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CARDIAC ARRHYTHMIAS

MYOCARDIAL MICRORNAS AND ION CHANNELS ARE DOWNREGULATED IN HEART FAILURE PATIENTS WITH SEVERE VENTRICULAR TACHYARRHYTHMIAS

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
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Session Title: Clinical Electrophysiology --Ventricular Arrhythmias
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Introduction: Ion channel expression is altered in heart failure and may underlie ventricular tachyarrhythmias (VT). Recently microRNAs (miRs) -1 and -133 have been shown to alter ion channel expression and induce VT in animal models. However, their role in human arrhythmias is poorly understood. We investigated whether myocardial miRs and their ion channel targets are differentially expressed in patients with significant VT versus those without VT.

Methods: Left ventricular cardiac tissue of patients with advanced nonischemic cardiomyopathy was obtained at the time of ventricular assist device implantation or orthotopic cardiac transplantation. Samples obtained from patients with significant VT (arrhythmic arrest requiring cardiopulmonary resuscitation and defibrillation, or multiple appropriate defibrillator shocks, n=10), were compared to samples from patients without any known VT (NVT; n=12). Myocardial expression of miRs identified by prior reports as playing key roles in heart failure and/or arrhythmias (miRs-1,-21, -133a, -133b, and-195) was measured by quantitative real time PCR (RT-PCR). Differential expression of potential mRNA targets of miRs was assessed using a PCR based array of 84 ion channel genes and confirmed using separate sets of primers.

Results: Data are presented as fold change in VT/NVT. miRs-1 (-1.4, $p<0.03$), and -133a (-1.2, $p<0.04$) were significantly downregulated in the VT group. By contrast, there was no significant difference in miRs-21 -133b, or -195 expression. miR target prediction databases (DIANA, miRGen, and MAMI), and prior literature reports were used to identify those ion channel mRNAs that contained potential target sites for miRs-1 and/or 133a. While many potential target mRNAs (SCN5A -1.5, $p<0.02$, KCNH2 -1.8, $p<0.05$, GJA1 -2.3, $p<0.05$, KCNJ2 -1.3, $p<0.05$) were significantly downregulated in the VT group, additional potential miR-1 and -133a target mRNAs showed no differences (CACA1C, KCNA5, or KCND2).

Conclusions: In patients with advanced nonischemic cardiomyopathy with VT, both miRs and their target mRNAs encoding ion channels are downregulated. Alterations in cardiac miRs and ion channel expression may predispose patients to VT.