Studies on the Mechanism of Sinus Node Dysfunction in the Sick Sinus Syndrome

Jay L. Jordan, M.D., Iwao Yamaguchi, M.D., and William J. Mandel, M.D.

SUMMARY The intrinsic heart rate (IHR) was determined in 17 patients with symptomatic sinus bradycardia by administering atropine 0.04 mg/kg and propranolol 0.2 mg/kg, i.v. In this way, sick sinus (SSS) patients with intrinsic sinus node (SN) dysfunction could be distinguished from those patients with disturbed autonomic regulation of SN function. Sick sinus syndrome patients with normal corrected sinus node recovery time (SNRTC), adjusted for the magnitude and direction of autonomic chronotropy, consistently had normal IHRs and therefore abnormalities of autonomic regulation. Sick sinus syndrome patients with abnormal adjusted SNRTC consistently had abnormal IHRs and therefore abnormalities of intrinsic SN function.

We conclude that more than one pathophysiological mechanism can produce the clinical manifestations of sick sinus syndrome and that abnormal prolongation of SNRTC is dependent upon the underlying mechanism of sinus node dysfunction.

Patient Population

Seventeen patients, 8 males and 9 females, ages 16 to 82 years, with symptomatic bradycardia were studied (table 1). Symptoms ranged from transient mild lightheadedness to syncope accompanied by bodily injury. All patients had sinus arrest or marked sinus bradycardia concomitant with symptoms documented by electrocardiogram, Holter monitor recordings or physical examination. Sinus arrest was documented in nine patients. Two patients had a history of paroxysmal atrial fibrillation and one patient had readily demonstrable carotid hypersensitivity. Although four patients had a history of ischemic heart disease and five patients had mild hypertension, none of these patients demonstrated congestive heart failure or cardiomegaly. All patients were New York Heart Association Class I. Excluded from the study were patients with pulmonary disease, glaucoma or urinary retention. All cardiac drugs and drugs known to interfere with sinus node and autonomic neural function were discontinued at least 48 hours or 2 half-lives prior to the study.

Methods and Parameters

After informed consent had been obtained, all studies were performed in the cardiac catheterization laboratory with the patient in the fasting state. A #6 Fr quadripolar catheter was passed through an antecubital vein into the high right atrium. Intra-atrial electrical activity as well as surface leads I, II, and III were recorded on a photographic oscillographic recorder at a paper speed of 50 mm/sec. Atrial pacing was performed at 90, 110, 130, 150 and 170 beats/min was carried out for 30 seconds and abruptly terminated. A one minute time interval was allowed to elapse between each pacing run. Without regard for the pacing rate at which it occurred, maximum sinus node recovery time was taken as the maximum time after the last paced P-wave to the appearance of the next atrial depolarization on the intra-atrial electrogram. P-wave configuration on the surface electrocardiogram was used to ascertain that the first escape beat terminating the pause was indeed sinoatrial in origin. The corrected sinus node recovery time (SNRTC) was derived by subtracting the resting sinus cycle length from the maximum sinus node recovery time (SNRTC = SNRT - sinus cycle length). No patient developed angina pectoris during overdrive atrial pacing.

The observed intrinsic heart rate (IHR), defined as the rate of spontaneous depolarization of the sinus node in-

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dependent of autonomic influences, was determined utilizing a modification of the protocol of Jose. With the transvenous temporary pacing catheter advanced into the apex of the right ventricle, sympathetic and parasympathetic blockade was achieved. Propranolol, 0.2 mg/kg of body weight, was administered intravenously at a rate of 1 mg/min. Ten minutes thereafter, atropine sulfate 0.04 mg/kg was administered as a single injection over 2 min. Sinus rate was measured on surface ECG continuously throughout the study. The maximum sinus rate following atropine administration was taken as the observed intrinsic heart rate. The IHR was usually reached a plateau at approximately 5 min and remained stable (±3 beats/min) for approximately 30 min. Existing pre-autonomic blockade sinus arrhythmia was invariably eliminated after atropine administration. Randomization of drug administration was not performed.

Predicted intrinsic heart rate (IHR) was determined for each patient utilizing the linear regression equation derived by Jose relating predicted intrinsic heart rate to age. According to this formula, IHR = 118.1 - (0.57 × age). For young individuals (≤ 45 years in our study) the 95% confidence limits of IHR was ±14%. For older individuals (> 45 years in our study), the 95% confidence limits of IHR was ±18%. An IHR falling within 2 standard deviations of the predicted intrinsic heart rate was considered indicative of normal sinus node function. Conversely, an IHR falling outside the 95% confidence limits of IHR was considered to be compatible with abnormal intrinsic sinus node function. This may be expressed by the equation: IHR - 2 SD ≤ IHR ≤ IHR + 2 SD.

In an attempt to develop a comparative measure of intrinsic sinus node function, the ratio of observed intrinsic heart rate to the lowest it could be and still be normal (i.e., IHR/IHR - 2 SD) was taken as a quantitative measure of the integrity of intrinsic sinus node function. By this method, a ratio of 1.0 or greater was thus indicative of normal sinus node function. By statistical definition, all patients determined to have normal sinus node function by this method also had an IHR, that fell within the 95% confidence limits of IHR. Conversely, all patients with an IHR/IHR - 2 SD < 1.0 had an IHR that fell outside the 95% confidence limits of IHR.

For each patient, the magnitude and direction of autonomic chronotropic influences present at the time of control sinus node recovery time determination were evaluated. The percent by which a patient's resting heart rate (RHR) deviated from his observed intrinsic heart rate was taken as a quantitative measure of positive or negative autonomic chronotropy present at that time. Thus, (

\[
\frac{\text{RHR} - 1.00}{100} = \text{percent positive or negative autonomic chronotropy.}
\]

The RHR was determined by measuring the average heart rates during electrocardiographic observation for one minute prior to the initiation of control overdrive atrial pacing and again prior to propranolol and atropine administration. Although many of the patients had demonstrated sinus arrhythmia during Holter monitoring, the degree of variability of resting heart rate was drastically reduced in the setting of the catheterization laboratory following the introduction of the catheters. Furthermore, overdrive pacing and IHR determination were intentionally performed at a time when sinus arrhythmia was minimal.

To adjust the measure of the corrected sinus node recovery time for the role that existing autonomic tone played in its value, two techniques were employed. 1) Sinus node recovery time determination was repeated after propranolol and atropine had been administered to give the observed adjusted SNRTC. Overdrive pacing trials were begun immediately after IHR determination and performed in the same manner as in the pre-blockade control state. 2) The predicted adjusted SNRTC, representing the SNRTC that would be anticipated if the control SNRTC were adjusted mathematically for the role that existing autonomic tone played in its value, was determined according to the following formula: Predicted Adjusted SNRTC = SNRTC + [SNRTC (RHR/IHR - 1.00)]

<table>
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**Table 1. Patient Population—Clinical Profile**

Abbreviations: Mod. = moderate; Sev. = severe; HTN = hypertension; CNS = central nervous system; ASHD = arteriosclerotic heart disease.
Results

Classification of Sick Sinus Patients on the Basis of Intrinsic Sinus Node Function

On the basis of observed intrinsic heart rates, the 17 sick sinus patients fell into two groups (table 1). Group I was composed of ten patients, five males and five females, with normal observed intrinsic heart rates i.e., IHR$_o$ falling within 2 standard deviations of IHR$_p$. Group II included seven patients, three males and four females, with abnormal observed intrinsic heart rates, i.e., IHR$_o$ falling outside the 95% confidence limits of IHR$_p$. Although statistically possible, no patient's IHR$_o$ was greater than the IHR$_p$ + 2 sd. It is not certain whether such an individual's intrinsic sinus node function should be properly classified as abnormal or supernormal. The mean age of group I patients was 41.4 ± 4.5 years. The mean age of group II patients was 63 ± 4 years. The age difference between the two groups was statistically significant. Furthermore, the occurrence of sinus arrest was statistically significantly greater in group II.

Pathophysiologic mechanisms could not be distinguished on the basis of severity of central nervous system symptomatology or on the basis of the presence or absence of ischemic heart disease or hypertension.

Adjusted SNRTC

The corrected sinus node recovery time, whether adjusted or unadjusted for autonomic chronotropic influences, was considered to be prolonged if greater than 450 msec. The corrected sinus node recovery time was thus abnormal in only 11 of the 17 patients (table 2).

When examined in the context of basic underlying mechanisms, the ten patients with normal observed intrinsic heart rates demonstrated both normal or abnormal corrected sinus node recovery times: 6, normal; 4 abnormal (table 2 and fig. 1). In contrast, all seven patients with abnormal observed intrinsic heart rates had abnormal corrected sinus node recovery times (table 2 and fig. 1).

When corrected sinus node recovery times were adjusted for autonomic chronotropic influences, either mathematically (predicted adjusted SNRTC) or by repeating atrial pacing after autonomic blockade (observed adjusted SNRTC), all ten patients with normal observed intrinsic heart rates had normal corrected sinus node recovery times (table 2): 6, unchanged; 4, changing to normal. In contrast, all seven patients with abnormal observed intrinsic heart rates continued to demonstrate abnormal corrected sinus node recovery times (table 2). Figure 1 is a flow chart that summarizes the relationship between IHR$_o$ and adjusted and unadjusted SNRTC.

No linear relationship existed between the magnitude of unadjusted SNRTC and the magnitude of deviation of the observed intrinsic heart rate from lower limits of predicted (fig. 2a). A similar lack of relationship existed for observed and predicted adjusted SNRTC (fig. 2b). Thus, individuals with equally abnormal intrinsic heart rates had markedly disparate abnormalities of adjusted sinus node recovery times.

![Flow sheet for evaluation of 17 patients with sick sinus syndrome utilizing intrinsic heart rate and sinoatrial nodal recovery time determinations. IHR$_o$ = observed intrinsic heart rate; NL = normal; ABNL = abnormal, SNRTC = sinus node recovery time corrected.](http://circ.ahajournals.org/)

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The value of the observed adjusted SNRTC resulting from overdrive pacing during autonomic blockade did not always equal the adjusted SNRTC that was predicted from mathematically adjusting the control SNRTC for the magnitude and direction of resting autonomic chronotropy (table 2). Seven patients demonstrated an observed adjusted SNRTC greater than predicted and ten patients demonstrated an observed adjusted SNRTC less than predicted.

Discussion

The complex pattern of interaction between intrinsic electrophysiologic properties of the sinus node and extrinsic factors must be reflected in any adequate explanation of the pathophysiologic mechanisms that underly the signs, symptoms, and electrocardiographic manifestations of the sick sinus syndrome. Before the site(s) of dysfunction can be identified, systematic techniques for isolating the many possible determinants of sinus node function must be found. The logical initial step toward establishing the specific site(s) of disturbance is the development of the general capability to distinguish those disturbances that are intrinsic from those that are extrinsic to the sinus node.

The present study has demonstrated that the sick sinus syndrome is clearly not a homogeneous entity in terms of underlying pathophysiologic mechanisms. Utilizing the technique of intrinsic heart rate determination, sick sinus patients with intrinsic sinus node dysfunction can be distinguished from those with disturbed autonomic regulation of sinus node function. Since the observed intrinsic heart rate is theoretically dependent upon only intrinsic electrophysiologic properties of the sinus node, an abnormal IHRc in patients with symptomatic sinus bradycardia reflects an abnormality of one or more of these intrinsic properties. In contrast, when the heart rate is "normal" (i.e., Jose) after autonomic blockade, it follows that disturbed autonomic regulation is most likely the underlying mechanism responsible for the manifestations of sinus node dysfunction.

In the present study, no clinical or electrocardiographic feature was diagnostic of the particular mechanism at fault in the sick sinus patients studied. Although the age difference between the two groups was statistically significant, 40% of patients with normal intrinsic sinus node function were over 45 years of age. Thus, age alone can not be regarded as a reliable indicator of the underlying pathophysiologic mechanism of sinus node dysfunction. Furthermore, although patients with sinus arrest are perhaps more likely to have intrinsic sinus node dysfunction than disturbed autonomic regulation of the sinus node, this finding in patients with normal intrinsic heart rates invalidates sinus arrest as a reliable differentiating marker.

As first described by Jose, intrinsic heart rate determination was neither designed nor employed as an experimental model to assess the underlying mechanisms of sinus node pacemaker dysfunction. Rather, his concern was primarily with the status of intrinsic myocardial function in cardiac disease of a variety of etiologies. Among the hemodynamic functions studied, a depression of intrinsic heart rate correlated with deterioration of left ventricular performance. Jose postulated that in the failing heart, the same biochemical fault in energy production may exist in both muscle fibers and pacemaker tissue.

It has been long recognized that the autonomic nervous system exerts profound and variable influences on sinus node function. Argus et al. demonstrated that the well-established phenomenon of slowing of the sinus rate with age may be, in part, secondary to increased parasympathetic tone in many elderly individuals. Other investigators have shown that, in some patients, sinoatrial block may be mediated by abnormal autonomic tone. Furthermore, it has been demonstrated that sinus arrhythmia is often produced primarily by periodic alterations in parasympathetic efferent cardiac activity. Particularly relevant to the results of the present study, Dighton found that individuals with symptomatic sinus bradycardia are more likely to have abnormal sinus rate responses to autonomic stimulation and inhibition than are asymptomatic patients. Similarly, patients with myocardial dysfunction have been shown to have profound abnormalities of reflex parasympathetic and sympathetic control of heart rate.

Surprisingly, despite intensive investigation of the interaction between normal and abnormal sinus node function and the autonomic nervous system, no standardized or systematic technique for quantitating the immediate influence of spontaneously occurring autonomic activity on sinus node function has been described. The present study details such a technique. Simply, the percent by which a subject's resting heart rate deviates from his observed intrinsic heart rate represents a quantitative measure of the magnitude and direction of autonomic chronotropic influences present at that moment in time.
A major diagnostic dilemma in the evaluation of patients with the sick sinus syndrome is that manifestations of sinus node dysfunction are only intermittently present. At the time of diagnostic evaluation, all objective evidence of sinus node dysfunction may be absent. Whereas the magnitude of sympathetic and parasympathetic tone varies from moment-to-moment and is dependent upon a host of variable internal and external stimuli and inhibitors, the intrinsic heart rate has been shown to be relatively constant and reproducible in any given patient. Thus, autonomic blockade provides a method of standardizing and controlling the diagnostic situation by eliminating the effects of beta-adrenergic and cholinergic activity on intrinsic sinus node function.

The importance of the autonomic nervous system on intrinsic sinus node function has led some investigators to recommend that heart rate response to sympathomimetic, sympatholytic, vagotonic and vagolytic drugs be employed routinely in the clinical evaluation of the sick sinus syndrome. Unfortunately, normal dose-response relationships have never been universally agreed upon nor systematically investigated.

Recently, investigators have begun to recognize that autonomic tone exerts a major influence on not only intrinsic sinus node function, but also on clinical parameters currently employed to assess sinus node function. For example, atropine administration has been shown to shorten sinoatrial conduction time in normal individuals as well as in some patients with the sick sinus syndrome. Furthermore, atropine and isoproterenol have been shown to shorten sinus node recovery time while vagal stimulation has been shown to prolong it in many individuals. Chadda et al. have suggested that the finding of an abnormal SNRTC should be evaluated in terms of the influence of the autonomic nervous system before concluding that sinus node dysfunction per se caused the abnormality. The present study outlines a logical approach for conducting such an evaluation, i.e., by determining the adjusted SNRTC. Thus, sick sinus patients demonstrating normal sinus node recovery times adjusted for the magnitude and direction of autonomic chronotropy consistently have normal intrinsic heart rates and therefore abnormalities of autonomic regulation. On the other hand, sick sinus patients demonstrating abnormal adjusted sinus node recovery times consistently have abnormal intrinsic heart rates and therefore abnormalities of intrinsic sinus node function.

The observation that not all patients with the sick sinus syndrome display abnormal prolongation of SNRTC provided a major stimulus for initiating the present study. While some investigators have cited the inconsistent nature of this measure as a cause for questioning the value of SNRTC in the diagnosis of the sick sinus syndrome, the present study has focused its attention upon the nature of this inconsistency. The present study suggests that SNRTC does not test an underlying mechanism of sinus node dysfunction that is common to all cases of the sick sinus syndrome. Specifically, sick sinus patients with primarily abnormal autonomic regulation of heart rate display normal adjusted SNRTC. Thus, the real value of adjusted SNRTC lies not only in the identification and diagnosis of many sick sinus patients, but also in identifying whether the dysfunction is intrinsic or extrinsic to the sinus node itself.

The intrinsic heart rate and adjusted SNRTC were not found to be linearly related. Several hypothetical explanations can be made:

1) Sinus node recovery time may be a more sensitive indicator of the degree or extent of abnormality of all intrinsic sinus node mechanisms than is the intrinsic heart rate. That is, only after stressing intrinsic electrophysiologic properties does the extent of dysfunction become truly apparent.

2) The absolute value of the adjusted SNRTC may depend not only upon the extent of the abnormality of intrinsic sinus node function, but also upon the precise electrophysiologic property that is abnormal. Rapid atrial pacing may not stress or challenge the integrity of all electrophysiologic properties equally. Furthermore, the abnormality of intrinsic sinus node mechanisms may lie at an even more basic level. Rapid atrial pacing may hypothetically have differential effects on sodium, potassium and calcium currents, possibly the elemental determinants of the intrinsic electrophysiologic properties of sinus node pacemaker cells.

3) As the intrinsic heart rate may be influenced by extrinsic factors other than the autonomic nervous system, so may the effects of rapid atrial pacing on sinus node automaticity be modified by other extrinsic factors.

4) The effects of rapid atrial pacing on intrinsic sinus node mechanisms may, in part, be dependent upon the etiology of intrinsic sinus node dysfunction. Coronary artery disease, atrial amyloidosis and fibrotic changes of the sinoatrial region may have differential effects on intrinsic sinus node function.

Finally, 5) subjects with similar intrinsic heart rates may differ considerably in the integrity of the conduction properties of the perinodal zone. Thus, one patient may have developed sinoatrial entrance block at an atrial pacing rate less than another patient with equally abnormal intrinsic sinus node function and would, therefore, display less “suppressibility” of sinus node automaticity at similar pacing rates.

An attempt must also be made to explain the minor disparity found between the observed adjusted SNRTC and the mathematically predicted adjusted SNRTC. It has been postulated that rapid atrial pacing causes a local release of neurotransmitters from nerve endings or myocardial tissue. If this hypothesis is true, the additional autonomic discharge provoked by rapid atrial pacing was not accounted for when the magnitude and direction of autonomic chronotropy present was determined prior to the initiation of control pacing. The majority of the patients studied demonstrated a mathematically predicted adjusted SNRTC greater than observed adjusted SNRTC, suggesting that additional cholinergic neurotransmitters were released by overdrive pacing that were not exerting an influence on sinus node function when resting autonomic tone was quantified. Conversely, those patients demonstrating a predicted adjusted SNRTC less than observed adjusted SNRTC presumably had a net release of sympathetic neurotransmitter during atrial pacing. The significance of this finding can not be overemphasized. Specifically, a difference between observed and predicted adjusted SNRTC provides an understanding of the mechanisms by which rapid atrial pacing may influence sinus node automaticity. The results of the present study suggest that the influence of rapid atrial pacing on sinus node automaticity is the net result of local release of autonomic neurotransmitters, as
represented by the difference between predicted and observed adjusted SNRT, and a direct influence on intrinsic electrophysiologic properties of the sinus node, as represented by the observed adjusted SNRT.

In conclusion, the present study has shown that: 1) the sick sinus syndrome is clearly not a homogeneous entity in terms of pathophysiologic mechanisms; 2) utilizing the technique of intrinsic heart rate determination, sick sinus patients with intrinsic sinus node dysfunction can be distinguished from those with disturbed autonomic regulation; 3) the subtypes of sick sinus patients can not be adequately differentiated on the basis of age, sex, associated cardiovascular disease, clinical presentation or electrocardiographic manifestations; 4) a standardized and systematic technique for quantitating the magnitude and direction of autonomic chronotropic effects on sinus node function has been described; 5) sick sinus patients demonstrating normal sinus node recovery times corrected for the magnitude and direction of autonomic chronotropy consistently have normal intrinsic heart rates and, therefore, abnormalities of autonomic regulation; on the other hand, sick sinus patients demonstrating abnormal adjusted sinus node recovery times consistently have abnormal intrinsic heart rates and, therefore, abnormalities of intrinsic sinus node function. It must be cautioned that a clear separation of patients with intrinsic versus extrinsic sinus node dysfunction on the basis of sinus node response to atrial overdrive is somewhat dependent on the value chosen as the upper limit of “normal” for SNRT. 6) a clinical method for identifying the mechanisms of suppression of sinus node automaticity by rapid atrial pacing is proposed; finally, 7) the ability to recognize sick sinus patients with normal intrinsic sinus node function may aid in selecting those patients who most likely would benefit from medical therapy.

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The Cellular Electrophysiologic Effects of Digitalis on Human Atrial Fibers

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SUMMARY
We used microelectrode techniques to study the indirect and direct actions of ouabain on human atrial fibers (HAF) obtained from patients with congenital heart disease undergoing open heart surgery. At 15 min of superfusion ouabain, 2 x 10^{-7} M, induced an increase in maximum diastolic potential (MDP), action potential (AP) amplitude and upstroke velocity of phase 0 depolarization (V_{max}) and a decrease in AP duration. Spontaneously beating HAF showed a decrease in automaticity. Acetylcholine (3 x 10^{-6} M) induced identical effects on AP characteristics and automaticity. Prior treatment with atropine (1 x 10^{-4} M) blocked these effects of ouabain and acetylcholine. Superfusion with ouabain (2 x 10^{-5} M) for 30 to 90 min resulted in decreased MDP, AP amplitude and V_{max}, and a further decrease in AP duration. Phase 4 depolarization and spontaneous rate increased and delayed afterdepolarization and tachyarrhythmias occurred. The ACh-like effects of digitalis decrease automaticity and increase MDP of HAF; the direct effects decrease MDP, increase automaticity, and induce tachyarrhythmias.

STUDIES OF DIGITALIS EFFECTS on mammalian atria have shown that low drug concentrations tend to slow sinus rate, whereas high concentrations induce ectopic pacemaker function and tachyarrhythmias. Toda and West demonstrated that ouabain, 2 x 10^{-5} M, augments the negative chronotropic response to vagal stimulation and to acetylcholine of rabbit sinus node. With higher concentrations of ouabain (1 x 10^{-4} M) the negative chronotropic responses to vagal stimulation and to exogenous acetylcholine application were inhibited. Ten Eick and Hoffman showed that the negative chronotropic effect of digitalis on rabbit sinus node was mediated primarily through the parasympathetic nervous system and was not the result of direct effects of the drug on the sinus node. The effects of ouabain were blocked by prior treatment with atropine. These investigators also demonstrated that digitalis increases the number of vagal fibers responding to a constant strength stimulus and enhances the effects of the vagus on the sinus node by increasing nerve excitability.

Studies done in intact animals also have shown that vagal afferent and efferent pathways must be intact for ouabain to exert its negative chronotropic effect on the sinus node. Whereas the effects of low concentrations of digitalis appear to be mediated through the autonomic nervous system, the actions of higher or toxic concentrations have been attributed to a direct effect on cardiac fibers. The toxic effects of digitalis on mammalian atrial fibers include decreases in membrane potential and action potential amplitude, increases in automaticity, and the occurrence of delayed afterdepolarizations.

The purpose of the present study was to investigate the therapeutic and toxic effects of digitalis on fibers obtained from diseased and from relatively healthy human right atria. In so doing, we intended to identify the cellular electrophysiologic mechanisms whereby 1) therapeutic digitalis concentrations may improve atrial electrophysiologic function and thereby suppress arrhythmias and 2) toxic concentrations may induce atrial arrhythmias.

Methods
Specimens of right atria were obtained from the hearts of 20 patients undergoing open heart surgery for treatment of congenital heart disease. The patients' ages ranged from 2-15 years (mean, 6.5 years). Their diagnoses are described below. None of the patients had received digoxin or an an-
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