Sino-Atrial Reciprocation in the Isolated Rabbit Heart

By Joak Han, M.D., Ph.D., Anna Mae Malozzi, B.S., and Gordon K. Moe, M.D., Ph.D.

ABSTRACT
Reciprocal beats between sinus node and atrium were studied in isolated rabbit heart tissue by microelectrode techniques. Early premature atrial responses which entered the sinus node frequently emerged to re-excite the atrium as "echoes." When the premature atrial beats discharged some but not all nodal areas, the atrial echoes, in turn, appeared to re-enter the sinus node. Repetitive reciprocation involving the sino-atrial circuit was occasionally observed. Anatomic and temporal patterns of excitation at multiple recording sites suggest that "entrance" block and slow conduction of premature impulses within the sinus node may explain the observed reciprocation. The results support the hypothesis that self-sustained reciprocation in a sino-atrial circuit might be responsible for some cases of paroxysmal atrial tachycardia.

ADDITIONAL KEY WORDS  
sinus node echoes  
atrial premature beats  
arrhythmia  
atrial echoes  
re-entry

It has been postulated that those paroxysmal supraventricular tachycardias which abruptly terminate upon reflexly induced vagal discharge may be the result of self-sustained re-entrant circuits involving either the A-V node or the sinus node (1, 2). Physiological evidence for A-V nodal reciprocation is well documented, and the effects of cholinergic discharge upon the refractory period and conductivity of the A-V node readily explain the response to vagal stimulation. Evidence for similar reciprocation in the sinus node is suggestive (3, 4), but the possibility of this mechanism has not been demonstrated.

A reciprocal rhythm between the atrium and sinus node should be possible if the intranodal conduction time between successive atrial discharges is greater than the duration of refractoriness of any element in the circuit. Slow propagation has been demonstrated in the sinus node (5). It has also been shown that the effective refractory period of sinus nodal tissue exceeds that of surrounding atrial tissue (6). A premature atrial response may therefore fail to engage one margin of the node, enter at another site, and traverse the relatively refractory nodal tissue so slowly that the atrium has recovered in time to respond again to the emerging response. The experiments described here were undertaken to test the possibility of this mechanism in isolated preparations of rabbit heart tissue.

Methods
Hearts excised from stunned rabbits were placed for dissection in a tissue chamber filled with continuously flowing Tyrode's solution. The solution was gassed with a mixture of oxygen (95%) and carbon dioxide (5%) and maintained at about 36°C. A preparation consisting of only the right atrium and the sinus nodal region was excised and flattened on a paraffin bed; the A-V node and ventricles were excluded to eliminate interference from possible A-V nodal reciprocation.

The preparation was driven by stimuli delivered through bipolar silver electrodes placed in the atrial roof or in the atrial septum. These stimuli were rectangular pulses of 2- to 5-msec duration obtained from a Tektronix pulse generator and passed through an isolation transformer. The pulse generator was triggered by a
Atrial "echo" induced by a premature atrial response. In each part, the upper trace (SN) shows transmembrane action potentials recorded from a single sinus nodal cell, and the lower trace (A) is a local atrial electrogram. S1 and S2, basic and premature stimuli applied to the atrium.

Results

Premature stimulation of the atrium commonly resulted in re-entrant activity. In the example shown in Figure 1, the preparation was driven by basic stimuli (S1) applied to the atrial roof at a cycle length of 400 msec; after each tenth driving stimulus a test pulse (S2) was applied to the same site at varying S1S2 intervals. The basic response was propagated to the recording site in the sinus node with a conduction time of 25 msec. In part A, the premature stimulus, S2, was applied 90 msec following the tenth S1; A2 failed to enter the node, and no reciprocal response occurred. When the S1S2 interval was increased to 115 msec (part B), the resulting response reached the impaled nodal cell with a conduction interval of 55 msec, and (apparently) returned to the atrium as an echo. In part C, at an interval of 140 msec between S1 and S2, the premature response was propagated to the nodal cell more rapidly (A2SN2 = 36 msec), but was not followed by an echo. Similar results were also obtained in experiments in which the driving and test stimuli were applied to the atrial septum.

The results illustrated in Figure 1 do not prove that the last atrial response shown in part B emerged as a re-entrant activation from the sinus node, but the time relations suggest that this is the most likely explanation. The alternative possibility, multiple responses due to stimulation of the atrium during its vulnerable period, would be expected only with the earliest possible premature stimulus. The earliest response (Fig. 1, A) did not result in a spontaneous atrial discharge, and it did not enter the node, which must therefore have been refractory. The nodal cell discharge recorded in Figure 1, B was delayed, presumably because of slow intranodal conduction, and it fell almost exactly halfway between the A2 response and the echo; sufficient time was available for a complete circuit through the node.
Finally, when a later atrial response penetrated the node more rapidly, no reactivation of the atrium occurred (Fig. 1, C). Similar findings were obtained in many experiments. The range of $A_1A_2$ intervals within which $A_2$ was regularly followed by atrial echoes varied from a very brief duration up to about 30 msec.

In some experiments, slow and apparently fractionated intranodal conduction of the premature response was more evident, as judged by the configuration of the SN action potentials. Figure 2 depicts the results of such an experiment, in which the $A_1A_2$ intervals were increased by increments of about 25 msec from 180 msec in part A to 305 msec in part F. In part A, $A_2$ failed to enter the sinus node; a spontaneous pacemaker discharge occurred 510 msec after the last basic response, and was propagated to the atrium. In part B, $A_2$ resulted in a low amplitude electrotonic depolarization in the impaled cell, indicating partial invasion of the node, but it obviously did not reach the site of the pacemaker, which discharged on schedule. When the $A_1A_2$ interval was further increased, in part C, $A_2$ was followed by a local potential of higher magnitude in the SN cell, followed in turn by a full action potential at an interval of 200 msec after $A_2$. Almost simultaneously, an atrial echo response was recorded. The delayed SN$_2$ appeared almost 60 msec earlier than the pacemaker responses in A and B; furthermore, the time relations of SN$_2$ and the associated atrial response are different from those shown in A and B. The results suggest that the SN recording site was passively depolarized but not discharged by the premature impulse entering an adjacent area of the sinus node, and completely depolarized later as the impulse emerged to re-excite the atrium. The delay during the first leg of intranodal conduction appears to have permitted recovery of the area of impalement in time to respond to the emerging impulse.

With still further delay of $S_2$ the premature impulse would be expected to enter the node more quickly, and perhaps over a broader pathway; less time would be available for recovery of the exit pathway, and the emerging impulse should therefore be delayed. In part D, the SN "local" response grew larger, and the delayed action potential appeared much earlier and at lesser amplitude. The $A_5SN_2$ interval was reduced to
Atrial echoes followed by re-entry of sinus node.

195 msec, and a second hump developed on the nodal action potential, suggesting the later discharge of adjacent elements. The echo response in the atrium occurred conspicuously later than in part C. In parts E and F, with further increments in the $A_1A_2$ interval, the impaled nodal cell developed an early action potential instead of a local response; no echo occurred, presumably because the return pathway was now occluded. The longer duration of the $SN_2$ action potentials in E and F probably reflect the electrotonic influence of nearby elements which discharged later, as previously observed during slow propagation of premature responses in the A-V node (7).

In a few preparations, atrial echo responses appeared to be followed by yet another entry of the sinus node. The results of such an experiment are shown in Figure 3. At the $A_1A_2$ interval of 95 msec in part A, the premature $A_2$ failed to enter the node and no atrial echo resulted. In parts B and C, at $A_1A_2$ intervals of 115 and 135 msec, respectively, $A_2$ entered the node and was followed by an atrial echo. In each case an additional nodal action potential was recorded subsequent to the atrial response. It is not certain from the available data whether the last nodal response represented re-entry from the atrium, or a delayed response to the same emergent impulse responsible for the earlier atrial echo. The time relations are compatible with either interpretation, but in comparable studies of A-V nodal reciprocation (8), re-entry of the node subsequent to an atrial echo was almost the rule.

The question raised above could be answered only by obtaining multiple records at different microelectrode puncture sites in the sinus node in an attempt to construct a complete map of the anatomic and temporal relationship of reciprocal responses. This was attempted in the same preparation as that of Figure 3, in which reciprocal responses were stable for a long enough period to permit recording of the time relations at 18 different puncture sites in the node and the neighboring atrial tissue. These results are illustrated in Figure 4. As shown in the diagram on the upper left, driving and test stimuli were applied to a point in the atrium indicated by S. An atrial electrogram taken from point A was used as a time reference (lower trace) in each part of the figure. The upper trace shows corresponding transmembrane action potentials recorded from each of the different puncture sites indicated by $A_a$ and $A_b$ in the atrium, and $SN_a$, $SN_b$ and $SN_c$ in the node. Each of these areas included 2 to 4 puncture sites which provided
almost identical temporal patterns, but records from only one puncture site were used to represent each area in the figure.

It is apparent from the reference atrial electrograms in all parts of Figure 4 that the atrial echo persisted with a constant temporal pattern while the various transmembrane potentials were sequentially recorded. In part A, the impaled atrial cell fired simultaneously with the response recorded from the reference site, both for the premature response and the echo, suggesting that the
two sites were temporally equidistant from the site of emergence of the echo. In part B, the impaled cell in the atrial septum responded later to the premature stimulus, and also to the echo; again the result indicates that the echo excited all three atrial sites in the same sequence as the premature stimulus, S2.

Within the node, the sequence of activation was conspicuously different for the premature response and the echo. At the site SNa, only a single response occurred, about 75 msec after S2. At SNb, two responses were recorded, and at SNc only a late response was observed, nearly 75 msec after the echo response in the atrial record. The temporal patterns of activity in these five different areas are plotted on the bottom graph, in which time is expressed in msec along the abscissas. The arbitrary position of each area is indicated along the ordinates as a horizontal line drawn according to the time interval between the basic stimulus (S1) and the corresponding action potential in the area. The ordinates, therefore, do not represent a true distance scale, but merely show the temporal sequence of normal activation, Aa-Ab-SNa-SNb-SNc, in response to the basic S1. A broken horizontal line was drawn to indicate the borderline between the atrium and the node. The premature impulse initiated by S2 entered slowly to activate areas SNa and SNb of the node in reverse sequence. Area SNc escaped direct activation by S2. The atrial echo was recorded first at Aa, propagated rapidly to Ab, and appeared to re-enter the node through the now-recovered area SNc. Re-activation of area SNb occurred before the re-entrant impulse was extinguished.

The results charted in Figure 4 suggest that the premature atrial impulse encoun-

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**Figure 5**

Repetitive reciprocation induced by atrial premature beat during sinus rhythm.

**Figure 6**

(A) Spontaneous atrial bigeminy during sinus rhythm. (B) Spontaneous atrial premature beats followed by re-entry of sinus node and atrial echoes. No electrical stimuli were applied to the preparation.
tered refractory tissue at the junction of the node with the crista terminalis, and traveled to the atrial septum before an excitable junction was encountered somewhere near the area SNb. The node was then excited from right to left (with respect to the map); the wave front, re-entering the atrium, swept downward and again invaded the node from below near area SNC. The time relationships also indicate that the late responses in Figure 3, B and C were indeed the result of re-entry; the impaled cell of Figure 3 was near the SNb area of Figure 4.

If sino-atrial reciprocation occurs in the human heart, the likeliest cause would be an early premature atrial response, coupled to an atrial response of normal sinus nodal origin. The experiment depicted in Figure 5 was designed to test whether premature atrial beats could initiate echoes when introduced during normal sinus rhythm. The preparation was beating spontaneously at a cycle length of about 370 msec. Stimuli (S) were applied to the atrium at a cycle length of about 410 msec, so that stimuli would fall at various intervals after each normal atrial beat. The first two stimuli shown in the figure fell during the atrial refractory period, but the third evoked a premature response which propagated into the node and returned to the atrium as an echo. Although no further stimuli were applied, two additional nodal responses and one atrial response were recorded before the sinus pacemaker resumed control.

Reciprocation through the sinus node has been suggested as a cause of coupled atrial rhythms (3). A spontaneous arrhythmia which may fit this pattern was observed in the records shown in Figure 6. In part A, the atrium responded bigeminally to each pacemaker discharge. In part B, each coupled premature atrial response entered the node (or electrotonically accelerated the pacemaker discharge) and was followed by a reciprocal atrial response, leading to a pattern of nodal bigeminy and atrial trigeminy.

**Discussion**

The mechanism of atrioventricular reciprocation, suggested on the basis of clinical observations half a century ago (9), has received ample confirmation from studies on the dog heart (10-12) and more recently by microelectrode mapping of activation sequences in isolated preparations of the rabbit A-V nodal area (8). The evidence obtained in the dog heart, although indirect, permits logical conclusions about the behavior of the A-V nodal black box, for the temporal relationships of both input and output events are available for analysis. Interpretation of the direct studies in the rabbit heart was facilitated by the relatively constant spatial organization of the A-V nodal conduction pathways from one preparation to another.

Comparable evidence for dissociation within the sinus node has not been so easily available. Definitive proof of a circuit within the sinus node would require a number of simultaneous impalements of intranodal cells, and a point-to-point demonstration of the course of the activation front during the whole interval between primary and re-entrant atrial responses. This level of resolution has not been achieved in the present study, and it is doubtful whether it could be obtained without a major effort.

The data we have obtained, incomplete as they may be, strongly support the concept that dissociation similar to that observed in the A-V node can also occur in the sinus node. In both cases a premature impulse must find one route of entry into the node that is excitable, while another portal remains refractory. Transmission within the node must be slow enough to permit recovery of extranodal tissue before the impulse emerges. To show that dissociation does in fact occur, it is necessary to demonstrate that the premature response discharges some nodal cells relatively promptly, while the response of other areas is significantly delayed. The data displayed in Figure 4, although they do not provide a continuous record of the passage of the impulse, do show that some areas escape excitation while others are excited. It would, in fact, be difficult to devise an alternative explanation for the recorded events.
As in the case of A-V nodal reciprocation, there is little reason to doubt that if an impulse can make one round trip from atrium through sinus node and back to atrium, repetition of the event as a self-sustained tachycardia may also occur. The responses shown in Figures 4 and 5 indicate that more than one round trip is possible even within the limited area of the rabbit sinus node. The sequence shown at the bottom of Figure 4, however, also indicates how the process may extinguish itself. The first circuit appeared to bypass the area represented by SNc, forcing a longer loop through the node. The atrial echo, returning to the lower pole of the node, was now able to enter this area, describing a shorter loop which was soon extinguished in refractory tissue within the node.

The efficacy of vagal stimulation in terminating episodes of paroxysmal supraventricular tachycardia is well known. On the assumption that the tachycardia represents reciprocation through either the sinus node or the A-V node, the effect of the vagus may be ascribed to prolongation of the nodal refractory periods, although it might be more accurately described as depression of nodal conductivity. The possible effects of vagal stimulation are, however, complex and perhaps biphasic. If nodal conductivity is irregularly depressed, the chance that an atrial premature beat can enter one area or one pathway while another remains incapable of supporting a propagated response will probably be increased. Slow intranodal transit of the impulse will permit adequate recovery of the atrium before the response emerges, particularly since vagal stimulation also abbreviates the atrial refractory period. Accordingly, moderate vagal activity could set the stage for sino-atrial reciprocation. More pronounced cholinergic influence, however, could depress nodal conductivity to the point where a premature atrial response, fractionated upon entry into the node, would “decrement” to extinction without ever emerging as an echo. In other words, vagal stimulation of moderate degree could facilitate the induction of a sino-atrial reciprocated tachycardia, while more intense stimulation could terminate the arrhythmia.

References
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