Premature Atrial Stimulation as a Key to the Understanding of Sinoatrial Conduction in Man

Presentation of Data and Critical Review of the Literature

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SUMMARY

Since recording potentials directly from the sinoatrial node (SAN) is not yet possible, the electrophysiologic evaluation of this structure in intact human subjects must be accomplished with indirect technics. Two technics have been used to study SAN function in man: premature atrial stimulation (PAS) and rapid atrial pacing. Recent discussions of data using these technics have emphasized their role in determining SAN automaticity, but their role in evaluating conduction from atrium to SAN or SAN to atrium has not been fully explored. Using the technic of PAS, we have studied five patients with sinus bradycardia and symptoms of dizziness or syncope. Our analysis of the results obtained from these studies discloses the unique ability of this technic to evaluate conduction into and out of the SAN. An atrial premature depolarization (APD) elicited late in atrial diastole is followed by a compensatory pause (nonreset of the SAN pacemaker). An APD elicited earlier in atrial diastole is followed by a pause that is less than compensatory (SAN reset). From these responses estimates of sinoatrial conduction time were made. In one patient reset was never seen, suggesting markedly prolonged sinoatrial conduction. With these results in mind, the literature was reviewed and an alternate interpretation posed for existing data. PAS is not only a means of determining SAN automaticity, but also a very useful means of unmasking sinoatrial conduction abnormalities.

Additional Indexing Words:

- Reset
- Nonreset
- Overdrive suppression
- Sinoatrial node function

Eyster and Evans\(^1\) and Levine\(^2\) emphasized the difficulties encountered in diagnosing abnormalities of sinoatrial conduction in man using the surface ECG. Although they described second-degree sinoatrial block in the electrocardiogram, they were aware that many of the possible sinoatrial conduction disturbances elude analysis. In 1962, Langendorf and co-workers\(^3\) presented an elegant analysis of a patient with atrial parasytostole, in which they estimated sinoatrial conduction delays. Since this outstanding contribution, little progress has been made in understanding sinoatrial conduction in human subjects.

Recently a heterogeneous group of elderly patients with sinus bradycardia and symptoms related to the slow heart rate has elicited great interest.\(^4\) The symptoms and signs characterizing this group have been termed “sick sinus syndrome.”\(^4\) Clinical,\(^5, 6\) hemodynamic,\(^7\) and electrophysiologic evaluations\(^8-11\) of these patients have recently appeared in the literature. As a result of the growing recognition of the prevalence of the syndromes of sinus node dysfunction\(^8-11\) an attempt to find useful tests of sinus node function has become an important problem in clinical electrophysiology. Recently, workers using the technics of

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rapid atrial pacing and/or premature atrial stimulation (PAS) evaluated sinoatrial node (SAN) function in normal and abnormal subjects.8-11 While these studies focused our attention on the ability of these two technics to evaluate SAN automaticity, the interpretation of the data derived from the use of PAS8,11 did not consider the possibility that this technic might be useful in estimating sinoatrial conduction time.

The purpose of this paper is to present our approach to the analysis of sinoatrial conduction using the technic of PAS and to advance alternate interpretations of recently published data.

Methods

Five patients, ages 46-76 years, with a recent, documented history of dizziness or syncope and sinus bradycardia were evaluated for sinus node dysfunction. None was on cardioactive medications at the time of the study. All gave informed, written consent.

Patients were studied in the cardiac catheterization laboratory in the resting, nonsedated, postabsorptive state. Catheter electrodes were positioned in the right atrium and across the tricuspid valve under fluoroscopic monitoring. Two no. 4 F bipolar electrodes, one for stimulating and one for recording, were passed via a right antecubital vein into the right atrium. The stimulating electrode was positioned at the junction of the superior vena cava and the right atrium; the recording electrode was positioned just caudad to the first, along the lateral wall of the right atrium. A no. 6 F tripolar catheter was passed percutaneously via the right femoral vein to the right atrium to lie across the tricuspid valve and used to record the His bundle electrogram. Signals from atrial and His bundle electrodes were simultaneously recorded with the body-surface ECG. All the above signals, along with 100- and 1000-msec time marks, from a time mark generator (Tektronix type 184) were simultaneously displayed on an Electronics for Medicine multichannel oscillograph and recorded on FM magnetic tape. Control recordings of spontaneous sinus rhythm were obtained for a period of 20 min. Thereafter, premature atrial stimuli were introduced via the stimulating electrode during spontaneous sinus rhythm. The atrial electrogram was used to initiate a programmable stimulator. In this way atrial premature stimuli, 2-2.5 times diastolic threshold, 2 msec in duration, were introduced via an isolation transformer after every eighth spontaneous sinus cycle. Stimuli were introduced late in atrial diastole and moved progressively earlier in 5-10-msec increments until the entire atrial diastolic period was scanned.

The data were transferred to photographic paper for analysis using the Electronics for Medicine recorder at a paper speed of 100 mm/sec. When the spontaneous sinus cycle was interrupted by an atrial premature depolarization (APD), the following atrial intervals were measured: (1) spontaneous sinus cycle length (A-A), i.e., the interval between the last spontaneous sinus P wave and the APD; (2) the test cycle (A-A), i.e., the interval between the last spontaneous sinus P wave and the APD; (3) the return cycle (A-A), i.e., the interval between the APD and the following spontaneous sinus P wave; and (4) the spontaneous sinus cycle immediately following the return cycle (A-A).

Definitions

The following terms used in the text are defined as follows:

Reset. Reset of the SAN pacemaker by an APD is said to occur when the sum of the test cycle and return cycle is less than the sum of two spontaneous sinus cycles.

Nonreset. Nonreset of the SAN pacemaker by an APD is said to occur when the sum of the test cycle and return cycle is equal to the sum of two spontaneous sinus cycles; i.e., the return cycle is fully compensatory.

Normalization. To allow data comparison despite differences in basic sinus cycle length the test and return cycle lengths were each divided by the A-A cycle. For example:

\[
A-A = 1000 \text{msec} \quad A-A = 900 \text{msec} \quad A-A = 1100 \text{msec}
\]

\[
\frac{A-A}{A-A} = \frac{900}{1000} = 0.90
\]

\[
A-A = 1100 \quad \frac{A-A}{A-A} = \frac{1100}{1000} = 1.10
\]

Results

In all patients the normalized return cycle was plotted as a function of the normalized test cycle (fig. 1). In four patients two types of return cycle responses occurred. In these four plots the return cycle responses fell into two distinct areas, zones I and II (fig. 1).

Zone I

Atrial premature depolarizations (APDs) elicited late in atrial diastole were followed by return cycles that were fully compensatory (fig. 2); i.e., the sum of the test (A-A) and return cycles (A-A) was equal to two spontaneous sinus cycles, two (A-A). In four patients this pattern of response was seen when the APD fell in the last 20% (mean value) of the spontaneous sinus cycle. In a plot of the normalized return cycle against the test cycle (fig. 1), these late APDs are seen to fall about line A. As the test cycle shortens, the return cycle lengthens in a reciprocal fashion. The sum of the values on the X and Y axes for any APD falling in zone I equals two spontaneous sinus cycles. This distribution of data points about line A in figure 1 defines the limits of zone I as from 0.83 to 1.02 of the spontaneous sinus cycle in this patient.

The mechanism we postulate for the relationship between the return cycle and test cycle is diagrammed in figure 2. An APD elicited late in
Figure 1

The return cycles plotted as a function of the test cycles for patient M.B. (figs. 2, 3). This graph depicts the relationship of the return cycle to the degree of prematurity of the test depolarization. Points falling on line A represent nonreset of the SAN pacemaker; i.e., a fully compensatory pause occurs when APDs are elicited late in atrial diastole. We have designated this portion of the graph as zone I extending from 0.83 to 1.02 of the abscissa. APDs elicited earlier in atrial diastole fall in zone II. Line B, projected from the y axis, is a reference line for one spontaneous sinus cycle. Zone II points could only fall on this line if conduction into and out of the SAN were instantaneous and the return cycle was identical to the SAN pacemaker cycle. The distance the zone II points fall above this line indicates the sum of conduction into and out of the SAN, assuming the SAN pacemaker cycle (SAN−SAN) immediately following the APD is identical to the preceding SAN pacemaker cycle (SAN−SAN). The slope of the line through zone II points between 0.65 and 0.80 is −0.036. The “sinoatrial conduction time” was calculated assuming conduction time to be approximately the product of one half the distance of a select group of zone II points above line B and spontaneous sinus cycle length. For example, mean A−A/A−A of zone II points between 0.65 and 0.80 = 1.17. Distance of these zone II points above line B = 0.17. Mean spontaneous sinus cycle length = 1179 msec. “Sinoatrial conduction time” = % \(\frac{1}{2}(0.17 \times 1179) = 100\) msec.

atrial diastole meets the emerging SAN impulse in the sinoatrial junction and they collide. The APD fails to enter the SAN and therefore fails to discharge the SAN prematurely (i.e., fails to reset it). The subsequent SAN impulse occurs at the expected time and conducts normally to the atrium. Thus, we postulate that when the sum of the test and return cycles is equal to two spontaneous sinus cycles, the SAN is not discharged prematurely because the APD has failed to reset the SAN pacemaker (nonreset).

**Zone II**

Earlier in atrial diastole, not only did progressive shortening of the test cycle (A−A) fail to result in reciprocal lengthening of the return cycle (A−A) but the return cycle duration remained nearly constant (fig. 1). The return cycle was no longer fully compensatory, but was greater than one spontaneous sinus cycle (A−A). This change in return cycle response marked the transition from zone I to zone II. In four of our patients the transition from zone I to zone II ranged from 0.67 to 0.90 of the spontaneous sinus cycle. In any one patient, the transition from zone I to II occurred at a constant time in the spontaneous sinus cycle. Linear regression analysis of points falling in the last third of zone II (adjacent to zone I) for patient M.B. gave a slope not significantly different from zero, indicating the remarkable constancy of the return cycle. In all four patients the slope of the line drawn through points falling in the last third of zone II was 0.051 ± 0.1081 (mean ± sd). The mean normalized return cycle length of these zone II responses was 1.17 for patient M.B. (fig. 1) and 1.20 ± 0.096 (mean ± sd) for all four patients studied; i.e., the return cycle length in zone II is 10–33% longer than the spontaneous sinus cycle. The mean normalized A−A cycle length for these zone II responses was 1.02 for patient M.B. and 1.02 ± 0.014 (mean ± sd) for all four patients studied.

The mechanism we postulate for events occurring in zone II is depicted in figure 3. In zone II, an APD enters the SAN and discharges it prior to its spontaneous discharge, resetting the SAN pacemaker. Since the return cycle remains constant despite shortening of the test cycle, one may postulate that the determinants of the return cycle also remain unchanged. These determinants are the conduction time of the APD into the SAN, the length of the SAN pacemaker cycle following the APD and the conduction time back to the atrium. If one assumes that the SAN pacemaker cycle is equal to the spontaneous sinus cycle (A−A) and that the SAN pacemaker cycle following the APD (SAN−SAN) is equal to the last preceding spontaneous sinus cycle (A−A), then the difference between A−A and A−A reflects conduction time into and out of the SAN. The “sinoatrial conduction time” was calculated to be approximately the product of one half the distance of a select group of zone II points above line B and the spontaneous sinus cycle length (fig. 1). Zone II was subdivided into three sections, and points in the section of zone II adjacent to zone I were selected for the calculation of a mean A−A/A−A and the distance of zone II points above line B. The calculated “sinoatrial
conduction time" was 100 msec for patient M.B. and ranged from 68 msec to 156 msec in our four patients.

In one patient studied, M.M., the sum of the test and return cycles remained equal to two spontaneous sinus cycles; i.e., reset did not occur despite increasing prematurity of the test depolarization (fig. 4). Figure 5 shows a possible mechanism for this behavior. An APD of sufficient prematurity to cause SAN reset in four other patients failed to excite the SAN prematurely in M.M. This suggests that prolonged sinoatrial conduction is present, blocking entrance of the APD into the sinus node. Even with very early APDs, premature discharge of the SAN did not occur. As can be seen in figure 4, all data points for this patient fall along line A; i.e., all premature depolarizations are followed by a compensatory pause. Reset never occurs. We have termed this phenomenon "first-degree sinoatrial block with interference" since reset of the SAN pacemaker is prevented by prolonged antegrade and retrograde conduction between the SAN and atrium.

**Discussion**

Dysfunction of the SAN in man has recently attracted increasing interest, particularly the "sick sinus syndrome," a heterogeneous patient population with a variety of ECG abnormalities. Out of this interest grew attempts to identify useful tests for SAN function. Two technics have emerged. The first termed rapid atrial pacing or overdrive suppression measures the pause following cessation of atrial pacing. This technic has proved helpful in distinguishing some patients with advanced SAN dysfunction from the larger group of patients with sinus bradycardia. It has been stated that overdrive suppression evaluates the automatic or generator characteristics of the SAN pacemaker. For this method to be valid, conduction between the atrium and SAN must be one to one and not greatly prolonged. Delay or block in conduction between atrium and SAN would lead to an irregular discharge of the SAN, even though atrial discharge remained regular. Such a delay or block in conduction might be anticipated as the rate of atrial pacing is increased. At slow pacing rates

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**Figure 2**

Nonreset of the SAN pacemaker. In the upper panel surface ECG (leads II and V1), high right atrial electrogram (HRA), and His-bundle electrograms (HBE) are recorded. In the lower panel is a ladder diagram showing the postulated sinoatrial junctional and SAN activity (stippled lines) and the recorded atrial activity (solid lines). A-A = spontaneous sinus cycle; A-A = test cycle; A-A = return cycle; and A-A = next spontaneous sinus cycle. Intervals are in msec; normalized values are in parentheses. The value [1159] for the SAN pacemaker cycle (SAN-SAN) is bracketed because it is assumed to be equal to the spontaneous sinus cycle (A-A).

In the upper panel, an APD, A, (arrow) is elicited 1010 msec after the last spontaneous sinus P wave. The sum of the test and return cycles is equal to two spontaneous sinus cycles. An explanation for this event is seen in the ladder diagram. The emerging spontaneous SAN impulse meets the APD in the sinoatrial junctional zone and they collide. The next sinus beat emerges unperturbed, i.e., sinoatrial conduction is identical with preceding unperturbed impulses and activates the atrium at the expected time. Throughout zone I there is a reciprocal relationship between the test and return cycles (see fig. 1).
(cycle lengths above 600 msec) 1:1 conduction from atrium to SAN could be expected with normal tissues.10, 14, 15 As the pacing rate is increased, gradual conduction delay followed by entrance block might be expected.14-16 This would lead to a paradox where faster atrial pacing rates cause slower discharge of the SAN. Sinoatrial entrance block would confound rapid atrial pacing as a means of estimating SAN automaticity. Conclusions in the literature concerning the generator function of the SAN following rapid atrial pacing are open to question due to the possibility of sinoatrial entrance block occurring during pacing. Mandel and co-workers10 found a sudden shortening in the pause following rapid atrial pacing when the pacing rate was increased to 150 beats/min. They interpreted this sudden shortening to the release of autonomic humoral mediators, causing a change in SAN automaticity. We think it more likely that this sudden shortening resulted from second-degree sinoatrial entrance block. Our interpretation is partially supported by the reports of sinoatrial entrance block3, 9, 11 when atrial premature depolarizations are closely coupled to the preceding spontaneous sinus beat.

In 1962, Langendorf and co-workers3 used the variably coupled atrial ectopic beats of spontaneous atrial parasystole to determine the relationship between the return cycle and the premature cycle. They estimated the role of conduction into and out of the SAN in the duration of the return cycle. Our analysis and interpretation parallel those used by these workers3 but differ significantly from the

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**Figure 3**

Reset of the SAN pacemaker. Both the recordings and diagrams are labeled as in figure 2. APDs are elicited at 892 msec and 588 msec, respectively. The sum of the test and return cycles is equal to less than two spontaneous sinus cycles. The return cycle in each example is approximately equal (see zone II, fig. 1). The ladder diagram below each figure suggests the mechanism for these events. The APD is early enough to gain access to the SAN and discharge it prematurely, causing reset of the SAN pacemaker. This perturbation of the sinus cycle allows an estimation to be made of conduction into and out of the SAN (see fig. 1).
The return cycle plotted as a function of the test cycle for patient M.M. The coordinates and lines on this graph are as in figure 1. The points on this graph all follow the line for a compensatory pause, despite the increasing prematurity of the test response. This suggests sinoatrial conduction is prolonged, i.e., first-degree sinoatrial block (see text for explanation).

Figure 4

The return cycle plotted as a function of the test cycle for patient M.M. The coordinates and lines on this graph are as in figure 1. The points on this graph all follow the line for a compensatory pause, despite the increasing prematurity of the test response. This suggests sinoatrial conduction is prolonged, i.e., first-degree sinoatrial block (see text for explanation).

interpretations put forward in several recent reports. We will now discuss the differences between our interpretations of the response of the SAN to PAS with the interpretations put forward by other workers.

Zone I

A fully compensatory pause follows an APD elicited late in atrial diastole. We have designated this portion of atrial diastole as zone I (fig. 1). Our observations are in agreement with those of Goldreyer and Damato and Narula et al. These investigators found a linear relationship between the test and return cycles from 100 to 70% of the spontaneous sinus cycle. However, we interpret this data differently than these investigators. They thought that this linear relationship represented "depression" of the SAN pacemaker, connoting a change in the automatic function of the SAN as a result of the APD. Our explanation of zone I events is that reset of the SAN does not occur (fig. 2). Events in zone I are entirely analogous to the compensatory pause usually seen after a ventricular premature depolarization with retrograde conduction into the A-V junction resulting in collision with the orthograde atrial impulse. We think it unlikely that impulse formation in the SAN is depressed by the late APD. Sinoatrial conduction time would

Figure 5

Response to an APD showing "first-degree sinoatrial block with interference." Selected recordings from patient M.M. show this unusual response. The recording and diagram are labeled as in figure 2. The degree of prematurity of the APD is similar to that in figure 3, i.e. 0.49 of the spontaneous sinus cycle (A-A). In this patient, however, the sum of the test and return cycles remains equal to two spontaneous sinus cycles; reset does not occur. Reset did not occur even when the coupling interval of the APD was as short as 450 msec. The ladder diagram shows the postulated mechanism for this event. Sinoatrial conduction is prolonged. The emerging SAN impulse collides with the APD conducting slowly toward the SAN. The next SAN impulse falls on time. The result is a fully compensatory pause.
have to be extraordinarily short for late APDs to enter the SAN. APDs during late atrial diastole would collide with the emerging spontaneous SAN impulse (fig. 2). The argument for “depression” of SAN automaticity neglects the fact that there is a considerable lag between SAN activation and atrial activation because of slow conduction of the emerging SAN impulse through the sinoatrial junction.\(^5,10\) In the isolated rabbit heart, Bonke et al.\(^1,7\) have demonstrated delay in conduction of premature impulses to the SAN. Thus, for an APD to enter the SAN pacemaker, it must precede atrial activation (P wave) by an interval of time equal to the sinoatrial conduction time, plus the retrograde atrium to SAN conduction time of the APD.

**Zone II**

As the APD is moved earlier in atrial diastole, increasing prematurity of the test depolarization produces no further prolongation of the return cycle, so that the sum of the test and return cycles is less than two spontaneous sinus cycles; i.e., the pause is not compensatory (fig. 1). We have called this portion of the cycle zone II. Previous reports\(^9,11\) call attention to the “plateau” occurring in zone II and attribute this to “maximum depression of the sinus node pacemaker.” The concept of “maximum depression of the sinus node pacemaker” is unclear to us. This concept probably stems from interpreting zone I events as depression of the SAN pacemaker. We postulate that the “plateau” occurs because the APD gains access to the SAN, discharging it prematurely and resetting it (fig. 3). Reset of the SAN pacemaker without alteration of the postextrasystolic SAN cycle length (SAN\(_R\)-SAN\(_R\)) would account for the “plateau” in zone II; i.e., as the degree of prematurity of the APD increases the duration of the return cycle remains constant. The return cycle (A\(_R\)-A\(_R\)) in zone II (reset) is longer than the spontaneous sinus cycle (A-A) by a fixed amount. The duration of the return cycle is determined by the following events: (1) the conduction time from the atrium to SAN (A\(_R\)-SAN\(_R\)), (2) the SAN firing rate (SAN\(_R\)-SAN\(_R\)), and (3) the conduction time from the SAN to the atrium (SAN\(_R\)-A\(_R\)). In figure 1 it can be seen that the line drawn through the return cycle responses falling in the last third of zone II has a slope that is very close to zero. This suggests that the first spontaneous SAN discharge following the APD is nearly identical to the previous spontaneous SAN discharge rate. Also, the spontaneous sinus cycle (A-A) preceding the test cycle, and the spontaneous sinus cycle (A\(_R\)-A\(_R\)) following the return cycle, are of near equal duration, adding further evidence that the SAN firing rate is almost constant despite the discharge of the SAN by the APD. We interpret the difference between the spontaneous sinus cycle (A-A) and the return cycle (A\(_R\)-A\(_R\)) to represent total conduction time into and out of the SAN.

To calculate “ sinoatrial conduction time” return cycle responses falling in the last third of zone II were used. These points in the graph were selected because during this portion of atrial diastole refactoriness of the tissues in and around the SAN is minimal.\(^5,10\) Hence, one would predict that an APD falling in the last third of zone II would conduct from the atrium to the SAN with about the same average velocity as an impulse propagating from the SAN to the atrium during a normal sinus cycle. Since the effect of a late zone II APD on the automaticity of the subsequent SAN response is less than it is for early zone II APDs,\(^5,10\) it is not unreasonable to assume that when the slope of zone II points is approximately zero, that one can estimate the sum of conduction time into and out of the SAN. Although one can never be certain how much of the total conduction time is apportioned to antegrade or retrograde conduction between the SAN and atrium, it is most probable that conduction times from the atrium to the SAN and from the SAN to the atrium are approximately equal late in zone II. However, the partition of conduction is of little consequence, since a prolonged total conduction time strongly suggests an abnormality in the SAN, its junction with the atrium, or both.\(^5,10\)

Although most patients studied to date have a clear-cut zone I and II,\(^9,11\) this is not invariably the case. For example, the patient illustrated in figures 4 and 5 has no zone II. A reasonable explanation for this behavior is that the APD does not propagate into the SAN because it collides with the slowly emerging SAN impulse (fig. 5). Despite increasing prematurity of the test depolarization, a compensatory pause occurs until the effective refractory period of the atrium is reached (at this point atrial depolarization is no longer possible). The fact that the APD never reset the SAN indicates that conduction from the SAN to the atrium must occupy a large portion of atrial diastole; i.e., first-degree sinoatrial block is present.

One can predict the response to PAS in patients with lesser degrees of impairment of sinoatrial conduction. In the presence of prolonged sinoatrial conduction, propagation of a premature impulse
into the SAN would be confined to an early portion of atrial diastole. Zone I would thus occupy an unusually large portion of atrial diastole; zone II would be abbreviated and located earlier in atrial diastole. Furthermore, the distance between the points in zone II and line B (fig. 1) would be increased because this distance represents the sum of conduction into and out of the SAN.

In two of our patients, when APDs were elicited very early in the spontaneous sinus cycle they were followed by return cycles shorter than anticipated. These short return cycles could result from interpolation of the APD, or from reentrance of the APD in the SAN and/or sinoatrial junction. Hence, this method offers the means to identify patients with first-degree sinoatrial block. Many other patterns of sinoatrial conduction should emerge as PAS is more widely applied in man. Indeed, PAS can be expected to provide new insight into the character of the human sinoatrial node.

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