Effects of Atrial Premature Systoles on Sinus Rhythm in the Rabbit

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ABSTRACT

Although it is well known that atrial premature depolarizations (APDs) frequently lead to lengthening of the next cycle (returning cycle), it is usually not appreciated that shortening of the returning cycle (RC) can also occur. Moreover, the mechanism for these alterations is not clearly understood. APDs were therefore electrically induced in rabbit sinoatrial (SA) preparations, and four basic patterns of alteration in the SA nodal rhythm were observed. The type of change depended very much on the timing of the APD in the cycle. The atrial events, more often than not, failed to reflect the underlying SA nodal events. Thus, lengthened atrial RCs occurred in spite of shortened SA nodal RCs. This and other discrepancies indicate that the extracellular records of atrial activity do not faithfully reflect the events within the SA node and that information gathered from them should be interpreted with caution. Timing of the APD in the cycle, antegrade and retrograde SA conduction time, SA nodal action potential characteristics, and shifts in pacemaker sites are important in the determination of the altered SA nodal and atrial responses to APDs.

KEY WORDS: returning cycle, conjoined cycle, reentry, fully compensatory pause, antegrade conduction, retrograde conduction, specialized atrial fibers, responsiveness of sinoatrial cells

Atrial premature depolarizations (APDs) exert variable effects on atrial rhythm. Lengthening of the postextrasystolic (or returning) atrial cycle has been repeatedly described in clinical and experimental studies (1-5), but it is less well known that returning cycles (RCs) may also equal (1,3,4-6) or be shorter than (1,3,4-13) the dominant cycle (DC). Various explanations have been offered for these differences in duration of atrial RCs. One attributes prolongation of the atrial RC to the conduction time for the APD from its site of origin to the sinoatrial (SA) node (1,5,14). This explanation implies that the RC would be directly influenced by any degree of prolongation of retrograde conduction time, especially if the APD arises early in the cycle. Another explanation attributes the change to the depressant effects of the APDs on SA nodal automaticity (5) and implies that alterations in atrial cycle length reflect changes in SA nodal activity. Neither explanation provides adequate mechanisms for RCs equal to or shorter than the atrial DC, although Lewis suggested that the shortening of the atrial RC might be due to "stimulation of the physiological impulse formation" (8) by the APD. A further weakness in these hypotheses is that they are based on information derived from the analysis of surface records of cardiac electrical activity, particularly the electrocardiogram. Since surface recording techniques do not provide direct information about SA nodal activity, they do not permit direct testing of the hypotheses. Proper understanding of the mechanisms responsible for the changes in atrial and SA nodal activity induced by APDs must be based on the simultaneous, direct demonstration of the effects on atrial and SA nodal electrical activity. Two recent studies by Bonke et al. (15,16) described the changes in transmembrane potentials which occur in rabbit SA preparations after extrasystoles. These studies documented an actual acceleration of the SA nodal rate after early APDs in contrast to the usual deceleration after late APDs, thus confirming a preliminary report from our laboratory (17). However, the studies did not sufficiently emphasize the correspondence, or the

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discrepancy, between SA nodal and atrial events after APDs.

The present report describes our own findings for a similar in vitro SA preparation with special emphasis on the correspondence, or the lack of it, between electrical events in the SA node and the atrium following electrically induced extrasystoles. The applicability of this information to changes in activity induced by APDs in the in situ heart is also considered.

**Methods**

Rabbits weighing 1–2 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv). The heart was rapidly removed. The right atrium, including short lengths of attached venae cavae and the SA node, was dissected free and pinned to a wax block in a Lucite bath (Fig. 1). The tissues were continuously perfused with modified Tyrode’s solution of the following millimolar composition: NaCl 137, NaHCO₃ 12, dextrose 11, KCl 2.7, NaH₂PO₄ 3.6, MgCl₂ 1.0, and CaCl₂ 2.7. The solution was equilibrated with 95% O₂-5% CO₂, and the pH was 7.35. Temperature in the tissue bath was maintained at 30–33°C.

Transmembrane potentials were recorded from the tissue through 3M KCl-filled glass microelectrodes with tip diameters of less than 0.5μm. The bath was connected to ground by a large electrode filled with 3M KCl and connected to a Ag-AgCl bar. The first stage of the recording system consisted of conventional cathode followers capable of input capacitance neutralization (Bioelectric Instruments model NF-1). The signals were led from the cathode followers through d-c amplifiers (Tektronix types 3A74 and 3A72) and then displayed on a dual-beam oscilloscope (Tektronix type 565). For voltage calibration, a 100-mv signal was introduced between the bath and ground. Bipolar surface electrograms were recorded through fine silver wires that were coated with Teflon except at the tip. Signals were photographed with a Grass oscilloscope camera.

Stimuli were applied regularly at a slow rate (approximately one-tenth of the spontaneous SA nodal rate) with fine Teflon-coated silver wires implanted in the right atrial appendage (Fig. 1). Stimuli introduced at such low rates resulted in random atrial responses of varying prematurity. Stimulation was accomplished with rectangular pulses generated by Tektronix pulse and wave-form generators (types 161 and 162) and led through radiofrequency oscillators isolated from ground.

Transmembrane potentials were recorded from cells in the SA node (Fig. 1) and, in some experiments, from atrial muscle cells in the right atrial appendage. In most instances, however, bipolar atrial electrograms served to define changes in atrial activity resulting from the extrasystoles. The following events were recorded: (1) spontaneous beats of the SA node (S) and the atrium (P), (2) premature depolarization of the SA node (S’) and the atrium (P’), (3) first postextrasystolic beat of the SA node (S₂) and the atrium (P₂), and (4) second postextrasystolic beat of the SA node (S₃) and the atrium (P₃). The following measurements, in milliseconds, were made in each experiment to assess the effects of premature stimulation of the atrium on subsequent SA nodal and atrial activity: (1) duration of SA nodal (S-S’) and atrial (P-P’) spontaneous cycles prior to introduction of an APD (i.e., the DCs), (2) duration of SA nodal (S-S’_) and atrial (P-P’_) curtailed cycles, (3) duration of SA nodal (S’-S₂) and atrial (P’-P₂) RCs, (4) conduction time of the APD from its site of origin to the SA nodal recording site (i.e., retrograde conduction time, P’-S’), and (5) conduction times of the dominant SA nodal impulse and the first returning SA nodal impulse from the SA node to the atrial recording sites (i.e., antegrade conduction times, S-P and S₂-P₂, respectively). In some experiments, studies were carried out not only under control conditions but
also after exposure of the preparation to acetylcholine
\((1 \times 10^{-7}-10^{-5} \text{ g/ml})\), atropine \((1 \times 10^{-8} \text{ g/ml})\), pro-
caine amide \((20-40 \text{ mg/liter})\), or ouabain \((1 \times 10^{-5}
\text{ mg/ml})\).

**Results**

The changes in activity induced by random stimulation of the atrium were dependent on the prematurity of the stimulus. The alterations in atrial activity often failed to reflect the alterations in SA nodal activity. The changes following premature atrial stimulation were of four basic types (Table 1). In type I, very early APDs resulted in a number of unusual phenomena. In type II, early APDs propagated to the SA node and resulted in shortening of the SA nodal RC. In type III, APDs initiated in the middle of the cycle propagated to the SA node and resulted in prolongation of the SA nodal RC. In type IV, late APDs failed to affect the SA node, since the next spontaneous SA nodal depolarization had already been initiated. SA nodal rhythm was uninterrupted.

For the sake of simplicity, these four types of responses will be discussed in increasing order of prematurity.

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Representative alterations after stimuli of decreasing prematurity (PT). Roman numerals in second column indicate the response type. DC = dominant SA nodal (SS) and atrial (PP) cycles, RC = returning SA nodal (S'Si) and atrial (P'Pi) cycles, SP = normal antegrade conduction time, P'S' = retrograde conduction time, and S,P1 = first postextrasystolic antegrade conduction time.

*Absence of SA nodal repolarization (SA entrance block).
ATRIAL EXTRASYSTOLES AND SINUS RHYTHM

TYPE IV RESPONSES

APDs initiated very late in the atrial cycle failed to reach the SA node before initiation of the next spontaneous SA nodal depolarization and did not affect the timing of subsequent SA nodal events (Fig. 2D). Although these late APDs did not disturb the SA nodal rhythm, they did cause prolongation of the atrial RC because of the premature depolarization of the atrium. The atrial RC was fully compensatory, and the conjoined atrial cycle was equal to twice the spontaneous atrial cycle (Fig. 2D). This type of response has been well described in the literature (5).

TYPE III RESPONSES

APDs initiated during the middle of the atrial cycle always depolarized the SA node and usually resulted in an SA nodal RC which was either unchanged (Fig. 2C) or prolonged (Fig. 3D). Usually the change in duration of the atrial RC closely paralleled that of the underlying SA nodal RC, with the atrial RC being somewhat more prolonged than the SA nodal RC. The degree to which the atrial RC exceeded the SA nodal RC reflected the time for retrograde conduction of the APD into the SA node (usually similar to antegrade conduction time or slightly more prolonged) and for antegrade conduction of the first returning SA nodal beat (usually normal). Sometimes, however, and for reasons that are not completely clear, retrograde and antegrade conduction delays of such magnitude were produced by the APDs that the first atrial RC was much more prolonged than the corresponding SA nodal RC. (Fig. 4F). In fact, the atrial RC was sometimes so prolonged that the conjoined cycle was equal to twice the DC. This occurrence of fully compensatory pauses is of particular interest in light of current views which maintain that fully compensatory pauses following APDs indicate that the SA nodal pacemaker site has not been depolarized by the APD (18).

A slight reduction in the slope of spontaneous depolarization was often observed, and an occasional slight increase in the level of maximum diastolic potential was seen. However, no single change in transmembrane potential was consistently responsible for prolongation of the SA nodal RC after these APDs (type III).

Changes induced by stimuli of decreasing prematurity. A: No response. B and C: Type II responses: stimulation 105 and 130 msec after P induces shortening of the SA nodal RC (DC = 670 msec, RC = 580 msec in B and 610 msec in C). Retrograde conduction time is not sufficiently increased (P-S' = 20 msec) to counteract shortening of the SA nodal RC; the atrial RC is therefore also shortened (500 msec in B, 520 msec in C). D: Type III response: stimulation 400 msec after P induces lengthening of both SA nodal and atrial RCs. The slightly greater duration of the atrial RC relative to the SA nodal RC is due to conduction time. Arrows represent stimulus artifacts. In B and C, there is an absolute shortening of the interval that encompasses the stimulus and the first SA nodal returning beat (see Discussion).

FIGURE 2
Simultaneous records of transmembrane potentials from the SA node and a bipolar atrial electrogram. Type II, III, and IV changes are illustrated in A-D. The spontaneous SA nodal cycle (DC) is 410 msec. The SA nodal RC is shortened (390 msec) in A and unchanged in B and C, whereas the atrial RC is lengthened in all three (430, 470, and 480, respectively). The discrepancy is due to conduction time. In D, the APD occurs too late to depolarize the SA node, and the postextrasystolic atrial cycle is compensatory (type IV response). P = spontaneous beat; P' = APD, and P₁ = first returning beat. Arrows indicate stimulus artifacts.
Type I, II, and III responses. The retrograde conduction time increases with prematurity of the stimulus. A: Stimulus 50 msec after P results in a delayed response which propagates to the atrial but not to the SA nodal recording site (type I). SA nodal cycles are unchanged and atrial RC is shortened. This phenomenon constitutes an interpolated APD. B, C, and D: Type II responses. With increasing prematurity, there is also less shortening of the SA nodal RC: 63 msec in B, 17 msec in C, and 8 msec in D. The atrial RC is lengthened in all three examples and the degree of lengthening is variably influenced by retrograde and antegrade conduction times. The atrial RC is of equal duration in C and D although the degree of SA nodal RC shortening is different due to the greater antegrade conduction time in C (35 msec) than in D (20 msec). E and F: Influence of the antegrade conduction time is again observed (type III responses). Antegrade conduction is normal in E (18 msec) but prolonged in F (34 msec). As a result, the atrial RC in F is virtually fully compensatory. Note that the stimulus-P' interval remains stable when the coupling interval is shorter (A-C). P = spontaneous atrial beats, P' = APD, and P1 = first returning beat.

Type II Responses

In sharp contrast to type IV and type III responses, APDs induced in the early part of the atrial cycle were followed almost uniformly by shortening of the first SA nodal RC (Figs. 2A, 3B, 3C, and 4B). No consistent mechanism could be found to explain this unexpected response of the SA node to early APDs. The slope of phase-4 depolarization was not consistently affected. However, the following factors could have contributed to the shortening of the RC. In some preparations, the premature SA nodal depolarization triggered by the early APD had a low amplitude and a short duration (Figs. 2A, 3B, 4B, and 5A). This shortening of the action potential duration would by itself be expected to contribute to the total shortening of the SA nodal RC. The second factor which could have contributed to RC shortening was the relatively less negative level of the maximum diastolic potential reached after these diminutive action potentials (Fig. 2A). In addition there was evidence for a shift of pacemaker activity to a different SA nodal site as manifested by the fact that the second and third SA nodal RCs also were sometimes shortened and were associated with alterations in atrial depolarization. This observation is particularly well illustrated in Figure 5B: the two RCs after the early APD were shortened, and they were determined by SA nodal beats associated with a shortened SA conduction time and an atrial electrogram of different configuration. This change, which lasted for another three beats, indicates that pacemaker function had shifted temporarily to a different pacemaker site with a faster rate and faster conduction to the atrium through different pathways of conduction. The change is also well demonstrated in Figure 6B–D where the returning SA nodal action potential was altered in appearance and the conduction time was shortened.

Shortening of the SA nodal RC induced by early APDs suggests the possibility that the first returning SA nodal action potential developed from reentrant excitation. To test this possibility, an effort was made to alter the conditions which favor reentry. Reentry is dependent on critical local differences in responsiveness and conduction; changes in these variables would be expected to affect the timing and the characteristics of reentrant activity or to abolish it entirely. Therefore, paired APDs were induced to cause conditions of responsiveness and conduction different from those resulting from single APDs of comparable prematurity. The same shortening of the SA nodal RC was found (not shown), indicating that RC shortening was probably not due to reentrant excitation.

Whatever the mechanism for shortening of the SA nodal RC, it is important to note that this
A and B: Type II responses recorded from a latent peripheral SA nodal cell. In A, extreme shortening of the SA nodal RC (from 380 to 290 msec) is paralleled by shortening of the atrial RC (330 msec). SA nodal conduction time is not altered. B suggests a shift in pacemaker site: the first and the second SA nodal RCs are shortened, and this shortening of the SA nodal RCs persisted for another three cycles (not shown). The first atrial RC is equal to the atrial DC because of the relative shortening of SA nodal conduction time and the relatively early occurrence of $P_1$. The next few atrial RCs are also shortened. The alteration of the atrial electrogram after the early APD indicates a difference in the pathways of depolarization.

C and D: Changes in the nature of very early responses with changes in stimulus strength. In C, a threshold stimulus 125 msec after $P$ results in a response which reaches the SA node but fails to propagate to the atrial recording site (i.e., no $P'$). Prolongation of the atrial cycle ($P-P_1$) after an apparently ineffective stimulus is due to the premature nodal depolarization and the absence of a propagated atrial response. In D, a suprathreshold stimulus 125 msec after $P$ results in a response which reaches both atrial and SA nodal recording sites with shortening of the SA nodal RC and lengthening of the atrial RC. Conduction time from the site of stimulation to the SA nodal recording site is the same (47 msec) in both C and D, suggesting that propagation to the SA node occurred along similar paths. $P =$ spontaneous atrial beat, $P' =$ APD, and $P_1 =$ first returning beat.

Simultaneous transmembrane potentials from the SA node and pectinate muscle of the right atrial appendage in a preparation exposed to ouabain ($1 \times 10^{-5}$ mg/ml). Control conditions (CONT.) were DC = 495 msec, antegrade conduction time = 25 msec. After exposure to ouabain (OUAB.) for 35 minutes, the DC is prolonged to 570 msec and the antegrade conduction time to 75 msec. A: No response to stimulus 80 msec after atrial depolarization. B: Stimulus 93 msec after $P$ results in a decremental SA nodal response, but no atrial action potential is induced. The SA nodal RC is shortened to 375 msec. The corresponding atrial RC is lengthened to 620 msec. The discrepancy between the durations of SA nodal and atrial cycles is due to the absence of an atrial response and to the 15-msec increase in antegrade conduction time. C: Stimulus at 120 msec initiates a type II response. SA nodal and atrial RCs are both shortened ($S'-S_j = 425$ msec, $P'-P_1 = 505$ msec). D: Stimulus at 150 msec induces another type II response: the SA nodal RC is shortened ($S'-S_j = 545$ msec); the atrial RC is prolonged ($P'-P_1 = 590$ msec), and there is a marked decrease in antegrade conduction time ($S_j-P_1 = 30$ msec). E: Stimulus 385 msec after $P$ causes a type III response with lengthening of both SA nodal and atrial RCs ($S'-S_j = 630$ msec, $P'-P_1 = 690$ msec). The antegrade conduction time ($S_j-P_1$) is also shorter than that of the dominant beats. This shortening and the alteration of the returning SA nodal action potential indicate a shift in pacemaker site.

shortening was most frequently not faithfully reflected by the atrial RC, the latter being longer than the atrial DCs (Figs. 2A and 4B–E). In the experiment illustrated in Figure 2A, the atrial RC was 30 msec longer than the atrial DCs, whereas the corresponding SA nodal RC was actually 26 msec shorter than the SA nodal DCs. Discrepancies between changes in timing of SA nodal and atrial events were frequently quite striking. In one experiment (not shown), the atrial RC was prolonged by 40–55 msec while the corresponding SA nodal RC was shortened by 40 msec.

These discrepancies between SA nodal and atrial cycle length were related to marked delays of retrograde conduction of the APD into the SA node and of antegrade conduction of the first returning SA nodal beat to the atrium. The extent to which retrograde conduction time was prolonged depended, in turn, on the degree of prematurity of the
stimulus (Fig. 4). To further investigate this relationship, random premature stimuli were introduced in a preparation driven at a rate faster than the intrinsic SA nodal rate. Figure 7 illustrates the increase in retrograde conduction time with increasing prematurity of the extrasystole. With very early extrasystoles, both intra-atrial and atrionodal conduction times were increased. In contrast, the degree of antegrade conduction delay of the first returning SA nodal beat was not directly related to the prematurity of the stimulus and persisted sometimes for several beats (five beats in the experiment of Figure 4B and C). As previously indicated, conduction time of the first returning SA nodal beat was sometimes unexpectedly shorter than that of the spontaneous beats, and the first postextrasystolic SA nodal or atrial complex (P1) had a different appearance (Figs. 5B and 6B-D), suggesting a transient shift of pacemaker activity to a different nodal site and different atrial activation pathways.

In some instances, as in Figures 3B and C and 5A, there was good correlation between atrial and SA nodal cycle length, i.e., the short SA nodal RC was reflected by a correspondingly short atrial RC. This phenomenon was usually due to shortening of the SA nodal RC extreme enough to counterbalance ultimate duration of the atrial RC. What has been said concerning the relative contribution of conduction delays and shortened SA nodal RCs to the ultimate atrial RC duration suggests that instances of atrial RCs equal to atrial DCs could be encountered. This supposition was in fact the case, as illustrated in Figure 5B.

**TYPE I RESPONSES**

The APDs induced in the first one-sixth or one-seventh of the atrial DC were of great interest because of the variable nature of the atrial and the SA nodal responses to them. In some instances, the premature responses failed to propagate to the SA nodal recording site, although they propagated to the atrial recording site (Fig. 4A). The actual site of this SA entrance block was not determined, but present evidence (19) suggests that it occurred in the perinodal fibers. In such instances, the timing of the subsequent SA nodal events was not altered (Fig. 4A), and the corresponding atrial beat occurred at its expected time, with the result that the atrial RC was abruptly shortened and the conjoined atrial cycle was equal to the atrial DCs (i.e., the APD was truly interpolated). In other instances, however, the premature response failed to propagate to the atrial recording site but propagated to the SA node (Figs. 5C and 6B). And in still other instances, the APD propagated to both the SA nodal and the atrial recording sites (Figs. 3B, 3C, 4B, 5A, and 5D and Table 1). One possible explanation for this variability is the marked difference in the responsiveness and the conductivity of ordinary and specialized atrial fibers during this portion of the cycle (20). Evidence for this explanation is provided by the observation that a slight variation in the intensity of the stimulus resulted in changes from one type of response to another. In the experiment shown in Figure 5C and D, threshold stimulation resulted in an SA nodal response only (Fig. 5C), but suprathreshold stimulation resulted in a response at both the SA nodal and the atrial recording sites (Fig. 5D). A possible explanation could be that the first stimulus was of a magnitude sufficient for initiating a propagated

**FIGURE 7**

Relationship between latency, retrograde conduction time, and prematurity of the stimulus. A: Conduction times of the premature responses from the site of stimulation to the SA nodal recording site (TS'). B: Conduction times of the premature responses from the site of stimulation to the atrial recording site (TP'). C: Conduction times from the atrial to the SA nodal recording sites (P'S'). Since the degree of prolongation of P'S', as well as TS' and TP', is directly related to the prematurity of the stimulus, the increase in retrograde conduction time with increasing stimulus prematurity cannot be attributed solely to increasing latency. See text for discussion.
response in specialized atrial fibers communicating with the SA node but insufficient for exciting ordinary atrial muscle (Fig. 5C). The suprathreshold stimulus excited both specialized and ordinary atrial fibers so that a premature atrial response also occurred (Fig. 5D). Similar differences in responsiveness and conduction within the SA node itself undoubtedly provide the best explanation for the frequent occurrence of repetitive responses (echoes, return extrasystoles) to single stimuli during this portion of the cycle (Fig. 8).

Altered timing of SA nodal and atrial activity induced by APDs reflects underlying changes in responsiveness, conduction, and automaticity of these tissues. Therefore, the response to premature stimulation was also studied in the presence of pharmacological agents which influence these variables. The basic pattern of SA nodal responses to early APDs (i.e., short RC) and late APDs (i.e., long RC) continued to occur in the presence of acetylcholine, atropine, ouabain, and procaine amide in concentrations sufficient to alter these variables (Fig. 6).

**Discussion**

In isolated preparations of rabbit atrium, electrically induced APDs result in alterations in subsequent atrial events that are in many ways similar to those observed previously in animal hearts in situ and in man (1–14). The atrial RC is usually prolonged to a variable extent, with restoration toward control values occurring within one to five beats. However, the atrial RC may be shortened after early APDs, or it may be unchanged (1, 3–5, 7–13, 21). What had not been anticipated by previous studies, however, is that the prolongation of the atrial RC often fails to reveal the true response of the SA nodal pacemaker cells to APDs: although the RC of SA nodal cells is lengthened after late APDs, the same pacemaker cells respond to early APDs by a shortening of their RCs, with RCs equal to DCs being occasionally observed. The present study not only establishes a sound explanation for this discrepancy between SA nodal and atrial responses based on SA conduction delays but also offers a reasonable electrophysiological correlate for the less commonly encountered types of atrial responses to APDs, namely RCs which are of equal or shorter duration than are the atrial DCs.

**ALTERATIONS IN SA NODAL ACTIVITY**

APDs which succeed in depolarizing the SA node induce changes in the timing of subsequent SA nodal events which can be predictably related to the prematurity of the stimulation. Early APDs (initiated roughly in the initial one-third of the atrial DC) usually result in a shortened SA nodal RC. Late APDs, however, usually cause prolongation of the SA nodal RC.

Lengthening of the SA nodal RC after late APDs (type III response) is readily explained in terms of normal automatic mechanisms, since the slope of
phase-4 depolarization is often depressed following late APDs (15). The mechanism responsible for this depression is not clear. It is probably not due to release of acetylcholine induced by electrical stimulation (22), since the prolongation of the RC is not abolished by atropine sulfate.

Shortening of the SA nodal RC after early APDs (type II response) was an unexpected finding, but its occurrence has been independently confirmed by others (16). Nevertheless, its occurrence is difficult to attribute to alterations in normal automatic mechanisms. Reduced levels of maximum diastolic potential (Fig. 2A) following early APDs and decreased duration of premature SA nodal action potentials (Figs. 2-7) would tend to result in the earlier appearance of the next spontaneous SA nodal beat. However, these factors are not sufficient to account for the extremely marked shortening seen in some experiments after very early APDs. A more plausible explanation is that early APDs may influence responsiveness and conductivity within the SA node to such an extent that certain latent SA nodal cells may transiently be able to take control of the atrium after partial SA nodal depolarization by the APD. The SA node is an agglomeration of automatic cells coexisting side by side with a variety of spontaneous firing rates, and the cells are not necessarily all depolarized by the fastest cell. This isolation of cells from each other is facilitated by very slow intranodal conduction (estimated to be as low as 0.05 m/sec) (23). Therefore, electrical activity originating in cells which reach threshold earliest may not spread far enough or quickly enough to prevent other cells from firing. Activity initiated by the first cell to attain threshold may not reach the atrium until the latter has already been activated by an impulse originating in another fiber which fires later but is in closer proximity to ordinary or specialized atrial fibers.

Because of their reduced amplitude and rate of rise, early SA nodal responses are even less likely to depolarize the entire SA node than are normal beats. Therefore, it seems reasonable to suppose that early responses could depolarize pacemaker cells in close anatomical or functional proximity to atrial muscle but fail to depolarize pacemaker cells in more distant portions of the node. This situation would result in usurpation of pacemaker function by subsidiary SA nodal cells. In instances where the spontaneous firing rate of the cell which transiently assumes pacemaking function is faster than that of the original pacemaker, shortening of the RC would ensue. Added support for this hypothesis is provided by observations that the configuration of the returning atrial electrogram (P1) and the time required for conduction of the returning SA nodal beats to the atrial recording site (S1-P1) sometimes differed from control conditions and that these alterations can last for several beats. These findings indicate a net acceleration of the SA nodal rhythm, presumably because a fast SA nodal cell has transiently taken over control of the atrium. These conclusions are somewhat different from those of Bonke et al. (15), who also observed lengthening of the atrial RC in spite of a shortening of the SA nodal RC (their Figs. 6 and 9 and their Table 2B-D) and postulated a shift of pacemaker site. These authors concluded that the long atrial RC indicates control of the atrium by a slow, latent SA nodal cell and that the first SA nodal action potential which terminates the shortened SA nodal RC does not propagate to the atrium. The fact that shortening of the SA nodal RC may persist for several beats indicates that usurpation of pacemaker function by an SA nodal cell endowed with a rate relatively faster than that of the initial cell. This cell may have been anatomically or functionally isolated from the atrium until depolarization of the SA node by the early APD opened up previously unavailable routes of access to the atrium by slight rearrangements of intranodal local responsiveness and conductivity.

In a subsequent study, Bonke et al. (16) suggest, as an alternate mechanism for SA nodal RC shortening, that early APDs discharge only a small part of the SA node and that the fibers in the vicinity of the depolarized area are electronically influenced to fire prematurely. The additional postulation must be made that a long-lasting state of depolarization in the center of the SA node could produce a persistent acceleration of the SA nodal rate over several beats.

Whatever the mechanism underlying it, the shortening of the SA nodal RC after early APDs must be regarded as real. Close examination of figures 3B and C, 5A, and 6B and C demonstrates that it is the entire interval between the stimulus artifact and the first returning SA nodal action potential (stimulus-S1) which is shortened and not just the S'-S1 interval. This observation indicates that the shortening of the SA nodal cycle is not an artifact due to failure to record the earliest possible SA nodal depolarization (S') induced by the APD. Early APDs may actually not induce a shift in pacemaker site as much as unmask the phenomenon of shift in pacemaker activity, which is an intrinsic
property of the SA node and which is found in a variety of other conditions such as acetylcholine release and vagal discharge (24), exposure to high potassium concentrations (25), or catecholamine release.

Reentry of impulses through the SA node has been shown to produce reciprocal depolarization of the atrium (26). We have observed similar phenomena after early APDs in what we have called type I responses, and several examples are found in Figure 8. These responses are distinctly different from the Type II responses. The atrial depolarization which initiates SA reciprocation occurs earlier in the DC, and the shortening of the cycle is much more precipitous with SA reciprocation than it is in type II responses.

ALTERATIONS IN ATRIAL ACTIVITY

It is evident that marked discrepancies exist between SA nodal and atrial RCs and that caution must be used when trying to guess at the SA nodal events from the atrial events. For example, moderately lengthened atrial RCs may be associated with lengthened, shortened, or unaltered SA nodal RCs. Similar discrepancies may exist when the atrial RC is markedly lengthened. Likewise, shortened atrial RCs after early APDs may result from three different mechanisms: (1) failure of the APD to depolarize the SA node (SA entrance block) as in Figure 4A, (2) depolarization of the SA node by the APD with marked shortening of the SA nodal RC as in Figure 3B, and (3) SA reciprocation as in Figure 8A. It may be very difficult to distinguish between these responses without direct SA nodal recordings. It should also be noted that there are two types of fully compensatory pauses. The first type (Fig. 2B) is encountered when the APD occurs late in diastole and fails to affect the SA node (18). The second type (Fig. 4F) is observed when the atrial RC is markedly prolonged and results from either marked lengthening of the SA nodal RC or from a combination of moderate SA nodal RC lengthening and marked prolongation of conduction time. In the second case, of course, the fully compensatory length of the postextrasystolic pause is purely fortuitous.

APPLICATIONS TO THE HEART IN SITU

Since the alterations in atrial RCs in the isolated rabbit atrium are similar to those seen in animal hearts in situ and in man after spontaneous and electrically induced APDs, it is quite likely that these alterations result from similar mechanisms, i.e., combinations of variously altered SA nodal RCs and altered retrograde and antegrade conduction times. It is generally not appreciated that shortening of the atrial RC has previously been amply documented experimentally and in man (1, 3–5, 7–13, 21, 27). One explanation for these shortened atrial cycles is that, as in Figure 4A, the APD fails to depolarize the SA node. The other explanation is that shortened atrial RCs are due to the same fundamental SA nodal event in the heart in situ as they are in the isolated rabbit atrium, that is, SA nodal depolarization by the APD and shortening of the SA nodal RC. Finally, SA reciprocation also cannot be completely ruled out in the heart in situ.

Thus, it would seem reasonable to propose that the entire spectrum of SA nodal responses and alterations of conduction times following APDs which is observed in isolated preparations may also occur in the heart in situ.

Conversely, the limited capability of electrocardiograms and surface or intracavitary electrograms to reveal the underlying SA nodal disturbances induced by APDs probably exists in the heart in situ as it does in the isolated rabbit atrium. Statements concerning depression of the SA node by single APDs should be accepted with some reservations if they are based on the electrocardiographic criterion of lengthening of the atrial RC. Recent attempts at assessing SA nodal function and entrance block (27–29) based on the study of atrial events following single APDs must be viewed in the same light. Since SA nodal electrical activity cannot be determined in man by presently available techniques, implications concerning SA nodal events from atrial recordings are somewhat speculative. So widespread is the concept of depression of the SA node by single APDs that strenuous explanations are often found to explain shortening of the atrial RC. Alteration in the appearance of the P wave is taken as evidence that the shortened RC is really due to premature interruption of the cycle by a second APD (10). It is evident from Figure 5B that alteration of the P wave after an APD does not militate against SA nodal origin of the first postextrasystolic beat.

One phenomenon, which is depicted in Figure 5C, may also have its counterpart in the heart in situ. A premature impulse may depolarize the SA node but fail to propagate to the atrial recording site. Although the SA nodal RC becomes shortened,
no P' is visualized on the atrial record and the P-P interval (which is actually P-Pi) becomes prolonged. A possible explanation is that, early in the cycle, responsiveness and conductivity may be greater in the specialized atrial fibers than in the ordinary atrial fibers (20). The premature impulse may reach the SA node via the specialized atrial fibers without spreading to any portion of the ordinary atrium. This explanation is supported by the fact that prolonged atrial pauses following apparently nonpropagated electrical impulses (i.e., no P' or atrial movement visible) have been observed not only on bipolar surface electrograms but also on electrocardiograms and records of muscle movement (myocardiograms) in the heart in situ (2, 3, 7). The known existence of propagation of an SA nodal impulse along specialized atrial pathways of conduction without registration of a P wave, sinoventricular rhythm (30), suggests that a similar phenomenon may take place in the reverse direction after early APDs. A similar explanation could be advanced for the rhythm disturbance clinically known as nonphasic sinus arrhythmia. Spontaneously occurring subthreshold atrial impulses may be unable to propagate through ordinary atrial fibers of the heart in situ but may succeed in reaching the SA node via the specialized atrial fibers. The consequent disturbance in SA nodal rhythmicity would be manifested, as after electrical stimulation of the isolated rabbit atrium or the heart in situ, only as a pause in the electrocardiogram.

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Effects of Atrial Premature Systoles on Sinus Rhythm in the Rabbit
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