAVI. We attained VP% data for 44 (94%) patients. Prior to TAVI, 55% of patients (n = 24) did not use pacing (VP < 1%) at baseline pre TAVI check. Pacing data was available both pre & post TAVI for 35 patients, with the first follow up check at 48 days (IQR 19 - 378) post TAVI, and for n = 26 with further follow up checks the final follow up was 759 days (IQR 411 - 1038) post TAVI. As shown in figure; 13 patients remained VP < 1% pre & post TAVI (nil-group), 10 had high VP% throughout (high-group), but the remaining 12 patients had a marked increase of VP% post TAVI (change-group). 83% (10/12) of change-group had right bundle branch block (RBBB) as PPM indication compared to only 31% (4/13; p = 0.03) of nil-group.

**Conclusion:** RBBB and negative delta MS-ID are associated with greater VP% need after TAVI for patients receiving prophylactic PPM.

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**POSTER PO-614-02: MICROTUBULE DETYROSINATION AND TRP1 DRIVE STRETCH-INDUCED ARRHYTHMIAS IN THE ISOLATED RABBIT HEART**

**Background:** In hypertension, acute fluctuations in ventricular load can trigger arrhythmias due to myocardial stretch. In single rabbit ventricular myocytes, the incidence of stretch-induced arrhythmias (SIA) is increased by microtubule (MT) densification or detyrosination and transient receptor potential ankyrin 1 channel (TRPA1) activation, as occurs in hypertension.

**Objective:** To determine the dependence of SIA on MT densification or detyrosination and TRPA1 in the whole rabbit heart.

**Methods:** Isolated rabbit hearts were instrumented with surface electrodes to monitor electrical activity and an intraventricular balloon to alter left ventricular (LV) load. Transient changes in LV volume were applied (50-500 μL; 10 mL/s, 20 repetitions of each volume separated by 30 s) and the volume that resulted in a 50% SIA incidence (V50) was determined (Fig. 1A). Paclitaxel (5 μM) was applied alone to increase MT density and detyrosination, with colchicine (10 μM) to prevent the increase in detyrosination, or with TRPA1 (10 μM) to prevent the increase in density, or with HC-030031 (10 μM) to block TRPA1. Immunofluorescence was used to determine MT density (Fig. 2A) and the nature of SIA was assessed by voltage optical mapping.

**Results:** Paclitaxel reduced the threshold for SIA (decreased $V_{50}$: 133±16 μL vs 173±11 μL in control; n = 8, p = 0.02 by paired t-test; Fig. 1A/B), which was associated with an increase in MT density (67±1% vs 56±2% in control; n = 17, p = 0.02 by one-way ANOVA Sidák post hoc test; Fig. 2A/B) and resulted in conversion of stretch-induced excitation to sustained activity. Parthenolide prevented the decrease in $V_{50}$ (256±27 μL vs 256±26 μL; n = 8, p = 0.73; Fig. 1B) but not the increase in MT density (58±3%; n = 17, p = 0.12; Fig. 2B). In contrast, colchicine prevented the increase in MT density (49±3%; n = 17, p < 0.01; Fig. 2B) but not the decrease in $V_{50}$ (190±36 μL vs 249±33 μL; n = 8, p = 0.04; Fig. 1B). The decrease in $V_{50}$ with paclitaxel was also prevented by HC-030031 (249±26 μL vs 237±27 μL; n = 8, p = 0.60; Fig. 1B). Optical mapping showed stretch-induced focal excitation originating from the LV free wall, which after paclitaxel lead to re-entrant activity in some cases.

**Conclusion:** MT detyrosination, not densification, leads to a reduced threshold for TRPA1-dependent SIA in the rabbit isolated heart.
ALTERED SUBCELLULAR CALCIUM RELEASE IN THE HEART FAILURE ATRIA

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Background: Transverse (t)-tubules enable close coupling between L-type calcium (Ca\(^{2+}\)) channels and ryanodine receptors (RyR) to facilitate triggered Ca\(^{2+}\) release throughout the cell. In heart failure (HF) there is disruption of the t-tubule network that contributes to dyssynchronous Ca\(^{2+}\) release. Despite the importance of t-tubules in triggering Ca\(^{2+}\) release in the atria of large mammals, little is known about Ca\(^{2+}\) release sites and how they are altered in HF.

Objective: To investigate Ca\(^{2+}\) release in the healthy and failing sheep atria and examine how this may be contributed to by t-tubule and RyR remodelling.

Methods: HF was induced in sheep by right ventricular tachypacing and left atrial myocytes isolated from control and HF animals. Cells were loaded with fluo-3 and stimulated under current clamp control. RyR structure was assessed using stochastic optical reconstruction microscopy (STORM).

Results: In control atrial myocytes, triggered Ca\(^{2+}\) release occurred at discrete sites on the surface and in the centre of the cell associated with t-tubules. In HF, t-tubule loss was accompanied by a reduction in central Ca\(^{2+}\) release sites. As such, triggered Ca\(^{2+}\) release was restricted to the cell surface with central Ca\(^{2+}\) release decreased and reliant on propagation. Ca\(^{2+}\) transient amplitude was decreased in both triggered and propagated sites in HF, and the difference between triggered and propagated release was exacerbated. The coefficient of variation for Ca\(^{2+}\) release was greater in HF indicating variable amplitude of release between beats. As RyR cluster properties can influence Ca\(^{2+}\) release, their structure was assessed. Atrial RyRs predominantly localise to the z-line but also to the cell surface. Compared to control, RyR clusters were smaller, more fragmented and further apart in HF which could perturb both triggered and propagated Ca\(^{2+}\) release.

Conclusion: Our data suggests loss of t-tubules, decreased Ca\(^{2+}\) release at triggered and propagated sites and RyR cluster remodelling all contribute to the decrease in the atrial systolic Ca\(^{2+}\) transient and dysynchrony observed in HF.

STABILIZING CARDIAC RYANODINE RECEPTOR WITH DANTROLENE PREVENTS BINGE ALCOHOL AND CAFFEINE INDUCED VENTRICULAR TACHYARRHYTHMIAS

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Background: Alcohol and caffeine are widely consumed worldwide. We have shown (Heart Rhythm 2021;18 [8 suppl]: S202) that binge alcohol and caffeine can synergistically induce spontaneous ventricular tachyarrhythmias in rats, yet the underlying mechanism is unclear.

Objective: We hypothesize that cardiac ryanodine receptor (RyR2) dysfunction may be responsible for alcohol and caffeine induced ventricular tachyarrhythmias. Thus, this study was designed to investigate whether stabilizing RyR2 with dantrolene treatment can prevent binge alcohol and caffeine induced ventricular tachyarrhythmias in rats.

Methods: A binge drinking model was established in adult rats (4-5 months old, both sexes) with alcohol injection (2g/kg, IP) every other day for 3 times. These binge drinking rats were divided into 2 groups: binge alcohol (A-group, n=8) and binge alcohol + dantrolene (A+D group, n=7). In A+D group, rats were pretreated with dantrolene (10mg/kg, IP) before each alcohol injection. Caffeine (60mg/kg, IP) was given 3 hours after the last alcohol injection in both groups. To investigate whether dantrolene can stabilize RyR2, ventricular myocytes were isolated and divided into control, alcohol (50mM) and alcohol + dantrolene (10mM) groups from 5 rats. The myocytes were treated for 24 hours and then underwent confocal microscopy with line scanning for Ca\(^{2+}\) sparks recording.

Results: Binge alcohol + caffeine induced various ventricular tachyarrhythmias (premature ventricular contractions and VT, predominantly in the form of bidirectional VT, Figure-ECG) in 8/8 rats. Dantrolene pretreatment prevented ventricular arrhythmia induction in all 7 rats (0/7, A versus A+D, p<0.001). In isolated ventricular myocytes, alcohol treatment significantly increased Ca\(^{2+}\) sparks and dantrolene treatment reduced alcohol induced Ca\(^{2+}\) sparks (Figure).

Conclusion: Stabilizing RyR2 with dantrolene can prevent binge alcohol and caffeine induced ventricular tachyarrhythmias in rats in vivo. Dantrolene treatment can stabilize RyR2 and decrease alcohol enhanced Ca\(^{2+}\) sparks in isolated ventricular myocytes.