Is Sick Sinus Syndrome an Adenosine-Mediated Disease?

Effects of Intravenous Aminophylline on Sick Sinus Node Function after Pharmacologic Autonomic Blockade

Wen-Ter Lai, M.D.; Hong-Ming Lai, M.D.; Ching-Teng Lin, M.D.; Sheng-Hsiung Sheu, M.D.; and Yeo-Shin Huang, M.D., F.C.C.P.

To assess the effects of intravenous aminophylline on the sinus node, 12 patients with clinical and Holter monitor-documented sick sinus syndrome were studied (1) during the control state, (2) after pharmacologic autonomic blockade and (3) 5 min after intravenous administration of aminophylline. The effects of aminophylline on sinus node function were compared with those after pharmacologic autonomic blockade. No significant improvement of sinus node function was found after intravenous aminophylline administration with a mean sinus cycle length and a mean maximum CSRT of 968 ± 218 and 1832 ± 1036 ms, respectively. The mean serum theophylline level was 10.9 ± 1.7 μg/ml. Since aminophylline is an adenosine receptor antagonist, these findings suggest that intrinsic adenosine may not play an important role in pathogenesis in patients with chronic and advanced sick sinus syndrome.

\[ AV = \text{atrioventricular node}; \ SA = \text{sinoatrial}; \ SNRT = \text{sinus node recovery time}; \ SACT = \text{sinoatrial conduction time}; \ CSRT = \text{corrected SNRT}; \ HRA = \text{high right atrium} \]

In 1909, Laslett\(^1\) described the clinical syndrome of syncope associated with profound intermittent bradycardia. Later, this condition was called the sick sinus syndrome.\(^2\) The clinical diagnosis of sick sinus syndrome is based on the electrocardiographic observation of marked sinus bradycardia, sinus arrest, sinoatrial block and alternating bradyarrhythmias and tachyarrhythmias. From previous studies, the nature of the bradyarrhythmias seen in sick sinus syndrome suggests that the defect of automaticity was not only confined to the sinus node but affected the latent cardiac pacemakers in the AV node and His-Purkinje tissue.\(^3,4\) However, the etiology of sick sinus syndrome remained obscure.

Normal sinus node function is regulated by a complex and delicately balanced interaction between intrinsic sinus node electrophysiologic properties, sinoatrial conduction properties and factors outside the sinoatrial region.\(^5\) Among the extrinsic factors capable of exerting modifying influences on the intrinsic sinus node function, the role of the autonomic nervous system is perhaps most important.\(^6\) In addition, another variety of chemical substances, the purine derivatives, also have pronounced effects on cardiac rhythmicity.\(^7\) The cardiac effects of the nucleotide adenosine, a derivative of purines, were first described in animals\(^8\) and man\(^9\) more than 60 years ago. Adenosine is now known to have wide modulation effects on cardiac automaticity and AV conduction, which (1) produce sinus bradycardia and even sinus arrest\(^10\) and (2) inhibit automaticity of the latent pacemakers in the AV node and His-Purkinje system.\(^10,11\) In addition, adenosine can shorten the atrial action potential duration,\(^12\) which may facilitate initiation of atrial fibrillation.\(^13\) The rapid metabolic change in adenosine\(^14\) also may provide an explanation for termination of tachyarrhythmias occurring in sick sinus syndrome. All these characteristic effects of adenosine, which are resistant to atropine, closely resemble the abnormalities of sick sinus syndrome. Recently Watt\(^15\) hypothesized that sick sinus syndrome might be an adenosine-mediated disease. Since theophylline has been shown to be able to antagonize the adenosine effects,\(^16,17\) in this prodromal study, we investigated the effects of intravenous aminophylline on the sinus node function in sick sinus patients in order to determine whether adenosine played a role in the mechanism of sick sinus syndrome.

METHODS

Study Patients

Twelve patients with the diagnosis of sick sinus syndrome were enrolled in this study. There were six men and six women ranging in age from 40 to 78 years (mean, 59.9 ± 10.0 years). The diagnosis of sick sinus syndrome was based on the presence of sinus bradycardia, sinus arrest and the bradycardiac syndrome documented in the 24-h ambulatory electrocardiographic Holter recordings. None of the patients had glaucoma, urinary retention or...
Electrophysiologic Study and Protocol

The study was performed with each patient in a postabsorptive, nonedated state. Using a conventional method, two quadripolar electrode catheters (USCI 6) with an interelectrode distance of 10 mm were introduced into the right femoral vein and extended separately to the high right atrium in close proximity to the anatomic location of the sinus node and the right ventricular apex. The distal pair of electrodes was used for electrical stimulation and the proximal pair for recording. A tripolar electrode catheter also was introduced into the right femoral vein and positioned at the level of the tricuspid valve for recording His bundle activity. Simultaneous body surface electrocardiographic leads 1, 2, V, and intracardiac electrograms from the high right atrium, His bundle and the right ventricular apex were displayed on a multichannel oscilloscope (Electronic for Medicine) using a filter setting between 30 to 500 Hz and recorded on photosensitive paper at a paper speed of 50 or 100 mm/s. Atrial and ventricular stimulation was administered at twice diastolic threshold and 2.0 ms in duration. During the control period, the SNRT and SACT were measured by the continuous pacing method. Autonomic blockade was given intravenously as proposed by Jordan et al, using 0.2 mg/kg body weight of propranolol at a rate of 1 mg/min. Ten minutes thereafter, 0.04 mg/kg of atropine sulfate was administered intravenously as a single bolus injection during a 2-min period. Sinus cycle length was measured from the oscillating record continuously. Five minutes after autonomic blockade, the SNRT and SACT were reassessed, as previously described. Right after completion of the autonomic blockade study, aminophylline (theophylline ethylenediamine), in a dose of 5 mg/kg, was given intravenously for 5 min. The sinus cycle length, SNRT and SACT, were reestimated within 15 min. A blood sample also was taken to document the theophylline serum concentration measured by fluorescence polarization immunoassay (TDx Abbott Lab).

Definitions

Maximum sinus node recovery time was defined as the longest interval from the last paced high right atrial electrogram to the first spontaneous sinus atrial electrogram after termination of any rate of pacing.

Maximum corrected SNRT was calculated by subtracting the mean sinus cycle length from the maximum SNRT.

Sinoatrial conduction time was estimated by a continuous pacing method as proposed by Narula et al. The high right atrium was paced for eight beats at a cycle length slightly shorter than the basic sinus cycle length. Pacing was abruptly stopped to allow the spontaneous sinus rhythm to return. This protocol was repeated three times at the same cycle length. Sinoatrial conduction time was calculated by subtracting the mean sinus cycle length from the interval between the last paced atrial electrogram and the atrial electrogram of the first return sinus cycle. The average of SACTs measured at three different times was taken as the representative SACT.

Statistical analysis was performed by utilizing the Student t test for paired data. All values represent mean ± SD.

Results

Control Measurements

During the control state, the mean sinus cycle length was 1,012.9 ± 208.1 ms (range 680 to 1,390 ms [Table 1]). The mean maximum SNRT and mean maximum corrected SNRT were 2,392 ± 817 and 1,379 ± 703 ms, respectively. The maximum corrected SNRT was abnormal (>525 ms) in 11 of 12 patients. The SACT was abnormal (>125 ms) in 9 of 12 patients with a mean SACT of 156 ± 66 ms.

Autonomic Blockade

After administration of pharmacologic autonomic blockade, the mean sinus cycle length was 953 ± 175 ms, corresponding to the mean intrinsic heart rate of 63.0 beats per minute (Table 2). The mean maximum SNRT and mean maximum corrected SNRT were 2,597 ± 1,126 and 1,644 ± 992 ms, respectively. The maximum corrected SNRT was abnormally prolonged in all 12 patients. The mean SACT was 125 ± 72 ms.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age (yr)</th>
<th>Clinical Diagnosis</th>
<th>Mean Sinus Cycle Length (ms)</th>
<th>Maximum SNRT (ms)</th>
<th>Maximum CSRT (ms)</th>
<th>SACT (ms)</th>
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</table>

Mean ± SD 60.2 ± 11.2 1,012.9 ± 208.1 2,391.7 ± 817.0 1,378.8 ± 702.6 156.5 ± 65.9

Is Sick Sinus Syndrome an Adenosine-mediated Disease? (Lai et al)
Table 2—Effects of Aminophylline on Intrinsic Sinus Node Function

<table>
<thead>
<tr>
<th>Mean Sinus Cycle Length (ms)</th>
<th>SNRT Maximum (ms)</th>
<th>CSRT Maximum (ms)</th>
<th>SACT (ms)</th>
<th>Serum Aminophylline Level (µg/ml)</th>
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<td>Autonomic Blockade</td>
<td>Aminophylline</td>
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<tr>
<td>12</td>
<td>840</td>
<td>900</td>
<td>1,860</td>
<td>1,960</td>
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<tr>
<td>Mean ± SD</td>
<td>952.5 ± 217.5</td>
<td>1,125.5 ± 1,153.1</td>
<td>991.5 ± 1,064.4</td>
<td>71.8 ± 52.6</td>
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</table>

Effects of Aminophylline on Sinus Node Function after Autonomic Blockade

After intravenous aminophylline administration, no significant change was found in the mean sinus cycle length (968 ± 218 ms [Table 2]). The mean maximum SNRT and mean maximum corrected SNRT were 2,799 ± 1,153 and 1,832 ± 1,036 ms, respectively. The mean SACT was 119 ± 53 ms. Compared with the data after autonomic blockade, none of these clinical electrophysiologic measurements of the sinus node function showed any significant change after intravenous aminophylline administration. The mean serum theophylline level of the 12 patients was 10.9 ± 1.7 µg/ml. Figure 1 is a representative example, in which patient 8 demonstrated no significant change in SNRT after intravenous aminophylline administration. The maximum SNRT during control, after autonomic blockade and after intravenous administration of aminophylline was 3,560, 3,520 and 3,540 ms, respectively.

Discussion

If adenosine played a role in the pathogenesis of sick sinus syndrome, intravenous aminophylline would improve the sinus node function by competitively antagonizing the adenosine effect through extracellular adenosine receptors. In this study, intravenous aminophylline in a dosage of 5 mg/kg did not improve sinus node function as shown by clinical electrophysiologic measurements in patients with sick sinus syndrome. These results indicate that intrinsic adenosine may not play an important role in the pathogenesis of sick sinus syndrome.

Electrophysiologic Effects of Adenosine

Adenosine produces significant negative chronotropic and dromotropic action on the SA node and AV node cells. Previous studies suggested that the main action of adenosine was through the extracellular receptor A1 adenosine receptors which could be antagonized by theophylline. Recently, the up-regulation of the adenosine receptor number after treatment with theophylline has also been proved. Atrioventricular block produced by adenosine was first reported in 1929 and has been well characterized in the human heart. An atropine-resistant but aminophylline-responsive AV block during inferior myocardial infarction was reported recently and adenosine was suggested as the mechanism of this AV block. The negative chronotropic effect of adenosine already had been described for both the animal and the human heart. The depressant effects of adenosine on the SA node include pacemaker shift, SA exit block and hyperpolarization of the pacemaker cells due to increase in the background potassium outward current.

Effects of Aminophylline on Sinus Node Function

Aminophylline, a theophylline derivative, has long been known to have positive chronotropic and dromotropic effects on the heart. The mechanisms attributed to these effects of aminophylline include (1) the inhibition of phosphodiesterase activity, (2) the release of endogenous catecholamines from sympathetic nerve terminals as well as the adrenal medulla, and (3) antagonizing the negative chronotropic and dromotropic effects of adenosine by competitive blocking extracellular adenosine R-site receptors. In this study, since we administered intravenous aminophylline after autonomic blockade, the sympathomimetic
action of aminophylline could be antagonized by the pharmacologic beta blocker propranolol. In addition, the mean serum concentration of theophylline was 10.9 ± 1.7 µg/ml, which was below the threshold concentration required to inhibit phosphodiesterase activity but was high enough to have a positive chronotropic effect by antagonizing the action of adenosine. In this study, after intravenous aminophylline administration, no significant improvement of the sinus node function could be observed. These findings indicate that endogenous adenosine may not play an important role in the pathogenesis of the sick sinus syndrome. Newby has referred to adenosine as a "retaliatory metabolite" which increases during a state of stress. Classic sick sinus syndrome, unrelated to an acute disease process, was known as a chronic degenerative disease and this may explain why adenosine is not important as a mechanism in the sick sinus syndrome. Although a previous study showed that theophylline could increase heart rate and improve the sinus node function in young patients with sinus bradycardia, the difference in results can be explained by positing that in young patients with symptomatic bradycardia, vagotonia may be the most important factor which can be antagonized by the sympathomimetic action of aminophylline.

Limitations of the Study

There are several limitations to the present study. These include: (1) The clinical therapeutic dosage of aminophylline (5 mg/kg) was used and the serum theophylline concentration was at the lower therapeutic range. Although this aminophylline dosage already had an anti-adenosine effect, we could not determine whether the higher theophylline dosage would improve the sinus node function. (2) In order to fit the definite diagnosis of sick sinus syndrome by Holter and electrophysiologic examination, the patients in this study all had relatively advanced sinus node disease. (3) The number of patients is small and there was no control group. Therefore, the results in this study against the role of adenosine in the pathogenesis of sinus node dysfunction can just be applied to patients with chronic and advanced sinus node dysfunction. Further studies regarding the response of sinus node function to theophylline in patients with relatively mild sinus node disease and those with sinus node disease related to acute disease entity may provide a more meaningful answer.

Conclusion

Thus, intravenous aminophylline after pharmacologic autonomic blockade cannot improve the sinus node function in patients with chronic and advanced sick sinus syndrome. Endogenous adenosine may not play an important role in the pathogenesis of advanced sick sinus syndrome. Clinically, aminophylline does not increase the intrinsic heart rate in patients with advanced sick sinus syndrome and pacemaker therapy is still the first choice for patients with symptomatic sick sinus syndrome.

References

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