Brugada syndrome and sinus node dysfunction

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Abstract
Brugada syndrome (BrS) is a well-known catastrophic disease first reported in 1992 by the Brugada brothers. Ventricular fibrillation (VF) is an essential arrhythmia in BrS. An association between BrS and atrial tachyarrhythmias is not uncommon. However, sinus node dysfunction (SND) associated with BrS has not been well discussed. In this review, we focus on the association between BrS and SND. Based on previous reports describing clinical, epidemiological, and genetic evidence, SND is not a rare concomitant disorder in BrS. BrS may be a multiple conduction or arrhythmogenic disorder including not only the His-Purkinje system and right ventricle, but also the sinus node and atrium, derived from ion channel mutations.

KEYWORDS
Brugada syndrome, overlap syndrome, sick sinus syndrome, sinus node dysfunction, sodium channel mutation

1 | INTRODUCTION
Brugada syndrome (BrS) is a well-known catastrophic disease reported in 1992 by the brother cardiologists Pedro and Josep Brugada.1 Although ventricular fibrillation (VF) is an essential arrhythmia in BrS, an association between BrS and atrial tachyarrhythmias is not uncommon. Atrial fibrillation (AF) is the most common arrhythmia other than VF in BrS, and AF is well known as a major cause of inappropriate shock from an implantable cardioverter defibrillator (ICD).2 However, sinus node dysfunction (SND) associated with BrS has not been well discussed. In this review, we focus on the association between BrS and SND.

2 | CLINICAL CASE REPORTS OF BRUGADA SYNDROME ASSOCIATED WITH SINUS NODE DYSFUNCTION
Twenty-four years ago, we treated a patient with idiopathic VF with incomplete right bundle branch block and persistent ST elevation in the right precordial leads, which was later named “Brugada syndrome,” the case report was published in 1993.3 One year ago, this patient was diagnosed as having sick sinus syndrome (SSS), and a cardiac pacemaker implanted (Figure 1).4 In 1993, we thought that the combination of BrS and SND occurred incidentally, and we had never imagined a genetic correlation between the two diseases.

We later reported three adult patients with BrS and SND in 2005: a 42-year-old man (the same case as3), a 62-year-old man, and a 49-year-old woman (the same case as5). Spontaneous sinus pause > 3 sec was observed clinically in all three patients, and a prolonged sinus node (SN) recovery time was observed during the electrophysiological study (EPS) in two of the patients. In all three patients, SND was recognized before an episode of VF. Two of the patients had a pacemaker implanted before the ICD implantation.

There have been several case reports of BrS associated with SND or SSS since 2005 as shown in Table 1.

Morimoto et al6 reported histopathologic evidence of SND in an autopsy case of BrS died suddenly. On histopathologic examination, the number of SN cells was reduced by one-half with prominent fatty tissue and fibrosis, which was compatible with SND. Namdar...
et al\textsuperscript{7} reported a 52-year-old man, who had the combination of hemochromatosis, SND, and BrS. Risgaard et al\textsuperscript{8} reported the case of a 75-year-old woman who was diagnosed with SSS and implanted a pacemaker 7 years ago. The patient was suspected to have BrS because of the family history and flecainide-induced type 1 ECG. A genetic test confirmed that she had the same mutation in SCN5A as her brother diagnosed with symptomatic BrS. As the patient had been asymptomatic for 7 years after pacemaker implantation, it was decided not to upgrade to an ICD.

There have been several reports of young patients (<30 years) with both BrS and SSS. Fazelifar et al\textsuperscript{9} reported a 23-year-old man with SSS and a Brugada-type ECG. Because of the absence of inducible ventricular tachyarrhythmias during the EPS, a dual-chamber pacemaker (DDDR) was implanted for SSS. Shimizu et al\textsuperscript{10} also reported a patient with both juvenile SSS and BrS followed up for 12 years. When the patient was 13 years old, he suffered from SND and AFL, and a pacemaker was implanted at the age of 15 years. At 25 years old, the patient was diagnosed with BrS based on pilsicainide-induced type 1 ECG and the induction of VF by the EPS. His pacemaker was upgraded to an ICD. Nakajima et al\textsuperscript{11} reported the case of a young patient with the overlapping phenotypes of juvenile SSS and BrS. When the patient was in elementary school, he was diagnosed as having SSS and underwent a pacemaker implantation. When he was a teenager, he experienced syncpe, and VF was induced by an EPS. When he was in his twenties, pilsicainide-induced type 1 ECG was documented. His pacemaker was then upgraded to an ICD.

The clinical course in two of the three young patients described above (ie, those in the Shimizu and Nakajima reports) is very interesting because BrS tends to become obvious after the diagnosis of SSS is made. The popularization of the challenge test using a sodium channel blocker may be one reason. In addition, the frequency of Brugada-type (type 1) ECG among adults has been reported as 0.05%-0.28%,\textsuperscript{12-17} which is higher than that among children (0.005%-0.06%).\textsuperscript{12,18-20} The age of phenotype manifestation has been reported to be different between SSS and BrS in family members with SCN5A mutations. Abe et al\textsuperscript{21} reported that the mean age of the SSS manifestation in individuals with SCN5A mutation was considerably less (20 ± 3.4 years) than the mean age of those affected with BrS, which typically manifests during adulthood at a mean age of around 40 years. Abe et al\textsuperscript{21} suggested that SND is the earliest electrophysiological manifestation of SCN5A mutation.
carriers. Therefore, in some juvenile SSS patients, the phenotype of BrS may become apparent in adulthood.

3 | PREVALENCE OF THE ASSOCIATION BETWEEN BRUGADA SYNDROME AND SINUS NODE DYSFUNCTION

The relationship between BrS and SND was first reported by Morita et al.\textsuperscript{22} in 2004. They performed an EPS in 60 patients with Brugada-type ECG. They divided the patients into two groups according to the inducibility of VF: 26 patients with EPS-induced VF (the VF group) and 34 patients without EPS-induced VF (the non-VF group). In the VF group, the corrected SN recovery time and the sinoatrial conduction time were both prolonged compared to the non-VF group: \( 452 \pm 126 \text{ ms} \) vs \( 324 \pm 146 \text{ ms} \) and \( 179 \pm 60 \text{ ms} \) vs \( 127 \pm 60 \text{ ms} \), respectively. Although clinical manifestations of SND were not observed, Morita et al revealed latent SND in the BrS patients with EPS-induced VF.

Table 2 shows the prevalence of the combination with BrS and SND in the previous studies. Bordachar et al.\textsuperscript{23} demonstrated a high prevalence of SND, in 10 (17%) of 59 patients with BrS. However, that high prevalence was derived from the EPS-induced SND cases, not the clinically documented SND or SSS cases. In adults, although the prevalence of clinically documented SND in patients with BrS was relatively high (7.9% and 8.8%) in the small-population studies,\textsuperscript{24,25} it was not so high (1.1%-1.7%) in the more recent large-population studies.\textsuperscript{24-28} In children, the prevalence of SND seems to be higher (6.7%-9.0%) compared to the adult patients.\textsuperscript{26,29,30} Conversely, we studied the prevalence of Brugada-type ECG in 487 consecutive patients who had been diagnosed as having SSS and were implanted with a cardiac pacemaker,\textsuperscript{31} and our analyses demonstrated that the prevalence of Brugada-type ECG in this SSS group was higher (0.82%) compared to the general population (0.005%-0.28%).\textsuperscript{12-20} Thus, SND seems to be not uncommon among individuals with BrS.

4 | GENETIC ASSOCIATION BETWEEN BRUGADA SYNDROME AND SINUS NODE DYSFUNCTION

In 1998, Chen et al.\textsuperscript{32} reported the first mutation linked to BrS in the sodium channel gene SCN5A. To date, 20 subtypes of gene mutation responsible for BrS have been identified.\textsuperscript{33} SC5A mutations are the most common type, found in 20%-30% of BrS probands.\textsuperscript{33} SND has also been reported in patients with a sodium channel mutation.\textsuperscript{34,35} Prolongation of the action potential of SN cells and slowing of diastolic depolarization due to an abnormal sodium channel gene may contribute to SND.\textsuperscript{36} In addition, reduced sodium current could account for both BrS and SND.

A possible bradycardic mode of death in carriers of the mutant SCN5A gene in a family with long QT syndrome (LQT) and BrS was proposed by van den Berg et al.\textsuperscript{36} They showed that one carrier who had a mutation of SCN5A (1795insD) suffered from sinus arrest > 9 second. A single mutation in SCN5A has been reported to be able to cause both the BrS and SSS phenotypes.\textsuperscript{24,37,38} Makiyama et al.\textsuperscript{24} screened for SCN5A gene mutations in 38 unrelated patients with clinically diagnosed BrS, and they identified four heterozygous mutations in four patients, all of whom had bradyarrhythmias including three with SSS (T187I, K1578 fs/52, R163X). Takehara et al.\textsuperscript{39} also reported a sodium channel mutation in SCN5A (R367H) identified in BrS associated with atrial standstill.
A new disease entity known as "overlap syndrome" of cardiac sodium channelopathy has been proposed: The mutation carriers tend to exhibit overlapping clinical properties including LQT, BrS, cardiac conduction disturbance, and SSS.40,41 Makita et al42 investigated a cohort of 44 genotyped LQT3 families with multiple ethnic backgrounds from seven institutions in Japan, Italy, Germany, UK, and the United States. E1784K was the most prevalent SCN5A mutation identified in 15 families. Of 41 mutation carriers in these families, the diagnosis of BrS was established in nine (22%) and SND was recognized in 16 (39%). Of these 16 mutation carriers with SND, four subjects also exhibited the BrS phenotype. Therefore, four (10%) of the 41 subjects with SCN5A (E1784K) mutation revealed the clinical overlapping phenotype, that is, BrS and SND.

The phenotype manifestation of patients with the same SCN5A mutations is variable. Some gene variants can modulate susceptibility to various arrhythmia phenotypes.33 Common genetic variants at SCN5A-SCN10A and HEY2 are reported to be associated with BrS.43 Yagihara et al44 revealed that variants in the core promotor region and the transcription regulatory region of SCN5A are associated with various arrhythmia phenotypes including BrS and SSS. Aoki et al45 showed that the phenotypic differences could be explained by modifiers such as SCN1B and DSG2 gene variants in a family with BrS and SSS with an SCN5A mutation.

A novel potential therapeutic approach was suggested in a 2013 in vitro study using mouse cardiomyocytes. Chakrabarti et al46 demonstrated that MOG1, a Na+,1.5-modulating protein, rescued the reduced plasma membrane expression of Na+,1.5 and sodium current densities due to the Na+,1.5 trafficking-defective mutations D1275N associated with SSS and G1743R associated with BrS. Thus, MOG1 may be a potential therapeutic option for some BrS and SSS patients with loss-of-function mutations in Na+,1.5.

5 | PROGNOSTIC VALUE OF SINUS NODE DYSFUNCTION IN PATIENTS WITH BRUGADA SYNDROME AS A POSSIBLE RISK FACTOR

In patients with BrS, SND was reported to be a risk factor significantly associated with future lethal arrhythmic events: sudden cardiac death (SCD), aborted SCD, or ICD shock.27,28,30 Sieira et al27 studied a total of 363 asymptomatic BrS patients with spontaneous or drug-induced type 1 ECG. After mean follow-up period of 73.2 ± 58.9 months, an annual incidence rate of lethal arrhythmic events was 0.5%. Although the multivariate analysis was not significant, univariate analysis identified that previous SND was a risk factor for arrhythmic events (hazard ratio, 8.0; 95% confidence interval, 1.0-63.9; P = .05).27 Sieira et al28 also studied a consecutive cohort of 228 women with spontaneous or drug-induced type 1 ECG (asymptomatic: 75%). They reported an event rate of 0.7% per year during a mean follow-up of 73.2 ± 56.2 months. Univariate analysis revealed that SND was one of the risk factors significantly associated with arrhythmic events (hazard ratio, 9.1; 95% confidence interval, 1.1-76.4; P = .04). Corcia et al reported the prognosis and risk in young (≤19 years) patients with BrS (N = 95, asymptomatic: 72%).30 During a mean follow-up of 59 months, the event rate was 1.9% per year. SND, atrial tachycardia, or a combination of both had a significantly worse prognosis than those without these findings (hazard ratio, 6.79; 95% confidence interval, 1.80-22.58; P = .01). The

| Study author, year (reference number) | Number of patients | Age, years | Men (%) | Asymptomatic (%) | Spontaneous Brugada-ECG | SND (%) |
|--------------------------------------|--------------------|------------|---------|-----------------|------------------------|--------|
| Adult                                |                    |            |         |                 |                        |        |
| Bordachar, et al 2004                | 59                 | 43 ± 9     | 74      | 76              |                        | 17 (EPS) |
| Makiyama, et al 2005                 | 38                 | 47 ± 17    | 92      | 47              |                        | 7.9    |
| Letsas, et al 2013                   | 68                 | 45 ± 13    | 81      | 59              | 40%                    | 8.8    |
| Conte, et al 2014                    | 465 (>12 y)        | 58         | 51      | (all drug-induced) |                        | 1.5    |
| Sieira, et al 2015                   | 363                | 41 ± 17    | 55      | 100             | 11%                    | 1.1    |
| Sieira, et al 2016                   | 542                | 41 ± 17    | 58      | 71              | 17%                    | 1.7    |
| Children                             |                    |            |         |                 |                        |        |
| Probst, et al 2007                   | 30 (<16 y)         | 8 ± 5      | 57      | 60              | 57%                    | 6.7    |
| Conte, et al 2014                    | 40 (<12 y)         | 8 ± 3      | 60      | 75              | (all drug-induced)     | 7.5    |
| Gonzalez Corcia, et al 2017          | 95 (<19 y)         | 13 ± 8     | 55      | 72              | 12%                    | 9.0    |

| Study author (year) | Number of patients | Age, years | Men (%) | Symptomatic (%) | Brugada-ECG (%) |
|---------------------|--------------------|------------|---------|-----------------|-----------------|
| Hayashi, et al 2010 | 487                | 70 ± 12    | 45      | 100             | 0.82            |

EPS, electrophysiological study-induced SND; SND, sinus node dysfunction.
incidence rate was 4.53% per year in patients with SND and 1.32% per year in those without SND and/or atrial tachycardia.

6 | MANAGEMENT OF BRUGADA SYNDROME PATIENTS WITH SINUS NODE DYSFUNCTION

In BrS patients with SND, the indication of an ICD should be basically same as that for BrS. Implantation of an ICD is first-line therapy for BrS patients presenting with aborted SCD or documented VF or polymorphic ventricular tachycardia (VT) (Class I recommendation). In the Japanese guideline in 2012, the Class IIa indication of an ICD for the primary prevention is that patients who have Brugada-type (coved-type) ECG (spontaneous or drug-induced, documented in the superior positions) and meet at least two of the following three conditions: (i) history of syncope (likely caused VT/VF), (ii) family history of sudden death (SD), and (iii) VF induced during EPS. As mentioned before, SND has been reported to be a risk factor for lethal arrhythmic events. Presentation of SND might be an additional factor for considering an ICD implantation. However, there has been not sufficient clinical evidence whether SND or SSS is a risk factor for future ventricular arrhythmic events. Presentation of SND might be an additional factor for considering an ICD implantation. However, there has been not sufficient clinical evidence whether SND or SSS is a risk factor for future ventricular arrhythmic events. The implantation of an implantable loop recorder should be considered when a syncope patient with Brugada-type ECG does not fulfill the indication of ICD (no family history of SD and negative EPS result). Concerning the pacing mode, a dual-chamber ICD is preferable because atrial pacing is more indicated especially in patients with clinically documented SND or SSS.

The indication of upgrade to an ICD in SSS patients who have proven to having a clinical manifestation of BrS should be considered according to the above-mentioned criteria. Although there are some concerns about sensing, a subcutaneous ICD may be an alternative choice in patients with a previously implanted pacemaker.

7 | CONCLUSIONS

Based on previous reports describing clinical, epidemiological, and genetic evidences, it is apparent that SND is not a rare concomitant disorder in BrS. Among patients with SSS, if they exhibit recurrent syncope after pacemaker implantation, the ventricular tachyarrhythmia is a possible cause. Repeated ECG recordings and provocation with a sodium channel blocker could unmask latent BrS. On the other hand, SND may be another cause of syncope in BrS. BrS may be a multiple conduction and arrhythmogenic disorder including not only the His-Purkinje system and right ventricle, but also the SN and atrium, derived from ion channel mutations.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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