Sleep Rate Mode of Pacemaker-Dependent Patients with Sick Sinus Syndrome Increases Dipper Blood Pressure and Dipper Heart Rate Patterns

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Summary

Cardiovascular event rates of patients with a dipper blood pressure (BP) and dipper heart rate (HR) pattern are lower than those of patients with nondipper BP and HR patterns. However, how the pacemaker mode affects the diurnal BP and HR patterns remains unclear.

We enrolled nine patients (average age 74.4 ± 6.6 years, 4 males and 5 females) with sick sinus syndrome who required atrial pacing. We investigated sequential 6-month pacing regimens (DDD mode at 60 bpm and sleep rate mode). We set the lower rate of sleep rate mode as follows: 60 bpm during the daytime and 50 bpm during the nighttime. The order of pacing mode was randomized, with crossover design. Ambulatory BP monitoring was performed at baseline, 6 months, and 12 months, BP category was classified into four groups (extreme dipper, dipper, nondipper, and riser pattern), and HR was classified into dipper and nondipper patterns.

Nighttime HR during the sleep rate mode was significantly lower than that at DDD (57.1 ± 6.2 versus 63.5 ± 3.8 bpm, P = 0.001). The dipper HR pattern was increased in the sleep rate mode compared with those at baseline or DDD mode (versus baseline: 89% versus 44%, P = 0.035; versus DDD: 89% versus 22%, P = 0.004). The dipper BP pattern significantly increased in the sleep rate mode compared with the baseline (56% versus 11%, P = 0.035), but the difference between the sleep rate mode and DDD mode was statistically marginal (56% versus 22%, P = 0.081).

The pacemaker settings in the sleep rate mode increased the dipper HR and BP patterns in pacemaker-dependent patients with sick sinus syndrome.

Key words: Diurnal rhythm, Circadian rhythm, Autonomic function

Blood pressure (BP) in humans exhibits a diurnal change, with BP levels generally being higher in early morning and during the daytime and decreasing during the nighttime. Among the types of diurnal BP change evaluated via a 24-hour ambulatory blood pressure monitoring (ABPM), the dipper BP pattern (with a 10% or greater decrease in BP during the nighttime compared with the daytime) has been associated with a lower rate of cardiovascular events and target organ damage compared with the nondipper BP pattern (less than a 10% decrease in BP during the nighttime compared with the daytime). In addition, when the diurnal BP pattern is classified into four groups based on the nocturnal fall in systolic BP at baseline, i.e., extreme dippers (20% or more), dippers (10% to below 20%), nondippers (0% to below 10%), and risers (any increase), stroke events are more frequent in the extreme dippers and risers, and there is a U-shaped curve relationship between the drop in nocturnal BP and cardiovascular events.

Heart rate (HR) also exhibits a diurnal variation with higher values in the morning. Several studies have investigated the dipper/nondipper HR pattern. The results revealed that both the cardiovascular event rates and BNP are lower in individuals with a dipper HR pattern than those in individuals with a nondipper HR pattern.

In pacemaker-dependent patients with sick sinus syndrome, HR is controlled by pacemakers. The sleep rate mode is used to reduce the nighttime HR to adjust the pacing rate to the physiological circadian rhythm. In pacemaker-dependent patients with sick sinus syndrome, the dipper HR pattern is expected to increase under sleep rate mode pacemaker operation compared to that by the usual DDD mode operation. However, the difference in HR and BP patterns between the sleep rate mode and DDD mode in pacemaker-dependent patients with sick sinus syndrome has not been elucidated.

The purpose of this study was to compare the rates of the dipper BP and HR patterns between the sleep rate...
mode and DDD mode in pacemaker-dependent patients with sick sinus syndrome.

**Methods**

**Subjects and pacemaker settings:** A total of 9 patients with sick sinus syndrome with the absence of spontaneous atrial activity during the atrial sensing test at AAI 40 bpm or atrial pacing percentage > 80% with a lower rate programmed at 60 bpm in DDD were included.

The baseline and DDD modes were set to a lower rate of 60 bpm, the sleep rate mode was set to a lower rate of 50 beats/minute during the nighttime and 60 beats/minute during the daytime, and all patients were adapted for rate response during the sleep rate and DDD modes. Figure 1 presents the details of the sleep rate mode. The sleep rate mode operates at a lower DDD rate of 60 beats/minute during the nighttime. At bedtime, the lower rate drops to 50 beats/minute. During waking, the lower rate increases to 60 beats/minute. We queried the patients directly to determine their individual bedtimes and waking times.

The study design is presented in Figure 2. Patient pacemakers were switched to the DDD mode for 6 months and the sleep rate mode for 6 months with a crossover design. Patients were randomized, and the ABPM and collection of blood sampling data were performed with the pacemaker settings masked to persons measuring ABPM.

This study was approved by the ethics committee of Jichi Medical University, and informed consent was obtained from all patients. The protocol was registered on the clinical trial registration site UMIN (University Hospital Medical Information Network) Clinical Trials Registry (UMIN-CTR) as no. 000020373, and the patients were enrolled from March 2016 to January 2018.

**ABPM and the definition of the dipping status of BP and HR:** ABPM was performed on a weekday using an automatic system that recorded the wearer’s BP and HR every 30 minutes for 24 hours. ABPM was performed using a validated machine: TM-2425 (A&D, Tokyo). Sleep BP was defined as the average of BP measurements from the time when the patient went to bed until the time he/she got out of bed; awake BP was defined as the average of BP measurements recorded during the rest of the day. The nocturnal systolic BP fall (%) was calculated as follows: $100 \times [1 - \text{sleep systolic BP/awake SBP ratio}]$. We subclassified the patients according to their nocturnal sys-
All data were expressed as mean ± SD or percentage. Paired t-tests were employed to compare the percentages of patients with a dipper HR or dipper BP pattern between the DDD mode and sleep rate mode groups and between baseline and the study period. The chi-squared test was employed to evaluate the differences in the percentages of patients with a dipper HR or dipper BP pattern between the DDD mode and sleep rate mode groups and between baseline and the study period. IBM SPSS Statistics version 20.0 was used for the statistical analysis. A probability value < 0.05 was considered statistically significant.

### Results

The baseline characteristics are presented in the Table. We enrolled 11 patients during the study period; one withdrew his/her consent, and one discontinued participation. Thus, a total of nine patients were analyzed. The average atrial pacing rate was 88% in the DDD mode and 74% in the sleep rate mode (P = 0.187).

Table. Patient Characteristics

| Variable               | n = 9 |
|------------------------|-------|
| Age (years)            | 74.4 ± 6.6 |
| Male/female            | 4/5   |
| 24 hour-SBP (mmHg)     | 131.3 ± 5.1 |
| 24 hour-DBP (mmHg)     | 78.6 ± 8.2 |
| 24 hour-HR (bpm)       | 67.6 ± 7.6 |
| Daytime SBP (mmHg)     | 136.2 ± 6.7 |
| Daytime DBP (mmHg)     | 82.5 ± 9.0 |
| Daytime HR (bpm)       | 69.7 ± 8.2 |
| Nighttime SBP (mmHg)   | 119.6 ± 13.6 |
| Nighttime DBP (mmHg)   | 69.7 ± 10.0 |
| Nighttime HR (bpm)     | 62.7 ± 7.3 |
| Epinephrine (pg/mL)    | 39.0 ± 17.7 |
| Norepinephrine (pg/mL) | 451.0 ± 162.5 |
| Dopamine (pg/mL)       | 18.7 ± 9.3 |

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

tonic BP fall as follows: extreme dippers, nocturnal systolic BP fall ≥ 20%; dippers, ≥ 10% but < 20%; nondippers, ≥ 0% but < 10%; and reverse dippers, < 0%. The HR dipper status was defined as (awake HR − sleep HR) / awake HR < 0.1. The HR nondipper status was defined as (awake HR − sleep HR) / awake HR < 0.1. The HR dipper status was defined as (awake HR − sleep HR) / awake HR < 0.1. The HR nondipper status was defined as (awake HR − sleep HR) / awake HR < 0.1.

Blood examination: Blood examinations were conducted at baseline, 6 months, and 12 months. We measured the epinephrine, norepinephrine, and dopamine levels.

Statistical analysis: All data were expressed as mean ± SD or percentage. Paired t-tests were employed to compare the percentages of patients with a dipper HR or dipper BP pattern between the DDD mode and sleep rate mode groups. The chi-squared test was employed to evaluate the differences in the percentages of patients with a dipper HR or dipper BP pattern between the DDD mode and sleep rate mode groups and between baseline and the sleep rate mode. IBM SPSS Statistics version 20.0 was used for the statistical analysis. A probability value < 0.05 was considered statistically significant.

### Discussion

In this study, the use of the sleep rate mode setting in the pacemaker increased not only the rate of the dipper HR pattern but also the rate of the dipper BP pattern in pacemaker-dependent patients with sick sinus syndrome. The HR during the nighttime decreased during the sleep rate mode compared with that during the DDD mode. Thus, the increase in the dipper HR pattern is reasonable. With respect to the change in the rate of the dipper BP pattern, we speculate that any of several mechanisms could account for the increase in the dipper BP pattern during the pacemaker operation in the sleep rate mode.

Increased sympathetic nerve activity during the nighttime has been considered a cause of the non-dipper HR pattern. Previous studies have demonstrated that frequent pacing and pacing irregularities increase sympathetic activity. The nighttime change in the sympathetic nerve activity due to the pacemaker operation in the sleep rate mode has not been evaluated, and thus, further studies will be required to investigate the relationship between the decrease in HR during the nighttime and the sympathetic nerve activity during the nighttime.

In this study, the epinephrine, norepinephrine, and dopamine levels were measured as indices of sympathetic nerve activity; however, no significant differences were observed between the pacemaker modes. Grassi, et al. revealed that diurnal BP changes are associated with sympathetic nerve activity in untreated hypertensive patients. The mean systolic BP in this study was less than 140 mmHg, and the large number of non-hypertensive patients may have been the result of significant catecholamine dif-
ferences between the DDD mode and sleep rate mode pacemaker operation. Därr, et al. showed that both the daytime and nighttime levels of urinary noradrenaline and adrenaline were associated with diurnal BP changes.\(^{16}\) Makimoto, et al. investigated the diurnal variation of sympathetic nerve activity and the effects of drugs in nondiabetic patients. They also observed diurnal variations of sympathetic nerve activity.\(^{17}\) The epinephrine, norepinephrine, and dopamine levels evaluated during the daytime may not adequately reflect the sympathetic nerve activity during the nighttime. Therefore, in the future, it will be necessary to determine a suitable method for evaluating sympathetic nerve activity to assess the effect of the sleep rate mode pacemaker operation on the reduction of HR during the nighttime.

We provide an example case presentation. The patient’s daytime BP/HR were higher in the sleep rate mode than in the DDD mode. The change to normal diurnal rhythm, i.e., the usual BP/HR pattern, first appeared in the sleep rate mode. Another explanation is that the dipper BP pattern and increased daytime BP might be due to an increase in physical activity. Nondipper BP was associated

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**Figure 3.** Changes in HR and BP. A: Daytime heart rate; B: daytime blood pressure; C: nighttime heart rate; D: nighttime blood pressure. BP indicates blood pressure; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

**Figure 4.** Changes in the HR and BP dipping status. A: Diurnal heart rate patterns at baseline, with DDD, and with the sleep rate mode. B: Diurnal blood pressure patterns at baseline, with DDD, and with the sleep rate mode. BP indicates blood pressure; and HR, heart rate.
with decreased daytime physical activity and increased nighttime sympathetic activity. The increase in daytime BP/HR is associated with exercise and might be a reflection of an increase in physical activity during the daytime.

By using the sleep rate mode, the physiological diurnal HR change can be maintained, and the pacemaker battery life can be extended due to a reduced pacing rate. Lower rates of atrial pacing have been demonstrated to reduce the rate of atrial fibrillation. Increased nighttime HR has been reported to be associated with mortality and organ damage, and lowering nighttime HR may improve prognosis. Ivabradine has also been reported to improve organ damage, thus reducing the HR in patients with heart failure.

The main limitation of this study was the small number of cases. With \( \alpha = 0.05 \) and power = 0.8, the number of samples required to detect catecholamine differences is 39. We could not enroll sufficient number of patients as this was a single-center study with a limited study period, and the number of patients requiring atrial pacing and having a setting the lower limit rate at 60 bpm was less than expected. In addition, the catecholamine levels were not measured during the nighttime or in the urine. Therefore, additional studies with large patient numbers and the measurement of nighttime catecholamine levels are required. In this study, the rate of BP and the HR pattern differed between those at baseline and during the DDD mode. We had a satisfactory crossover period, but the DDD mode might still be slightly affected by a carryover effect of the sleep rate mode. Other potential reason why the rates of BP and HR patterns differed between those at the baseline and during the DDD mode is that the first, second, and third ABPM measurements were conducted under different conditions (e.g., the temperature and the use of ABPM). Evidence regarding the association between the dipping HR pattern and improved prognosis has not been obtained for pacemaker-dependent patients. Thus, further large-scale studies with longer follow-up periods are necessary to determine the relationship between the sleep rate mode and diurnal BP patterns.

**Conclusions**
The pacemaker settings in the sleep rate mode increased the dipper HR and dipper BP patterns in pacemaker-dependent patients with sick sinus syndrome.

**Disclosure**
Conflicts of interest: None.

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