Influences of Autonomic Changes on the Sinus Node Recovery Time in Patients with Sick Sinus Syndrome

Takao Mitsuoka, M.D., Chiaki Ueyama, M.D., Yoriaki Matsumoto, M.D., and Kunitake Hashiba, M.D.

Summary

To assess the relative contribution of sympathetic and vagal influences on diurnal variation of sinus node recovery time (SNRT) in sick sinus syndrome (SSS), the diurnal changes of SNRT and the effects of propranolol and subsequent atropine on SNRT were examined in 39 patients with SSS.

SNRT was measured before and after intravenous propranolol (0.1 mg/kg), and after subsequent intravenous atropine (0.02 mg/kg) in the cardiac catheterization laboratory. After completion of the electrophysiologic studies in the laboratory, SNRT was measured at 0 a.m. (midnight), 6 a.m. and 12 noon on the following day in the ward. After propranolol, SNRT was prolonged in 22 of 26 patients and shortened in 4 patients. After subsequent atropine, SNRT was prolonged in 5 of 26 patients and shortened in 21 patients. The patients with SNRT longer than 3 sec had a tendency to have greater diurnal variation of SNRT than those with SNRT less than 3 sec. A strong correlation (r=0.98) was found between SNRT after propranolol and the longest SNRT in a 24-hour period. A difference of SNRT between after propranolol and after subsequent atropine was significantly correlated (r=0.88) with a difference between the longest and the shortest SNRT in a 24-hour period.

These results suggest that the diurnal changes in SNRT are regulated by the autonomic nervous system in SSS. SNRT after propranolol may be useful in estimating the longest SNRT in a day.

Additional Indexing Words:
Autonomic blocking  Autonomic influences  Diurnal variations  Sinus node recovery time  Sick sinus syndrome

SINUS node recovery time (SNRT) has been utilized in confirming sinus node dysfunction. However, some patients with clinical manifestation of sinus node dysfunction show normal SNRT. It appears that

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one of the most important factors related to this discrepancy between clinical symptoms and SNRT is the reproducibility of SNRT. Only two previous studies are available on the reproducibility of SNRT in sick sinus syndrome.\textsuperscript{5,6} One showed a marked variation of SNRT in a 24-hour period, especially in cases with prolonged SNRT.\textsuperscript{5} The other showed that the diagnostic value of SNRT in sick sinus syndrome was influenced by the time of the day because SNRT was variable from time to time in a 24-hour period.\textsuperscript{6}

On the other hand, previous investigators reported that SNRT was prolonged after propranolol\textsuperscript{7–9} and shortened after atropine\textsuperscript{1–3,10} in most patients with sick sinus syndrome.

Therefore, one of the major factors responsible for the variability of SNRT can be alterations of vagal and sympathetic tone. However, up to now clear evidence has not been reported for the relation between diurnal changes of SNRT and alterations of autonomic tone in patients with sick sinus syndrome.

The aims of the present study were (1) to evaluate the diurnal changes of SNRT in a 24-hour period, (2) to determine the effects of propranolol and subsequent atropine on SNRT and (3) to examine the relation between the diurnal changes of SNRT and the effects of propranolol and atropine on SNRT in patients with sick sinus syndrome, in order to assess indirectly the relative contribution of sympathetic and vagal influences on diurnal changes of SNRT.

\textbf{Subjects and Methods}

\textit{Patients:}

Thirty-nine patients (15 males and 24 females), aged 30 to 77 years (mean 59.7±1.8 years), with sick sinus syndrome were studied.

The clinical background including age, sex, clinical diagnosis, symptoms and electrocardiographic findings are presented in Table I. Twenty of the 39 patients had symptoms of dizziness and/or syncope. The remaining 19 patients had no cerebral symptoms. However, some of them complained of other symptoms including palpitations, malaise and easy fatigability. Eleven patients showed at least one documented episode of sinus arrest and/or sinoatrial block, 18 documented bradycardia-tachycardia syndrome, and 10 persistent sinus bradycardia (rate<50/min) on the resting electrocardiogram (ECG).

Two patients had ischemic heart disease, 11 mild hypertension, 2 valvular disease and 1 cardiomyopathy.
All cardiac drugs and also non-cardiac drugs known to interfere with the sinus node and autonomic nervous function were discontinued at least 48 hours or 3 half-lives prior to the study.

Study protocol:

After informed consent was obtained, an electrophysiologic study (EPS) were performed in the electrophysiologic laboratory in the nonsedated, post-absorptive state. Overdrive suppression tests were performed before and after propranolol, and also subsequent atropine in the electrophysiologic (EP) laboratory. After completion of EPS in the laboratory, overdrive suppression tests were repeated 3 times in the patient’s ward in the subsequent 24-hour period as described below.

1. Measurement of SNRT in the electrophysiologic laboratory

Three quadripolar catheters with an interelectrode distance of 10 mm were positioned in the cardiac chambers via the femoral vein: one in the
Table II. Electrophysiological Data

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<tr>
<th>Case</th>
<th>P-P int (sec)</th>
<th>SNRT (sec)</th>
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Atrop.=atropine; Cont.=control; j=junctional escape beat; Prop.=propranolol; p=pacing; SNRT=sinus node recovery time; s=secondary pause; v=ventricular escape beat.
high right atrium used for recording the atrial activity and atrial pacing; one across the tricuspid valve for recording the His bundle potential; and the third one at the right ventricular apex for ventricular pacing. The two proximal electrodes were used for recordings and the distal two electrodes for stimulation. Atrial stimulation was performed with stimuli of 2 msec duration at twice the diastolic threshold using a programmed cardiac stimulator (Fukuda Denshi Co., BC-02A). Intracardiac electrograms and leads I, aV\textsubscript{F} and V\textsubscript{1} were continuously displayed on a polygraph (Fukuda Denshi Co., MCM 8000) and recorded simultaneously with a chart recorder (Siemens-Elema Co., 804) at a paper speed of 25, 50 or 100 mm/sec as necessary. Atrial overdrive pacing for measurements of sinus node recovery time (SNRT) was performed at rates of 90, 110, 130, 150, 180 and 210 beats/min for 2 min. The interval between each determination of SNRT was approximately 1 min to allow the spontaneous sinus rhythm to resume. Measurement of SNRT before drugs was done approximately at 12 noon.

(2) Measurements of SNRT after propranolol and after subsequent atropine
After measurement of SNRT was completed without drugs, propranolol (0.1 mg/kg) was given intravenously at a rate of 1 mg/min to 26 patients (cases No. 1 through 26 in Table II). Overdrive suppression test was repeated 3 min after the administration of propranolol. Atropine (0.02 mg/kg) was added intravenously over a 1-min period, approximately 20 min after the administration of propranolol. Overdrive suppression test was performed again 3 min after the administration of atropine.

(3) Serial measurements of SNRT in the ward
After the electrophysiologic study was completed in the laboratory, 30 patients (cases No. 10 through 39 in Table II) were returned to their ward with an electrode catheter left in the high right atrium. The same protocol of atrial overdrive pacing as described above was repeated in the ward at 0 a.m. (midnight), 6 a.m. and 12 noon on the following day. During this 24-hour period patients were kept at bedrest. Atrial electrograms and leads I and aV\textsubscript{F} were simultaneously recorded with a 3 channel electrocardiographic recorder (Nihon Kohden Co., 5303) at a paper speed of 50 mm/sec.

Measurements:
SNRT was measured as the interval from the last paced atrial electrogram to the first atrial electrogram of sinus origin, or to the first QRS if an escape beat from a lower focus appeared. If a more prolonged cycle subsequent to the first beat called a "secondary pause"\textsuperscript{11} was found, it was used as the SNRT. If patients complained of dizziness or showed prolonged cardiac arrest of over 10 sec, ventricular pacing was started with a pacing rate of 50/min. In such a case SNRT was determined from the last paced
atrial electrogram to the first ventricular paced beat. The longest SNRT among those obtained by pacing at rates of 90–210 beats/min was taken as the representative SNRT in each overdrive suppression test.

**Definitions:**
The following abbreviations were used for simplification.

- **SNRT (cont)** = control SNRT before drugs, determined approximately at 12 noon on the day of EPS in the electrophysiologic laboratory.
- **SNRT (prop)** = SNRT after propranolol.
- **SNRT (prop+atrop)** = SNRT after subsequent atropine in addition to propranolol.
- **SNRT (L)** = the longest SNRT between SNRT (cont) and SNRT determined at midnight, 6 a.m. and 12 noon on the following day.
- **SNRT (S)** = the shortest SNRT determined in the same way as the above.
- **dSNRT (L−S)** = the difference between SNRT (L) and SNRT (S).
- **dSNRT (prop−cont)** = the difference between SNRT (prop) and SNRT (cont).
- **dSNRT (prop−prop+atrop)** = the difference between SNRT (prop) and SNRT (prop+atrop).

**Number of patients in each overdrive suppression test:**
In this study, SNRT (cont) was obtained in 39 patients, SNRT (prop) and SNRT (prop+atrop) in 26 patients, SNRT (L) and SNRT (S) in 30 patients. In 17 patients SNRT (prop), SNRT (prop+atrop), SNRT (L) and SNRT (S) were all obtained.

**Statistical analysis:**
Correlations of the following variables were examined: (1) between SNRT (cont) and SNRT at 12 noon on the following day, (2) between SNRT (L) and SNRT (prop), (3) between SNRT (L) and SNRT (prop+atrop), (4) between dSNRT (L−S) and dSNRT (prop−cont) and (5) between dSNRT (L−S) and dSNRT (prop−prop+atrop).

Statistical analyses were performed by the Student’s t-test for paired data. All values were expressed as the mean±standard error (SE). Values were considered significant at the level of p<0.05.

**Results**

**Basic sinus cycle length:**
P-P interval and SNRT before and after propranolol, and after subsequent atropine in the laboratory, and SNRT at midnight, 6 a.m. and 12 noon on the following day in the ward are presented in Tables II and III.
Eight patients showed "relative" sinus tachycardia, namely P-P interval <1.0 sec, before the autonomic blockade during EPS in the laboratory. In the electrocardiogram (ECG) taken before hospitalization, 4 of the 8 patients (cases No. 6, 10, 15 and 27) showed persistent bradycardia (rate <50/min) and the remaining 4 patients (cases No. 5, 22, 25 and 35) showed sinoatrial block or sinus arrest with "relative" sinus tachycardia, which would be considered as a "high rate response group" of the sick sinus syndrome by Kasanuki, et al.12)

Changes of SNRT after propranolol and after subsequent atropine:
Changes of SNRT after propranolol and after subsequent atropine are shown in Tables II and III and Fig. 1.

As shown in Fig. 1, SNRT (prop) was longer than SNRT (cont) in 22 of 26 patients (85%) and shorter in the remaining 4 patients (15%). SNRT (prop+atrop) was shorter than SNRT (prop) in 21 of 26 patients (81%) and was longer in the remaining 5 patients (19%). In 3 of 5 remaining patients (cases No. 8, 13 and 25) SNRT (cont) was longer than SNRT (prop).

Diurnal variation and reproducibility of SNRT:
SNRT (L) and SNRT (S) were determined following the study protocol as described above in 25 of 30 patients. In the remaining 5 patients, these were determined without the 12 noon measurement on the following day.

As shown in Fig. 2A, fluctuation of SNRT during the 24-hour period
Fig. 1. Change of SNRT after propranolol and subsequent atropine. Numbers in figure are case numbers and are discussed in detail in the text.

Fig. 2. A: Diurnal changes of SNRT. B: Percent changes of SNRT in a day. Numbers in figures are case numbers and are discussed in detail in the text.
was shorter than 1.0 sec in 9 of 10 patients with SNRT (L) shorter than 3.0 sec and it was longer than 1.0 sec in 18 of 20 patients with SNRT (L) longer than 3.0 sec.

SNRT at midnight was significantly longer than SNRT both at 6 a.m. (4.23±0.44 sec vs. 3.69±0.44 sec; p<0.01) and at 12 noon on the following day (4.23±0.44 sec vs. 3.47±0.41 sec; p<0.01) (Tables II and III). However, there was no significant difference between SNRT at 12 noon in the laboratory (SNRT (cont)) and SNRT at midnight (0 a.m.) (4.13±0.43 sec vs. 4.23±0.44 sec; ns).

Percent changes of SNRT to SNRT (cont) in a 24-hour period are presented in Fig. 2B. SNRT at midnight and 6 a.m. was longer than SNRT (cont) in 13 of 30 patients (43%) and shorter in 10 patients (33%) as shown in Fig. 2B. In the remaining 7 cases (24%), SNRT at midnight was longer than SNRT (cont) and SNRT at 6 a.m. and shorter than SNRT (cont) in 5 cases; and SNRT at midnight was shorter than SNRT (cont) and SNRT at 6 a.m. and longer than SNRT (cont) in 2 cases. Percent change of SNRT with respect to SNRT (cont) in 18 patients was within ±30% at 12 noon on the following day. Namely, SNRT at 6 a.m. tended to converge to 0% at 12 noon on the following day.

Six patients (cases No. 5, 8, 13, 18, 20 and 25) showed SNRT (prop) shorter than SNRT (cont) and/or SNRT (prop+atrop) longer than SNRT (prop) as shown in Fig. 1. In 4 (cases No. 13, 18, 20 and 25) of these 6 patients, SNRT was shorter both at midnight and at 6 a.m. than at 12 noon on the day of EPS as shown in Fig. 2B.
As shown in Fig. 3, a close correlation \((r=0.794, \text{n}=25)\) was found between SNRT at 12 noon in the laboratory and SNRT at 12 noon on the following day in the ward. The former tended to be longer than the latter, although this did not reach statistical significance \((4.13\pm0.43 \text{ sec vs. } 3.47\pm0.41 \text{ sec}; \text{ns})\).

**Correlation between SNRT after propranolol and the longest SNRT in the day:**

Correlation between SNRT (prop) and the longest SNRT in a 24-hour period was examined in 17 patients. SNRT (prop) was longer in 14 of 17 patients and was shorter in the remaining 3 patients (Table II). In the 14 patients which showed SNRT (prop) longer than SNRT (cont), a very strong correlation \((r=0.980)\) was found between SNRT (L) and SNRT (prop) (Fig.
4A). On the other hand, a weaker correlation ($r=0.831$) was found in the 17 patients (Fig. 4B) between SNRT (L) and SNRT (prop+atrop).

Correlation between $dSNRT$ (prop−cont) and $dSNRT$ (L−S), and between $dSNRT$ (prop−prop+atrop) and $dSNRT$ (L−S):

Correlation between $dSNRT$ (prop−cont) and $dSNRT$ (L−S), and between $dSNRT$ (prop−prop+atrop) and $dSNRT$ (L−S) were examined in 17 of the 39 patients. As mentioned above, SNRT (prop) was longer than SNRT (cont) and SNRT (prop+atrop) was shorter than SNRT (prop) in 13 of the 17 patients. In the remaining 4 patients, 3 showed SNRT (prop) shorter than SNRT (cont) and one SNRT (prop+atrop) longer than SNRT (cont). In the former 13 patients, a close correlation was found between $dSNRT$ (L−S) and $dSNRT$ (prop−cont) (Fig. 5A) and between $dSNRT$ (L−S) and $dSNRT$ (prop−prop+atrop) (Fig. 5B).

**DISCUSSION**

The major observations in this study are: (1) a strong correlation was found between SNRT after propranolol and the longest SNRT in a 24-hour period, (2) a close correlation was found between change of SNRT in a 24-hour period and change of SNRT after propranolol, (3) a close correlation was found between change of SNRT in a 24-hour period and change of SNRT after subsequent atropine, and (4) a close correlation was found between SNRT at 12 noon in the laboratory and SNRT at 12 noon on the following day in the ward.

In addition, we observed in the present study that: (1) SNRT was prolonged after propranolol and shortened after subsequent atropine in the majority of the patients with sick sinus syndrome; and (2) the patients with long SNRT had a tendency to have greater diurnal variations in SNRT. These observations support the findings of previous studies.1)-3),5),7),8),10)

*Autonomic influences on diurnal changes of the sinus node recovery time:*

It is generally recognized that vagal tone increases and sympathetic tone decreases at night, and that the reverse situation occurs during daytime. In normal subjects SNRT is prolonged after propranolol and shortened after atropine.13)-16) Also an experimental study has shown that vagal stimulation prolongs corrected SNRT while beta-adrenergic stimulation decreases it. Therefore, it is suggested that increased sympathetic tone generally acts to shorten SNRT and increased vagal tone acts to prolong SNRT. In fact, a previous study of normal subjects showed that SNRT became significantly prolonged between midnight and early morning and returned to baseline at 12 noon.18) In the present study, also in patients
with sick sinus syndrome, SNRT was significantly longer at midnight than at 12 noon on the following day. However, evaluation of the individual cases in the present study revealed that SNRT was prolonged at midnight in approximately 60% of patients and SNRT shortened at midnight in the remaining 40%. This "paradoxical" response in the latter might be explained as follows: (1) normal diurnal change of the autonomic tone was disturbed in some patients with sick sinus syndrome, and (2) increased vagal tone induced entrance block of atrial stimuli to the sinus node, which resulted in decreased numbers of effective atrial stimuli to overdrive the sinus node.

It can be theoretically speculated that dSNRT (L−S), namely the difference between SNRT (L) and SNRT (S), is brought about by a change of sympathetic tone from a decreased state to an increased state or by a change of vagal tone from an increased state to a decreased state. In the present study, a close correlation was found between diurnal change in SNRT (dSNRT (L−S)) and change in SNRT after propranolol (dSNRT (prop−cont)), namely after removing sympathetic tone, and was also found between diurnal change in SNRT (dSNRT (L−S)) and change in SNRT after subsequent atropine (dSNRT (prop−prop+atrop)), namely after removing vagal tone additionally, when SNRT was prolonged after propranolol and shortened after subsequent atropine. Therefore, changes in SNRT in a 24-hour period probably stem from changes in both sympathetic and vagal tone in patients with sick sinus syndrome. Also, a very strong correlation was found between the longest SNRT in a 24-hour period and SNRT after propranolol when SNRT was prolonged after propranolol. This result suggests that the longest SNRT could be estimated by SNRT after propranolol.

On the other hand, if patients showed a "paradoxical response" to drugs, namely, SNRT was shortened after propranolol or prolonged after subsequent atropine, a majority of the patients showed profoundly shorter SNRT at midnight than at 12 noon on the following day. In those patients with "paradoxical" response to the autonomic blocking agents, it is necessary to measure SNRT after both propranolol and subsequent atropine to estimate the longest SNRT in the day.

Reproducibility of sinus node recovery time:

Several investigators reported that corrected SNRT was reproducible when measurement was repeated 3 to 8 months later, although the numbers in those studies were small. However, just one previous comparative study of this kind reported that a marked variation of SNRT in a 24-hour period was observed when control SNRT was especially prolonged. In the present study, fluctuation of SNRT was larger in patients with SNRT more than 3.0 sec than in those with SNRT less than 3.0 sec. Thus, our
results are consistent with earlier work.

In the present study, a close correlation was found between SNRT at 12 noon in the laboratory and SNRT at 12 noon on the following day in the ward, although SNRT at 12 noon in the laboratory tended to be longer of the two. These results are consistent with the results of a previous study,\textsuperscript{21} which showed that SNRT in sick sinus syndrome patients repeated the day after EPS was not significantly different from that obtained during EPS in the laboratory. Also, it was shown that EPS performed in the laboratory does not elicit a continuous hyperadrenergic response in most patients, but on the contrary it appears to induce an absolute or relative increase in parasympathetic tone in some patients. Therefore, SNRT may have better reproducibility if it is measured at the same time of the day. Also, it seems likely that this relatively longer SNRT in the laboratory comes from increased parasympathetic tone.

\textit{Limitations of the present study:}

To evaluate autonomic influences on SNRT, 0.1 mg/kg of propranolol and 0.02 mg/kg of atropine were used in the present study. These doses were only half the amount of propranolol and atropine that was administered by Jose et al.\textsuperscript{22}-\textsuperscript{24} Half doses were used for autonomic blockade so as to avoid serious side effects including sinus arrest or hypotension in older subjects with associated cardiac disease, especially when propranolol was administered first. Several previous reports using half doses for autonomic blockade\textsuperscript{14},\textsuperscript{25} or of propranolol\textsuperscript{7},\textsuperscript{8},\textsuperscript{13},\textsuperscript{26} suggested that even "half" doses were enough to achieve adequate autonomic or beta-adrenergic inhibition.

In the present study, SNRT instead of corrected SNRT was used to evaluate the sinus automaticity. Cerebral symptoms including syncope and dizziness in sick sinus syndrome are related to SNRT itself. Therefore, from a clinical point of view, SNRT is more relevant. Also, previous studies\textsuperscript{6},\textsuperscript{18} suggested that corrected SNRT produced a larger dispersion of SNRT during 24 hours, which resulted in wide variation and a comparable lack of reproducibility in corrected SNRT. Further, previous studies\textsuperscript{27},\textsuperscript{28} using direct sinus node recordings showed that atrial pauses after overdrive suppression were usually caused by sinoatrial block and did not reflect abnormal sinus node automaticity in patients with sick sinus syndrome. Thus, SNRT itself seems to be more adequate than corrected SNRT in a comparison of changes of SNRT in a 24-hour period or after drugs.

\textit{Clinical implications:}

In the previous studies\textsuperscript{5},\textsuperscript{27},\textsuperscript{29}-\textsuperscript{32} the combined effect of atropine and propranolol on sinus node function, including intrinsic heart rate, sinoatrial conduction time and SNRT, was investigated to evaluate the autonomic
dysfunction of sick sinus syndrome. In those studies, atropine was first administered and followed by propranolol, or atropine and propranolol were administered simultaneously. No systematic study evaluating SNRT both after propranolol and atropine similar to the present study was available. Another study reported that prolonged SNRTs suggesting sinus node dysfunction may be found at midnight in patients with normal SNRT during daytime. From a practical point of view, it is difficult to repeat SNRT at midnight. As shown in the present study, SNRT was prolonged after propranolol in most patients with sick sinus syndrome and sometimes prolonged profoundly in patients who showed normal SNRT before the drug. Therefore, it is suggested that the longest SNRT in a day can be estimated by the SNRT after propranolol in most patients with sick sinus syndrome, although SNRT shortens after propranolol or prolongs after subsequent atropine in some patients with sick sinus syndrome. No adverse effects such as long pauses or hypotension were observed after the administration of propranolol in our series. Based on the present observations, we recommend that in patients suspected of having sinus node dysfunction, propranolol should be given first and then followed by atropine; SNRT should be measured after each drug. This method will improve the diagnostic value of SNRT.

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