BRUGADA SYNDROME AND SINUS NODE DYSFUNCTION

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SCN5A gain-of-function mutations

- Long QT syndrome type 3
- Familial atrial fibrillation
- Brugada syndrome
- Sick sinus syndrome
- Cardiac conduction diseases
- Dilated cardiomyopathy

SCN5A loss-of-function mutations

- Peak $I_{Na}^-$
- Late $I_{Na}^+$
SCN5A Mutations Associated with Overlap Syndromes

- Brugada ECG + Progressive Conduction disease
- Brugada ECG + Sinus node disease
- Brugada ECG + Paroxysmal complete AV block
- Brugada ECG + Conduction disease + Sinus node disease
- Brugada ECG + Conduction disease + Long QT 3 syndrome
- Brugada ECG + Atrial flutter + Conduction disease
- Brugada ECG + Atrial standstill

JCE 2015
A four-generation family with the \textit{SCN5A} mutation \textit{ΔK1500} exhibited long QT syndrome, BrS and conduction system disease.
The study population consisted of 68 individuals (55 males, mean age 44.8 ± 12.8 years) with spontaneous (n = 27) or drug-induced (n = 41) type 1 ECG pattern of BS.

Twenty-eight subjects were symptomatic with a history of syncope (41.2%).

SND was observed in 6 symptomatic subjects (8.8%), and was mainly attributed to sino-atrial block with sinus pauses.
Ambulatory monitoring showing episodes of sinus arrest in a patient with BrS
ECG tracing and endocardial signals showing a spontaneous episode of sinus arrest during electrophysiological study.
Patients with SND displayed an increased P-wave duration in leads II and V2, PR interval in leads II and V2, QRS duration in leads II and V2, and increased QTc interval in lead V2 (p < 0.05).

AH and HV intervals as well as corrected sinus node recovery time (cSNRT) were significantly prolonged in subjects with SND (p < 0.05).

During a mean follow-up period of 5.0 ± 3.6 years, five subjects with a history of syncope suffered appropriate implantable cardioverter defibrillator (ICD) discharges due to ventricular arrhythmias (7.4%).
SCN5A gene mutations underlie both SND and BrS

- Experimental studies in heterozygous SCN5A knockout mice have shown that SND attributed to sodium current reduction involves **reduced automaticity** and conduction slowing or blocking of action potentials from the sino-atrial node to the surrounding atrial muscle (J Physiol 2005;567:38-400).

- In 2005 a novel SCN5A mutation was identified in patients presenting with both SND and BrS, showing that in the same family, both diseases may be related to the expression of a loss-of-function mutation in INa (Journal of Molecular and Cellular Cardiology 2005; 38:969-981).
SND and atrial arrhythmias

- In our study, a trend toward a higher rate of atrial arrhythmias was observed in subjects with SND.
- SND is often associated with atrial tachyarrhythmias (tachy–brady syndrome) (JCE 2005;16:345–7).
- BrS is also associated with atrial fibrillation/flutter (PACE 2009;32:500–505).
- Fibrotic atrial cardiomyopathy may be the underlying pathophysiology even in the young subjects with SND and atrial arrhythmias (JCE 2012;23:797–9).
- Morimoto et al. reported an autopsy case of BrS with significant lesions in the sinus node, including reduction of the nodal cells and fibrosis (JCE 2005;16:345–7).
**SND and BrS phenotype: Which is the clinical course of these patients?**

- In our series, none of those diagnosed with SND suffered syncope or ICD therapies.
- Two of these patients were initially diagnosed with SND, and received a PM. These patients remained asymptomatic during a long-term follow-up period (25 and 7 years, respectively).

**Possible explanations for this benign clinical course:**
- SND may be the predominant phenotype in these patients, a fact that may explain their benign clinical course (Circulation 1999;100:1660-6)
- Another possible explanation is that cardiac pacing (lower rate of 60 b/min) may protect these patients from severe bradycardia that could induce augmentation of the ST-segment elevation and VT/VF events (Circulation 1996;93:372–9, J Clin Invest 2003;112: 1019-28).
6.5% of asymptomatic BrS displayed SND.

Previous SND was not predictive of a worse outcome.
SND and drug-induced type 1 BrS ECG

Which is the appropriate management of this patient???
SND and BrS phenotype: PM or ICD??

- HOW TO MANAGE ASYMPTOMATIC SUBJECTS WITH SND AND BrS?
- WHICH IS THE PREDOMINANT PHENOTYPE?
- The incidence of sudden cardiac death in patients with SND is very low.
- BrS is a highly lethal disease.
SND and BrS phenotype: PM or ICD??

Brugada Syndrome: Report of the Second Consensus Conference
Circulation. 2005;111:659-670
Heart Rhythm 2011;8:1595–1597

HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes
Heart Rhythm 2013;10:1932–63
The role of EPS in subjects with Brugada phenotype

- **VF inducibility** (>50% in BrS populations vs. 5% in general population) (Heart Rhythm 2011;8:1595-1597). This obviously reflects an electrical instability.

- EPS might be valuable in the clinical evaluation of patients with syncope to rule out the presence of SND or supraventricular arrhythmias as potential causes of the event.

- EPS may guide the proper device selection (dual chamber ICD) in these patients.
Meta-analysis on Risk Stratification of Asymptomatic Patients With the Brugada Phenotype

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The prognosis of asymptomatic subjects remains the most controversial issue in Brugada syndrome (BS). A meta-analysis on the prognostic role of spontaneous type 1 electrocardiographic (ECG) pattern and programmed ventricular stimulation (PVS) in asymptomatic subjects with Brugada electrocardiogram was performed. Current databases were searched until March 2014. Fourteen prospective observational studies were included in the present meta-analysis, accumulating data on 3,536 asymptomatic subjects (2,820 men) with BS phenotype. The mean follow-up period varied from 20 and 77 months. Data regarding 1,398 asymptomatic subjects with spontaneous type 1 ECG pattern of BS were retrieved from 6 studies. During follow-up, arrhythmic events (sustained ventricular tachycardia/fibrillation, appropriate device therapies, or arrhythmic death) occurred in 42 patients (3%). The meta-analysis of these studies demonstrated that asymptomatic subjects with spontaneous type 1 ECG pattern of BS exhibit an increased risk of future arrhythmic events (odds ratio = 3.56, 95% confidence interval 1.70 to 7.47, Z = 3.37, p = 0.0008); 1,104 asymptomatic subjects with BS ECG pattern from 12 studies underwent PVS and were available for analysis. During follow-up, arrhythmic events occurred in 36 subjects (3.3%). Inducible ventricular arrhythmias at PVS were predictive of future arrhythmic events (odds ratio = 3.51, 95% confidence interval 1.60 to 7.67, Z = 3.14, p = 0.002). In conclusion, this meta-analysis showed that asymptomatic subjects with either spontaneous diagnostic ECG pattern or inducible ventricular arrhythmias at PVS are at increased risk. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015; ■ ■ ■ ■)
Inducible sustained VT/VF during EPS confers a 3.5-fold higher risk of future arrhythmic events in previously asymptomatic subjects.
THANK YOU VERY MUCH FOR YOUR ATTENTION
Within the same family, SCN5A mutations may manifest with:

- BrS phenotype
- Atrial arrhythmias, SND or progressive conduction disease with negative intravenous INa blocking test for BrS!

**IS IT POSSIBLE TO IDENTIFY THE PREDOMINANT PHENOTYPE?**

**HOW DOES THIS INFLUENCE OUR THERAPEUTIC APPROACH?**
Sodium channel blocking test in patients with SND

- Should we perform INa blocking test in young patients with SND?
How a single mutation can produce multiple phenotypes?

- Potential explanations include:
  - the phase of the action potential that is affected (early vs. late),
  - the presence of more than one biophysical alteration in channel function from a single mutation, and
  - modifying factors, whether clinical or genetic, that modulate biophysical function.
Progressive Cardiac Conduction Defect is the Prevailing Phenotype in Carriers of a Brugada Syndrome SCN5A Mutation

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Progressive Conduction Defects in Brugada Syndrome. Introduction: Loss-of-function mutations in the SCN5A gene encoding the cardiac sodium channel are responsible for Brugada syndrome (BS) and also for progressive cardiac conduction disease (inherited Lenègre disease). In an attempt to clarify the frontier between these two entities, we have characterized cardiac conduction defect and its evolution with aging in a cohort of 78 patients carrying a SCN5A mutation linked to Brugada syndrome.

Methods and Results: Families were included in the study if a SCN5A mutation was identified in a BS proband and if at least two family members were mutation carriers. Sixteen families met the study criteria, representing 78 carriers. Resting ECG showed a spontaneous BS ECG pattern in 28 of 78 (36%) gene carriers. Intraventricular conduction anomalies were identified in 59 of 78 gene carriers including complete (17) or incomplete (24) right bundle branch block, right bundle branch block plus hemiblock (6), left bundle branch block (1), hemiblock (1), and parietal block (10). PR and QRS duration were longer in the gene carrier cohort in comparison with their relatives carrying no mutation. Finally, in the gene carrier cohort conduction defect progressively aggravated with aging leading in five occasions to pacemaker implantations.

Conclusion: The present study shows that the most common phenotype of gene carriers of a BS-type SCN5A mutation is progressive cardiac conduction defects similar to the Lenègre disease phenotype. In consequence, we propose that carriers of a SCN5A mutation need a clinical and ECG follow-up because of the risk associated with severe conduction defects. (J Cardiovasc Electrophysiol, Vol. 17, pp. 270-275, March 2006)
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OBJECTIVES The purpose of this study was to determine the clinical and biophysical characteristics of a novel SCN5A mutation.

BACKGROUND Brugada syndrome and isolated cardiac conduction defect have been linked to SCN5A mutations.

METHODS Eleven members of a western European family underwent electrophysiologic investigations and mutation analysis of the SCN5A gene. Wild-type and mutant SCN5A channels were expressed in HEK293 cells, and whole cell currents were studied using patch clamp procedures.

RESULTS A novel mutation, R376H, in the first pore segment of SCN5A variably causes Brugada syndrome and/or conduction disease in a single family. Biophysical analysis demonstrated a significant current reduction for the mutant, a pathophysiologic profile consistent with Brugada syndrome and isolated cardiac conduction defect. Among 11 family members, 9 were carriers of the mutation. The proband’s initial presentation was a saddleback Brugada ECG, atrial flutter, and diffuse conduction disturbances. He had no inducible ventricular arrhythmias but experienced sudden cardiac death. His brother was affected by atrial flutter and had a clear conduction disorder, but he did not display baseline or evocable ECG signs of Brugada syndrome. He received an implantable cardioverter-defibrillator that delivered one appropriate shock after 1 year of follow-up. The phenotype in the family members was highly variable and ranged from noninducible and inducible asymptomatic carriers of the mutations to isolated conduction disease and to symptomatic Brugada syndrome.

CONCLUSIONS We describe the functional characterization of a novel SCN5A pore mutation, R376H, with variable clinical expression in the same family. Differentiating between electrophysiologic entities (Brugada syndrome–isolated cardiac conduction defect) is more challenging. Recognition of factors modifying the clinical presentation may be important for clinical decision making.

KEYWORDS Brugada syndrome; SCN5A; sudden cardiac death

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Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A)

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Sick sinus syndrome (SSS) describes an arrhythmia phenotype attributed to sinus node dysfunction and diagnosed by electrocardiographic demonstration of sinus bradycardia or sinus arrest. Although frequently associated with underlying heart disease and seen most often in the elderly, SSS may occur in the fetus, infant, and child without apparent cause. In this setting, SSS is presumed to be congenital. Based on prior associations with disorders of cardiac rhythm and conduction, we screened the α subunit of the cardiac sodium channel (SCN5A) as a candidate gene in ten pediatric patients from seven families who were diagnosed with congenital SSS during the first decade of life. Proband s from three kindreds exhibited compound heterozygosity for six distinct SCN5A alleles, including two mutations previously associated with dominant disorders of cardiac excitability. Biophysical characterization of the mutants using heterologously expressed recombinant human heart sodium channels demonstrate loss of function or significant impairments in channel gating (inactivation) that predict reduced myocardial excitability. Our findings reveal a molecular basis for some forms of congenital SSS and define a recessive disorder of a human heart voltage-gated sodium channel.

p. Y1449C SCN5A Mutation Associated with Overlap Disorder Comprising Conduction Disease, Brugada Syndrome, and Atrial Flutter
During a mean follow-up period of 4.6 ± 2.2 years, 24% of subjects (9/38) suffered ATs. Six subjects displayed paroxysmal atrial fibrillation and three typical atrial flutter.

Among the studied 12-lead ECG parameters, subjects with ATs exhibited

- increased values of P-wave duration in lead II,
- P-wave dispersion
- PR interval in leads II
- QRS duration in leads II and V2
- Tpeak-end interval in lead II, and
- Tpeak-end dispersion of the 12 leads in relation to those without ATs (P < 0.05).

Among the assessed electrophysiological parameters, atrial-His (AH) and His-ventricular (HV) intervals were significantly prolonged in subjects with ATs (P < 0.05).