SEVERE LOSS-OF-FUNCTION SCN5A MUTATIONS ASSOCIATED WITH SINUS NODE DYSFUNCTION, ATRIAL ARRHYTHMIAS, AND POOR PACEMAKER CAPTURE

Poster Contributions
Poster Hall B1
Saturday, March 14, 2015, 3:45 p.m.-4:30 p.m.

Session Title: Contemporary Issues in Pediatric Arrhythmia
Abstract Category: 11. Congenital Heart Disease: Pediatric
Presentation Number: 1152-329

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Background: Mutations in the SCN5A gene, which encodes the NaV1.5 channel, have been implicated in inheritable cardiac diseases, primarily long QT and Brugada syndromes. We now report an association between severe SCN5A mutations, sinus node dysfunction, atrial arrhythmias and poor pacemaker capture.

Methods: A retrospective chart review of all SCN5A mutations at a single center was conducted. Patients with a diagnosis of Brugada or long QT syndrome were excluded.

Results: There were a total of 23 patients with SCN5A mutations, 15 of whom had a definitive diagnosis of Brugada or long QT syndrome. Of the remaining 8 patients, 7 were diagnosed with sinus node dysfunction, atrial arrhythmias, and poor pacemaker capture either in the atria, ventricles or both. In all 7 patients, inability to capture myocardium or excessive capture thresholds was found at pacemaker implant. Capture thresholds have remained elevated in all; however some patients have demonstrated a waxing and waning course with intermittent complete loss of capture resulting in syncpe. Genetic testing revealed 6 distinct SCN5A mutations, one of which has never been previously reported. Bioinformatic analysis and literature review demonstrated: 1) a frame-shift mutation leading to an early stop codon and protein truncation, 2) a splice site mutation resulting in inclusion of an intron which then lead to early stop codon and protein truncation, 3) missense mutation resulting in a protein trafficking defect, and 4) missense mutations that may affect either NaV1.5 activation or inactivation or both. Together, all of these 6 SCN5A mutations are predicted to result in severely compromised or complete ablation of NaV1.5 function, albeit via distinct molecular mechanisms.

Conclusion: This is the first series of poor pacemaker capture associated with SCN5A mutations. Significant decreases in NaV1.5 function appear to be involved in fluctuating capture thresholds and intermittent complete loss of pacemaker capture. Recognition of this association in a subset of patients with SCN5A mutations will be important for future management.