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Original article

Sinus node disease in subjects with type 1 ECG pattern of Brugada syndrome

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ABSTRACT

Background: The spectrum of phenotypes related to mutations of the *SCN5A* gene include Brugada syndrome (BS), long QT syndrome, progressive cardiac conduction defect, and sinus node disease (SND). The present study investigated the incidence of SND in subjects with type 1 electrocardiogram (ECG) pattern of BS.

Methods and results: 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. Two patients were initially diagnosed with SND, and received a pacemaker. 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%). None of those diagnosed with SND suffered syncope or ICD therapies.

Conclusion: SND is not an uncommon finding in subjects with type 1 ECG pattern of BS. The occurrence of SND in relatively young patients may deserve meticulous investigation including sodium channel blocking test.

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Introduction

The Brugada syndrome (BS) is an arrhythmogenic entity that typically manifests with syncope or cardiac arrest due to ventricular arrhythmias in individuals with structurally normal hearts [1–4]. The *SCN5A* gene encoding for the cardiac sodium channel was the first gene linked to BS [2]. Apart from BS, the spectrum of phenotypes related to mutations of the α-subunit of the *SCN5A* gene include long QT syndrome, progressive cardiac conduction defect (Lenègre syndrome), atrioventricular (AV) block, atrial arrhythmias, and sinus node disease (SND) [5–7].

It has been reported that the loss of function of single *SCN5A* gene mutations can be responsible for both BS and SND [8,9]. In previous case studies, the diagnostic type 1 electrocardiogram (ECG) pattern of BS was identified after pacemaker implantation for SND [10–15]. SND may be implicated in the pathophysiology of ventricular arrhythmic events in BS, since bradycardia-dependent augmentation of ST-elevation has been previously demonstrated in patients with BS [16]. The coexistence of SND and BS raises severe diagnostic and therapeutic dilemmas in symptomatic subjects, particularly in the case where SND is the initial diagnosis. Patients with symptomatic SND are typically treated with pacemaker (PM) implantation, while an implantable cardioverter defibrillator (ICD) is currently indicated in symptomatic patients with BS [17]. The present study investigated the incidence and the prognostic significance of SND in patients with type 1 ECG pattern of BS.

Methods

Patient population

The clinical records of consecutive individuals diagnosed with spontaneous or drug-induced (ajmaline 1 mg/kg, flecainide

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2 mg/kg, procainamide 10 mg/kg) type 1 ECG pattern of BS from 1999 to 2011 were retrospectively analyzed. The ECG diagnosis of BS was strictly based on the recommendations of the Second Consensus Conference on BS [2]. All subjects underwent transthoracic echocardiography in order to rule out the presence of structural heart disease including myocardial ischemia. Laboratory tests were performed to exclude any electrolyte or metabolic disturbances including thyroid dysfunction. Subjects with established neurally mediated syncope were excluded from the study. The following clinical data were collected in all patients: age, gender, family history of sudden cardiac death (SCD) (<45 years of age), family history of BS, and history of atrial tachyarrhythmias. Screening for *SCN5A* gene mutations was performed in selected cases. Subjects with a previous history of syncope or aborted SCD were classified as symptomatic.

Baseline 12-lead ECGs were recorded at a paper speed of 25 or 50 mm/s and an amplification of 10 mm/mV. The following parameters were reviewed in the absence of antiarrhythmic medication: (i) the P-wave duration in leads II and V2; (ii) the PR duration in leads II and V2; (iii) the QRS duration in leads II and V2; and (iv) the QTc interval in leads II and V2 (corrected using Bazett's formula). ECG measurements were performed by two independent cardiologists. When measurements were not identical, the mean of the values were calculated. To avoid diurnal variation, ECGs performed during the same time interval (09.00–12.00 h) were evaluated. The inter-observer and intraobserver variability was less than 5%. Ambulatory 24 or 48 h Holter ECG recordings were evaluated in all subjects.

An electrophysiological study (EPS) was carried out in selected cases based on the judgment of the treating physician. The baseline AH and HV intervals were measured. The corrected sinus node recovery time (cSNRT) was calculated following burst atrial pacing at different cycle lengths. A cSNRT of more than 550 ms was considered abnormal. Programmed right ventricular stimulation was performed at three running cycle lengths (600, 500, and 430 ms) with up to triple extrastimuli (minimum coupled extrastimuli of 200 ms). Inducible ventricular arrhythmia was defined as ventricular tachycardia/fibrillation (VT/VF) lasting >30 s, causing syncope/circulatory collapse, or requiring intervention to be terminated. The study was approved by the medical ethical review committee of the participating centers. Informed consent was obtained from all patients.

Definition of sinus node disease

SND was defined when one of the following was present: (i) sinus bradycardia <40 beats/min while awake; (ii) sino-atrial block or sinus arrest with pauses >3 s; (iii) bradycardia–tachycardia syndrome defined as episodes of atrial tachyarrhythmias coexisting with sinus bradycardia, sino-atrial block, or sinus arrest; and (iv) cSNRT >550 ms at EPS in previously symptomatic patients (syncope or dizziness).

Statistical analysis

All continuous variables had a normal distribution, according to Shapiro–Wilk's corresponding test. All continuous data are presented as mean ± standard deviation, while categorical variables are reported as absolute and relative (percentages) frequencies. Differences in categorical variables were evaluated using Pearson's chi-square or Fisher's exact test. Student's *t*-test was used for comparison of continuous variables. All reported probability values (*p*-values) were based on two-sided tests and compared to a significance level of 0.05. Data were analyzed using SPSS.17 for Windows (SPSS, Chicago, IL, USA).

Results

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. All subjects displayed a structurally normal heart. Twenty-eight subjects were symptomatic with a history of syncope (41.2%), and 18 displayed a positive family history of BS and/or sudden cardiac death (26.5%). EPS was performed in 37 subjects, and programmed right ventricular stimulation induced VT/VF in 25 of them (67.5%). There were no significant differences between subjects with and without spontaneous type 1 ECG pattern regarding the cSNRT (640.00 ± 763.54 vs. 403.33 ± 370.91, $p = 0.543$), AH (104.58 ± 33.81 vs. 102.26 ± 34.61, $p = 0.863$), and HV intervals (55.27 ± 10.98 vs. 49.40 ± 16.05, $p = 0.279$). Genetic test was performed in 6 subjects (one with SND), and identified one positive proband without SND (exon 26, 4477–4479delAAG, *K1493del*). An ICD was implanted in 28 individuals (41.1%).

SND was observed in 6 subjects (8.8%). All subjects with SND were symptomatic. The clinical data of these individuals are depicted in Table 1. Four patients exhibited sino-atrial block with sinus pauses >3 s (Figs. 1 and 2), and two patients displayed sinus bradycardia <40 beats/min while awake. Two of them received a dual-chamber PM (lower rate of 60 beats/min), while the other four a dual-chamber ICD (lower rate of 60 beats/min). The patients who received a PM were initially diagnosed as having SND, while the diagnostic Brugada ECG phenotype was unmasked after sodium channel blocking test with ajmaline during follow-up. An ICD upgrade was offered in both patients. As shown in Table 2, subjects with SND displayed an increased P-wave duration in leads II ($p < 0.001$) and V2 ($p = 0.009$), PR interval in leads II ($p < 0.001$) and V2 ($p = 0.009$), QRS duration in leads II ($p = 0.036$) and V2 ($p = 0.001$), and increased QTc interval in lead V2 ($p = 0.009$). AH ($p < 0.001$) and HV ($p = 0.011$) intervals as well as cSNRT ($p = 0.027$) were significantly prolonged in subjects with SND. Fourteen subjects suffered atrial tachyarrhythmias (20.5%), mainly atrial fibrillation. Although not statistically significant, subjects with SND displayed a higher rate of atrial fibrillation or atrial flutter in relation to those without SND (50% vs. 17.7%, $p = 0.062$).

During a mean follow-up period of 5.0 ± 3.6 years, five previously symptomatic subjects suffered appropriate ICD discharges due to ventricular arrhythmias (7.4%), and one died due to non-cardiac causes. None of those diagnosed with SND suffered syncope or ICD therapies. None of the asymptomatic individuals had syncope or ICD therapies. There were no inappropriate ICD therapies in our cohort. Two complications related to the implantation procedure were noted (one pneumothorax and one pocket infection).

Discussion

The main findings of the present study are as follows: (i) the incidence of SND in subjects with type 1 ECG phenotype of BS is comparatively high given the relative young age of this population and (ii) subjects with BS phenotype and SND display prolonged P-wave duration, PR interval, QRS duration, and QTc interval compared to those without SND.

Sodium channels play an important role in pacemaking of the heterogeneous sinus nodal tissue [18]. *SCN5A* gene mutations lead to loss of function of the cardiac sodium current, resulting in reduced action potential upstroke velocity and slowed impulse propagation [8]. Two different mechanisms have been suggested to underlie SND due to *SCN5A* gene mutations: (i) a slowed conduction between the sino-atrial node and the atria, due to an increased stimulus threshold in the atrial myocardium and (ii) a disorder of the sino-atrial node itself; although predominantly calcium

Table 1
Clinical and electrophysiological characteristics of patients with SND.

	Age at diagnosis of BS ECG	Sex	BS ECG type	Symptoms	AT	Sinus pauses	Bradycardia (<40 beats/min)	EPS	Inducible VT/VF	cSNRT (ms)	AH interval (ms)	HV interval (ms)	Management	Follow-up
Patient 1	38	M	2	Yes	Yes	Yes	No	Yes	No	–	194	90	PM implantation 25 years ago	Asymptomatic, no VT/VF events
Patient 2	46	M	2	Yes	No	Yes	No	No	–	–	–	–	ICD implantation 12 years ago	Asymptomatic, no VT/VF events
Patient 3	50	F	1	Yes	Yes	No	Yes	Yes	Yes	–	180	80	ICD implantation 10 years ago	Asymptomatic, no VT/VF events
Patient 4	45	F	2	Yes	No	No	Yes	Yes	Yes	1100	140	44	ICD implantation 10 years ago	Asymptomatic, no VT/VF events
Patient 5	32	M	3	Yes	Yes	Yes	No	Yes	No	1000	140	60	PM implantation 7 years ago	Asymptomatic, no VT/VF events
Patient 6	48	F	1	Yes	No	Yes	No	Yes	No	2000	145	55	ICD implantation 1 year ago	Asymptomatic, no VT/VF events

SND, sinus node disease; BS, Brugada syndrome; ECG, electrocardiogram; AT, atrial tachyarrhythmias; EPS, electrophysiological study; VT/VF, ventricular tachycardia/ventricular fibrillation; cSNRT, corrected sinus node recovery time; ICD, implantable cardioverter defibrillator; PM, pacemaker.

Fig. 1. Ambulatory monitoring showing several episodes of sinus arrest (patient 2).

currents are responsible for the action potential upstroke in sino-atrial and atrioventricular nodal cell, sodium channels also play a significant role in pacemaking of the heterogeneous sino-atrial nodal tissue [18]. 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 [19].

Previous studies have indicated that single *SCN5A* gene mutations can be responsible for both BS and SND. In a previous study, among 38 patients clinically diagnosed with BS, heterozygous *SCN5A* gene mutations were identified in 4 subjects. All of them had bradyarrhythmic complications including three with SND and one with paroxysmal complete atrioventricular block. None of these probands had additional *SCN5A* mutations, suggesting that this type of "loss of function" overlap syndrome (BS plus SND/atrioventricular block) may result from a single *SCN5A* mutation [9]. Morita et al. have shown that sinus node function is impaired in patients with Brugada ECG pattern and inducible ventricular fibrillation at EPS compared with those without inducible arrhythmias. In this study, abnormal values of cSNRT occurred in 6% of patients without induced arrhythmias and 31% of patients with induced VT/VF [13]. Sumiyoshi et al. reported 3 patients with symptomatic BS and documented sinus pauses >3 s. EPS demonstrated prolonged SNRT in 2 patients, and a PM was initially implanted before the diagnosis of BS [14]. In the study of Bordachar et al., the incidence of SND (diurnal heart rate <55 beats/min and prolonged cSNRT >525 ms) in patients with BS was 17% [20]. In a retrospective analysis, among 487 patients diagnosed with SND, BS ECG phenotype was found in 14 patients (2.87%) including 4 (0.82%) with type 1 and 10 (2.05%) with type 2. During follow-up, 2 out of the 4 patients with type 1 ECG pattern experienced a VT/VF episode [21]. Spontaneous augmentation of ST-segment elevation in daily life has been described along with an increase in vagal activity in BS patients [22]. A circadian variation of fluctuation in ST-segment elevation has been demonstrated, and ST-segment elevation always becomes prominent just before VT/VF episodes [23]. In BS, VT/VF and sudden cardiac death mainly occur in the resting state, predominantly during sleep [24]. Previous studies have also demonstrated a rate dependence of both the J-wave amplitude and ST-segment elevation [25]. These phenomena could be caused by a slow recovery from the inactivation of the Ito current [26]. Sino-atrial block with sinus pauses or sinus bradycardia may therefore lead to augmentation of the ST-segment elevation and VT/VF events. Thus, the possibility of SND should be taken into consideration in patients with BS.

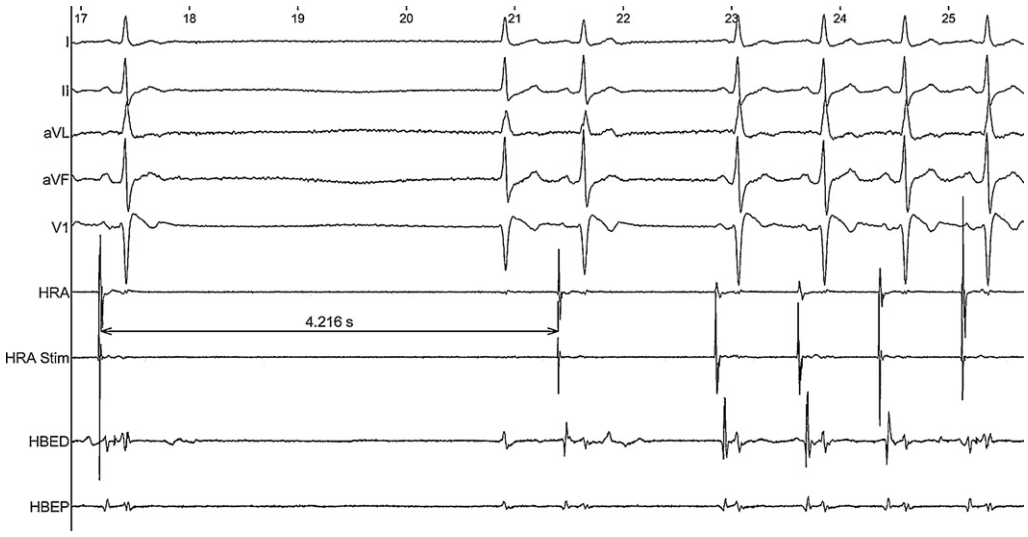

Fig. 2. Electrocardiographic tracing (25 mm/s) and endocardial signals from the high right atrium and the His-bundle region showing a spontaneous episode of sinus arrest during electrophysiological study (patient 6). HRA, high right atrium electrogram recorded from proximal bipole; HRA STIM, high right atrium electrogram recorded from distal bipole (used for stimulation); HBED, His-bundle electrogram recorded from the distal bipole; HBEP, His-bundle electrogram recorded from the proximal bipole.

Table 2
Clinical, electrocardiographic and electrophysiological data of subjects with and without SND.

Variables	Subjects with SND ($n=6$)	Subjects without SND ($n=62$)	p-Value
Age (years)	43.16 ± 6.82	44.93 ± 13.23	0.749
Males (n)	3 (50%)	52 (83.9%)	0.044
History of syncope (n)	6 (100%)	22 (35.5%)	0.002
Family history of BS/SCD (n)	2 (33.3%)	16 (25.8%)	0.690
Spontaneous ECG type			0.721
Type 1 (n)	2 (33.3%)	25 (40.3%)	
Type 2 (n)	3 (50%)	21 (33.9%)	
Type 3 (n)	1 (16.7%)	16 (25.8%)	
P-wave duration in lead II (ms)	148.33 ± 31.25	113.25 ± 17.04	<0.001
P-wave duration in lead V2 (ms)	110.00 ± 24.49	90.73 ± 16.01	0.009
PR interval in lead II (ms)	231.66 ± 44.90	174.35 ± 28.45	<0.001
PR interval in lead V2 (ms)	219.16 ± 48.82	164.11 ± 26.77	0.009
QRS in lead II (ms)	119.16 ± 13.57	101.20 ± 20.07	0.036
QRS in lead V2 (ms)	131.66 ± 12.11	109.67 ± 15.59	0.001
QTc in lead II (ms)	423.13 ± 42.77	408.32 ± 30.35	0.275
QTc in lead V2 (ms)	463.18 ± 45.88	417.31 ± 39.49	0.009
EPS (n)	5 (83.3%)	32 (51.6%)	0.136
AH interval (ms)	154.80 ± 30.90	89.76 ± 19.66	<0.001
HV interval (ms)	65.80 ± 18.79	48.57 ± 11.00	0.011
cSNRT (ms)	1366.66 ± 550.75	283.33 ± 15.27	0.027
Inducible VT at EPS (n)	2 (40%)	23 (65.4%)	0.267
ICD implantation (n)	4 (66.6%)	24 (38.7%)	0.184
PM implantation (n)	2 (33.3%)	0 (0%)	<0.001
Atrial arrhythmias during follow-up (n)	3 (50%)	11 (17.7%)	0.062
Ventricular arrhythmic events during follow-up (n)	0 (0%)	5 (8.1%)	0.470

SND, sinus node disease; BS, Brugada syndrome; SCD, sudden cardiac death; ECG, electrocardiogram; EPS, electrophysiological study; cSNRT, corrected sinus node recovery time; VT, ventricular tachycardia; ICD, implantable cardioverter defibrillator; PM, pacemaker.

In the present report, we showed that a significant number of subjects with type 1 ECG pattern of BS display SND (8.8%). The most common cause of SND in these patients was sino-atrial block leading to sinus pauses >3 s. 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). SND may be the predominant phenotype in these patients, a fact that may explain their benign clinical course [27]. Another possible explanation is that cardiac pacing (lower rate of 60 beats/min) may protect these patients from severe bradycardia that could induce augmentation of the ST-segment elevation and VT/VF events [22–25]. Based on the current recommendations, an ICD should be implanted in symptomatic patients with the diagnostic ECG of BS [2]. In our study, an upgrade to an ICD was offered in both patients who initially received a PM. We additionally showed that subjects with type 1 ECG pattern of BS and SND display increased P-wave duration and PR interval. Furthermore, cSNRT was abnormal in all cases with SND who underwent an EPS. Previous studies have shown that patients with BS display an increased P-wave duration and PR interval, particularly those with an *SCN5A* gene mutation [28,29]. These findings suggest that the reduced sodium current and the intra-atrial conduction velocity possibly underlie the mechanisms of increased P-wave duration and PR interval in patients with BS. In addition, the PROSPER study has demonstrated that prolonged P-wave duration and PR interval provides significant information on the risk of developing atrial fibrillation [30]. 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) [31,32]. Fibrotic atrial cardiomyopathy may be the underlying

pathophysiology even in the young subjects with SND and atrial arrhythmias [32]. Morimoto et al. reported an autopsy case of BS with significant lesions in the sinus node, including reduction of the nodal cells and fibrosis [15]. Subjects with BS ECG pattern and SND exhibited increased QRS duration and QTc interval compared to those without SND, an event that possibly reflects an advanced electrical disease. However, none of those diagnosed with SND suffered syncope or ICD therapies.

Limitations

The present study has several limitations. First, it is a retrospective analysis and hence is subject to the limitations inherent in any retrospective study. Second, a small number of subjects with SND were studied. Third, chronotropic incompetence which is a manifestation of SND was not evaluated. Fourth, EPS was not performed in all subjects. Finally, screening for *SCN5A* gene mutations was performed in only 6 subjects.

Conclusions

SND is not an uncommon finding in subjects with type 1 ECG phenotype of BS. The occurrence of SND in relatively young patients is puzzling, and deserves meticulous investigation including sodium channel blocking test. In patients with SND and Brugada sign who display recurrent arrhythmogenic syncope following PM implantation, an upgrade to an ICD should be offered. The prognostic significance of SND in BS should be evaluated in prospective studies.

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