Measurement of Sinoatrial Conduction Time by Premature Atrial Stimulation in the Rabbit

By Hugh C. Miller and Harold C. Strauss

ABSTRACT

The premature atrial stimulation technique was investigated as a method of measuring sinoatrial conduction time in the rabbit. Fifteen studies were performed in which intracellular recordings were obtained from a sinus node cell and atrial electrical activity was recorded from the crista terminalis by a surface electrogram. An additional ten studies were performed without microelectrode recordings. Atrial premature depolarizations late in the cardiac cycle produced compensatory atrial return cycles, but earlier premature depolarizations produced less than compensatory return cycles. Compensatory return cycles only occurred with atrial premature depolarizations that failed to capture the sinus node cell. The transition from compensatory to less than compensatory return cycles occurred with late atrial premature depolarizations that failed to capture the sinus node cell. Therefore, the transition from compensatory to less than compensatory atrial return cycles failed to indicate sinus node capture by an atrial premature depolarization. Although these premature depolarizations were too late to capture the sinus node cell, they still shortened the sinus node and atrial return cycles to make the atrial return cycle less than compensatory. This shortening of the sinus node return cycle was due to a shortening of the sinus node action potential by electrotonic interaction between sinus node and adjacent cells during repolarization. The electrotonic effect resulted in shortening of the sinus node action potential and accounted for the poor correlation (r = 0.64) between estimated and measured values of sinoatrial conduction time. These data indicate that there are significant limitations to the use of the premature atrial stimulation technique for estimating sinoatrial conduction time.

KEY WORDS
electrotonic effects
sinus node
return cycle
action potential shortening
crista terminalis
repolarization
compensatory return cycle

A satisfactory technique for measuring conduction time between the sinus node and the atrium would represent a considerable advance in our ability to evaluate sinus node function. It has been suggested that sinoatrial conduction time can be derived by assessing the atrial response to atrial premature depolarizations, but this procedure is still unsubstantiated (1) even though several studies have analyzed the atrial response to atrial premature depolarizations (1–19). An atrial premature depolarization elicited late in the atrial cycle is followed by a return cycle that is compensatory. Progressively earlier premature depolarizations are followed by return cycles that lengthen proportionally to remain compensatory. At some critical coupling interval, an atrial premature depolarization is followed by a return cycle that is just less than compensatory, and thereafter progressively earlier premature depolarizations are followed by less than compensatory return cycles. It has been postulated that late atrial premature depolarizations are followed by compensatory return cycles because these depolarizations fail to capture the sinus node (1, 2, 7); somewhere between the site of stimulation and the sinus node they collide with the emerging sinus node impulse and are blocked. It has similarly been postulated

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that the atrial premature depolarizations that result in the transition from compensatory to less than compensatory return cycles capture the sinus node and “reset” the sinus pacemaker. If it is assumed, as Wenckebach (2) did, that a premature beat capturing the sinus node resets it in the same way that a spontaneous discharge of the node itself does, then the duration of a noncompensatory atrial return cycle equals the basic cycle length plus the time necessary for retrograde conduction of the atrial premature depolarization from its site of origin to the sinus node and for antegrade conduction from the sinus node to the atrium. If “sinoatrial conduction time” is considered to comprise the sum of retrograde and antegrade conduction times, then the sinoatrial conduction time equals the noncompensatory return cycle duration minus the basic cycle length.

Analysis of the atrial response to atrial premature depolarizations has been used to evaluate human sinus node function (1, 7, 12-14, 17), to describe sinoatrial entrance block with late premature depolarizations (1), and to delineate the effects of drugs on sinoatrial conduction time (17), even though no experimental verification of the technique is available. It was therefore the purpose of this study to investigate the atrial response to atrial premature depolarizations in the isolated rabbit heart and to examine the relation between the atrial response and the sinoatrial conduction time. Changes in conduction time and changes in automaticity can occur with early atrial premature depolarizations, and these changes can affect return cycle duration (5, 10, 11, 16, 19). Therefore, the response to the latest atrial premature depolarization consistently giving noncompensatory return cycles was used in the derivation of sinoatrial conduction time in the present study (Fig. 1). The results showed that in this experimental model the atrial response to atrial premature depolarizations did not accurately reflect sinoatrial conduction time due to previously unsuspected effects of the premature depolarizations; atrial premature depolarizations caused shortening of sinus node action potentials and, consequently, shortening of the sinus node return cycle duration.

**Methods**

Studies were performed on 25 rabbits (1.5-3 kg). They were anesthetized with sodium pentobarbital (100-150 mg/kg, ip), and their hearts were then rapidly removed and dissected in cool, modified...
Tyrode's solution. The right atrium, including the sinus node but excluding the atrioventricular node, was dissected free and pinned to the wax bottom of a Lucite tissue chamber with the endocardial surface uppermost (20). In some preparations with ectopic rhythms, the atrial appendage was trimmed.

The modified Tyrode's solution had the following millimolar composition: NaCl 130.0, KCl 4.0, NaH,PO4 1.8, CaCl2 2.7, MgCl2 0.5, dextrose 5.5, and NaHCO3 18.0 in deionized, distilled water. The solution was bubbled with a 95% O2-5% CO2 gas mixture in both the reservoir bottles and the tissue bath to establish a pH of 7.40. The bath was maintained at 36.0 ± 0.5°C and perfused with Tyrode's solution at approximately 10 ml/min.

Transmembrane potentials were recorded through glass microelectrodes filled with 3M KCl and having tip resistances of 18–35 Mohms. The microelectrodes were connected by silver-silver chloride wires to a high-input impedance, capacitance-neutralizing amplifier,1 and the transmembrane potentials were displayed on a Tektronix type 565 dual-beam oscilloscope. Calibration was performed by applying a 50-mv signal in series with the ground of the tissue bath.

A bipolar surface electrogram was recorded from the crista terminalis, usually at its upper end, through silver wires insulated except at the tip. This signal was amplified by a Tektronix 262A differential amplifier and displayed on the oscilloscope screen.

The preparations beat spontaneously, and after every eighth to tenth beat a premature depolarization at a predetermined coupling interval was evoked by stimulating the atrium through bipolar silver electrodes placed immediately adjacent to the surface electrogram electrodes. Stimuli were rectangular constant-voltage pulses 4 msec in duration and less than twice diastolic threshold voltage in intensity. The atrial premature depolarizations were evoked late in the atrial cycle and then at progressively earlier intervals, usually in 5-10-msec decrements.

The action potential, the atrial electrogram, and the signal from a 50-msec time-mark generator (Tektronix model 2901) were recorded on magnetic tape at 7.5 inches/sec. Records for analysis were subsequently obtained by playback to an Elema Mingograf 800 recorder (frequency response 0-750 Hz) at a paper speed of 200 mm/sec or by Polaroid photography of a storage oscilloscope display (Tektronix model D11). During playback, intervals between depolarizations on the atrial electrogram were measured using a Hewlett-Packard model 5304A interval counter coupled to a voltage-triggered time circuit2 and a Hewlett-Packard model 5055A digital recorder. This system was accurate within ±1 msec.

Before commencing the studies, preparations were allowed to stabilize for at least 1 hour following dissection until the basic cycle length was steady. Action potentials were only accepted as sinus node recordings if they were at least 50 mv in total amplitude and had a slow phase 0 depolarization which developed smoothly from a spontaneous phase 4 depolarization. The action potential always preceded the atrial electrogram by at least 25 msec and during any one experiment was always recorded from the same cell. In 15 experiments, action potentials meeting these requirements were obtained for a sufficient period of time to allow scanning of the diastolic period with atrial premature depolarizations. In many experiments, it was not possible to locate cells with sinus node action potentials meeting these rigid criteria in spite of systematic search of the endocardial surface; these studies were therefore abandoned. In an additional 10 experiments, premature stimulation was performed in the absence of microelectrode recordings.

Time intervals measured from the sinus node action potential were taken from the junction of tangents drawn to the steepest portion of phase 0 and the most prominent part of phase 4 depolarization. Capture of the sinus node by a premature beat occurred when the basic sinus cycle measured in this way was shortened.

DEFINITIONS

A premature cycle is a cycle ending in an atrial premature beat, and a return cycle is a cycle following an atrial premature beat. The sinus node premature and return cycles are those corresponding to the relevant atrial cycles.

RESULTS

Only the responses to late atrial premature depolarizations occurring in the last 50% of the atrial cycle were analyzed. Mean cycle length of the preparations was 533 msec (400-650 msec) for the 15 experiments with microelectrode recordings (Table 1) and 509 msec (400-650 msec) for the 10 experiments without microelectrode recordings. In all experiments the durations of the premature and the return cycles were normalized using the duration of the last spontaneous cycle as the denominator (5). The normalized return cycle was then plotted as a function of the normalized premature cycle using the same format as that shown in Figure 1. Normalization allowed the ready identification of the atrial response to atrial premature depolarizations as compensatory or non-compensatory, permitted comparison of responses in spite of changes in basic cycle length, and facilitated comparison of data from different experiments.

1 Designed by Dr. William New, Jr, Stanford University School of Medicine, Palo Alto, California.
2 Designed by Jack Kasell, Duke University Medical Center, Durham, North Carolina.

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TABLE 1
Results of 15 Experiments in which Microelectrode Recordings Were Made

<table>
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<tr>
<th>Expt.</th>
<th>Cycle length</th>
<th>Conduction time: crista to SAN</th>
<th>Conduction time: SAN to crista</th>
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<th>Action potential shortening</th>
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**MEAN** 533 37 54 91 49 27

SAN = sinoatrial node.

**ATRIAL RETURN CYCLE DURATION**

The results of two experiments which illustrate the range and the variability of response to atrial premature depolarizations are shown in Figure 2. In experiment A, the introduction of premature depolarizations later than 87% of basic cycle length resulted in compensatory return cycles. An atrial premature depolarization at 87% of basic cycle length marked the transition between compensatory and noncompensatory return cycles. Earlier premature depolarizations then caused progressively longer return cycles, but they remained less than compensatory.
Curves with a similar configuration were obtained in 20 experiments.

In experiment B (Fig. 2) the plot of the normalized return cycle versus the normalized premature cycle showed a plateau over which the return cycle duration was virtually constant with increasing prematurity of the atrial premature depolarizations. A plateau-shaped curve was obtained in 5 experiments. The position of the curve for all 25 experiments was usually between A and B.

The transition from compensatory to noncompensatory return cycles with progressively earlier atrial premature depolarizations was similar for curves with or without a plateau and varied between 72% and 97% of basic cycle length. However, this value varied with the site of stimulation. Stimulation further from the sinus node on the atrial appendage caused a shift of the curve upward, and noncompensatory return cycles first occurred with earlier premature depolarizations compared with results obtained when the crista terminalis was stimulated.

**SINUS NODE RESPONSE TO ATRIAL PREMATURE DEPOLARIZATIONS**

Microelectrode recordings from experiment A in Figure 2 showed that atrial premature depolarizations earlier than 70% of basic cycle length captured the sinus node but that later premature depolarizations blocked somewhere between their point of origin on the crista terminalis and the recording site in the sinus node. Although atrial premature depolarizations between 70% and 87% of the basic cycle length failed to capture the sinus node, they caused noncompensatory return cycles, demonstrating that the occurrence of noncompensatory return cycles is not a reliable indicator of sinus node capture. On the other hand, compensatory responses only occurred with premature depolarizations that failed to capture the sinus node. Similar observations were made in 13 other experiments both in the presence and the absence of plateau-shaped curves. Sinus node capture first occurred with atrial premature depolarizations between 53% and 92% of basic cycle length in these experiments in contrast to the transition from compensatory to noncompensatory return cycles which occurred with later premature depolarizations between 72% and 97% of basic cycle length. In one experiment, sinus node capture coincided with the appearance of noncompensatory return cycles.

In experiment A (Fig. 2), atrial premature depolarizations later than 87% caused compensatory return cycles, those between 70% and 87% caused noncompensatory return cycles without sinus node capture, and those earlier than 70% caused sinus node capture and noncompensatory return cycles. The sinus node response to atrial premature depolarizations in these different ranges is shown in Figure 3. In Figure 3A, an atrial premature depolarization at 90% of basic cycle length had no effect on the sinus node action potential, and a compensatory return cycle occurred. In B, a premature depolarization at 80% of basic cycle length failed to capture the sinus node but caused early and more rapid phase 3 repolarization of the sinus node action potential, followed by the early onset of phase 4 depolarization, a shortened sinus node return cycle, and an early noncompensatory atrial response. The unchanged slope of phase 4 depolarization is noteworthy. In C, an even earlier premature depolarization at 75% also failed to capture the sinus node; the same phenomena seen in B were present to a more marked degree. In D, an atrial premature depolarization at 60% of basic cycle length captured the sinus node, reset the node, and resulted in a noncompensatory atrial response.

Figure 3 shows that, for atrial premature depolarizations that failed to capture the sinus node, shortening of the sinus node action potential approximately equaled shortening of the sinus node return cycle and accounted for the amounts by which the atrial return cycles were less than compensatory. Similar results were found in 13 other experiments (Fig. 4). The maximum shortening seen in 14 experiments was 54 msec, and the mean maximum shortening was 27 msec. In the one experiment in which sinus node capture coincided with the appearance of noncompensatory atrial return cycles, shortening of action potentials occurred but there was no change in return cycle duration (see Discussion). The maximum amount of shortening of the sinus node action potential in milliseconds was not related to the basic cycle length (Table 1).

Following sinus node capture by earlier atrial premature depolarizations, several
patterns of response of the sinus node return cycle occurred. In four experiments, the sinus node return cycle, which had been shortened by late premature depolarizations that failed to capture the sinus node, remained short with earlier atrial premature depolarizations that did capture the sinus node (Fig. 5A). In eight experiments, the sinus node return cycle rapidly lengthened with atrial premature depolarizations that captured the sinus node and returned to within 2% of the control value (Fig. 5B). In two experiments, depression of sinus node automaticity occurred with early premature depolarizations, and the sinus node return cycle lengthened to 106% and 114% of control, respectively (Fig. 5C).

There was no evidence that shortening of the sinus node action potential was mediated by humoral factors. Stimulation at ten times threshold voltage did not affect the return cycle response to premature beats. Also stimuli during the atrial refractory period did not

**FIGURE 3**

Sinus node response to atrial premature depolarizations. Abbreviations are the same as in Figure 1. In A-D, a sinus node action potential is shown in the top tracing and the crista terminalis electrogram in the bottom tracing. Each trace comprises several oscilloscope sweeps which were superimposed by triggering the sweep at the same voltage level. A: Compensatory responses follow two late atrial premature depolarizations which fail to capture the sinus node. B and C: Noncompensatory atrial response follows a premature depolarization which failed to capture the sinus node. D: Noncompensatory atrial responses follow premature depolarizations which did capture the sinus node. See text for further details.

**FIGURE 4**

Results of 15 experiments with plot of the shortening of sinus node action potential duration (measured at 90% of amplitude) and shortening of sinus node return cycle following atrial premature depolarizations that failed to capture the sinus node. There was a tendency for action potential shortening to be more marked than shortening of cycle length. The line of identity is shown.
affect the basic rhythm of the preparation. In the presence of $3.4 \times 10^{-4}$ M propranolol or $2 \times 10^{-4}$ M atropine, comparable shortening of the sinus node action potential occurred and similarly accounted for shortening of the atrial return cycle.

ELECTROTONIC INTERACTION

Demonstration of shortening of the sinus node action potential by electrotonic interaction between the sinus node and adjacent cells is shown in Figure 6. In this experiment simultaneous microelectrode recordings were made from a sinus node cell meeting all of the criteria for this study (Methods) and from a cell 0.3 mm closer to the crista terminalis. The figure shows the smooth onset of phase 0 depolarization of the sinus node action potential which preceded the action potential of the adjacent cell and preceded the atrial electrogram by 32 msec. The action potential of the peripheral cell had spontaneous phase 4 depolarization but abrupt onset of phase 0 depolarization typical of a latent pacemaker. An atrial premature depolarization at a coupling interval of 442 msec captured the peripheral cell but failed to penetrate and capture the more central sinus node cell as shown by its undisturbed basic sinus cycle length. The action potential of the peripheral cell on the other hand had a more rapid upstroke and an early repolarization following capture by the premature depolarization. Although the central sinus node cell was not captured, shortening of the sinus node action potential accompanied shortening of the action potential of the peripheral cell. The shortening of the two action potentials ran a parallel course in keeping with electrotonic interaction between the cells. The shortening of the sinus node action potential was followed by early spontaneous
Simultaneous action potential recordings from a sinus node cell and a latent pacemaker 0.3 mm closer to the crista terminalis. **Top:** Action potential and crista terminalis electrogram responses to an atrial premature depolarization at 442 msec, showing the values of the sinus node (upper values) and atrial cycles (lower values). **Bottom Left:** Sinus node action potential before (broken line) and after (solid line) the premature depolarization. **Bottom Right:** Action potential of the latent pacemaker before (dotted line) and after (solid line) the atrial premature depolarization. The crista terminalis electrogram common to both action potentials is shown in both bottom sections. See text for further details.

Phase 4 and phase 0 depolarizations and an early atrial response like that seen in Figure 3.

**Conduction time: crista terminalis to sinus node**

Retrograde conduction time from the crista terminalis to the sinus node ranged from 12 msec to 78 msec (mean 37 msec) for the latest atrial premature depolarization that just captured the sinus node (Table 1). In 13 of 15 experiments, this value was less than the value for antegrade conduction time from the sinus node to the crista terminalis. With progressively earlier premature depolarizations the retrograde conduction time from the crista terminalis to the sinus node increased strikingly, the increase being more marked in experiments with longer conduction times (Fig. 7, solid circles) and less marked in experiments with shorter conduction times (Fig. 7, open circles).

**Conduction time: sinus node to crista terminalis**

The antegrade conduction time from the sinus node to the crista terminalis ranged from 25 msec to 90 msec (mean 54 msec) (Table 1). In seven experiments atrial premature depolarizations that captured the sinus
node caused shortening of antegrade conduction time, and in one experiment shortening occurred with premature depolarizations that were not early enough to capture the sinus node. There was no other evidence of pacemaker shift. Shortening of antegrade conduction time was only detected in experiments with conduction times greater than 45 msec, and in these experiments shortening became more marked with early premature depolarizations (Fig. 8).

**Estimation of Sinoatrial Conduction Time**

Estimation of sinoatrial conduction time from the latest atrial premature depolarization giving a noncompensatory return cycle (Fig. 1) consistently underestimated the true sinoatrial conduction time. The consistent underestimation reflected the fact that noncompensatory return cycles occurred with atrial premature depolarizations that failed to capture the sinus node. In the one experiment in which this phenomenon did not occur, the estimated and measured values for sinoatrial conduction time agreed closely.

The correlation coefficient for estimated versus measured values of sinoatrial conduction time for 15 experiments was 0.64. Results from each experiment are shown in Table 1. The results in experiments with a plateau-shaped curve did not differ significantly from those in the other experiments. Also use of the plateau value for the duration of the noncompensatory return cycle in these experiments did not improve our ability to predict sinoatrial conduction time.

**Discussion**

The most important observation in this study is that late atrial premature depolarizations which fail to capture the sinus node can cause shortening of the sinus node action potential by as much as 54 msec. Shortening of the action potential in turn causes shortening of the sinus node return cycle so that atrial premature depolarizations which fail to capture the sinus node can shorten the sinus node return cycle duration.

There is good evidence that action potential shortening is not mediated indirectly by catecholamines or acetylcholine released as a result of electrical stimulation; action potential shortening occurred even in the presence of effective beta-receptor (21) and cholinergic receptor blockade (22).

Mendez and Moe (23) have demonstrated that electrotonic interaction can occur in the rabbit atrioventricular (AV) node and cause alteration of action potential duration of AV nodal cells. We demonstrated that atrial premature depolarizations could similarly cause alteration of action potential duration in the sinus node. Depending on their prematurity, late atrial premature depolarizations penetrated a variable distance into the sinus node before blocking at the site of collision with the emerging sinus node impulse. Normally the impulse formed in the sinus node would proceed toward the crista terminalis and sequentially depolarize the cells lying in between. Repolarization would occur in a similar sequence. However, when an atrial premature depolarization was introduced, the sequence of activation peripheral to the site of block was reversed. This reversal of activation permitted repolarization peripheral to the block to precede its expected time of occurrence and caused disparity of repolarization between cells on either side of the

![Figure 8](http://circres.ahajournals.org/)

**Figure 8**

Plot of antegrade conduction time from the sinus node to the crista terminalis versus premature atrial cycle duration in one experiment in which antegrade conduction time was longer than average and one in which it was shorter than average. Abbreviations are the same as in Figures 1 and 2. The vertical lines indicate the latest atrial premature depolarizations that captured the sinus node. Following capture the antegrade conduction time decreased with earlier premature depolarizations. This effect was not seen in experiments with short conduction times.
site of block. The early repolarization peripheral to the block then caused early repolarization central to the block by electrotonic interaction. The early repolarization caused shortening of the sinus node action potential. As the site of the block moved closer to the pacemaker cell, shortening of the sinus node action potential increased. This proposed mechanism for electrotonic interaction is demonstrated in Figure 6.

In the majority of experiments, shortening of the sinus node action potential was accompanied by similar shortening of the sinus node and atrial return cycles, but this similarity was not always the case. When Bonke (24) applied hyperpolarizing and depolarizing current to sinus node cells during phase 4 depolarization, he found that in some instances did the cycle length of the preparation change appropriately. In those cases in which no change in cycle length occurred, he concluded that the true pacemaker was distant from the polarizing electrode and was therefore unaffected. He reemphasized that several areas within the sinus node can have action potential morphology typical of pacemaker cells but that these areas do not necessarily drive the heart and can in fact depolarize after atrial depolarization (24, 25). In the present study, records were only taken from cells discharging at least 25 msec before the atrial electrogram. Also in 14 of 15 experiments, shortening of the sinus node action potential was followed by shortening of the sinus return cycle duration, indicating that the cell being recorded from was either the true pacemaker or close to it. When some action potential shortening occurred without a change in return cycle duration (Fig. 4), the true pacemaker was presumably slightly more central in the sinus node than the cell from which the recordings were being made. Electrotonic effects could then shorten the recorded action potential without affecting the more centrally placed true pacemaker, but slightly earlier atrial premature depolarizations would penetrate farther and affect both. In one experiment, the recorded cell and the true pacemaker were presumably farther apart, since action potential shortening occurred with late atrial premature depolarizations but no change in cycle length occurred until the premature depolarizations were early enough to capture the recorded cell. This phenomenon presumably coincided with the onset of electrotonic effect on the pacemaker due to deeper penetration by the atrial premature depolarization. In several experiments, the electrotonic effect did not completely account for the disparity between estimated and measured values for sinoatrial conduction time. In these experiments, measured values of sinoatrial conduction time were high; the true pacemaker might have been nearer the crista terminalis than the recorded cell.

Electrotonic effects provide a significant source of error in determining sinoatrial conduction time by premature atrial stimulation, as shown in Table 1. A further shortcoming relates to the uncertainty of the relative contributions of intra-atrial conduction as opposed to conduction between the atrium and the sinus node. When the atrial component was increased by placing stimulating and recording electrodes on the atrial appendage farther from the sinus node, the estimated sinoatrial conduction time increased appropriately. Also, antegrade and retrograde conduction time differed (Table 1), suggesting that the antegrade and retrograde conduction pathways differed slightly (26). Both this result and the effect of stimulation from different atrial sites indicate that the atrial components of sinoatrial conduction time are important and that their relative contributions are not assessed by premature atrial stimulation. The atrial component of the sinoatrial conduction pathway in the antegrade direction can be effectively eliminated by using a surface P wave, since the beginning of the P wave coincides with activation of the crista terminalis (27).

The diagram in Figure 1 is drawn on the assumption that antegrade and retrograde conduction times are equal; however, this assumption was incorrect for most experiments. Retrograde conduction time is usually less than antegrade conduction time for an atrial premature depolarization just capturing the sinus node (10, 16). With earlier atrial premature depolarizations, retrograde conduction time is prolonged (10, 16). The slowing of conduction which this phenomenon must reflect indicates a prolonged relative refractory period of cells between the atrium and the sinus node. In a previous study, the recovery of phase 0 Vmax of rabbit perinodal fibers has been shown to be strikingly time dependent, suggesting that
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the fibers have a prolonged relative refractory period (28).

Shortening of the sinus node return cycle with late premature beats occurred in all experiments except one. Shortening persisted in four experiments with atrial premature depolarizations as early as 50% of the basic atrial cycle length, although with this prematurity there was a tendency for the sinus return cycle duration to increase toward the control value. In eight experiments, sinus return cycle duration returned to near the control value following the initial shortening. In such experiments, shortening of the return cycle length due to action potential shortening was presumably counterbalanced by a depression of automaticity resulting from the atrial premature depolarization. In two experiments, this depression was the predominant effect, and, following initial shortening, sinus return cycle duration increased, in one case to 114% of normal. Eccles and Hoff (5) thought that the major response of the sinus node to an atrial premature depolarization was a depression of automaticity. This depression, in fact, appears to be an unusual response, and shortening of the return cycle length or no change in rhythm is much more common.

The shortening of conduction time from the sinus node cell to the crista terminalis following atrial premature depolarizations confirms earlier studies (10, 16). These studies showed convincing evidence that shortening resulted from a shift in the pacemaker toward the origin of the premature beat; the shift could persist for several cycles and occurred because latent pacemakers at the periphery of the sinus node were depolarized early by an atrial premature depolarization. Although the natural cycle length of the latent pacemaker would normally be slightly longer than that of the true pacemaker, following an atrial premature depolarization its depolarization precedes sinus node depolarization and with this early start it has an advantage over the true pacemaker. A further factor may be shortening of action potential duration which also permits early onset of phase 4 depolarization. Both factors are exaggerated by earlier atrial premature depolarizations, thus accounting for more marked pacemaker shifts with early premature depolarizations. However, with the late premature depolarizations used in the present study, pacemaker shifts were only detected in one experiment, and this phenomenon did not otherwise contribute to action potential shortening.

Comparison of the graphs obtained from experiments on rabbit atria with those obtained from other animal species and man shows similarities and differences. In some of these studies the transition from a compensatory return cycle to a constant but less than compensatory return cycle has been interpreted as signifying the transition from noncapture to capture of the sinus node by the atrial premature depolarization (1, 17). In studies in man and dogs, this transition occurs over a relatively long diastolic interval (5, 19). Although sinus node action potentials were not recorded in these studies, we now believe that this long transition period reflects electrotonic shortening of the sinus node action potential at a time when the premature depolarization has still not captured the sinus node. Hence, in these studies curves with long transition periods should preclude an accurate estimation of sinus node capture by the atrial premature depolarization and therefore preclude an accurate estimation of sinoatrial conduction time.

In the human studies reported thus far, the curves depicting the atrial return cycle response to atrial premature depolarizations differ significantly from those obtained in animal studies (1, 12, 13). Typically, a fully compensatory response in the later portion of diastole is followed on the graph by a sharp transition to a constant, less than compensatory return cycle, the transition occurring over a narrow range of atrial premature depolarization coupling intervals. Since we did not obtain such responses in our rabbit studies, the sinus node response to atrial premature depolarizations in this situation is unknown. One can speculate that the difference in response may in part reflect the longer cycle lengths of human studies. If the absolute shortening of sinus node return cycles occurring with atrial premature depolarizations that fail to capture the sinus node is comparable at long and short cycle lengths, then the relative shortening of the return cycle at long cycle lengths would be small, possibly undetectable.

Another difference between the curves obtained in rabbit and human studies is the
infrequent occurrence of a plateau response in the rabbit studies. In five such experiments, the pattern of sinus node response was inconsistent. In the majority of our experiments, the increasing value of the atrial return cycle was due to an increase in the conduction time of the premature depolarization into the sinus node as the coupling interval of the atrial premature depolarization decreased. The long cycle lengths recorded in human studies may permit greater recovery from the refractory state and hence a more uniform conduction time of the atrial premature depolarization into the sinus node.

In conclusion, we were unable to validate the premature atrial stimulation technique as an accurate method of assessing sinoatrial conduction time in the rabbit, primarily because atrial premature depolarizations caused shortening of the sinus node action potential. This shortening in turn caused shortening of the sinus return cycle duration and the appearance of noncompensatory atrial responses in the absence of sinus node capture. The premature atrial stimulation technique therefore remains unsubstantiated as a means of accurately measuring sinoatrial conduction time in man.

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