Role of Autonomic Regulatory Mechanisms in Sinoatrial Conduction and Sinus Node Automaticity in Sick Sinus Syndrome

Pritpal S. Kang, M.D., Joseph Anthony C. Gomes, M.D., George Kelemen, M.D., and Nabil El-Sherif, M.D.

SUMMARY To assess the role of autonomic regulatory mechanisms on sinoatrial conduction and automaticity in patients with clinical evidence of sick sinus syndrome, electrophysiologic studies were conducted in 12 male patients, mean age 64 ± 7 years. Heart rate, sinus node recovery time (SNRT) and sinoatrial conduction time (SACT) were determined before and after autonomic blockade with atropine (0.04 mg/kg) and propranolol (0.2 mg/kg). The mean sinus cycle length was 1033 ± 208 msec (± SD) before autonomic blockade and 1016 ± 188 msec after autonomic blockade. The observed intrinsic heart rate (1HRo) after autonomic blockade was abnormal in nine of 12 patients. The mean corrected SNRT before autonomic blockade was 606.5 ± 432 msec and was abnormal (> 450 msec) in six of 12 patients (50%). After autonomic blockade the mean SNRT was 661.8 ± 604.8 msec and was abnormal (> 450 msec) in eight of 12 (67%). Six of nine patients (66%) with an abnormal intrinsic observed HR had an abnormal SNRT before autonomic blockade. After autonomic blockade, eight of these nine (88%) had an abnormal SNRTc.

SACT was estimated by continuous pacing and by premature stimulation. The mean SACT estimated by continuous pacing before autonomic blockade was 190.3 ± 99.6 msec and decreased significantly after autonomic blockade (140.6 ± 53.4 msec, p < 0.05). The mean SACT estimated by premature stimulation before autonomic blockade was 218 ± 87.6 msec and decreased significantly after autonomic blockade (143.7 ± 49.9 msec, p < 0.01). The coefficient of correlation between the two methods was 0.8 before autonomic blockade and 0.85 after autonomic blockade. SACT was abnormally prolonged (> 206 msec) in five of 12 patients (41%) during control studies and in two of 12 patients (16%) after autonomic blockade. SACT by either method decreased in eight of 12 patients (67%) and increased in four of 12 patients (33%) after autonomic blockade. Changes in SACT after autonomic blockade could not be predicted from symptoms, electrocardiographic findings or determination of intrinsic HR.

In conclusion, assessment of IHR, SNRT and SACT after autonomic blockade can differentiate patients with sick sinus syndrome, whether due to intrinsic or extrinsic abnormality of sinus node automaticity or conduction. The significant decrease in SACT in most patients with sick sinus syndrome after autonomic blockade suggests enhanced basal parasympathetic tone and normal intrinsic conduction in the perinodal region. The increase in SACT in a minority of patients after autonomic blockade suggests that enhanced basal sympathetic tone can mask an underlying intrinsic abnormality of sinoatrial conduction.

SICK SINUS SYNDROME encompasses a group of cardiac rhythm disturbances and their corresponding clinical manifestations that are a consequence of impaired formation and/or conduction of sinus node impulses. Normal sinus node function depends on a complex and delicately balanced interaction between intrinsic electrophysiologic characteristic of sinus node impulse formation, its conduction to the atrium and factors outside the sinus node region. Among the extrinsic factors that have modifying influences on intrinsic sinus node function, the role of the autonomic nervous system may be most important. Patients with sick sinus syndrome may have an intrinsic or extrinsic abnormality of sinus node automaticity. However, the role of extrinsic regulatory mechanisms (i.e., autonomic influences) in regulating sinoatrial (SA) conduction has not been systematically studied.

In this study we assessed the role of the autonomic nervous system on SA conduction and other measurements of sinus node functions in patients with the sick sinus syndrome.

Material and Methods

Twelve male patients, mean age 64 ± 7 years, with the clinical diagnosis of sick sinus syndrome were studied. The diagnosis was suggested by the presence of sinus bradycardia, sinus arrest and brady-tachyarrhythmia with or without symptoms of light-headedness, and syncope documented by ECG or 24-hour Holter tape recordings.

Clinical features are provided in table 1. Although four patients had hypertension and four had ischemic heart disease, none of the patients had congestive heart failure in the past or at the time of the study. Patients with pulmonary disease, glaucoma or urinary retention were excluded from the study. None had a recent myocardial infarction, electrolyte or metabolic disturbances, or atrioventricular or intraventricular conduction abnormalities. All cardiovascular drugs and drugs known to interfere with sinus node and autonomic neural functions were discontinued at least 48 hours or 2 half-lives before the study.

All patients gave informed signed consent and were studied in the electrophysiology laboratory in the non-
Table 1. Heart Rates

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
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<th>SA block arrest</th>
<th>Bradycardia symptoms</th>
<th>Control heart rate</th>
<th>After autonomic blockade</th>
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<tr>
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<td>+ 61</td>
<td>30</td>
<td>+ Severe</td>
<td>923</td>
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<td></td>
<td>Moderate</td>
<td>1014</td>
<td>59 69 57–82 921 65</td>
</tr>
</tbody>
</table>

Mean ± SD 64 ± 7 1033 ± 208 1016 ± 188 0.0025 ± 0.168

Abbreviations: RHD = rheumatic heart disease; HCVD = hypertensive cardiovascular disease; ASHD = arteriosclerotic heart disease; SA = sinoatrial; CNS = central nervous system; SCL = sinus cycle length; RHR = resting heart rate during electrophysiological studies; IHRp and IHRo = predicted and observed intrinsic heart rates; + = present.

seded, postabsorptive state. Two quadripolar catheters with interelectrode distance of 10 mm were introduced percutaneously under local anesthesia from an antecubital vein and groin and positioned in the region of the sinus node in the high right atrium and at the level of tricuspid valve for recording atrial activity and His bundle activity respectively. The proximal poles of atrial catheter were used for recordings and distal poles for stimulation. Two or more standard electrocardiographic leads, intracardiac electrograms at frequency settings of 40–500 Hz and time lines generated at 40,200 and 100 msec were displayed on a multichannel oscilloscope (VR-12) and reproduced on thermal paper at a paper speed of 50–100 mm/sec. Atrial stimulation studies were performed at twice diastolic threshold with stimuli 2 msec in duration.

Sinus node recovery time (SNRT) was estimated using atrial pacing at rates ranging from 60 (if possible) to 200 beats/min at increments of 20 beats/min for 30 seconds. The interval between two pacing periods was at least 15 seconds to allow the spontaneous sinus rhythm to resume.

Sinoatrial conduction time (SACT) was estimated by the continuous pacing method* and premature stimulation.

To achieve sympathetic and parasympathetic blockade, the quadripolar catheter across the tricuspid valve was advanced to the right ventricular apex and distal two poles were connected to the pulse generator for ventricular pacing, in case of marked sinus bradycardia. Autonomic blockade was achieved as proposed by Jose and Collison, modified by Jordan et al., with propranolol, 0.2 mg/kg of body weight, administered intervenously at a rate of 1 mg/min, and atropine sulphate, 0.04 mg/kg of body weight, administered thereafter as a single injection over 2 minutes. Sinus rate was continuously monitored. Five to 10 minutes after autonomic blockade, SNRT and SACT were remeasured. The studies were completed within 1 hour and 15 minutes, and in no case more than 30 minutes after autonomic blockade.

Definition of Terms, Measurements and Calculations

Resting heart rate (RHR) is the average heart rate observed before autonomic blockade.

Predicted intrinsic HR is the calculated HR after autonomic blockade. It is calculated by using the linear regression equation relating predicted intrinsic HR to age. According to this formula, predicted intrinsic HR = 118.1 – (0.57 × age),

Observed intrinsic HR is the maximum sinus rate observed 5 minutes after autonomic blockade.

For each patient, the magnitude and direction of autonomic chronotropic influences present at the time of control study were evaluated. The percent by which the resting HR deviated from the observed intrinsic HR was taken as quantitative measure of positive or negative autonomic chronotropy present at that time. Thus, (resting HR/intrinsic observed HR - 1) × 100 = the percent positive or negative autonomic chronotropy.
Corrected SNRT (SNRTc) is the maximum corrected SNRT before autonomic blockade, regardless of the pacing rate at which it occurred.

Predicted adjusted corrected SNRT represents the SNRT that would be anticipated if the control SNRTc were adjusted mathematically for the role that existing autonomic tone played in its value. It was determined according to the formula:

\[
\text{SNRTc} + \left( \frac{\text{resting HR} - 1.00}{\text{observed intrinsic HR}} \right)
\]

Observed SNRTc is the maximum SNRTc after autonomic blockade regardless of the pacing rate at which it occurred.

Statistical evaluation was performed using the t test for paired data. Regression analysis was performed using a computer program. Values are mean ± SD.

**Results**

The clinical data and electrophysiologic findings in the 12 patients are presented in tables 1 and 2. All patients were in sinus rhythm before and after autonomic blockade. Control sinus cycle length ranged from 687-1414 msec (mean 1033 ± 208 msec) and did not significantly change after autonomic blockade (range 614-1384 msec, mean 1016 ± 188 msec). Seven patients had sinus arrhythmia with a variation in spontaneous cycle length > 120 msec during the control period and only two patients had sinus arrhythmia after autonomic blockade. The observed intrinsic heart rate (HR) decreased after autonomic blockade in patients 1, 2, 4, 5, 7 and 9) and increased in patients 3, 6, 8, 10, 11 and 12). Patients 1-9 fell outside the 95% confidence limit of predicted intrinsic HR, whereas patients 10-12 had an observed intrinsic HR within the 95% confidence limit of predicted intrinsic HR. None of the 12 patients had HRs greater than the predicted HR after autonomic blockade.

**SACT**

The results of estimated SACT before and after autonomic blockade by SACTc and SACTp are shown in table 2.

**SACT Assessed by Continuous Pacing**

The SACTc ranged from 83-454 msec (mean 190.3 ± 99.6 msec) during the control study and decreased significantly after autonomic blockade (range 50-250 msec, mean 140.6 ± 53.4 msec, p < 0.05). The SACTc decreased in patients 2-7, 10 and 11 and increased in patients 1, 8, 9 and 12.

**SACT as Assessed by Premature Stimulation**

The various patterns of A2 A3 in 12 patients during SACTp in response to premature atrial stimuli (A1 A2) and their duration, before and after autonomic blockade, are given in table 3.

The SACTp, estimated in 10 patients during the control period, ranged from 108-416 msec (mean 218.6 ± 87.6 msec). The SACTp was abnormally prolonged (> 206 msec) in patients 2, 4, 5, 6, and 10 and was normal < 206 msec) in the five other patients. The SACTp could not be estimated in patients 1 and 8 because all of the A2 A3 responses were fully compensatory. After autonomic blockade, SACTp decreased significantly (range 87-244 msec, mean 143.7 ± 49.9 msec, p < 0.01). In the five patients in whom SACTp was abnormally prolonged during control, it decreased after autonomic blockade and normalized in patients 2, 5, 6 and 10). Of the five patients who had normal SACTp during control studies, it decreased in patients 3, 7 and 11 and increased in patients 9 and 12.

<table>
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<th>Table 2. Electrophysiologic Data</th>
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<td>12</td>
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<td>Mean ± SD</td>
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</table>

Abbreviations: SACTc = sinoatrial conduction time by continuous pacing; SACTp = sinoatrial conduction time by premature stimulation; SNRTc = corrected sinus node recovery time; ND = nondefinable.
<table>
<thead>
<tr>
<th>Pt</th>
<th>Zone I</th>
<th>Zone II</th>
<th>Zone of incomplete interpolation</th>
<th>Zone of sinus echoes</th>
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<th>Zone II</th>
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<td>-</td>
<td>100-66%</td>
<td>66-28%</td>
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</tbody>
</table>

Zone I = zone of nonreset of the sinus node; zone II = zone of reset of the sinus node.

In patient 12, SACTp became abnormal after autonomic blockade.

**Correlation Between SACTc and SACTp**

There was a good correlation between mean SACT determined by pacing or by premature stimulation during control studies (r = 0.8) and after autonomic blockade (r = 0.85).

**Postspacing Sinus Cycles**

After atrial stimulation, the subsequent spontaneous sinus cycles were analyzed during SACTc and SACTp. With SACTc, the postspacing sinus cycles were longer than the mean sinus cycle during control (range 1–10%, mean 2.2%) and after autonomic blockade (range 1–10.9%, mean 2.3%). With SACTp, the postreturn sinus cycle (A2 A3) were longer than the mean sinus cycle during control (range 1–7.9%, mean 2.3%) and after autonomic blockade (range 1–8.5%, mean 2.5%).

**SNRT**

The SNRTc ranged from 300–1960 (mean 606.5 ± 432 msec) and was prolonged (> 450 msec) in patients 1–6. After autonomic blockade, observed SNRTc ranged from 200–2530 msec (mean 661.8 ± 604.8 msec). The SNRTc before and after autonomic blockade correlated well (r = 0.965) (NS). Mean predicted adjusted SNRTc was 635.1 ± 531.6 msec, and correlated well with observed SNRTc (r = 0.986). Of the nine patients whose observed intrinsic HR fell outside the 95% confidence limit of predicted intrinsic HR, eight had prolonged observed SNRTc after autonomic blockade and one (patient 7) had a decrease in observed SNRTc and intrinsic observed HR. Patients 1–6, who had prolong control SNRTc, had prolonged abnormal observed SNRTc after autonomic blockade. Patients 8 and 9, with normal control SNRTc, had prolonged abnormal observed SNRTc after autonomic blockade. Patients 10–12, with an observed intrinsic HR that fell within the 95% confidence limit of predicted intrinsic HR, had normal control and normal observed SNRTc after autonomic blockade.

**HR vs SACT**

No statistically significant correlation was found between HR and SACT by either method before or after autonomic blockade.

**SNRTc vs SACT**

No statistically significant correlation was found between SNRT and SACT by either method before and after autonomic blockade.

**Discussion**

The sinus node and atrium are richly innervated by both adrenergic fibers (sympathetic) and cholinergic fibers (parasympathetic). That the autonomic nervous system has a profound but variable influence on sinus node function has been recognized for a long time. Arguss et al demonstrated that the well-established observation of slowing of the sinus rate with age may in part be secondary to increased parasympathetic tone. Sinus arrhythmia is often a reflection of periodic alterations in parasympathetic efferent cardiac activity. The autonomic nervous system not only influences sinus node automaticity, but can also lead to SA block. Thus, the importance of the autonomic nervous system in the regulation of sinus node function has led some investigators to recommend that HR responses to sympathomimetic, sympatholytic, parasympathomimetic and parasympatholytic drugs be used routinely in the clinical evaluation of patients with sick sinus syndrome. With the assessment of intrinsic HR after
complete autonomic blockade, Jordan et al.\(^8\) could distinguish intrinsic dysfunction of the sinus node from abnormal autonomic regulation in patients with symptomatic sinus bradycardia. Other investigators\(^9,\)\(^10\) have assessed the effect of parasympathetic blockade on SNRT to distinguish intrinsic sinus node dysfunction from abnormally exaggerated parasympathetic influences.

The sick sinus syndrome is a disorder of sinus node automaticity or of SA conduction, so it is of paramount importance to assess SACT and measurements of sinus node automaticity before and after autonomic blockade to quantify the magnitude and direction of autonomic influences on the sinus node. Various investigators\(^37-39\) have studied the effect of atropine or propranolol alone on SACT; however, the effect of complete autonomic blockade on SACT has not been reported.

**Effect of Autonomic Blockade on SACT**

To assess SACT and to study the effects of autonomic blockade on the latter, we calculated SACT by the methods proposed by Strauss et al.\(^8\) and Narula et al.\(^4\) SACT as assessed by the Strauss method and, as assessed by Narula’s method, correlated very well \((r = 0.80)\) during control and after autonomic blockade \((r = 0.85)\). However, discrepancies were observed between the two methods in a few patients. Narula and co-workers\(^4\) reported a similar good correlation \((r = 0.97)\), while Breithardt and Seipel\(^4\) reported a poor correlation \((r = 0.45)\) between the two methods.

The range of values reported for the upper limits of normal for SACTp (antegrade + retrograde), 198–304 msec, is wide.\(^41-46\) However, in patients without abnormalities of distal conduction system and in the absence of any evidence clearly favoring one value over another, we have chosen 206 msec\(^46\) to represent the upper limit of normal for SACTp. The SACTp in five of 12 patients (41\%) was more than 206 msec during control studies. Strauss and co-workers\(^8\) also reported similar (38\%) incidence of abnormal SACT in a group of 16 patients with clinical sick sinus syndrome. Although SACTp of more than 206 msec may represent abnormal conduction time with intact innervation, because of lack of data on normal values of SACT after autonomic blockade, this value cannot be considered abnormal with certainty. Nonetheless, SACTp after autonomic blockade was more than 206 msec in two of 12 patients (16\%). One of these, patient 12, had normal SACTp during control studies but had electrocardiographically documented SA block and severe central nervous system symptoms.

Previous studies on the effects of atropine on SACT in patients with sinus node dysfunction demonstrated marked shortening of SACT in some patients; in others, the decrease was minimal.\(^37-39\) Strauss and co-workers\(^8\) reported that propranolol (0.1 mg/kg) significantly prolonged SACT in patients with sick sinus syndrome, but Narula et al.\(^4\) did not observe any significant effect of propranolol on SACT in patients suspected of having sinus node dysfunction. Goodman et al.\(^40\) found that SACT and SNRT were significantly shorter in the transplanted heart than in those with intact innervation, but correction of SACT and SNRT for HR abolished these differences. The findings in this study demonstrated a significant decrease in mean SACT in the majority of patients after autonomic blockade as assessed by either of the two methods. This finding may be related to enhanced resting parasympathetic tone or parasympathetic blockade predominating over, sympathetic blockade after autonomic blockade. It is also possible that these patients have no abnormalities of intrinsic SA conduction, the sinus node dysfunction being primarily a result of abnormal autonomic regulations of SA conduction. The latter possibility is substantiated by the observation that SACT normalized after autonomic blockade in four of five patients, who had abnormally prolonged SACT during the control study. In addition, in two patients in whom SACT could not be estimated by premature stimulation during the control basal state, SACT could be estimated after autonomic blockade. The findings of fully compensatory A\(_2\) A\(_3\) cycles during the control period and the demonstration of clearly definable zone II responses after autonomic blockade in the latter two patients suggests the presence of SA block due to enhanced vagal tone, which was abolished after autonomic blockade. The increase in SNRTc after autonomic blockade in these patients was probably related to abolition of SA block during overdrive atrial pacing.

In patients 1, 8, 9 and 12, SACT prolonged after autonomic blockade as assessed by SACTc and or SACTp. In patient 12, the SACT became abnormal. The observed increase in SACT in these four patients may be related to intrinsic abnormality of SACT masked by sympathetic overactivity, the former made manifest after autonomic blockade; sympathetic blockade predominating over parasympathetic blockade; or depressed sinus node automaticity. However, the analysis of postspacing cycles failed to reveal a significant increase of sinus cycle length, so the latter possibility seems unlikely. In addition, our observation that patients demonstrating an increase or decrease in SACT after autonomic blockade do not differ in respect to their symptoms or electrocardiographic findings suggests that it is difficult to assess clinically whether abnormalities in SA conduction are primarily the result of autonomic dysfunction or intrinsic SA conduction abnormality.

**Effect of Autonomic Blockade on Sinus Node Automaticity**

Jordan et al.,\(^8\) in their group of patients with symptomatic sinus bradycardia, found that 10 of 17 patients (59\%) had abnormal intrinsic HRs after autonomic blockade. They found that all 10 patients had abnormal SNRTc before and after autonomic blockade. In four of the seven other patients, the SNRTc was abnormal during control studies; however, after autonomic blockade, the SNRTc and
observed intrinsic HR normalized, suggesting that sinus node dysfunction in these patients was secondary to exaggerated autonomic influences. We found that nine of 12 patients (75%) had abnormal observed intrinsic HR. However, six of nine patients (66%) had abnormal SNRTc during control and after autonomic blockade. Three of nine patients (33%) had a normal SNRTc during control. In two of these three patients, the SNRTc became abnormal after autonomic blockade, suggesting that in these patients, abnormal intrinsic sinus node automaticity was masked by increased sympathetic tone. The increase in SACT in these two patients after autonomic blockade suggests increased basal sympathetic activity. These findings and those of Jordan and co-workers\textsuperscript{8} suggest that most patients with sick sinus syndrome have intrinsic abnormality of sinus node automaticity, while a few may have extrinsic abnormality of sinus node automaticity mediated by autonomic nervous system, intrinsic abnormalities of sinus node automaticity masked by exaggerated sympathetic activity, and normal sinus node automaticity as assessed by overdrive stimulation and observed intrinsic HR obtained after autonomic blockade.

Implications

The sick sinus syndrome is not a homogenous entity in regard to its pathophysiologic mechanisms.

The autonomic nervous system exerts varying degrees of effect on sinus node automaticity and sinoatrial conduction.

Using autonomic blockade to determine intrinsic HR, sick sinus patients with intrinsic sinus node dysfunction can be reliably distinguished from those with disturbed autonomic regulation. Thus, patients with abnormal intrinsic HR are more likely to have prolonged SNRTc. However, it is difficult to predict the directional change in SACT from intrinsic HR determination, percent chronotropic effect of autonomic chronotropic influences and SNRTc. The last is difficult probably because determination of intrinsic HR and SNRTc are dependent primarily upon sinus node automaticity, while estimation of SACT is dependent primarily upon conduction properties of perinodal region and surrounding atrium. Nonetheless, the technique of estimating SACT before and after complete autonomic blockade distinguishes patients with prolonged SACT due to intrinsic slowing of conduction velocity from those in whom it is due to exaggerated autonomic influences.

Prolonged SACT due to decreased intrinsic conduction velocity is found only in a small percentage of patients with sick sinus syndrome, while it may be prolonged in the majority due to extrinsic autonomic influences.

A standardized and systematic technique for quantitating the magnitude and direction of autonomic chronotropic effect on sinus node function and on SACT in the intact human heart should be used to detect the effect of various pharmacologic agents in patients with or without sick sinus syndrome to determine if a given drug effects sinus node automaticity and sinoatrial conduction velocity directly or indirectly through autonomic influences. Breithardt and co-workers\textsuperscript{42} used this technique to delineate the effect of verapamil on the sinus node; however, the doses of propranolol and atropine used for autonomic blockade were inappropriate. Other investigators\textsuperscript{61, 62} used atropine only in similar drug trials, leaving the influence of sympathetic nervous system unopposed. The decreased fluctuation in sinus cycle length after complete autonomic blockade helps assessing sinus node functions more accurately and with less difficulty.

SACT estimated by both the methods gives comparable results. The continuous atrial pacing method is simpler and quicker than premature stimulation method. Despite its advantages, Grant et al.,\textsuperscript{68} in isolated rabbit right atrial preparations, found that the constant pacing technique is subject to sources of error similar to those of the premature atrial stimulation technique. Shortening of the paced action potential duration, depression of automaticity and the shifts in the site of the primary pacemaker. The range of normal for continuous method has to be delineated before this method can be used to evaluate patients with sinus nodal dysfunction. Further validation of SACT estimated by either method can probably be accomplished by direct recording of sinus node potentials.\textsuperscript{64}

The ability to recognize sick sinus patients with normal intrinsic sinus node automaticity and sinoatrial conduction may theoretically help patients who most likely would benefit from medical therapy. However, the feasibility of long-term medical management in this subset of patients as contrast to conventional pacemaker management requires further observation.

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