Clinical and Electrophysiological Characteristics of Binodal Disease

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Background Although coexistence of atrioventricular conduction disturbances with sick sinus syndrome (SSS), so-called binodal disease (BND), is a frequently encountered disorder, its clinical significance and electrophysiological characteristics remain unknown.

Methods and Results One hundred and seven patients with SSS were divided into BND (n=30) and N-BND groups (n=77). Sinus cycle length, sinus node recovery time (SRT), sino-atrial conduction time (SACT), the number of isolated sinus node electrograms, atrio-His (AH) interval, His-ventricular (HV) interval, intra-atrial conduction time (PA intervals) and QRS width were measured. In addition, the prevalence of bundle-branch block was obtained. The parameters of sino-atrial and intra-atrial conduction were significantly longer in the BND group: SRT (5.070±2.628 vs 3.122±1.856 ms, p<0.05), SACT (115±30 vs 87±21 ms, p<0.05), PA intervals (56±13 vs 41±8 ms, p<0.05). The BND group was more likely to have atrial fibrillation than the N-BND group (83.3% vs 53.2%, p<0.01). HV interval, QRS width and the prevalence of associated bundle-branch block did not differ between the 2 groups.

Conclusion BND patients not only had sino-atrial and atrioventricular node dysfunction, but also widespread atrial conduction disturbances. Thus, in the clinical setting BND should be categorized as severe SSS. (Circ J 2006; 70: 1580–1584)

Key Words: Binodal disease; Sick sinus syndrome; Sinus node electrocardiography

The concept of sick sinus syndrome (SSS) was first described by Ferrer1 and by Rubenstein et al.2 Clinically, it is recognized as bradycardia that is induced by a transient or persistent functional disorder of sino-atrial nodal automaticity or sino-atrial conductivity. In particular, a morbid condition accompanied not only by functional disorder of the sino-atrial node but also by atrioventricular node conduction disturbance was reported by Kaplan et al in 19733 and since then, this condition has been referred to as “binodal disease” (BND). However, the frequency of the association of BND with SSS ranges from 23% to 58%, showing marked variation among previously published reports.4–6 Although the pathogenesis and clinical features remain unknown, we have previously reported that transient cardiac arrest in SSS patients is actually sino-atrial block caused by disturbed conduction adjacent to the sino-atrial node.7,8 There is also another report that the lesions that may cause SSS involve not only the sino-atrial node, but also the entire atrium.9 These observations raise the possibility of BND being based not merely on isolated lesions of the sino-atrial and atrioventricular nodes but also on wide-ranging lesions of the atrium or of the cardiac conduction system. The objective of this study was to elucidate BND by investigating its clinical and electrophysiological characteristics in patients with SSS.
Characteristics of Binodal Disease

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Fig 1. Measurements of P duration, PA interval and sino-atrial conduction time (SACT) was measured using sinus node electrogram. RAA, right atrial appendage; HBE, His bundle electrogram; SNE, sinus node electrogram.

Fig 2. Intracardiac electrogram showing transient sino-atrial block following frequent stimulation from the right atrial appendage (RAA). There are 4 isolated sinus node electrograms (*) following rapid atrial stimulation. SRTi, sinus node recovery time (indirect; measured by atrial potential); HBE, His bundle electrogram; SNE, sinus node electrogram; SRTd, sinus node recovery time (direct; measured by SNE); arrow heads, onset of SNE.

ter was inserted and placed at that site for recording the His bundle electrogram (HBE). Next, an 8F sheath (length: 85 cm) to introduce the sinus node electrogram (SNE) catheter was inserted into the right femoral vein. After this sheath had been placed in the right atrium, a 5F and 10-polar catheter (1085-150-S, Webster Co) was inserted through the sheath for recording SNE. The catheter provided 9 electrodes for recording SNE (inter-polar distance of 1.5 mm and electrode length of 1.0 mm) and with 1 indifferent electrode (45 mm proximal to the tip). The catheter for SNE was reversed in the superior vena cava. The indifferent electrode was placed in the superior vena cava, and the electrode for SNE was placed in the transition area from the superior vena cava to the right atrium. A low-end filter and a high-end filter were set at 0.05–0.1 Hz and 40–50 Hz, respectively. The extent of amplification was set at 100–200μV/cm, and SNE was recorded directly.7,8,11,12 The mean sinus cycle length (SCL) of 10 heart beats during sinus rhythm and the duration from the onset of SNE to the onset of atrial potential (sino-atrial conduction time: SACT) were determined from SNE. The width of the P wave (P duration) and QRS width were measured on the body surface ECG, and the duration from the onset of the P wave and atrial potential recorded by the HBE catheter (PA interval), atrio-His (AH) interval, and His-ventricular (HV) interval were also measured (Fig 1). The sino-atrial function was evaluated using an overdrive suppression test in which the atrium was frequently stimulated at 80–200 beats/min for 30 s through the electrode catheter placed in the RAA. The duration from the last pacing spike to the onset of SNE determined directly through the catheter for SNE was defined as the direct sinus node recovery time (SRT direct: SRTd), and the duration from the last pacing spike to recovery of the atrial potential through the catheter maintained in the RAA as the indirect sinus node recovery time (SRT indirect: SRTi). The number of isolated SNEs, which could not capture the atrium, through the catheter used for SNE during the SRTi was also determined (Fig 2). The minimum pacing rate at which grade II atrioventricular block occurred (ie, Wenckebach point) was determined by RAA pacing.
A 24-h ambulatory ECG was recorded from the CM 5 and NASA leads, and the data were analyzed by DMW-7000H (Fukuda Denshi Co, Ltd). Total heart beats (THB), the minimum heart rate (Min. HR), the maximum duration of atrial pause (clinical max. atrial pause), and the number of premature atrial contractions (PACs) were determined.

Echocardiography

The maximum (end-diastolic) diameters of the long and short axis of the right and left atria were determined on the 4-chamber view using transthoracic echocardiography.

Statistical Analysis

Statistical analysis was performed with the Mann-Whitney U test for comparison of all parameters between the 2 groups. All the data are expressed as the means±standard deviation, and a p-value <0.05 was considered significant.

Results

Patient Characteristics

Patient characteristics are shown in Table 1. Thirty of the 107 patients with SSS (28%, 17 males, 13 females, mean age: 65±8 years) were assigned to the BND group. Grade I or greater atrioventricular block was recognized in 19 of these 30 patients on 12-lead or 24-h ambulatory ECG monitoring during sinus rhythm. Grade II or greater atrioventricular block was induced by right atrial low frequency stimulation (≤120 beats/min) in 21 of the 30 patients. All 19 patients with grade I atrioventricular block during sinus rhythm had prolonged AH interval, and did not show prolongation of the HH or HV interval. All the 21 patients with atrioventricular block ≥grade II induced by right atrial stimulation (with a low frequency) had AH block. The N-BND group consisted of 77 patients (72%, 33 males, 44 females, mean age: 61±11 years). There was no significant difference in age or gender between the 2 groups. The incidence of patients with Rubenstein classification type III corresponding to paroxysmal atrial fibrillation was significantly higher in the BND group than in the N-BND group (25/30 vs 41/77 patients or 83.3% vs 53.2%, respectively, p<0.01). There was no significant difference between the 2 groups in the atrial diameters on echocardiography. In patients who underwent 24-h ambulatory ECG monitoring before the EPS, there was no significant difference between 2 groups in the THB, Min. HR or the number of PACs on 24-h ambulatory ECG monitoring, whereas the clinical max. atrial pause was significantly longer in the BND group (4,691±2,084 ms (BND) vs 3,401±1,863 ms (N-BND); p<
The prevalence of syncope was 7/30 patients (23.3%) in the BND group and 9/77 patients (11.7%) in the N-BND group.

**Discussion**

Several reports have described a morbid condition (BND) of atrioventricular node conduction disturbance in patients with sinus node dysfunction, but the incidence of BND varies considerably among those studies. Rubenstein et al reported that abnormalities in atrioventricular conduction were noted in 33 (58%) of 56 patients with SSS. In contrast, according to Vallin et al, atrioventricular block induced by low-frequency atrial stimulation (≤130 beats/min) was recognized in only 7 (23%) of 30 SSS patients. Kudo et al reported that BND occurred in 7 (37%) of 19 SSS patients. Rosen et al and Katoh et al reported an incidence of 40% (6/15) using the same method as in the reports by Vallin et al. Furthermore, Rosen et al reported that atrioventricular conduction disturbance in their patients was located above the His bundle recording site.

**Evaluation of Atrioventricular Conduction**

In the present study, SSS accompanied by grade I or greater atrioventricular block in sinus rhythm, or by grade II or greater atrioventricular block induced by low-frequency atrial stimulation (≤120 beats/min), was defined as BND. Using this definition, 30 patients (28%) were diagnosed: 19 had accompanying grade I atrioventricular block without conduction disturbance below the His bundle and in 21 atrioventricular block of grade II or greater was induced by atrial stimulation with a low frequency and that atrioventricular block was caused by AH block in all of them.

**Conclusion**

Previously, a conduction disturbance below the His bundle has been observed in 8–10% of SSS patients. Kudo et al who compared 26 SSS patients with 14 healthy subjects, reported that there was no significant difference in HV interval between the 2 groups. Our study demonstrated that the HV interval was not significantly different between the 2 groups, and the mean HV interval was normal in both groups when the normal range was defined as 35–55 ms, as described by Josephson. There was no difference in the QRS width between the 2 groups nor was there a difference in the incidence of abnormal prolongation of the HV interval or of the association of bundle-branch block. Our results indicate that the main lesion to atrioventricular conduction in BND is localized to the conduction system above the His bundle, in accordance with the report by Rosen et al.

**Evaluation of Sino-Atrial Node Function**

We have previously found that the affected lesions in cases of SSS were not limited within the sino-atrial node but also involved the adjacent area. Based on this observation, we also have presumed that atrial bradyarrhythmia might be caused by sinus node-atrial exit block occurring in the peri-sino-atrial nodal area. In the present study, there was no difference between the 2 groups in SCL and SRTd, whereas SACT and SRTi were significantly longer and the number of isolated SNEs was significantly larger in the BND group than in the N-BND group.
in patients with SSS and we considered it to be caused by atrial muscle conduction disturbance localized in the area adjacent to the sinus node. Thus, an intra-atrial conduction abnormality is considered to exist in patients with SSS. In the present study, the prolonged PA interval and P duration in the BND group indicated that the conduction time was prolonged not only in the area adjacent to the sinus node but also in the entire atrium of these patients. Raybaud et al. reported a positive correlation between the atrial diameter measured on echocardiography and the intra-atrial conduction time; however, there was no difference between the present BND and N-BND groups in atrial diameters, which suggests that prolongation of the intra-atrial conduction time in BND is caused by an increase in the conduction time as a result of degeneration of the atrial myocardium.

Clinical Features of BND
The 24-h ambulatory ECG monitoring disclosed that the maximum duration of the atrial pause was significantly greater in the BND group, suggesting that BND is a more severe stage of illness than ordinal SSS. Nakata et al. considered that the coexisting atrial fibrillation was caused by wide-ranging atrial myocardium degeneration rather than by a disturbance in the sino-atrial node itself. The coexistence of paroxysmal atrial fibrillation with SSS was 58% among the present patients, and the coexistence was significantly higher (77%; 23/30) in the BND group. Although the number of PACs was not statistically significantly different between the 2 groups, the number of PACs tended to higher in the BND group. Thus, patients with BND were considered to have more severe intra-atrial conduction disturbance.

Study Limitations
The major limitation of our study is the lack of pathologic assessment. However, previous reports have suggested that BND is associated with myocardial fibrosis, edema, fatty degeneration and inflammatory cell infiltration, not only in the sinus node and the area adjacent to the sinus node, but also in the atrial area remote from the sinus node. The present study was retrospective and did not include long-term follow-up examinations. Thus, the progression or regression of BND remains unknown.

Conclusion
The results of the present study strongly suggest that BND does not represent a simple co-existence of 2 independent lesions involving the sino-atrial node and the atrioventricular node separately, but should be categorized as a subtype of severe SSS, because it manifests various conduction disturbances that include the sino-atrial node, intra-atrial conduction and the atrioventricular node.

References

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