during the VP was greater in SI compared to CTL (7 *vs* 1% of stretches induced arrhythmias; $n=50$, $N=6$; $p<0.005$) but was similar in diastole. Arrhythmias during the VP were more complex than in diastole (100 *vs* 69% had sustained activity; $n=50$, $N=6$; $p<0.05$). In the VP, arrhythmia incidence was reduced by BAPTA (2%; $p<0.05$), HC-030031 (1%; $p<0.005$), NAC (1%; $p<0.005$), or DPI (2%; $p<0.05$), while dantrolene had no effect. Fluorophore photoexcitation caused an increase during both the VP and diastole (29 and 14%, $n=42$, $N=4$; $p<0.05$). Glibenclamide reduced the size of the VP (109±6ms; $p<0.0001$), with an associated decrease in arrhythmia incidence (2%, $n=50$, $N=6$; $p<0.05$). SI increased diastolic Ca^{2+} (9±1%, $n=25$, $N=5$; $p<0.0001$), which was not prevented by NAC or HC-030031.
Conclusion: Mechano-arrhythmogenicity in ischemia is enhanced during the VP and involves TRPA1, Ca^{2+}, and ROS, representing potential anti-arrhythmic targets.

B-YIA2-02

CELLULAR AND ELECTROPHYSIOLOGICAL CHARACTERIZATION OF TRIADIN KNOCKOUT SYNDROME USING HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

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Background: Triadin knockout syndrome (TKOS) is a malignant arrhythmia disorder caused by recessive null variants in *TRDN*-encoded cardiac triadin. TKOS is characterized by QT prolongation, T-wave inversions in the precordial leads, ectopy upon stress testing, and a severe disease expression of cardiac arrest in childhood.
Objective: To characterize the cellular and electrophysiological phenotype of TKOS using induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).
Methods: iPSC-CMs were generated from two unrelated patients with TKOS and an unrelated control (TKOS Patient 1: p.D18fs*13/D18fs*13; TKOS Patient 2: p.N9fs*5/K147fs*0). CRISPR/Cas9 was used to insert homozygous p.D18fs*13 into a different healthy control line thereby generating a patient-independent TKOS model (TRDN-/-) and isogenic control iPSC-CMs. Protein expression was measured using immunofluorescence. Action potential duration (APD) and L-type calcium channel (LTCC) properties were measured by whole cell patch-clamp. Calcium handling was assessed using Fluo-4 calcium indicator.
Results: APD90 was prolonged significantly from 507±20 ms (n=9) in the unrelated control to 662±62 ms (n=9; $P<0.05$) in TKOS Patient 1 and 653±39 ms (n=9; $P<0.05$) in TKOS Patient 2. This was confirmed in TRDN-/- iPSC-CMs compared to isogenic control (518±27 ms, n=17 vs. 312±20 ms, n=16; $P<0.0001$). Additional work in TRDN-/- iPSC-CMs revealed that loss of triadin underlies decreased expression and co-localization of RyR2 and Casq2 leading to slow and decreased calcium release from the sarcoplasmic reticulum. These abnormal calcium transients lead to slow inactivation of the LTCC which contributes to the observed APD prolongation. Finally, these changes underlie frequent cellular arrhythmias including early- and delayed afterdepolarizations and APD alternans.
Conclusion: Here, we characterized the first set of iPSC-CM models of TKOS and provide further evidence for recessive null variants in *TRDN* as a self-sufficient monogenetic substrate for potentially lethal genetic heart disease. These cells display APD prolongation, calcium handling abnormalities, and arrhythmias which likely underlie the unique clinical and arrhythmogenic phenotype observed in patients with TKOS.

B-YIA2-03

A GOVERNING EQUATION TO EXPLAIN THE NUMBER OF WAVELETS AND ROTORS OBSERVED IN HUMAN VENTRICULAR FIBRILLATION

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Backgroundbackground: VF is commonly characterised by two mechanisms, multi wavelet reentry and rotors, but no governing equation exists to explain and predict their population dynamics.
Objective: We hypothesized a single equation derived from an M/G/∞ renewal process could explain rotor and wavelet numbers in VF.
Methodsmaterials-methods: Phase singularity (PS) and wavefront (WF) tracking was used to identify wavelets and rotors in epicardial recordings of induced VF during cardiac surgery (n=13 patients). Autocorrelation and distributions of PS and WF lifetimes and inter-formation times were assessed to verify an underlying renewal process. Distributions were fitted using maximum likelihood to calculate formation (λ_f) and destruction (λ_d) rates, and combined in an M/G/∞ process to develop a potential governing equation of VF dynamics.
Results: PS and WF inter-event-time distributions were consistent with the Weibull in all 210 epochs (PS: mean X^2 P=0.23(95%CI,0.18,0.28); WF: mean X^2 P=0.19(95% CI,0.13,0.27)), with zero autocorrelation at non-zero lags, indicative of an underlying renewal process over all stages (perfusion, ischemia and reflow). The M/G/∞ equation accurately predicted average PS and WF number (R>0.90) and population distribution (X^2 P>0.05) in all epochs. Differences in λ_f (term: 0.015/ms (95%CI,0.010,0.020), non-term 0.023/ms (95% CI,0.019,0.027)), and average PS number (term: 1.68 (95%CI, 1.36, 2.00), non-term: (2.00 (95%CI, 1.86, 2.15)) was observed in spontaneous VF termination.
Conclusion: M/G/∞ renewal process provides a governing equation to explain the number of wavelets and rotors in VF, which could be used in mechanistic studies to guide development of new therapies.