Development of Atrioventricular Block and Diagnostic Value of Stored Electrograms in Patients With Sick Sinus Syndrome and Implanted Pacemaker

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Background: The incidence of atrioventricular block (AVB) in pacemaker patients with sick sinus syndrome (SSS) is not yet known. The aim of this study was to analyze AVB episodes in SafeR mode based on stored electrograms (EGM), and determine the occurrence rate and risk factors for advanced AVB in a pacemaker population with SSS.

Methods and Results: The study included 50 consecutive patients with SSS without a history of advanced AVB who had a dual-chamber pacemaker programmed in SafeR mode. A total of 377 EGM stored in the pacemakers as AVB episodes fulfilling the second- or third-degree criterion were analyzed. Of 377 EGM, 73 EGM (19.4%) were appropriate episodes, whereas the other EGM did not show actual AVB, and showed atrial tachyarrhythmia, ventricular event in the blanking period, or premature atrial contractions with block. On EGM analysis, advanced AVB occurred in 9 patients (18%), and the occurrence rate was 11.7% per year. Moreover, on multivariate analysis β-blocker use was an independent risk factor for advanced AVB (OR, 9.10; P=0.004).

Conclusions: The occurrence rate of advanced AVB in patients with SSS is much higher than previously reported, and β-blocker use is an independent risk factor for advanced AVB. SafeR is useful to detect latent AVB. Stored EGM, however, sometimes include inaccurately classified events. (Circ J 2015; 79: 1263–1268)

Key Words: Beta-blocker; Electrogram; Pacemaker; Sick sinus syndrome

Several studies have suggested that unnecessary right ventricular pacing increases the risk of atrial fibrillation and hospitalization for heart failure, despite the preservation of atrioventricular (AV) synchrony. AAI pacing mode has long been considered safe and reliable for patients with sinus node disease or bradycardia-tachycardia syndrome. It has never been widely used, however, because patients with sinus node disease have an increased risk of developing AV block (AVB). Several studies reported an annual incidence of second- and third-degree AVB of between 0.6% and 1.8% per year. These incidents of AVB, however, included asymptomatic episodes detected on only a few Holter electrocardiogram (ECG) recordings or only symptomatic episodes. The actual number of AVB during the entire follow-up period is not yet known. In recent years, new pacing modes have been developed. SafeR™ (SORIN Group CRM SAS, Clamart, France) pacing mode was designed to combine the advantages of AAI with the safety of DDD mode. The cardiovascular implantable electronic device (CIED) mounting SafeR mode can be programmed to record and store intracardiac electrograms (EGM) of AVB episodes. To our knowledge, research on EGM during AVB episodes in SafeR mode has not yet been reported. The aim of this study was to analyze AVB episodes in SafeR mode based on stored EGM, and determine the occurrence rate and risk factors for advanced AVB in pacemaker patients with sick sinus syndrome (SSS).
Wenckebach block rate (WBR) was measured on electrophysiological study during implantation. The patients were followed at 1 month after implantation of the pacing system and every 5 months thereafter during the study. At each follow-up, the stored data on the pacemaker memory were retrieved, and a total of 377 EGM related to the AVB episodes fulfilling the second- or third-degree criterion were collected. Each waveform of these stored EGM was carefully analyzed.

This study was approved by the Yokohama City University Hospital Ethics Committee.

**Statistical Analysis**

Comparisons of quantitative and categorical variables between groups were performed using Pearson chi-squared test or Student’s t-test. All continuous data are expressed as mean ± SD. Univariate or multivariate Cox regression models with a forward stepwise approach were run to assess crude and multi-

Figure 1. Electrograms (EGM) of 2:1 atrioventricular block (AVB). AVB with a conduction ratio of 2:1 occurred with a consequent switch in pacing mode to DDD in response to second-degree AVB criterion. Atrial and ventricular EGM are shown in the upper tracings, and atrial and ventricular markers in the lower tracing.

Figure 2. Electrograms (EGM) of high-degree atrioventricular block (AVB). Two consecutive atrial events with conduction block to the ventricle occurred with a consequent switch in pacing mode to DDD in response to third-degree AVB criterion. Atrial and ventricular EGM are shown in the upper tracings, and atrial and ventricular markers in the lower tracing.
Heart rhythm disorder and Value of Pacemaker EGM

Effectiveness of SafeR Mode

The mean follow-up period was 18.4±14.0 months. No pacemaker was reprogrammed from SafeR to DDD mode during the follow-up period, because of permanent AVB. At each follow-up, ventricular pacing data were also collected. The mean percent of ventricular pacing in all patients was 2.5±8.1%. No

Results

Baseline Characteristics

Mean subject age was 71.4±10.7 years, and 46% of the patients were male. In all patients, the indication for original pacemaker implantation was SSS, including bradycardia-tachycardia syndrome in 54%. The underlying disease was hypertension in 44%, diabetes mellitus in 20%, paroxysmal atrial fibrillation in 46%, cerebral infarction in 10%, and coronary artery disease in 12%. All patients had WBR ≥110/min. The proportion of patients receiving warfarin at the time of discharge after pacemaker implantation was 24%, that receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was 40%, and that receiving anti-arrhythmic drug (AAD) was 40%, including a β-blocker in 16%, class Ia or Ic AAD in 12%, bepridil in 6%, and verapamil in 10%. The β-blockers consisted of carvedilol in 3 patients, bisoprolol in 2 patients, atenolol in 2 patients, and metoprolol in 1 patient.

Effective mode of SafeR

The mean follow-up period was 18.4±14.0 months. No pacemaker was reprogrammed from SafeR to DDD mode during the follow-up period, because of permanent AVB. At each follow-up, ventricular pacing data were also collected. The mean percent of ventricular pacing in all patients was 2.5±8.1%. No

Figure 3. Electrograms (EGM) of junctional rhythm. Ventricular events with a blanking period occurred with a consequent switch in pacing mode to DDD in response to second-degree atrioventricular block criterion. Atrial and ventricular EGM are shown in the upper tracings, and atrial and ventricular markers in the lower tracing.

Figure 4. Electrograms (EGM) of premature atrial contraction with block. Atrial events, which are earlier than the atrial cycle length, with conduction block to the ventricle, occurred with a consequent switch in pacing mode to DDD in response to second-degree atrioventricular block criterion. Atrial and ventricular EGM are shown in the upper tracings, and atrial and ventricular markers in the lower tracing.
Occurrence Rate and Risk Factors for Advanced AVB

Advanced AVB was defined as second-degree type II (Mobitz) AVB, high-degree AVB, 2:1 AVB, or third-degree AVB. On EGM analysis, advanced AVB occurred in 9 patients (18%) during the follow-up period. Therefore, the annual occurrence rate of advanced AVB in this study was 11.7% per year. All 9 patients were free of symptoms.

On univariate Cox regression analysis, β-blocker use was associated with a higher risk of advanced AVB (OR, 9.098; 95% CI: 2.010–41.18, P=0.004; Table 2). On multivariate Cox regression analysis controlling for age and sex, β-blocker use was an independent risk factor for advanced AVB (OR, 9.100; 95% CI: 2.010–41.18, P=0.004; Table 2).

Table 1. Univariate Risk Factors for Advanced AVB

| Variable                  | OR    | 95% CI       | P-value |
|---------------------------|-------|--------------|---------|
| β-blocker                 | 5.867 | 1.550–22.20  | 0.009   |
| PQ interval (per 10-ms increase) | 1.018 | 0.990–1.047  | 0.202   |
| Age (per 1-year increase) | 1.046 | 0.967–1.132  | 0.263   |
| Hypertension              | 2.052 | 0.548–7.693  | 0.286   |
| Class Ia or Ic AAD        | 1.788 | 0.443–7.223  | 0.415   |
| LBBB                      | 2.362 | 0.293–19.04  | 0.419   |
| Male                      | 0.588 | 0.155–2.223  | 0.434   |
| WBR (per 10/min increase) | 0.993 | 0.959–1.027  | 0.670   |
| Atrial fibrillation       | 0.826 | 0.221–3.085  | 0.776   |
| ACEI or ARB               | 1.109 | 0.297–4.145  | 0.878   |
| RBBB                      | 0.855 | 0.107–6.861  | 0.883   |
| Diabetes mellitus         | 1.074 | 0.223–5.181  | 0.929   |

AAD, anti-arrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVB, atrioventricular block; CI, confidence interval; LBBB, left bundle branch block; OR, odds ratio; RBBB, right bundle branch block; WBR, Wenckebach block rate.

Table 2. Multivariate Risk Factors for Advanced AVB

| Variable                  | OR    | 95% CI       | P-value |
|---------------------------|-------|--------------|---------|
| β-blocker                 | 9.098 | 2.010–41.18  | 0.004   |

Abbreviations as in Table 1.

Discussion

Several studies have shown that frequent right ventricular pacing has long-term adverse effects.1–4 The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial compared ventricular back up pacing at 40/min (VVI-40) with dual-chamber rate responsive pacing at 70/min (DDDR-70) in patients with indications for implantable cardioverter defibrillator and no indications for pacing.1 Mortality was significantly higher in patients with DDDR-70 than in those with VVI-40 (OR, 1.61). In the Mode Selection Trial (MOST), a high cumulative percentage of right ventricular pacing was associated with high rates of atrial fibrillation and hospitalization for heart failure.2 Therefore, new pacing modes, such as managed ventricular pacing (MVP; Medtronic, Minneapolis, MN, USA) and SafeR, which were designed to combine the advantages of AAI with the safety of DDD mode, have been developed in recent years. These pacing modes were associated with a marked decrease in the percentage of ventricular pacing. In the Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial, the median percentage of ventricular pacing in MVP mode was significantly lower than that in conventional dual-chamber pacing mode (9.1% vs. 99.0%, P<0.001).20 The first large study of SafeR mode enrolled 147 consecutive patients with all pacing indications, and showed that the median percentage of ventricular pacing was 9.0% in SafeR mode and 95.0% in DDD mode.21 In the present study, the mean percent of ventricular pacing was 2.5±8.1%, similar to that in previous studies.16,17,21–23 Furthermore, no major adverse clinical event or symptom related to SafeR was observed. SafeR mode was safe, and significantly decreased the percent of ventricular pacing compared with DDD mode.

In the present study, EGM analysis revealed that 9 patients (18%) had EGM of advanced AVB, which consisted of high-degree AVB, 2:1 AVB, and second-degree type II (Mobitz)
AVB. The occurrence rate of advanced AVB in this study was 11.7% per year. In previous studies, the annual incidence of AVB in patients with SSS was 0.6–2.8%, which was much lower than that in the present study.10–15 In a prospective randomized evaluation by Andersen et al, AVB occurred at a rate of only 0.6% per year.15 The difference in the occurrence rates of AVB between the present study and previous studies is likely to have been due to the different procedure of AVB detection. In previous studies, asymptomatic episodes detected on only a few Holter ECG recordings or only symptomatic AVB episodes were collected. Accordingly, most asymptomatic AVB episodes might not have been detected in the previous studies. In contrast, a CIED in SafeR mode is known to be able to automatically detect and store EGM of AVB episodes during the entire follow-up period. Therefore, we considered that EGM analysis in SafeR mode could be more suitable and useful to detect latent AVB and determine the occurrence rate of AVB in patients with SSS. To our knowledge, research on EGM during AVB episodes in SafeR mode has not yet been reported. Patients with asymptomatic AVB might have had some risk of development of symptomatic AVB or higher degree AVB. Therefore, the early detection of asymptomatic AVB is important.

As described, the storage of EGM by CIED offers the opportunity to visualize and retrospectively evaluate events. These EGM, however, sometimes included events that had been inaccurately classified by the CIED.24,25 Nowak et al suggested that 45% of EGM that were recorded as atrial high rate episodes were false-positive events due to far-field sensing, noise, sinus tachycardia, double counting, or under-sensing.24 In the present study, a total of 304 EGM (80.6%) did not show actual second- or third-degree AVB, and showed atrial tachycardia or atrial fibrillation, premature ventricular contractions in the blanking period or AV junctional rhythm, and premature atrial contractions with block. The episodes of atrial tachyarrhythmia and premature atrial contraction with block, however, were not completely incorrect detections and were therefore classified as AVB, because AV conduction block actually occurred in these events. Making a diagnosis of arrhythmia on CIED should be based not only on diagnostic counters but also on physician review of stored EGM.

Considering the risk factors for AVB, we found that the only significant risk factor for advanced AVB was use of a β-blocker, a drug that can affect AV conduction. Beta-blockers have a negative dromotropic effect on the AV node and prolong the AH interval and AV nodal refractory period.27 Andersen et al reported that the reduction of Wenckebach block point at follow-up was associated with the patient starting to receive β-blocker.15 Of 50 patients in the present study, β-blocker was administered to 8 patients at discharge after pacemaker implantation. On EGM analysis, advanced AVB occurred in 4 (50%) of them. The 4 patients with advanced AVB were individually given carvedilol 7.5 mg, 5.0 mg, bisoprolol 2.5 mg and metoprolol 120 mg. The other 4 patients without advanced AVB were individually given carvedilol 2.5 mg, atenolol 25 mg, 12.5 mg and bisoprolol 2.5 mg. Carvedilol tended to cause a dose-related increase in advanced AVB, which needs further investigation due to the present small sample size. In contrast, the occurrence rate of advanced AVB in 42 patients without β-blocker treatment was 7.8% per year, which was also higher than previously reported. Thus, patients with SSS had an increased risk of advanced AVB irrespective of β-blocker treatment. These findings suggest that the use of a dual-chamber pacemaker rather than a single-chamber atrial pacemaker was preferred in patients with SSS in terms of development of AVB.

Other clinical variables, including BBB, WBR and other drugs, did not correlate with advanced AVB in the present study. Bepridil and verapamil are known to be able to depress AV node conduction. Of the 8 patients in whom these drugs were administered, however, no patients had advanced AVB in the present study. Some reports suggested that the presence of BBB at the time of implantation was associated with an increased risk of development of AVB.10,15 Matsumoto et al reported that WBR <120/min was a predictor of high-degree AVB, whereas other groups reported that WBR had little predictive value.12,14,15,16 Thus, the risk factors for AVB in SSS patients have not yet been completely clarified. Further analysis is required to establish the risk factors for AVB.

The present study has several limitations. One possible limitation is the small sample size, with analysis of only 2 centers. Another possible limitation is that a limited number of EGM can be stored due to the finite storage capabilities of the pacemaker, although all of the AVB episodes can be counted. Further study with a larger sample size is needed to confirm the present results.

Conclusions

The occurrence rate of advanced AVB in patients with SSS is much higher than previously reported, and β-blocker use is an independent risk factor for advanced AVB. SafeR is useful to detect latent AVB. EGM analysis, however, should be based on careful review by a physician, because stored EGM sometimes include inaccurately classified events.

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