A novel association between sinus node dysfunction and an *SCN5A* variant presenting as persistent symptomatic bradycardia in a young adult

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Introduction

Sinus node dysfunction (SND), historically referred to as sick sinus syndrome, is characterized by symptomatic bradycardia due to an abnormality of the sinoatrial (SA) node or the interface between the SA node and the atrial tissue. SND encompasses inappropriate sinus bradycardia, ectopic atrial bradycardia, SA exit block, sinus pause, sinus node arrest, tachycardia-bradycardia syndrome, chronotropic incompetence, and isorhythmic dissociation. Causes of SND are divided into intrinsic and extrinsic. Extrinsic causes include autonomic dysfunction, high vagal tone, metabolic disturbances, obstructive sleep apnea, and medications. Intrinsic causes include degenerative fibrosis, infiltrative cardiomyopathies, SA node remodeling owing to systemic disease, and ion channel dysfunction. The *SCN5A* gene encodes for a sodium ion channel. Pathogenic variants in *SCN5A* have been associated with a diverse set of cardiac conditions, including Brugada syndrome (BrS), dilated cardiomyopathy, long QT syndrome (LQTS), atrial fibrillation, and SND. LQTS is due to a gain-of-function *SCN5A* variant, whereas BrS is due to a loss-of-function *SCN5A* variant. *SCN5A* variants demonstrate variable expressivity, and some individuals may have clinical features of multiple *SCN5A*-related conditions. SND has been described in individuals with heterozygous, as well as homozygous or compound heterozygous, *SCN5A* variants.[1,2] The *SCN5A* gene is expressed throughout the atria and ventricles.[3] Though the expression of this gene is relatively low in the SA node compared to the myocardium and conductive tissue, recent studies have demonstrated that sodium channels are involved in normal SA node function.[4,5] Though the *SCN5A* protein is not present in the central portion of the SA node, it has been shown to be present in

KEY TEACHING POINTS

- The majority of symptomatic sinus node dysfunction (SND) should be treated with permanent pacemaker implantation unless a reversible cause can be identified.
- In cases where a definitive mechanism of SND needs to be established and the usual diagnostic evaluation has not yielded a mechanism, genetic testing and an electrophysiology study can be useful.
- The intrinsic heart rate and the corrected sinus node recovery time measure the intrinsic function of the sinus node, whereas the sinoatrial conduction time evaluates the interface between the sinus node and the atrial tissue.
- Even though management of SND is unlikely to change based on etiology, it is important to identify the cause of SND whenever possible, as many causes can have other cardiac effects or multisystem implications.
- Variants in the *SCN5A* gene can lead to a variety of cardiac abnormalities, including Brugada syndrome, long QT syndrome, and SND. Understanding these variants is critical to anticipating and treating the disorders that they cause.

KEYWORDS Sinus node dysfunction; *SCN5A* gene variant; Intrinsic heart rate; Corrected sinus node recovery time; Sinoatrial conduction time; Electrophysiology study; Symptomatic sinus bradycardia; Atrial flutter

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the SA node periphery.[6] Therefore, loss-of-function *SCN5A* variants may result in electric decoupling of the sinus node and surrounding atrial cells.[7] Gain-of-function variants may induce an increase in cardiac action potential duration because of persistent activation during the systolic phase, and the prolonged SA node action potential would then lead to bradycardia.[8]

Suspected SND should initially be evaluated with the use of a history, physical examination, and surface electrocardiogram (ECG), as well as transthoracic echocardiography, advanced imaging, and exercise ECG testing, depending on the clinical scenario. In cases where this evaluation has been completed, and a diagnosis still needs to be made, patients should undergo ambulatory ECG monitoring. Rarely will patients complete ECG monitoring without a precise diagnosis or a clear etiology of their conduction system disease. In these cases, an electrophysiology study (EPS) and consideration of genetic testing can be helpful.

We describe a case of a 22-year-old man who presented with SND of unclear etiology after routine evaluation. We performed an EPS, which demonstrated a very low intrinsic heart rate (IHR), which is a rare finding and one of unclear significance beyond suggesting an intrinsic SND. Genetic testing in this case identified a pathogenic variant in *SCN5A*, c.611+1G>A. This is the first case, to our knowledge, where this *SCN5A* variant has been observed in a patient with a primary presentation of SND without evidence of other *SCN5A*-related conditions.

Case report

A 22-year-old active-duty male patient presented to the emergency department with persistent fatigue and lightheadedness following an episode of intense exertion. He had just completed a military physical fitness test during which he completed a 3-mile run in 17 minutes and other exercise events. During the test, he experienced no abnormal symptoms and was not limited from a cardiovascular perspective. Before the test, he was in his usual state of health, was well-hydrated, and had been exercising without issue.

He had a medical history of atrial flutter. At 17 he experienced a witnessed loss of consciousness immediately following a cross-country race, and a cardiac evaluation was reportedly normal. Later that year, he experienced another witnessed loss of consciousness with a prodrome of dyspnea, palpitations, and blurry vision immediately after another episode of intense physical exertion. He spontaneously regained consciousness after several minutes. Upon emergency medical services arrival, he was found to be in a typical atrial flutter at a rate of 216 beats per minute (bpm). He was admitted to a nearby hospital, where cardioversion was required to achieve sinus rhythm. His ECG and transthoracic echocardiogram showed no abnormalities, and he was referred for an EPS. The EPS demonstrated normal baseline intracardiac intervals. There was no evidence of conduction system abnormalities. Atrial and ventricular burst and programmed extrastimulus testing were performed with and without isoproterenol infusion and revealed no inducible arrhythmias. No accessory pathways were identified. A cavotricuspid isthmus ablation was performed with successful bidirectional block.

Upon arrival to our emergency department during this encounter, he was found to be in sinus bradycardia with junctional escape complexes at a rate of 31 bpm (Figure 1). His vitals were otherwise normal. He continued to report lightheadedness with activity. A review of systems was otherwise normal. He denied recent medication or substance use. He reported a maternal second cousin who had a pacemaker implanted at the age of 16 after surgical complications. His father, mother, and sister had no history of cardiac structural abnormalities, arrhythmias, or sudden cardiac death. Laboratory evaluation including CBC, CMP, TSH, free T4, ESR, CRP, UDS, respiratory viral panel, iron panel, ceruloplasmin, ACE level, and Lyme antibody titer were all unremarkable. A transthoracic echocardiography revealed normal function and no structural abnormalities. A head computed tomography without contrast ruled out intracranial pathology. An exercise stress test was performed to assess chronotropic competence. He exercised according to the standard Bruce protocol for 10:33 minutes, and his heart rate increased from 41 bpm to 118 bpm, 59% of his age-predicted maximal heart rate. Lightheadedness occurred after 4 minutes of exercise, gradually progressed, and was the reason for test termination. Cardiac magnetic resonance imaging showed no evidence of scar, infiltrative disease, myocarditis, or a mass. The patient was monitored for 5 days as an inpatient, and continuous telemetry revealed persistent sinus bradycardia with sinus pauses up to 5.5 seconds (Figure 2). The decision was made to perform an EPS to define the mechanism of the patient's inappropriate sinus bradycardia, sinus pauses, and chronotropic incompetence.

Intracardiac electrocardiograms were measured at rest. At baseline there was normal atrioventricular (AV) nodal conduction with evidence of dual AV nodal physiology. There were no echo beats or inducible AV nodal reentrant tachycardia, orthodromic reciprocating tachycardia, atrial tachycardia, or other inducible supraventricular tachycardias on or off isoproterenol infusion. At baseline, there was no ventriculoatrial conduction. No ventricular tachycardia was induced with burst pacing. Sinoatrial conduction time (SACT) was normal. Corrected sinus node recovery times (CSNRT) were prolonged up to 775 ms at long cycle lengths and only improved to 563 ms at faster pacing intervals. After administration of intravenous propranolol (16 mg) and intravenous atropine (3.2 mg), an IHR was measured at 75 bpm, which was abnormally low for his age. A procainamide infusion showed no evidence of BrS. Additionally, 2 detailed >1000-point sinus node maps were made at baseline and after isoproterenol infusion, confirming a high right atrial sinus focus (Figure 3).

Owing to the unknown significance of the patient's abnormal CSNRT and IHR, genetic testing was performed and revealed a pathogenic variant in *SCN5A*. This specific variant, c.611+1G>A, is expected to be a loss-of-function

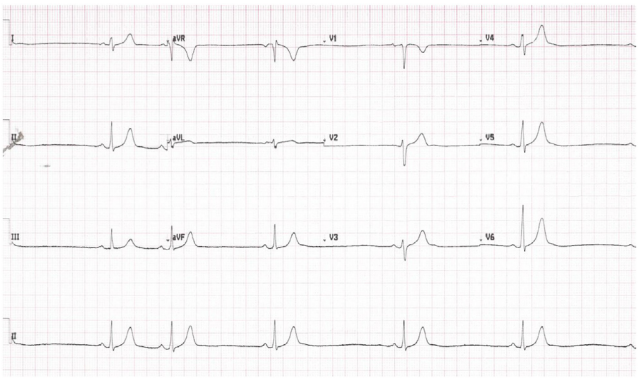

Figure 1 Electrocardiogram obtained at the time of presentation demonstrating sinus bradycardia with a premature atrial contraction.

variant, as it is believed to disrupt RNA splicing at a donor splice site within intron 5. This variant has been reported in individuals with BrS and LQTS and is likely contributing to this patient's SND.[3,9,10]

Gradually his lightheadedness improved, and he could ambulate with minimal symptoms. The patient desired to avoid permanent pacemaker implantation owing to the impact it would have on his military career. An implantable loop recorder was inserted, and he was discharged. At follow-up, the patient's exertional lightheadedness persisted and was causing significant limitations. His resting heart rate remained in the 30s to 50s. Oral theophylline marginally improved his symptoms but not significantly enough to return him to his prior quality of life. Given the genetic etiology of his SND and the lack of reversible causes, a permanent pacemaker (PPM) was recommended. After extensive discussion, the patient elected to proceed with dual-chamber pacemaker implantation.

Discussion

The treatment for nearly all cases of symptomatic SND without a reversible cause is a PPM. Theophylline can be used in cases of SND in which it is unclear if the patient's symptoms are secondary to bradycardia or in which the mechanism of bradycardia is unclear. Though PPM therapy and oral theophylline have both been shown to decrease the incidence of heart failure and minor symptoms in SND, PPM therapy has been shown to decrease rates of recurrent syncope, while oral theophylline has not.[11]

The optimal treatment of SND does not change based on the mechanism of disease, apart from treating reversible causes. Regardless, it is crucial to identify the cause of SND whenever possible, as many causes can have other cardiac effects or multisystem implications. Additionally, future treatment options may become available for specific etiologies. For our patient, the usual diagnostic evaluation failed to identify the etiology of SND. In an elderly patient, it is reasonable to implicate degenerative fibrosis of the SA node or the surrounding tissue and to forgo additional diagnostic evaluation. Owing to our patient's age and exercise-associated episodes, we opted to pursue a definitive diagnosis with genetic testing and EPS. EPS of the SA node includes measurement of SACT, CSNRT, and IHR.

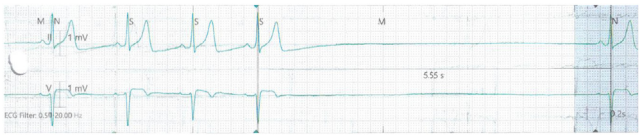

Figure 2 Telemetry monitoring during the patient's inpatient evaluation demonstrating a 5.5-second sinus pause.

IHR is uncommonly measured but can reveal an essential mechanism of SND. It measures SA node function without sympathetic and parasympathetic effects. Propranolol provides nonselective beta-adrenergic blocking effect, which isolates the heart rate from epinephrine and norepinephrine, and atropine strongly antagonizes acetylcholine at muscarinic receptors. This virtually eliminates heart rate variability. The strongest predictor of IHR is age, and the formula for a normal IHR is as follows[12,13]: $IHR_{normal} = 118.1 - (0.57 \times Age)$.

The predicted IHR for our patient's age would be 105 bpm. Based on the data used to generate the linear regression defined by the above equation, the lower limit of normal that would tolerate 95% of variability would be 90 bpm at our patient's age.[13] Meanwhile, the measured IHR for our patient was 75 bpm.

The sinus node recovery time (SNRT) is the amount of time required for sinus rhythm to resume after overdrive atrial pacing. The CSNRT is the sinus cycle length subtracted from the SNRT, which accounts for SNRT variability with sinus rate. A normal CSNRT value is less than 550 ms. The longest CSNRT value obtained should be used. Our patient had CSNRTs from 563 ms to 775 ms at varying pacing rates. While CSNRT measures the intrinsic function of the SA node, the SACT attempts to evaluate for delayed conduction at the interface between the SA node and the atrial tissue. However, accurate measurement of the SACT is technically difficult, as it relies on resetting the SA node with a single extrastimulus delivered to the high right atrium. Our patient's normal SACT suggests that his atrial tissue is normal. Meanwhile, his abnormal CSNRT and IHR suggest that his SND is secondary to a phase 0 etiology in the sinus node. Regardless of the metrics used to evaluate sinus node function, the most significant limitation of these tests is their lack of therapeutic value. As discussed above, there is no evidence for adjusting treatment based on SND mechanism.

The *SCN5A* variant, c.611+1G>A, has been reported in 11 individuals across 3 publications.[3,9,10] Of the individuals with this variant, 9 had BrS, 1 had LQTS, and 1 individual identified on cascade screening was asymptomatic. *SCN5A* variants demonstrate variable expressivity and reduced penetrance. In a study of SND among 5 families with *SCN5A*

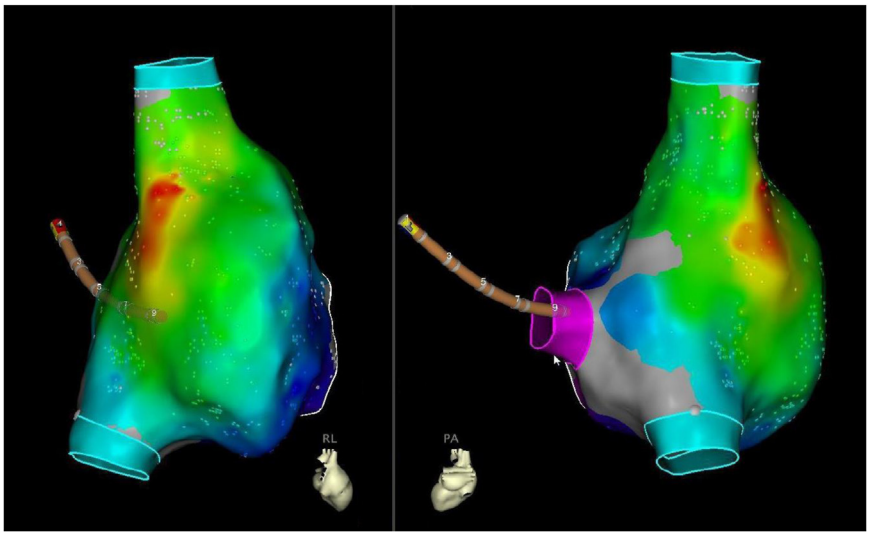

Figure 3 Sinus node electroanatomical maps depicted from the right lateral view (left) and posterior view (right), which were obtained at baseline and which confirmed a high right atrial sinus focus. The sinus node is depicted in red, which represents the earliest electrical impulse.

variants, 37% of subjects (7/19) had isolated SND or SND along with other *SCN5A*-related conditions, 26% had other *SCN5A*-related arrhythmias, and 37% were asymptomatic.[7] Although our patient's specific *SCN5A* variant is previously unreported in association with SND, his presentation fits into the spectrum of phenotypes observed among *SCN5A* variants. In pediatric patients with *SCN5A* variants, the most common presentation in one study was multiple *SCN5A*-related conditions (overlap syndrome), followed by isolated SND and isolated BrS. Another important consideration in patients with *SCN5A* variants is atrial standstill, which is a rare form of atrial cardiomyopathy characterized by a transient or persistent absence of electrical and mechanical activity that can affect the entire atrium or only part of the atrium.[14] *SCN5A* variants have been associated with atrial standstill in isolation and in association with other cardiomyopathies. Our patient currently has no evidence of other arrhythmias or cardiomyopathy, but we cannot exclude the possibility that he will develop other *SCN5A*-related conditions. Periodic cardiac evaluation, including ECG and echocardiogram, was recommended to monitor for new developments.

Identification of the pathogenic *SCN5A* variant in this patient also has important implications for family members. Most *SCN5A*-related conditions are inherited in an autosomal-dominant manner, so there is up to a 50% chance that each of the patient's first-degree relatives have the *SCN5A* variant and are at increased risk for *SCN5A*-related conditions. Based on these genetic test results, family members were recommended to undergo clinical cardiac evaluation and targeted genetic testing. Though none of his immediate family members have presented with phenotypic abnormalities, they have not opted to pursue genetic testing to date. As such, it remains unclear if this is a de novo or inherited variant for our patient. Additionally, because of the lack of familial genetic testing, it is unclear if there was cosegregation with other genes in this case.

Current theories of sinus node automaticity include a contribution from a "voltage clock" driven by the inward "funny current" I_f and a contribution from a "calcium clock" driven by spontaneous calcium release from the sarcoplasmic reticulum with inward sodium-calcium exchange resulting in membrane depolarization.[15] More recent data demonstrated that the spontaneous beating rate of human sinus nodal tissue is depressed by tetrodotoxin, a specific inhibitor of neuronal and, to a lesser extent, cardiac sodium channels.[5] The apparent depression of sinus node automaticity associated with loss-of-function variants in *SCN5A*, as seen in this patient, supports the heterodoxical notion the cardiac sodium channels play a role in SA nodal automaticity.

Conclusion

SND is increasingly common and can be caused by intrinsic or extrinsic etiologies. Treatment of irreversible SND is PPM implantation, especially in cases of *SCN5A* variants that impart a risk for other atrial and ventricular arrhythmias. Though knowing the mechanism of SND may not change pacemaker recommendation, it may impact other aspects of the patient's care and provide important information for family members. For this purpose, IHR, CSNRT, SACT, and genetic testing are crucial tools in the assessment of the mechanism of SND. *SCN5A* variants such as the loss-of-function splice donor variant c.611+1G>A on intron 5 found in our patient may lead to a variety of clinical syndromes, including the atrial flutter and SND that we described. Further research is warranted to determine the optimal management of these patients.

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References

1. Benson DW, Wang DW, Dyment M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (Scn5a). J Clin Invest 2003;112:1019–1028.
2. Ziyadeh-Isleem A, Clatot J, Duchatelet S, et al. A truncating SCN5A mutation combined with genetic variability causes sick sinus syndrome and early atrial fibrillation. Heart Rhythm 2014;11:1015–1023.
3. Robyns T, Nuyens D, Vandenberk B, et al. Genotype–phenotype relationship and risk stratification in loss of function SCN5A mutation carriers. Ann Noninvasive Electrocardiol 2018;23:e12548.
4. Veerman CC, Wilde AAM, Lodder EM. The cardiac sodium channel gene SCN5A and its gene product NaV1.5: role in physiology and pathophysiology. Gene 2015;573:177–187.
5. Li N, Kalyanasundaram A, Hansen BJ, et al. Impaired neuronal sodium channels cause intranodal conduction failure and reentrant arrhythmias in human sinoatrial node. Nat Commun 2020;11:512.
6. Lei M, Jones SA, Liu J, et al. Requirement of neuronal- and cardiac-type sodium channels for murine sinoatrial node pacemaking: sodium channels in the SA node. J Physiol 2004;559:835–848.
7. Abe K, Machida T, Sumitomo N, et al. Sodium channelopathy underlying familial sick sinus syndrome with early onset and predominantly male characteristics. Circ Arrhythm Electrophysiol 2014;7:511–517.
8. Wilders R. Sinus bradycardia in carriers of the SCN5A-1795insD mutation: unraveling the mechanism through computer simulations. Int J Mol Sci 2018; 19:634.
9. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm 2010;7:33–46.
10. Christiansen M, Hedley PL, Theilade J, et al. Mutations in Danish patients with long QT syndrome and the identification of a large founder family with p.F29L in KCNH2. BMC Med Genet 2014;15:31.
11. Alboni P, Menozzi C, Brignole M, et al. Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. Circulation 1997;96:260–266.
12. Craft N, Schwartz JB. Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. Am J Physiol 1995;268:H1441–H1452.
13. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 1970;4:160–167.
14. Zaklyazminskaya E, Dzemeshkevich S. The role of mutations in the SCN5A gene in cardiomyopathies. Biochim Biophys Acta 2016;1863:1799–1805.
15. Maltsev VA, Vinogradova TM, Lakatta EG. The emergence of a general theory of the initiation and strength of the heartbeat. J Pharmacol Sci 2006; 100:338–369.