Sinus Node Response to Premature Atrial Stimulation in the Rabbit Studied with Multiple Microelectrode Impalements

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SUMMARY In this study we investigated the response of the isolated rabbit sinus node to ectopic atrial premature beats elicited late in the atrial cycle. In three experiments the response of at least 45 different fibers of the sinus node was recorded, whereas, in other experiments, investigation was less extensive. In this way the spread of activation of the total pacemaker area could be mapped accurately both during spontaneous beating and the induction of ectopic atrial beats of different degrees of prematurity. We found that: (1) The conduction of an impulse from the dominant pacemaker area to the atrium during spontaneous rhythm (antegrade conduction) is slower than the conduction of an ectopic atrial impulse towards the center of the sinus node (retrograde conduction). (2) The action potential of the dominant pacemaker fibers in the sinus node is shortened because of premature activation caused by an ectopic impulse from the atrium. Late premature beats had no effect on diastolic depolarization. If the retrograde activation wave did not reach the area of the dominant pacemaker before the spontaneous discharge of these fibers, there was electrotonic influence demonstrable over a distance of about 0.5 mm. (3) Comparison of the true sinoatrial conduction time with the estimated sinoatrial conduction calculated indirectly from the length of the postextrasystolic atrial cycle revealed that, in the isolated rabbit heart, the calculated value is a serious underestimation of the true antegrade sinoatrial conduction time.

THE response of the natural pacemaker of the heart to ectopic beats has been a matter of debate among electrophysiologists for a long time. Progress in this field was made following the advent of the microelectrode technique, which made it possible to study the effect of premature atrial beats on single sinoatrial pacemaker cells. Recently, Strauss et al. suggested that the premature atrial stimulation technique may be used for indirect assessment of sinoatrial conduction time in man: if spontaneous action potential generation in the pacemaker is assumed to be uninfluenced by the premature beat, and furthermore if antegrade and retrograde conduction velocities are equal, half of the difference between postextrasystolic and basic atrial cycles should be equivalent to unidirectional sinoatrial conduction time.

In two experimental studies, the effect of premature atrial stimulation on fibers in the sinoatrial node of the rabbit has been investigated extensively. The results of both studies are not completely in agreement. Klein et al. pointed out that a premature beat initiated during the middle of the atrial cycle always depolarized the sinus node and usually resulted in a postextrasystolic pacemaker cycle which was either unchanged or prolonged. However, Miller and Strauss found a shortening of the pacemaker cycle following a premature beat that was elicited late in the atrial cycle. An earlier premature beat resulted in a postextrasystolic pacemaker cycle that was shorter than normal, or about normal, or longer than normal. Inherent in all electrophysiologic studies on this subject hitherto reported is the tentative assumption that the cell under investigation was representative of the group of dominant pacemaker fibers and truly reflected the behavior of the sinus node as a whole. Because we believe that the function of the sinus node as a whole is not adequately described by the study of only a single fiber out of the total population, we decided to reinvestigate the matter. In this study, the responses to premature atrial stimulation of at least 45 fibers of each of three sinus node preparations were investigated. In other studies, records were obtained from fewer cells. In this way, spread of activation of the total pacemaker area could be mapped both during spontaneous beating and induction of single ectopic beats of differing prematurity. This resulted in a clear image of the response of the sinus node as a whole to premature atrial stimulation.
Methods

Young New Zealand rabbits were anesthetized with a mixture of fluanison and fentanyl (Hypnorm) (1 mg/kg, im) and were given heparin, 1500 IU, intravenously. While under artificial endotracheal respiration, the thorax was opened and the heart rapidly removed.

The right atrium including the superior vena cava and the right atrial appendage, but without the AV node, was isolated and mounted in a tissue bath with its endocardial surface uppermost. The perfusion fluid contained (in mM): NaCl, 130; KCl, 5.6; CaCl2, 2.2; MgCl2, 1.7; NaHCO3, 24; NaH2PO4, 1.2; glucose 11; and saccharose, 13. The pH was kept at 7.35 ± 0.05 and temperature at 37 ± 0.1°C. The fluid, oxygenated by bubbling with a gas mixture containing 95% O2 and 5% CO2, entered the tissue bath at the bottom and was sucked off from the surface at a rate of 100 ml/min.

The preparations were allowed to beat spontaneously; the basic cycle length varied from preparation to preparation between 350 and 450 msec during the course of the experiments. To record a bipolar surface electrogram, a pair of Teflon-coated silver wires was placed on crista terminalis. A second pair of Teflon-coated silver wires placed on the right atrial appendage was used for stimulation (see Fig. 1). A programmable stimulator was used which, after 15 spontaneous beats, delivered a premature stimulus (rectangular in shape, 2 msec in duration, and twice diastolic threshold) via an isolation unit. The last 100 msec of the spontaneous atrial cycle were scanned by premature atrial depolarizations in 5-msec steps.

Transmembrane potentials of fibers in the sinus node area were recorded through glass microelectrodes filled with 2.7 M KCl and 2.0 mM potassium citrate. Electrical resistances ranged from 10 to 35 MΩ. The microelectrode was connected by a chlorided silver wire to a high input impedance, capacitance-neutralizing amplifier. An Ag-AgCl plate served as indifferent electrode. The microelectrode was rigidly mounted on a micromanipulator provided with an electrode steering device; horizontal movement of the microelectrode was possible in an area of 25 times 25 mm with an accuracy of 10 μm. When enough measurements of a single fiber had been obtained, the microelectrode was withdrawn and moved to another place. Thus, the whole pacemaker area was consecutively studied by one microelectrode, using a random mapping procedure. Mostly, only superficial endocardial layers of fibers were impaled; however, if this was not possible at some locations, the microelectrode penetrated to deeper layers. Distances between neighboring places were between 0.25 and 1.0 mm, the small ones in the vicinity of the pacemaker center and the larger ones farther away from it. With this method, it was possible to analyze the responses to premature stimulation of 45 to 60 sinus node fibers within 3–4 hours.

The nomenclature used is illustrated in Figure 1. As an indication of the moment of activation, the 50% amplitude of the transmembrane potential during depolarization and the intrinsic deflection of the surface electrogram were used. Time intervals were measured by feeding the signals into a time-interval counter (HP 5300 B measuring system). Following digital-analog conversion, the curve relating curtailed to postextrasystolic cycles of a nodal cell was plotted on-line by an XY-plotter. All signals were stored on magnetic tape for subsequent additional analysis (Ampex PR 2200; tape speed 15 inches/sec).

We assume that the pacemaker location and the spread of impulse propagation remained the same during the course of the experiments. This is based upon the following observations: (1) Reevaluation of the same places, especially at the pacemaker...
center which was looked for at least four times during the mapping procedure, yielded reproducible results at different stages of the experiment (data not shown). (2) The configuration of the electrogram recorded from the reference electrode on the crista terminalis was constant throughout the experiment. (3) No sudden changes in cycle length during spontaneous rhythm were observed, whereas the relationship between atrial curtailed and postextrasystolic cycles, determined as a control during evaluation of every fiber was essentially unchanged during the course of the experiment. Hence, we feel justified in combining the results obtained at different times and locations as if they had been recorded simultaneously.

**Results**

In three sinus node preparations we were able to impale at least 45 fibers and to record their responses to premature atrial stimulation (experiments marked by an asterisk in Table 1). In three other experiments, the sinus node area was investigated less extensively but enough to construct maps of the activation pattern both during spontaneous rhythm and premature atrial stimulation. In five further experiments, evaluation was incomplete because of substantial changes in cycle length or irregularity, or because of technical problems such as breakage of the microelectrode before the whole pacemaker area was mapped. In the experiments presented, the beat-to-beat variations were never more than 2 msec. During the course of an experiment, spontaneous cycle length generally increased slightly, but by less than 10 msec/hour. Maximal change of cycle length did not exceed 30 msec in any of these experiments.

Because of the striking similarity of the different experiments, one single experiment is described in detail. Figure 2 depicts a surface electrogram (A) and three action potential recordings (B, C, and D) obtained from one sinus node preparation. The places at which recordings were obtained are indicated in the sketch. Spontaneous discharge is earliest in D, followed by activation of C, B, and A. The first two discharges are the last of a series of 15 spontaneous beats. Thereafter a premature beat (curtailed atrial cycle 389 msec) is induced and is retrogradely conducted to the sinus node. This causes a reversal of activation and the sequence of discharges now progresses from A to D as schematically indicated by the arrows. The original spread of activation is reestablished in the first postextrasystolic beat which is of sinus origin. Whereas the time of the premature stimulus is identical for all

**Table 1**  
**Measured vs. Calculated Sinoatrial Conduction Time**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Antegrade conduction time (msec)</th>
<th>Retrograde conduction time (msec)</th>
<th>Noncompensatory phase (msec)</th>
<th>Transition (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2*</td>
<td>25</td>
<td>15</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>3*</td>
<td>23</td>
<td>14</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>18</td>
<td>23</td>
<td>12</td>
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<tr>
<td>5</td>
<td>25</td>
<td>13</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23.5 ± 2.3</td>
<td>14.7 ± 2.2</td>
<td>14.2 ± 4.4</td>
<td>10.2 ± 1.2</td>
</tr>
</tbody>
</table>

* Experiments in which 45 fibers or more were analyzed.
records, the curtailed and postextrasystolic cycles differ markedly in duration at the different recording sites. The curtailed cycle becomes longer from A up to D while the postextrasystolic cycle gets shorter. In A, the postextrasystolic cycle (464 msec) is 18 msec longer than the basic cycle (446 msec). In B, this prolongation is less (14 msec). In C, there is practically no difference between the basic cycle and postextrasystolic cycle (446 and 448 msec), whereas in fiber D the postextrasystolic cycle is clearly shorter than the basic cycle. From this figure it can be concluded that in one and the same sinus node preparation, the postextrasystolic cycle can be either prolonged, unchanged, or shortened in different fibers. In Figure 3, the whole set of data from the atrial and the three nodal recording sites, as indicated in Figure 2, is plotted. In the four panels, the duration of the curtailed and postextrasystolic cycles are plotted against the coupling interval (time between the last spontaneous atrial complex and the moment of stimulation). In A, the usual atrial response to premature stimulation is shown: a1 - a2 progressively decreases with shortening of the coupling interval, whereas a2 - a3 exhibits a compensatory pause following long coupling intervals when (a1 - a2) + (a2 - a3) = 2 times (a1 - a2); data points fall along the theoretical line indicating a compensatory pause. With further shortening of coupling intervals, a2 - a3 cycles become noncompensatory, i.e., (a1 - a2) + (a2 - a3) < 2 times (a1 - a2); data points fall below the theoretical line). These atrial curves are repeated as interrupted lines in panels B, C, and D. In B, s1 - s2 is slightly longer than a1 - a2 and s2 - s3 slightly shorter than a2 - a3 for all prematurities of stimulation tested. The differences between atrial cycles and corresponding intervals in the sinus node are even more marked for fiber C and most marked for fiber D.

Hence, after curtailing the basic atrial cycle by up to 100 msec, three types of responses can be recognized in different sinus node fibers: lengthening of the postextrasystolic cycle (panel B), constancy of s2 - s3 (panel C), and shortening of the postextrasystolic cycle (panel D). In some fibers a mixed response was found. For instance, some fibers showed a slight shortening of s2 - s3 after a late premature beat and a normal (unchanged) s2 - s3 after premature beats elicited somewhat earlier in the atrial cycle. In the present experiment 54 fibers were analyzed and classified according to the main type of response. Figure 4 shows the spatial distribution within the sinus node of these three types. Fibers along the sinoatrial border show a prolongation of s2 - s3 (open circles) whereas the fibers exhibiting a shortening of the postextrasystolic cycle are located more in the center of the node (filled circles). Between these areas are fibers which exhibit a constancy of s2 - s3 (crosses). The type of fiber response is closely related to the spread of activation during spontaneous rhythm: the farther a fiber is from the dominant pacemaker site and the later it is activated during spontaneous rhythm, the more its s2 - s3 cycle is prolonged, and vice versa (see Fig. 5). This statement does not hold for the fiber near the atrial septum (caval area). Although these fibers are activated even later than the atrium, they had s2 - s3 cycles equal or shorter than the normal cycle (s1 - s1).

**Antegrade and Retrograde Conduction Time**

Our approach of multiple microelectrode recordings in the sinus node enabled us to get an accurate image of the spread of activation within the sinus node. From measurements of activation time of all the fibers, evaluated maps of impulse propagation could be constructed both for spontaneous rhythm and single ectopic atrial beats of differing prematurity.

In Figure 5, two maps of the excitation of the sinoatrial junction are shown. The left map repre-
o Lengthening of $s_2 - s_3$

x Constancy of $s_2 - s_3$

• Shortening of $s_2 - s_3$

**FIGURE 4** Sketch of sinus node preparation indicating the spatial distribution of three different types of fiber responses to premature atrial stimulation. The fibers showing a lengthening of the postextrasystolic cycle of more than 5 msec compared to the basic cycle are indicated by open circles. The fibers in which the $s_2 - s_1$ interval was more than 5 msec shorter than $s_1 - s_1$ are indicated by filled circles. If the postextrasystolic cycle was not more than 5 msec shorter or longer than the basic cycle, the fiber response was classified as constant (crosses).

sent antegrade sinoatrial conduction during normal spontaneous rhythm. The earliest activity is taken as zero reference. For each impaled fiber, the latency between this earliest activation and the action potential of the respective fibers is given in milliseconds. From these activation times, isochrones are drawn. The impulse arising in the dominant pacemaker fibers does not take the shortest route toward the atrium. Conduction from the pacemaker center directly toward the crista terminalis is very slow or even blocked. Instead, there is preferential conduction from the pacemaker center toward the cranial end of the crista terminalis. In this case, the crista terminalis is activated 25 msec after excitation of the crista terminalis. Thus, retrograde sinoatrial conduction time (15 msec) is shorter than antegrade sinoatrial conduction time (24 msec). It appears that conduction into the caval area during retrograde conduction is about as slow as during spontaneous rhythm.

Retrograde conduction time to the pacemaker center in all experiments depended to some extent on the prematurity of stimulation. However, within the range of $a_i - a_i$ cycles analyzed in this study (last 100 msec of $a_i - a_i$), this effect was small, retrograde conduction time prolonging by about 5 msec with increasing prematurity of stimulation. Apart from that, no qualitative differences were apparent between maps of retrograde conduction of premature beats just early enough to capture the pacemaker center and earlier premature beats. The spread of activation during retrograde conduction differed slightly from experiment to experiment, as was the case for antegrade conduction. However, maps of retrograde conduction from different preparations were uniform insofar as the ectopic impulse penetrated the sinus node area always as a more or less broad wavefront.

**Response of Dominant Pacemaker Fibers to Ectopic Premature Discharge**

From Figure 4 and the left map of Figure 5, it can be seen that the fibers in the area of the dominant pacemaker show a shortening of the postextrasystolic cycle. Detailed analysis of the course of the transmembrane potential revealed that, following a relatively late premature beat which just did not capture the dominant pacemaker fiber, shortening of postextrasystolic cycle is caused by shortening of the action potential duration due to acceleration of the repolarization, as described by Miller and Strauss (see their Fig. 3). In case of capture of a dominant pacemaker fiber, the premature action potential is shortened both by an acceleration of the upstroke of the action potential.
and by an acceleration of repolarization. In contrast, the process underlying diastolic depolarization is not substantially affected by single premature beats (at least in the last part of the atrial cycle).

Collision between an Ectopic Impulse and the Impulse Coming from the Dominant Pacemaker

In case of premature beats elicited late in the atrial cycle and followed by a compensatory postextrasystolic cycle, two wavefronts collide somewhere in the sinus node. This means that there is antegrade conduction of the impulse arising in the dominant pacemaker together with retrograde conduction through the sinoatrial junction of an ectopic impulse. Depending on the degree of prematurity of the ectopic impulse, the collision between the antegrade and retrograde wavefronts can be expected to occur in different regions within the sinus node. Since the ectopic impulse invades the sinus node more or less as a broad wavefront (see Fig. 5), the sites of collision will be determined almost exclusively by the pattern of antegrade conduction of the spontaneous impulse.

Figure 6 shows the collision lines in the sinus node between nomotopic and ectopic activation as varied by the prematurity of stimulation. This map was constructed from the data of the same experiment as in Figures 4 and 5. To do so, first the $a_1 - a_2$ cycle at which capture of sinus node cells occurred was determined for every fiber. This degree of prematurity (i.e., the critical $a_1 - a_2$ interval at which the $s_1 - s_2$ starts to shorten) can be easily derived from a diagram, as shown in Figure 3, which was elaborated for every fiber. Next, the difference between this critical $a_1 - a_2$ interval and basic cycle $a_1 - a_1$ was calculated; this represents the time in msec by which $a_1 - a_1$ has to be shortened in order to lead to capture of a certain fiber. These differences are plotted in minus values for every fiber in a map. For simplicity, in Figure 6 not all the individual values are given, but only four collision lines are constructed on the basis of these data. The resulting map shows the sites of collision for four premature beats of differing prematurity. For example, if the curtailed atrial cycle $a_1 - a_2$ is shorter than $a_1 - a_1$ by 5 msec, the line indicated by "-5"...
represents the collision between the ectopic wave coming from the left, and the spontaneously emerging sinus impulse coming from the right. The earlier the ectopic beat occurs, the more the line of collision is shifted toward the pacemaker center. If \( a_1 - a_2 \) is more than 35-40 msec shorter than \( a_1 - a_0 \), the pacemaker center is discharged prematurely by the ectopic impulse.

Electrotonic Interaction within the Sinus Node

Figure 7 shows the effect of the penetrating ectopic wave front on the dominant pacemaker. In the left part of this figure, the course of the transmembrane potential of the dominant pacemaker fiber is shown during the induction of three ectopic beats of different prematurity (curtailed atrial cycle length 405, 385, and 370 msec, respectively). In the right part of the figure the changes in curtailed and postextrasystolic cycle of this fiber are given, together with a sketch of the preparation in which the site of recording is indicated as well as the lines of collision between the nomotopic wavefront and the ectopic wavefront for the different prematurities. In the left part of the figure, the curtailed cycle and the postextrasystolic cycle are superimposed on the recording during normal rhythm. In the upper panel, a premature beat is elicited late in atrial diastole at a coupling interval of 405 msec. The curtailed atrial cycle is shortened by 10 msec. However, in the fiber from which the record is taken, no change in cycle length or action potential configuration occurred under the influence of the atrial premature beat. As can be seen in the sketch of the preparation, the ectopic wave collided with the sinus impulse more than 1 mm from the place where the microelectrode was impaled. In the middle panel, a coupling interval of 385 msec produced a curtailed atrial cycle which is 30 msec shorter than \( a_1 - a_0 \). Again, the pacemaker fiber is not captured by this premature beat, as can be concluded from the fact that \( s_1 - s_2 \) is equal to \( s_1 - s_0 \), and from the unchanged rate of rise and amplitude of the action potential upstroke. However, repolarization is accelerated and leads to shortening of the action potential duration. As phase 4 depolarization during the postextrasystolic cycle is unaffected, this shortening of the action potential leads to shorten-

![Figure 7](image-url)
ing of the $s_2 - s_3$ cycle, although the fiber is not captured. Construction of the collision lines reveals that, at a coupling interval of 385 msec, the ectopic wave has approached within 0.5 mm of the site of microelectrode recording. Thus, it must be concluded that the pacemaker center is influenced electronically over this distance.

When the coupling interval is further shortened—as in the lower panel—the pacemaker fiber is prematurely discharged by the premature impulse as judged from the earlier onset and increased steepness of the upstroke of the action potential (phase 0). Following a premature beat curtailing the atrial cycle by 45 msec (coupling interval is 370 msec), the action potential is shortened more than in the case of the middle panel. This shortening is based on both a faster upstroke and a more rapid repolarization. Accordingly, the postextrasystolic cycle $s_2 - s_3$ is shortened further. At this panel also, a slight change in the diastolic potential following this premature discharge of the fiber can be noticed. Both the maximum diastolic potential and the slope of diastolic depolarization are slightly increased. However, because these changes are counteracting each other, they seem not to contribute to the shortening of the $s_2 - s_3$ interval at the present degree of prematurity of the $s_1-s_2$ interval.

**Measured vs. Calculated Sinoatrial Conduction Time**

In Table 1, directly measured antegrade and retrograde conduction is shown, together with the calculated values for six sinus node preparations in which the spread of activation was mapped completely. Retrograde conduction time was measured following a curtailed cycle, $a_1 - a_2$, which was just early enough to capture the pacemaker center.

In each experiment, antegrade conduction time is longer than retrograde conduction time. In these six experiments the mean antegrade conduction time was $23.5 \pm 2.3$ msec, whereas the mean retrograde conduction time was $14.7 \pm 2.2$ msec ($P < 0.001$, paired $t$-test).

For the calculation of sinoatrial conduction time (SACT) in man, two modes have been used. Both are based on the relation between the atrial curtailed cycle and the postextrasystolic cycle as can be determined by the premature atrial stimulation technique. From this curve the SACT has been estimated either using the so-called plateau phase of the noncompensatory part of the curve or the point of transition from compensatory to noncompensatory values as reference point. According to these criteria we have calculated the sinoatrial conduction for our rabbit preparations. Since in our experiments the atrial curves did not show a plateau phase, we decided to use as reference the postextrasystolic cycle following a premature beat that curtailed the atrial cycle by 100 msec. By subtracting the normal interval ($a_1 - a_2$) from the value of this postextrasystolic cycle and dividing by two, the calculated unidirectional conduction time was derived (see "noncompensatory phase" of Table 1). In the same way the calculation was done using the point of transition as reference. Table 1 shows that both methods seriously underestimate antegrade sinoatrial conduction time, since the calculated values are $14.2 \pm 4.4$ msec and $10.2 \pm 1.2$ msec, respectively, compared with the true value for antegrade conduction of $23.5 \pm 2.3$ msec. Underestimation is slightly less when the "noncompensatory phase" method is used.

**Discussion**

In the literature there is disagreement between investigators concerning the effect of ectopic atrial premature beats on the automaticity of the sinus node. Klein et al. concluded that the response of sinus node fibers to a premature atrial beat depended on the timing of the premature beat in the atrial cycle. In case of premature beats in the second half of the atrial cycle, they found that the postextrasystolic cycles of sinus node fibers were unchanged or prolonged. Miller and Strauss investigated the effect of ectopic atrial premature beats on the automaticity of the sinus node and reported three types of sinus node responses: (1) in 8 of 14 preparations, the postextrasystolic cycle, $s_2 - s_3$, shortened after late premature beats, and returned to control values following earlier premature beats; (2) in 4 of 14 experiments, $s_2 - s_3$ shortened with both late and early premature beats; (3) in 2 of 14 experiments, $s_2 - s_3$ shortened after some initial shortening with late premature beats, prolonged with ectopic beats introduced earlier in atrial diastole. This was interpreted as some depression of sinus node automaticity. Thus, there is a shortening of the $s_2 - s_3$ with late premature beats in all their experiments. Since we studied only late premature beats with a curtailment of the spontaneous cycle by no more than 100 msec or about 25% we can only partially compare our results with those of Miller and Strauss. Our description of the response of dominant pacemaker fibers to late premature atrial stimulation is in agreement with the majority of experiments (type A and B; that means 12 out of 14) in the latter study. In two experiments, Miller and Strauss described a lengthening of $s_2 - s_3$ in case of atrial premature beats curtailing the atrial cycle by more than 15%. Since they did not make a complete map of the activation pattern of the sinus node, it might be that the fiber under investigation was not a true dominant pacemaker fiber. Since the identification of the group of dominant pacemaker fibers is more reliable if a complete map of the activation pattern in the sinus node is made, it might be that Miller and Strauss, in the two experiments in which they got results different from ours, have studied a fiber lying between the area of the pacemaker and the crista terminalis. Furthermore, it is important to realize that Miller and Strauss and Klein et al. also investigated the effect of curtailment of the
atrial cycle with more than 25%. In those cases, a shift of the dominant pacemaker might be caused by the premature beat as was demonstrated by Bonke et al. Such a shift may hinder the interpretation of the data.

As is demonstrated in Figure 7, the shortening of the postextrasystolic cycle of the dominant pacemaker fibers is caused by a shortening of the premature action potential. In case of a spontaneous discharge of the sinus node, the dominant pacemaker fibers start to repolarize at a moment when the surrounding fibers are still depolarized. Because of the presence of electrotonic interaction between fibers in the node, this will lead to a retardation of the repolarization of the dominant pacemaker fibers.

In contrast, after the occurrence of an atrial premature beat the impulse propagates from the atrium into the sinus node. Therefore, the fibers in the sinoatrial border are depolarized earlier than the fibers in the pacemaker area. Concomitantly the process of repolarization also starts earlier in the former group of fibers. This early repolarization of the fibers surrounding the dominant pacemaker fibers will accelerate the repolarization of these dominant fibers because of electrotonic interaction. This may explain that, in case of an ectopic atrial beat, the action potential of the dominant pacemaker fibers is shorter than during spontaneous sinus rhythm. It should be noted that this shortening of the action potential and of the postextrasystolic cycle of dominant pacemaker fibers already is apparent when the ectopic wave is approaching but still not yet capturing the pacemaker center (see Fig. 7). As to this electrotonic influence, our measurements allow some quantitative description of the distance across which it can take place in the sinus node. The study of the collision between the ectopic and spontaneous wavefront, and the resulting influence on the postextrasystolic cycle, revealed that the ectopic wave had to approach within 0.5 mm of the pacemaker center to exert an electrotonic effect. Thus, two depolarizations occurring at a distance of about 0.5 mm in the sinus node will influence each other, and it seems reasonable to assume that, also, during the repolarization, electrotonic interaction might be possible over such a distance. This is in agreement with the values for the space constant measured by use either of a large extracellular suction electrode ($\lambda = 465 $ $\mu$m, Bonke \textsuperscript{12}) or the voltage clamp technique with a single sucrose gap ($\lambda = 828 $ $\mu$m, Seyama \textsuperscript{13}).

In case of an early capture of the pacemaker fibers in the sinus node also the maximal diastolic potential and the slope of diastolic depolarization may change. In the last panel of Figure 7, the first indications of such changes become apparent. At the induction of earlier premature beats, the effects on the diastolic depolarization will become more marked, and even a shift of the site of the dominant pacemaker with the concomitant changes in diastolic depolarization might occur.\textsuperscript{4}

**Difference between Antegrade and Retrograde Conduction in the Sinus Node**

As shown in Table 1, antegrade sinoatrial impulse propagation differs markedly from retrograde invasion of the node after an atrial ectopic beat. In six experiments, antegrade conduction time (time between discharge of dominant pacemaker fiber and earliest activation of crista terminalis) was $23.5 \pm 2.3$ msec, whereas retrograde conduction time amounted to $14.7 \pm 2.2$ msec. Thus, antegrade conduction is slower than retrograde conduction in the sinus node. This is in accord with the observation that dominant pacemaker fibers exhibit action potentials of higher amplitude and steeper rise of phase 0 when the impulse is coming from the atrium than in case of spontaneous discharge. A possible explanation is that, in case of spontaneous discharge of the sinus node, the impulse diverges from the group of dominant pacemaker fibers in all directions. In such a situation a relatively small number of fibers has to generate the excitatory current for a relatively large amount of surrounding fibers. Therefore, the depolarization of a dominant pacemaker fiber will be of small amplitude and a low rate of rise. If the impulse is coming from the atrium, the sinoatrial border is reached over a broad front. In the center of the sinus node more fibers now are discharged simultaneously. Therefore, the action potential in these fibers will show a high amplitude and a high rate of rise. Since the rate of rise of the upstroke of the action potential is an important factor for the conduction velocity, this might be the cause of the difference between antegrade and retrograde conduction within the sinus node. As shown in Figure 5, there is a marked difference between retrograde invasion of the node and antegrade impulse propagation in terms of the activation pattern. This also will influence the conduction time.

While a similar spread of activation during spontaneous sinus rhythm was demonstrated by Sano and Yamagishi,\textsuperscript{10} these authors found, in contrast to our results, retrograde sinoatrial conduction time to be longer than antegrade conduction time. Explanation for these differences may lie in the methods used: while we introduced only single premature impulses, sinus node impulses were constantly overdriven by electrical impulses applied at a rate of 2.5–3/sec in the other study. It has been shown that recovery of excitability in sinus node border fibers is strongly time dependent, full recovery time being longer for sinus node border fibers than for crista terminalis fibers.\textsuperscript{14} On the basis of these findings, we think it not inconceivable to assume that the time for recovery of full excitability is even more prolonged during constant overdrive: thus, while one premature atrial beat still may be conducted rather rapidly into the sinus node, retrograde conduction velocity could progressively decelerate dur-
ing constant overdrive and this ultimately may lead to a retrograde conduction time longer than antegrade sinoatrial conduction time. Direct comparative studies of retrograde conduction during premature atrial stimulation and constant overdrive is needed to test this hypothesis. Furthermore, in the present study, only late premature beats were given, but it is obvious that the conduction through the atrium and the sinus node border depends on the prematurity of the premature beat, and this becomes more pronounced if premature beats are elicited earlier in the atrial cycle.

Reevaluation of the Method of Calculating Sinoatrial Conduction Time (SACT)

The data presented in this paper clearly show that: (1) the postextrasystolic cycle of the dominant pacemaker fiber might be shortened by an atrial premature beat that is elicited late in the atrial cycle (curtailment by less than 25%). This shortening of cycle length is caused by a shortening of the captured pacemaker action potential; (2) antegrade and retrograde conduction times in the sinus node are not equal, antegrade conduction being considerably slower than retrograde conduction. These findings give a satisfactory explanation for the fact that the method of calculating the SACT seriously underestimate the sinoatrial conduction time. It demonstrates that the two prerequisites for indirect calculation of SACT are not met. It may be argued whether the underestimation, implicit to this method, when used in man, is as serious as it is in the rabbit.

References

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