Triple Mutation of SCN5A Associated with Sinus Bradycardia and Conduction Disease

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Introduction: Mutations in SCN5A have been associated with a wide variety of rhythm disorders, including Brugada syndrome, LQT3 and conduction disease. The role of SCN5A in sinus node dysfunction is still in debate. Furthermore, it is not known whether mutations in SCN5A may interact to cause a more severe phenotype.

Methods: An 18 year old man with long-standing bradycardia presented with syncope during physical exercise and a documented wide complex tachycardia (WCT) on exercise testing. Evaluation included echocardiography, exercise testing, 24-hr Holter recording, EPS and cardiac MRI. Genetic screening involved direct sequencing of all exons and intron borders of HCN4, KCNJ2, KCNJ12 and SCN5A.

Results: ECG demonstrated junctional rhythm with a RBBB pattern. 24- hr Holter recording showed an average heart rate of 50 (range: 24 – 110) due to sinus bradycardia and occasional junctional rhythm with sinus pauses up to 5.8 seconds. Exercise testing did not reveal any chronotropic incompetence but induced a hemodynamically stable WCT (CL: 310 ms, RB & northwest axis). Echocardiography and MRI did not reveal any structural defects. EPS demonstrated a prolonged A-H of 260ms and H-V of 75 ms. During rapid pacing (420 CL) the H-V interval increased to over 100 ms. Atrial flutter (AFL) was inducible with 1:1 conduction leading to "clinical" WCT. Genetic screening revealed that the father had 2 missense mutations (V1251M, V1924T) and the mother had a K1492del in SCN5A. The proband inherited all 3 variations. 24-hr Holter recording showed no bradycardia in either parent, but the father displayed 1700 VPCs with a RBBB pattern.

Conclusions: Mutations in SCN5A may cause not only conduction disease but also sinus node dysfunction. Only a combination of the 2 SCN5A mutations and the amino acid deletion resulted in clinical bradycardia. Despite a markedly diseased conduction system the proband did not have any chronotrpic incompetence and had fast AV nodal conduction during AFL. This suggests that other ion channel currents may compensate or a may have a similar role to I_{Na} under hyper adrenergic states.