POSTER B-PO05: Poster Session V

Friday, July 30, 2021
1:30 pm - 4:00 pm

B-PO05-001

ARRHYTHMOGENIC AND MOLECULAR MECHANISMS OF SHORT QT SYNDROME TYPE 3

Ana Isabel Moreno Manuel MSci, Álvaro Macías, Francisco Miguel Cruz Uréndez, Lilian Karina Gutiérrez Espinosa de los Monteros, Isabel Martínez Carrascoso, Francisco José Bermúdez Jiménez, María Linarejos Vera Pedrosa, Juan A. Bernal and Jose Jalife MD, FHRS

Background: Short QT Syndrome type 3 (SQTS3) is a rare and deadly arrhythmogenic disease caused by gain of function mutations in the *KCNJ2* gene coding Kir2.1, a strong inward rectifier potassium channel. SQTS3 patients present an abnormally short QT interval on the electrocardiogram (ECG) and are at a high risk for AF, VF and sudden cardiac death (SCD).
Objective: To analyse the severity of SQTS3 causing mutations $Kir2.1^{D172N}$ and $Kir2.1^{E299V}$ and correlate it with their respective molecular and arrhythmogenic mechanisms.
Methods: We generated mouse models for each of the mutations and the wild type (WT) condition via single i.v. injection of cardiac specific adeno-associated virus. We compared the risk of arrhythmias and underlying mechanisms in each model using ECG, immunofluorescence, intracardiac stimulation and patch-clamping.
Results: $Kir2.1^{E299V}$ mice recapitulated the SQTS3 ECG phenotype, showing a remarkably briefer corrected QT interval than WT mice (43.7 $\pm$ 5.8 *vs* 74.4 $\pm$ 27.3 ms). On intracardiac stimulation, 89% of $Kir2.1^{E299V}$ mice (n=9) had increased vulnerability to AF, of which 22% also presented serious VT events. Action potentials recorded from $Kir2.1^{E299V}$ cardiomyocytes were extremely short (10.7$\pm$1.6 ms *vs* 35.0$\pm$3.9 ms in WT mice at 5 Hz of stimulation) due to the lack of inward going rectification (outward current at -20 mV, 3.0$\pm$0.5 pA/pF in E299V *vs* 0.5$\pm$0.2 pA/pF in WT mice). In contrast, $Kir2.1^{D172N}$ mice did not show an obvious QTc abbreviation nor increased susceptibility to cardiac arrhythmias compared to $Kir2.1^{E299V}$, although it was somewhat higher than control. Our initial results show alterations in the PR and QRS intervals at high frequencies in SQTS3 models, which possibly favours defects in the specialized cardiac conduction system underlying arrhythmias.
Conclusion: SQTS3 mouse models accurately recapitulate the electrophysiological phenotype of patients with each mutation, dysfunction produced by $Kir2.1^{E299V}$ mutant channels being more pathogenic. These models provide the appropriate tools to investigate in detail the arrhythmogenic and molecular mechanisms underlying each SQTS3 subtype. Translation of the results to the clinic should help establish robust diagnosis and prognosis of SQTS3 patients, and hopefully prevent SCD.

B-PO05-002

DIFFERENTIAL GENE EXPRESSION BY AGE AND ATRIAL FIBRILLATION IN THE HUMAN LEFT ATRIUM

Samuel Harwood, Sojin Youn Wass MD, Han Sun MS, A. Marc Gillinov MD, Christine Moravec PhD, Jonathan Smith PhD, Julie H. Rennison PhD, David R. Van Wagoner PhD, FHRS, John Barnard PhD and Mina K. Chung MD, FHRS

Background: The incidence of atrial fibrillation (AF) increases with age. Identification of genes differentially expressed by age and AF may improve our understanding of AF pathogenesis.
Objective: We aimed to determine whether there are age related differences in the expression of AF-associated genes in human left atria.
Methods: RNA sequence data from 314 left atrial appendages was processed and aligned using best practices. The expression of 24,002 left atrial genes was jointly modeled using sex, race, rhythm (in the age analysis) and age (in the rhythm analysis), and 25 expression surrogate variable analysis covariates using the limma-voom approach. Genes that showed both differential expression (DE) by age and by AF vs sinus rhythm at time of surgery were selected for analysis.
Results: The median age of patients included in the analysis was 61 (IQR 53-69). The majority of patients were male (67%), white (84%), and in sinus rhythm at the time of surgery (55%). 599 genes were significantly ($q \leq 0.05$) differentially expressed by age and 592 by rhythm. 68 genes were differentially expressed by both age and rhythm. Of those genes, only *CDH2* (age FC 1.002 per year, $q = 0.046$; rhythm FC 1.081, $q = 0.016$) and *MYBBP1A* (age FC 1.002 per year, $q = 0.012$; rhythm FC 1.073, $q = 0.010$) displayed significant concordant age and rhythm effects.
Conclusion: After controlling for sex, race, and multiple testing in our dataset, we saw limited gene expression concordance between age and AF. This may reflect prior reported ventricularization of atrial gene expression in permanent AF that has been speculated to move toward a dedifferentiated fetal phenotype in response to stress. *CDH2*, which encodes N-cadherin, has been implicated in atrial remodeling and may contribute to the role of age in AF.

B-PO05-003

EFFECT OF BARIATRIC SURGERY ON VENTRICULAR REPOLARIZATION

Erden Goljo BS, MD, Abhijeet Singh MD, Ibrahim O. Almasry MD, FHRS, Roger Fan MD, FHRS, Aurora Pryor MD, Kan Liu MD, PhD, Richard Lin MD and Eric J. Rashba MD, FHRS

Background: Obese patients with insulin resistance have a greater prevalence of QTc interval prolongation, which is an independent risk factor for cardiovascular death in diabetic patients. Phosphoinositide 3-kinase (PI3K) is the key cellular effector activated by insulin, and insulin resistance and diabetes are associated with decreased PI3K signaling. Decreased PI3K signaling in cardiac myocytes of mice with genetic and diet-induced diabetes increases the persistent inward sodium current, resulting in QT interval prolongation.