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Aditya Vaze
University of Massachusetts Medical School

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TRANSCRIPTIONAL REGULATION OF CARDIAC REMODELING IN A PORCINE MODEL WITH VALIDATION IN HUMAN SUBJECTS

Aditya Vaze MD[1], David McManus MD[*2], Kevin Donahue MD[*2]
[1]Department of Medicine, [2]Division of Cardiology, Department of Medicine, University of Massachusetts Medical School (*contributed equally as senior authors)

Introduction: The majority of new atrial fibrillation (AF) cases occur in elderly patients with cardiac remodeling (CR) in the setting of structural heart disease and heart failure (HF). We leveraged a unique animal model to identify cardiac microRNAs (miRNAs) and gene regulatory mechanisms that drive this process.

Methods: We prospectively quantified atrial expression of 48 miRNAs by high-throughput qRT-PCR in 15 pigs with right-atrial pacing-induced heart disease (5 pigs with AF/severe HF, 5 pigs with AF/mild HF, and 5 control pigs) as well as in 21 patients (11 with AF and CR and 10 controls) undergoing cardiac surgery. CR and HF were defined through a metric of left atrial volume index, BNP and ejection fraction. MiRNA levels were normalized to global mean and expression compared across pig subtypes and between the two human groups.

Results: In the porcine model, miR-208b was upregulated at week 1 (ΔC_T = -3.9, $p<0.01$) and week 3 (ΔC_T = -5.5, $p<0.05$) after induction of AF compared to sinus rhythm animals. The increase persisted at week 3 compared to week 1 (ΔC_T = -1.5, $p<0.05$). Similarly, humans with AF and HF had higher tissue expression of miR-208b compared to controls (ΔC_T = -1.5, $p<0.05$).

Conclusions: Dysregulation of miR-208b is confirmed in our porcine model and is validated in humans. Prior studies have identified miR-208b in both myosin isoform switching and conduction disease. We theorize that dysregulation of miR-208b may play a critical role in atrial structural remodeling and vulnerability to AF.

Contact:
Aditya Vaze
UMass Memorial Medical Center
Aditya.Vaze@umassmemorial.org