Interaction of Inhomogeneities of Repolarization With Anisotropic Propagation in Dog Atria
A Mechanism for Both Preventing and Initiating Reentry

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Having found the regional differences in right atrial action potentials shown in an accompanying article, we tested two seemingly paradoxical hypotheses: 1) The spatial pattern of repolarization provides a protective mechanism against reentry, and 2) repolarization inhomogeneities interact with anisotropic discontinuous propagation to produce reentry. Measurement of multidimensional refractory periods demonstrated an anisotropic distribution within large bundles with the longest refractory periods in the medial upper crista terminalis (sinus node area), a distribution similar to that of action potential durations. Also, discontinuities of repolarization were found at muscle bundle junctions. Early premature impulses originating in the sinus node area propagated throughout the right atrial preparations without conduction disturbances or reentry. Conversely, early premature impulses that originated at sites distal to the sinus node area resulted in localized conduction block at multiple sites, which frequently produced complex conduction changes and reentry. The critical nature of the site of origin of a premature impulse in initiating reentry was related to locations where the steepest repolarization gradients occurred: within anisotropic bundles in the direction of highest axial resistance (across fibers) and at muscle bundle junctions that represented localized discontinuities of axial resistance. The multiple conduction abnormalities at localized sites interacted to produce different types of reentry at a larger size scale (25 mm to several cm²). In each case, neither repolarization inhomogeneities (leading circle concept) nor anisotropic discontinuous propagation was the only "mechanism" involved. That is, reentry at a macroscopic size scale occurred as a result of a combined repolarization-anisotropic discontinuous propagation mechanism. (Circulation Research 1989;65:1612–1631)

It is generally thought that the only electrophysiological consequence of the spatial dispersion of repolarization of cardiac action potentials is the enhancement of reentry. It is also widely considered that the spatial nonuniformity of refractory periods (spatial dispersion of action potential durations) is the only "mechanism" involved in the production of conduction disturbances that initiate circus movement reentry following premature impulses. In this article, however, we present experiments that use new information to reassess both of these long-standing ideas.

Approximately a decade ago, we presented new evidence that in cardiac muscle anisotropic propagation was discontinuous, with directional differences in electrical load that lead to unidirectional block without requiring nonuniformities of refractory periods. Subsequently, we found that anisotropic discontinuous propagation can produce all of the conduction disturbances leading to reentry without the presence of spatial differences in refractory periods. That is, the passive anisotropic properties of cardiac muscle have an independent role in determining excitability and the safety factor of propagation, in addition to producing very low effective conduction velocities of premature impulses. The safety of propagation of early premature impulses also is critically dependent on the specific type of anisotropic electrical properties, which we have designated simply as uniform and nonuniform anisotropy. For example, we found that unidirectional block of premature action potentials can occur along the long axis of the fibers in nonuniform anisotropic atrial bundles, and this can...
lead to reentry within areas as small as 1–2 mm² (microreentry) based on the mechanism of anisotropic discontinuous propagation in the absence of nonuniformities of repolarization.  

The above studies of anisotropic propagation, however, provide quantitative information concerning the relative roles of these two general mechanisms (anisotropic discontinuous propagation and the spatial inhomogeneities of repolarization) only at the small size scale of a few millimeters. At a larger size scale the relative contributions and interactive effects of these two mechanisms likely are different. Two widely applied methods, the measurement of refractory periods and of strength-interval curves, have contributed to the belief that the spatial inhomogeneity of refractory periods is the only mechanism that needs to be considered in the origin of conduction disturbances associated with circus movement reentry. This is likely due to the highly successful use of these methods in preparations that approximate one-dimensional structures in which the major mechanisms for altering propagation are limited to the sarcolemmal membrane. The most frequently used method to measure refractory periods is to determine if a premature response elicited by a test ( premature) stimulus propagates to a distant recording site. An immediate problem arises, however, in the interpretation of such results in some anisotropic preparations because, following the initiation of a premature impulse, conduction may change differently in different directions with respect to the fiber orientation. For example, we recently found that a new type of conduction, “dissociated microscopic” longitudinal conduction (LP-dm), can occur when measuring strength-interval curves, a change in conduction that would be missed at a distal recording site. Thus, new types of “local” multidimensional strength-interval curves are needed to evaluate propagation in anisotropic preparations.

Available models of reentry due to the spatial dispersion of repolarization depend on experimental documentation of different refractory periods within the area containing the reentrant circuit. Critical information, however, has been missing about the multidimensional spatial relations of refractory periods within specific atrial structures. Consequently a quantitative two-dimensional analysis of the differences in action potential duration and anisotropic propagation cannot be made at a macroscopic level from published experimental information. We therefore measured the spatial distribution of action potential shapes and durations throughout major bundles of the right atrium, the results of which are presented in an accompanying article. The results demonstrated that there were multiple differences in the action potential shape and duration from region to region. However, the multiple regional differences were organized into an overall simple pattern in relation to the sinus node area. The longest action potentials occurred in the area where normally atrial excitation was initiated from sinus node impulses, and there was progressive shortening of the action potential duration with increasing distance from the sinus node via all routes by which propagating impulses could eventually reach the atrioventricular (A-V) node. Also, there was an anisotropic distribution of the duration of the action potentials in prominent atrial bundles.

Based on the above, in this study we test two seemingly contradictory hypotheses. The first hypothesis is that the overall spatial pattern of repolarization of the right atrium provides a fundamental protective mechanism against the development of reentrant arrhythmias when “premature” atrial impulses arise at the usual site, that is, when impulses invade atrial muscle from the sinus node after abrupt increases in pacemaker activity. Knowledge of the overall spatial pattern of repolarization also provided a way to test the second hypothesis: The spatial dispersion of repolarization interacts with anisotropic discontinuous propagation to produce the conduction disturbances necessary to initiate reentry at a macroscopic size scale (several to many millimeters).

Materials and Methods

Electrical Methods

Most of the preparations were the same as those described in detail for the accompanying analysis of the spatial distribution of right atrial action potentials. The right atrial specimens consisted of the crista terminalis, the pectinate muscles (pectinati), and limbus of the fossa ovalis (limbus), and accompanying lower atrial septum. Twenty-three preparations were studied from adult dogs. Each animal was anesthetized with sodium pentobarbital (30 mg/kg i.v.). An accompanying article presents the details of the composition of superfusate, the large tissue bath, the measurement of intracellular action potentials, and the high flow rate of the superfusate used to ensure a “normal” status of the preparations at 35°–36° C.

Unipolar extracellular potential waveforms were recorded with flexible tungsten wire electrodes, 50 μm in diameter, which were insulated except at the tip. Unipolar, rather than bipolar, waveforms were measured because they can be interpreted for differences in shape in terms of the underlying membrane events at a single site, and complex wave-
form shapes with multiple deflections (similar to “fractionated” waveforms) can be interpreted in terms of asynchronous excitation of small groups of fibers within distances of 50–100 μm; we know of no way to use bipolar recordings in this manner because the waveform shapes are rarely the same at two sites located as much as 300 μm apart. A dissecting microscope equipped with a Nikon F250 35-mm camera was used to document all recording positions. Each unipolar extracellular electrode was connected to an AC-coupled differential amplifier having a frequency response flat between 0.1 and 30,000 Hz. Separate reference electrodes for each electrode were located in the bath 3–5 cm from the measurement sites.

A small unipolar stimulus electrode 50 μm in diameter was used to initiate excitation at different sites; the reference for the stimulus was located 7–9 cm away in the bath. A cathodal stimulus 1 msec in duration and 1.5 times threshold was applied to the endocardial surface of the preparation for regular paced sequences. A PDP-11/44 computer system (Digital Equipment, Maynard, Massachusetts) controlled the rate and synchronized the timing of the stimuli with the data recording. The outputs of the recording amplifiers were sampled at rates between 6,600 and 40,000 per second (12-bit samples). The computer stored the data and displayed the waveforms on a Tektronix 4014 (Beaverton, Oregon) unit with a persistent screen.

Two types of measurements were made to evaluate refractoriness within individual muscle bundles and at the junction of the crista terminalis (crista) and limbus of the fossa ovalis (limbus): 1) “Local” multidimensional strength-interval curves (minimum current required to initiate propagation in different directions at different premature intervals) were constructed for different stimulus sites in the crista. For each stimulus site, conduction was monitored by recording extracellular depolarization waveforms at six positions, which were located on imaginary lines extending from the stimulus electrode along the longitudinal and transverse axes in relation to the fiber orientation (Figure 1). Along the longitudinal axis two electrodes were located in the superior direction and two in the inferior direction, and along the transverse axis one electrode was positioned medially and another laterally to the stimulus electrode.

The stimulus duration was maintained constant at 1 msec, and premature stimuli were delivered at variable intervals after 10 consecutive pulses at a constant cycle length between 600 and 800 msec (75–100/min). A computer-controlled programmable switch was used to vary the current strength of the premature stimulus, while the stimuli for the regular paced beats remained constant at 1.5 times threshold. A minimum current was identified that just produced longitudinal propagation in the superior and inferior directions and transverse propagation in the medial and lateral directions. If conduction block occurred in one or more of the four directions, two additional electrodes were used to confirm the failure of propagation past the most distal electrode in each direction. Each premature interval produced a specific shape and timing of the extracellular depolarization deflections, which were usually reproducible for several minutes. This provided time for measurements at additional sites to verify changes in conduction within small areas (several mm²). The maximum current of the stimulus was limited to 10–12 mA because larger stimuli occasionally initiated excitation at sites distant from the stimulus electrode and produced ill-defined time boundaries of the absolute refractory period.

2) Multidimensional local refractory periods were measured with an electrode arrangement similar to that used for the strength-interval curves. The threshold current of a 1-msec duration stimulus was determined at each site as the minimum stimulus required to initiate propagation on an every-beat basis during steady-state at a constant cycle length between 700 and 800 msec. Then the stimulus strength was set at 1.5 times threshold for all stimuli, and the premature interval after each tenth beat was progressively shortened. The shortest time interval between the last stimulus at a constant cycle length and the premature stimulus (premature or S1–S2 interval) that just produced a propagated response in each direction was noted. The absolute refractory period for each site was taken as the shortest premature interval that produced propagation in any direction. Repeated measurements were performed at each stimulus site to ensure reproducibility of the results.

After the pattern of repolarization was determined by measuring refractory periods at multiple sites, changes in the premature interval at different stimulus locations were introduced to determine the associated changes in conduction that occurred throughout the preparation. For this, extracellular waveforms were measured simultaneously at nine to 12 selected sites to detect changes in conduction that involved anisotropic propagation (propagation along axes in different directions relative to the fiber orientation) versus changes due to spatial inhomogeneities of the refractory periods. When a change in conduction (e.g., conduction block) occurred within a small area, the waveforms were reproducible long enough to use several electrodes to confirm the events at an additional six to 14 locations surrounding the area of interest. This also allowed us to determine at selected sites the shortest time between the depolarization waveforms of the last normally propagated impulse and the earliest propagated premature impulse (the shortest A1–A2 interval). The A1–A2 interval involves a “latency” component. That is, there are no wavefronts or nodes in the myocardium between the stimulus artifact and the depolarization waveform at any given location due to changes in the effective conduction velocity that alter the con-
duction time from the stimulus electrode to the monitoring site. This provided a way to evaluate the success or failure of propagation in specific small regions in relation to the pattern of repolarization by comparing the $A_1$-$A_2$ and the $S_1$-$S_2$ intervals measured in the same area.

After each experiment, the digitally stored waveforms were displayed again and photographed for initial analysis. The propagation events of premature action potentials often were so complex at a microscopic size scale that we could not resolve the events in sufficient detail to represent the excitation spread as an average "wavefront" by the widely used isochrone method. Therefore, the general pattern of excitation spread was estimated from the extracellular waveforms based on recent experimental and theoretical results on the origin of polyphasic waveforms and their derivatives at a microscopic level.

**Morphological Methods**

The crista-limbus (C-L) junction was singled out for special attention since there was a marked discontinuity in action potential durations at the junction (see "Results"). For light microscopic study of the C-L junction, six preparations were immersion-fixed for at least 24 hours in Bouin's fixative and then routinely processed and embedded in paraffin. Three of the preparations (all from adults) were studied in the tissue bath before fixation; three others (one adult, two neonates) were fixed immediately on excision. All of the preparations were serially sectioned at 7 μm through the entire junctional region, with three being sectioned en face (sections in planes parallel to the endocardium) and three being cut so that the crista was cross-sectioned and the limbus longitudinally sectioned. The sections were stained by a modification of the picrosiris red method for collagen (the PMA/PSR method) or with a Masson trichrome. To produce a figure for this article (i.e., Figure 6), the stained slide was mounted in a photographic enlarger and the image of the section was projected onto red-insensitive Kodak Electrophoresis Duplicating Paper.

**Results**

In presenting the results we show typical experiments, with each result followed by an interpretation of the effects of the spatial dispersion of refractory periods (differences in action potential duration) versus the effects of anisotropic discontinuous propagation. Because multiple intracellular impalements within small areas produce local injury that alters microscopic propagation, we made a more indirect interpretation from a large number of simultaneously measured extracellular waveforms. Thereby, the results are interpreted on the basis of 1) the reproducible spatial pattern of atrial action potentials presented in an accompanying article, and 2) prior combined simulation-experimental analyses of intracellular-extracellular potential relations in uniform and nonuniform anisotropic cardiac muscle.

**Local Multidimensional Strength-Interval Curves and Refractory Periods**

Figure 1A shows the arrangement of the extracellular electrodes and an example of the waveforms used to obtain local multidimensional strength-interval curves at each of two stimulus sites in the upper crista. The locations of these two stimulus sites, and those of subsequent figures, were chosen because they provided a way to investigate the functional implications of the highly organized repolarization pattern demonstrated in an accompanying paper (see Figures 1 and 2 of Reference 15). The stimulus site in the medial zone of the crista (M) was located in the region of longest atrial action potentials where the earliest site of excitation occurred from impulse invasion from the sinus node. The duration of the action potential decreased markedly along the transverse axis from this site to the lateral zone (L) of the crista, with continuing decreases of action potential duration in the pectinate. Also, from both stimulus sites, along the longitudinal axis of the fibers there were small but definite decreases in action potential duration in the superior and inferior directions.

The threshold current varied between 0.5 and 1.0 mA, and the regular paced beats (cycle length, 600 msec) produced extracellular waveforms characteristic of nonuniform anisotropic bundles (Figure 1B and 1C, 600). That is, there were large amplitude smooth biphasic waveforms of fast longitudinal propagation in the superior and inferior directions and low amplitude multiphasic waveforms of slow transverse propagation in the medial and lateral directions. The multiphasic or "fractionated" waveforms during transverse propagation were associated with normal action potentials (not shown) that had more rapid upstrokes than those of fast longitudinal propagation.

For the largest current strength (7–8 mA) applied at the medial stimulus site, the shortest premature interval that produced a propagated response was 150 msec (Figure 1B, 150). This multidimensional response consisted of stable propagation in both transverse directions while simultaneously drastic changes occurred in the waveforms in both longitudinal directions. Dissociated microscopic longitudinal conduction was indicated by the change from a single large biphasic deflection to multiphasic low amplitude deflections in both the superior and inferior directions; also, unidirectional decremental conduction to block occurred inferiorly (Figure 1B, 150, arrow). The longitudinal changes of dissociated microscopic conduction and decrement to block can be attributed to anisotropic discontinuous propagation. Both conduction abnormalities occurred as excitation progressed from an area of longer action potentials into an area of slightly shorter action potentials.
FIGURE 1. Arrangement of stimulus and recording electrodes (A) and typical extracellular waveforms (B and C) used to construct local multidimensional strength-interval curves. Panel A illustrates that six extracellular recording electrodes were positioned around each stimulus electrode to monitor propagation along longitudinal and transverse axes related to the orientation of the fibers. L, C, and M mark the lateral, central, and medial zones of the crista, respectively. Panels B and C show selected waveforms of premature impulses originating from stimulus sites in the medial (B) and lateral (C) zones of the upper crista terminalis. Normal waveforms are shown on the left and early premature impulses on the right. The numbers in the boxes indicate the normal cycle length and premature intervals in milliseconds. Solid arrows on selected premature waveforms designate conduction block at or proximal to the recording electrode. LP Sup, longitudinal propagation in the superior direction; LP Inf, longitudinal propagation in the inferior direction; TP med, transverse propagation toward the medial border of the crista; TP lat, transverse propagation toward the lateral border of the crista.

With the largest current strength (7–8 mA) applied at the lateral stimulus site, the shortest premature interval that produced a propagated response was 120 msec (Figure 1C, 120). From this site, the earliest propagated response consisted of the following: In both longitudinal directions, there was decremental conduction to block. This was evidenced by the uniphasic small positive deflection at the most superior electrode (upper arrow) and the absence of a deflection at the most inferior electrode (lower arrow). Again, the decremental conduction can be attributed to anisotropic discontinuous propagation; that is, there was block along the long axis of the fibers as propagation occurred into regions of slightly shorter action potentials in non-uniform anisotropic muscle.6–9 Along the transverse axis, however, there were marked differences in the propagated responses in the medial and lateral directions. Conduction failed in the medial direction (Figure 1C, 120, middle arrow), while stable transverse propagation continued in the lateral direction. The conduction differences in the two transverse directions from the lateral stimulus site can be attributed to the spatial inhomogeneity of repolarization. Conduction block in the medial direction occurred in the region where the action potentials were progressively longer than at the lateral stimulus site. As a consequence, the marked increase in the action potential duration in the central and medial zones of the crista overrode the effect of the greater “safety factor” of transverse conduction provided by the nonuniform anisotropic tissue (i.e., a decreased electrical load in the transverse direction compared with the longitudinal direction of the...
fibers). In the lateral direction from the stimulus site, however, conduction of the early premature impulse was enhanced by the progressively shorter action potentials at the lateral border of the crista and in the pectinate area.

**Local multidimensional strength-interval curves of adjacent areas.** Figure 2 shows multidimensional strength-interval curves for three adjacent areas (the medial and lateral zones of the upper crista and the proximal portion of an attached pectinate muscle) in which there was a unidirectional decrease (or increase) in action potential duration in going from one area to the next. The shortest premature interval that produced a propagated response in each area decreased in going from the medial crista to the lateral crista and then to the nearby pectinate. During the relative refractory part of each curve (i.e., the portion of the curve requiring increased current above the threshold value of regular paced beats), the multidimensional propagation events were different for each area. As can be seen, the different events in each curve were related to the relative time of each curve on the abscissa with respect to the curves of the neighboring areas. For example, conduction block did not occur along the transverse axis from the medial crista stimulus site, the curve with the longest premature intervals during the absolute and relative refractory portion of the curves. The lateral crista, however, produced a curve of duration intermediate between that of the medial crista (longer) and the proximal pectinate (shorter). From the stimulus site in the lateral crista, transverse propagation persisted in the lateral direction (i.e., the pectinates) to the earliest propagated response at a premature interval of 120 msec (7.0 mA); however, conduction block occurred in the direction of the medial crista at 150 msec (2.6 mA) and at all shorter premature intervals at greater current strengths. When conduction block occurred along the transverse axis in the medial direction at a premature interval of 150 msec at 2.6 mA, an increase in the stimulus current to 6 mA at this premature interval still failed to induce propagation in the medial direction. This indicated that the simultaneous directional different propagation events were caused by inhomogeneities of the preparation and not by different magnitudes of the stimulus current. In the pectinate muscle, decrement to block occurred in both longitudinal directions as the premature interval was shortened from 130 to 100 msec, while transverse propagation to both sides of the pectinate bundle continued to the earliest propagated response at 100 msec.

These multiple "local" multidimensional strength-interval curves obtained in adjacent areas provided a way to identify different mechanisms associated
with the directionally different propagation events in each curve of Figure 2. 1) The different positions of the curves on the abscissa were consistent with the different times of phase 3 repolarization of the action potentials in each region (i.e., more positive transmembrane potentials required more stimulus current to initiate propagation). 2) Longitudinal propagation was subject to unidirectional changes with the abrupt development of dissociated microscopic longitudinal conduction and/or decremental conduction to block (anisotropic propagation phenomena). 3) Transverse propagation was stable when conduction occurred into regions of equal or shorter action potentials but it failed when conduction occurred into a region of longer action potentials (directional differences due to inhomogeneities of repolarization).

The absence of conduction block of the earliest propagated response along the transverse axis in either direction from the stimulus site in the medial zone of the crista can be accounted for by the lack of longer action potentials in any direction from that site. However, during a considerable portion of the relative refractory part of the curve at the stimulus site in the lateral zone of the crista, transverse conduction block occurred in the medial direction while simultaneously there was stable conduction in the lateral direction toward the pectinates. The three curves of Figure 2 demonstrate that the same premature interval, within the range of 120-150 msec, required markedly different current strengths to initiate propagation in each of the juxtaposed areas. At a premature interval of 150 msec, for example, 8.0 mA were required to initiate propagation in the medial zone of the crista, 2.6 mA in the lateral zone of the crista, and only 1.0 mA in the adjoining pectinate muscle.

**Influence of Anisotropic Distribution of Refractory Periods Within Crista on Propagation of Premature Impulses Arising at Different Locations**

In presenting spatial maps of the refractory period measurements, we wish to emphasize for clarity that the time interval measured as the "refractory period" at any given site was highly dependent on the current strength. As an example, in the strength-interval curve for the medial crista in Figure 2, the absolute refractory period at a maximum current strength of 8 mA was 150 msec. If the refractory period at that site was measured at a current strength of 2.3 mA (a value two times threshold), the refractory period would be 230 msec, and if measured at 1.7 mA (1.5 times threshold), the refractory period would be 265 msec. In the following experiments we use "refractory period" to indicate the shortest premature interval at 1.5 times threshold strength that produced stable (1.5 times threshold) propagation in any direction from a stimulus site.

Figure 3A shows a spatial map of refractory periods that was obtained while pacing the preparation at a constant cycle length of 800 msec. The isochrones (dashed lines) and times marked on the map represent interpolated values of the refractory periods measured at 29 sites (solid dots) located in different regions of the crista, pectinates, and the adjoining limbus. The arrow in Figure 3A indicates the area where earliest atrial excitation occurred from impulse invasion from the sinus node, a region in the medial crista we refer to as "the sinus node area." As can be seen, the refractory periods were organized spatially within the crista as an anisotropic distribution with the longest refractory periods in the area of the sinus node and with progressive decreases in the refractory period with increasing distance from the area of the sinus node, including the pectinates and the limbus. Thus, the overall spatial pattern of the distribution of refractory periods was quite similar to the spatial distribution of the durations of atrial action potentials as presented in the accompanying paper.

Figures 3B and 3C show the patterns of excitation spread when a premature impulse originated in different regions of the crista at premature intervals slightly longer (2-18 msec) than the local refractory periods. Shown with each propagation pattern are five extracellular waveforms, recorded in the local areas marked by the rectangles in Figure 3A. When early premature impulses were initiated in the medial zone of the upper crista (Figure 3B1) in the sinus node area, stable propagation occurred throughout the preparation; that is, there was no conduction block in any of the prominent atrial bundles. This can be accounted for by the following considerations. From the spatial distribution of refractory periods of Figure 3A, it is evident that the earliest propagated response that could be induced in this area would correspond to the longest refractory period present throughout the preparation. Thus, as the premature impulse propagated from this site in any direction, each area encountered would be at a progressively shorter refractory period as excitation progressed further away from the sinus node region. Consequently, all premature impulses that originated in the medial zone of the upper crista, including the earliest responses initiated there, should propagate throughout the preparation by continually entering tissue with the same or a more negative takeoff potential. As a consequence, propagation from one region to the next would be enhanced by the impulse continually entering tissue with equal or enhanced excitability.

The influence of the spatial pattern of refractory periods on early premature impulses initiated at sites away from the sinus node area was quite different, and the multidimensional responses depended on the exact location of the stimulus site in relation to the repolarization pattern of Figure 3A. When the site of origin of the premature impulse was moved to the lower crista along its medial border (Figure 3B2), propagated premature responses could be initiated at much shorter inter-
FIGURE 3. Propagation of premature impulses from different sites in relation to anisotropic distribution of refractory periods in the crista. Panel A shows the repolarization map constructed from multidimensional refractory periods measured at sites marked by solid circles. Isochrone (dashed) lines were constructed by interpolating values of the refractory periods at each measurement site. The numbers within the five boxes indicate the sites of the recording electrodes for the waveforms shown with each sequence in panels B and C. The arrow in panel A indicates where atrial excitation was initiated from invasion of the sinus node impulse. The number in the large rectangle with each sequence in panels B and C indicates the premature interval (msec) of the accompanying excitation sequence and set of waveforms; darkened areas superimposed on the excitation patterns indicate the distribution of refractory periods that were the same or greater than the associated premature interval. The pattern of propagation is indicated by lines with arrows; straight lines signify longitudinal propagation; irregular curved lines signify transverse propagation. ‘‘T’’ symbols at the border of the light and dark areas indicate the approximate area where propagation failed (conduction block); the small boxes with solid circles in each drawing reproduce the sites of the recording electrodes shown in panel A. The solid arrows on some of premature waveforms indicate sites at which no excitation occurred. Med and lat, medial and lateral sides, respectively, of the crista. The dark area beneath the limbus represents the fossa ovalis.

Vals than the shortest premature interval of 220 msec at which propagation could be initiated in the medial zone of the upper crista. This result is consistent with the refractory period map of Figure 3A. When the premature interval was 170 msec at this medial site in the lower crista (Figure 3B2), stable propagation occurred in all directions from the site of origin, for example, laterally across the crista and medially across the lower part of the C-L junction where the refractory period of the crista was 160–165 msec. However, although stable propagation extended superiorly into the lateral half of the upper crista and adjoining pectinates, all regions where the refractory periods were less than 170 msec, propagation did not extend into the medial half of the upper crista (Figure 3B2, waveform 3) where the refractory periods were longer than 170 msec. This resulted in the absence of premature
excitation of atrial muscle surrounding the sinus node. Thus, the premature atrial impulse would not have been able to influence or interact with pacemaker action potentials within the sinus node due to the refractory period (action potential duration) being significantly longer in the medial zone of the upper than in the lower crista where the early premature impulse originated; that is, the premature impulse failed before it could enter the medial zone where the perinodal fibers were located. The stimulus site was next moved to the lateral zone of the upper crista where, according to the refractory period map of Figure 3A, it should be possible to initiate propagated impulses at much shorter premature intervals than at the two previous upper and lower medial zone stimulus sites. Accordingly, Figure 3C1 shows the propagation pattern induced when the premature interval was reduced to 140 msec at this stimulus site. Fast longitudinal conduction occurred down the length of the lateral zone of the entire crista with further excitation spread into the adjoining pectinate muscles. These regions of stable propagation corresponded to areas where the refractory period decreased progressively with increasing distance from the stimulus site (Figure 3A). Propagation did not extend, however, into the central and medial zones of the upper crista nor into the medial zone at a lower level. The line of intrabundle block (Figure 3C1, "T" symbols) corresponded to the regions where the anisotropic distribution of refractory periods was greater than 140 msec (Figure 3A). In the medial zone of the crista, the distribution of refractory periods greater than 140 msec extended inferiorly below the C-L junction; thus, excitation did not reach the limbus because conduction failed in the crista before it arrived at the C-L junction (Figure 3C1).

In the lateral zone of the lower crista, the local refractory period was only 100 msec. As the premature interval was shortened from 120 to 105 msec at a stimulus site in this area, the premature impulses produced propagation patterns similar to that shown for the premature interval of 118 msec in Figure 3C2. From this site, stable propagation occurred inferiorly in the lateral zone from which excitation extended into the nearby pectinate muscles. However, propagation failed to enter the entire upper crista and the medial zone of the lower crista. The separation of the small region of stable propagation within the lateral zone of the lower crista from the remainder of the crista where the premature impulse did not propagate corresponded with the spatial demarcation of areas where the refractory periods were shorter and longer than 120 msec, respectively. Note that, due to the spatial distribution of the refractory periods (Figure 3A), the early premature impulse arising from the inferior lateral site in the crista failed to propagate to the C-L junction to excite the perinodal fiber and failed to propagate to the lateral zone in the upper crista to excite the superiorly located pectinate muscles.

Repolarization Discontinuity at the Crista-Limbus Junction: Effect on Bidirectional Propagation of Premature Impulses

The junctions of anisotropic atrial muscle bundles frequently represent macroscopic discontinuities of axial resistance where localized conduction block of premature action potentials can occur in the absence of spatial differences in the refractory period. To determine if discontinuities of repolarization can also occur at the junctions of muscle bundles, we investigated the C-L junction while the preparation was paced at constant cycle length of 800 msec. Figure 4A shows an example of two action potentials recorded at sites 200 μm apart but on different sides of the C-L junction. As can be seen, the time of repolarization at −30 mV was 40 msec shorter on the limbus side than on the crista side of the junction (Figure 4A2). In eight other preparations, the time of repolarization at −30 mV was 10−45 msec less on the limbus side than on the crista side of the C-L junction. Thus, the decrease in action potential duration with increasing distance from the sinus node area occurred with an abrupt decrease (discontinuity) across the C-L junction.

Such a repolarization discontinuity at a muscle bundle junction (which electrically represents a localized increase in axial resistance?) could have major effects on the bidirectional propagation of early premature impulses across the junction. This possibility was investigated in another preparation in the experiment shown in Figure 4B. After 10 beats at a constant cycle length of 800 msec, premature impulses at 1.5 times threshold were initiated at a site in the medial zone of the crista 1 mm above the C-L junction and then at another site in the distal limbus 4 mm from the junction. The drawing (Figure 4B, top) shows the locations of the two stimulus sites (C and L) and the recording positions of four extracellular waveforms (waveforms 1 and 2 in the crista, waveforms 3 and 4 in the limbus). Premature responses initiated at the crista stimulus site resulted in successful conduction down the crista and across the C-L junction to induce propagation in the limbus, including the earliest propagated response (175 msec) that could be initiated in the medial zone of the crista just above the C-L junction (Figure 4B1, 175).

When progressively earlier premature impulses were initiated in the distal limbus, however, there were marked changes in conduction to the crista while simultaneously there was little or no change in conduction in the limbus. For example, at a premature interval of 190 msec there was a prominent delay in the transmission of excitation to the crista (Figure 4B2, 190), but no detectable change in conduction occurred in the limbus. When the premature interval was decreased further to 175 msec at the distal limbus stimulus site, there was no excitation of the crista (Figure 4B2, arrows) while fast longitudinal conduction continued in the lim-
bus. We alternated the site of origin of the premature impulse between the distal limbus and crista stimulus sites while maintaining the premature interval constant at 175 msec; this demonstrated that the same unidirectional propagation failure occurred repeatedly for many minutes. As the premature interval was reduced further from 175 to 155 msec at the distal limbus stimulus site, stable propagation continued in the limbus but there was no transmission of excitation to the crista.

To evaluate the unidirectional propagation block between the crista and limbus, strength-interval curves were measured at the above stimulus sites (Figure 5A1), maintaining a constant cycle length of 800 msec for the regular paced beats. In the medial zone of the crista just above the C-L junction, decreases in the premature interval below 225 msec required increases in current strength to initiate propagation (Figure 5A1); however, propagation of these premature responses continued at all monitoring sites in both the crista and the limbus until no responses could be elicited at the crista site at a current strength of 10 mA at premature intervals less than 170 msec. Note that for the distal limbus stimulus site, however, when the premature interval was reduced from 200 to 175 msec, a smaller increase in current was required to initiate propagation in the limbus than was required to induce conduction in the crista at the same premature intervals (Figure 5A1). When the premature interval was decreased from 170 to 145 msec in the distal limbus, considerable increase in current was necessary to initiate stable propagation in the limbus (relative refractory part of the curve), while simultaneously propagation could not be initiated in the crista by direct stimulation or by propagated impulses from the limbus (Figure 5A1, open triangles on the limbus curve).
To directly demonstrate that the site of unidirectional block was localized to the C-L junction, we measured strength-interval curves at two stimulus sites positioned as close as possible, one on either side of the C-L junction (Figure 5A2), and the waveforms were recorded at the same monitoring sites shown at the top of Figure 4B. As the premature interval was decreased at each stimulus site, unidirectional propagation failure occurred across the C-L junction in going from the limbus to the crista for a 6-msec range of intervals (175 to 169 msec) over which propagation could be induced in either bundle by direct stimulation on the respective side of the C-L junction (Figure 5A2, vertical darkened area). Decreases in the premature interval between 169 and 151 msec at the stimulus site on the limbus side of the junction continued to produce stable propagation in the limbus during its period of relative refractoriness; however, propagation across the C-L junction failed to excite the crista, which was completely refractory at premature intervals less than 170 msec (Figure 5A2).

The above confirmed that the unidirectional block was localized to the C-L junction. However, the question arose as to how to interpret the unidirectional block across the junction for the 6-msec range of intervals.
premature interval during which propagation could be induced in the respective bundles by direct stimulation on either side of the junction. The strength-interval curves of Figure 5A2 provided the following way to interpret the unidirectional block during the 6-msec interval. At a premature interval of 175 msec, the crista side of the C-L junction required 5.6 mA to initiate propagation while the limbus side required only 2.8 mA. At the slightly shorter premature interval of 169 msec, the current strength required to initiate propagation on the crista side of the C-L junction increased considerably to 10 mA, but only a slight increase to 3.6 mA was necessary on the limbus side. Successful antegrade propagation from the crista to limbus during the 6-msec interval, therefore, was associated with a decrease in the current strength needed to initiate propagation in going across the junction to the limbus; that is, the upstroke of the premature action potential encountered progressively less refractory tissue (increase in excitability across the junction).

In the opposite direction (limbus to crista), propagation failure was associated with an increase in the current strength required to initiate propagation in going across the junction to the crista; in this direction the upstroke encountered progressively greater refractory tissue (decrease in excitability across the junction).

These results show that the C-L junction has several features in common with the A-V node: 1) Both are associated with marked changes in action potential shape within small distances; 2) both represent localized regions of high axial resistance; and 3) both are associated with the occurrence of unidirectional block. These results show that the C-L junction has several features in common with the A-V node: 1) Both are associated with marked changes in action potential shape within small distances; 2) both represent localized regions of high axial resistance; and 3) both are associated with the occurrence of unidirectional block. Merideth et al demonstrated delayed recovery of excitability beyond full repolarization of A-V nodal action potentials (postrepolarization refractoriness) at slow and fast stimulation rates. The question naturally arose as to whether this phenomenon occurs at muscle junction sites.

To test this possibility, we measured action potentials at successive impalement sites from the limbus to crista across the junction in steps of 100 μm. Premature stimuli were delivered after 10 beats at a constant cycle length of 800 msec. To achieve the earliest possible propagated responses on each side of the C-L junction, one stimulus electrode was placed in the lateral zone of the crista and another stimulus electrode was placed in the limbus 2 mm from the junction. Figure 5B shows premature action potentials measured at the two sites that resulted in the largest difference in action potential duration of the regular paced beats at any two consecutive sites 100 μm apart, that is, action potentials at sites within the smallest area identifying the repolarization discontinuity. Note that the upstrokes of the premature action potentials at both sites occurred before full recovery of the preceding action potential. Comparison of the action potentials in Figure 5B with the strength-interval curves in Figure 5A2 shows that the period of relative refractoriness in the strength-interval curves corresponded to the repolarization phase of the action potentials; that is, full excitability was restored by the completion of repolarization.

Thus, we did not observe postrepolarization refractoriness at the C-L junction for impulses that propagated in either direction. Steady-state action potentials measured at all sites across the junction were of normal amplitude with resting potentials more negative than -78 mV, which contrasts with the smaller (less negative) resting potentials of A-V nodal cells. We concluded therefore that localized differences in cell-to-cell electrical coupling that produce local increases in effective axial resistance do not contribute to postrepolarization refractoriness. The mechanism of that phenomenon likely resides solely in the delayed kinetics of the sarcolemmal membrane net depolarization current, as occurs in the A-V node and in depressed fibers.

Structural correlations. All of the C-L junctions studied showed several features in common, which are demonstrated in Figure 6. This figure shows the junction in one of over 500 PMA/PSR-stained serial sections from the same preparation from which the electrical data in Figures 4B and 5 were obtained. The junctional region was divided into sheets, one superficial and one deep, by a thick collagenous "knot" whose superior and inferior connections were not observed. This knot acted as a tendon, with the majority of the myocytes from the limbus and from deep within the crista inserting upon it. The superficial junctional region was at most 500-1,000 μm thick and was often thinner. At the endocardial side of the crista, the myocytes ran parallel to the long axis of the crista; they were separated from parallel myocytes overlying the knot by an obliquely running collagenous septum (Figure 6, filled arrows), which serial section study showed to be seldom interrupted. This septum is one of two candidates for the site of the major electrical discontinuity. The other, on the limbus side of the junctional region, was marked by a sudden shift of myocyte orientation (Figure 6, open arrow), the myocytes of the limbus running parallel to the long axis of the limbus and thus perpendicular to the crista. Deep to the knot there was also muscle, this connecting the deepest part of the crista, whose myocytes ran parallel to the long axis of the limbus, with the deepest part of the limbus (near to the left atrial endocardium). There was some discontinuity between the endocardial and epicardial portions of the crista, whose myocytes generally ran perpendicular to one another. Large deposits of fat broke up the muscular connections deep to the collagenous knot.

Interaction of Anisotropic Discontinuous Propagation and Inhomogeneities of Repolarization as a Mechanism of Complex Conduction Disturbances and Reentry

A major correlation with the spatial pattern of refractory periods (Figure 3A), as well as with the
regional differences in action potential duration, was the lack of conduction disturbances throughout the preparation secondary to premature impulses that originated in the sinus node area (medial zone of upper crista). In two of 12 preparations, however, the earliest propagated responses produced in this area resulted in local unidirectional longitudinal decrement to block and subsequent microreentry, both anisotropic propagation phenomena originally demonstrated in bundles with nonuniform anisotropic properties. On the other hand, except for these two instances there was no reentry and all propagated premature responses generated in this zone of the upper crista were conducted across the C-L junction to the limbus and throughout the preparation.

In contrast to the rare occurrence of conduction disturbances secondary to early premature impulses initiated in the medial zone of the upper crista, early premature impulses initiated at other sites usually produced conduction disturbances. These occurred in multiple small areas and frequently generated complex changes in the time of local excitation at locations far from the stimulus site. An example is shown in Figure 7 for a stimulus site in the lateral zone of the upper crista, located only 1.6 mm from the medial zone in which premature stimuli produced no conduction disturbances. Figure 7A shows the normal pattern of excitation spread of the regular beats at a cycle length of 700 msec and the associated waveforms at four positions (numbered boxes). These normal waveforms were typical for bundles with microscopic nonuniform anisotropic properties. That is, fast longitudinal conduction (large biphasic waveform 3) occurred within a narrow region in the lateral zone, slow transverse propagation (multiphasic low-amplitude waveform 2) occurred in the medial zone along the entire crista, and there was a slight delay in conduction across the C-L junction to the limbus (waveform 4).

When the premature interval was reduced to 175 msec (Figure 7B), fast longitudinal conduction continued inferiorly in the narrow region of the lateral crista (waveform 3) and in the pectinates (waveform 1), but localized block of transverse propagation occurred to the medial zone of the upper crista (waveform 2). Stable propagation continued, however, to the medial zone of the crista located inferiorly at the C-L junction, where there was successful but quite delayed propagation to the limbus (Figure 7B, waveform 4). The simultaneous presence of conduction block in the upper medial zone and stable propagation in the lower medial zone at the C-L junction corresponded with the spatial distribution of refractory periods that were longer and shorter, respectively, than 180 msec in the crista (Figure 7B, darkened area). In the crista at the level of the C-L junction (position 3) the time between the last normal depolarization and that of the premature depolarization (A1-A2 interval) was 178 msec. This time interval was longer than the longest refractory periods in the medial zone of the crista along the C-L junction (160 to 175 msec), which provided recovery of excitability for propagation to continue across the C-L junction to the limbus.

When the premature interval was decreased further to 150 msec (Figure 7C), fast longitudinal conduction continued in the lateral zone of the crista and into the pectinates; however, failure of transverse propagation into the medial zone of the crista now extended inferiorly along the entire C-L junction. As can be seen in waveform 4 (Figure 7C), there was no propagated impulse in the limbus. The failure to propagate into the limbus can be accounted for by the fact that in the crista at the level of the C-L junction the time interval between the last normal depolarization and that of the premature depolarization was 156 msec. This interval was shorter than the shortest refractory period of 160...
FIGURE 7. Interaction of anisotropic pattern of repolarization with anisotropic discontinuous propagation in crista to produce complex conduction events. Each panel shows the pattern of excitation spread and the waveforms recorded at four sites (identified in panel A) following stimulation of the lateral zone of the upper crista. Panel A shows the normal pattern and waveforms, and panels B–D show the conduction patterns and waveforms associated with progressive shortening of the premature interval, which is indicated in milliseconds in each large rectangle. In panel D, the "sawtooth" line represents dissociated microscopic longitudinal propagation (waveform 3). Conduction patterns are based on extracellular waveforms recorded at 12 positions. The repolarization distribution (isochrone dashed lines and darkened areas) was constructed from measurements of local multidimensional refractory periods at 21 sites. The time (msec) of each repolarization isochrone is identified by its associated number.

msec in the medial crista area bordering the C-L junction (Figure 7C, darkened area) where the prolonged refractory periods produced conduction block of the premature impulse proximal to the C-L junction.

From the above, continued decreases in the premature interval below 150 msec would be expected to produce continued failure of excitation of the limbus due to block of the earlier premature impulses in the crista before they arrived at the C-L junction. However, when the premature interval was decreased another 5 msec, propagating premature impulses reappeared in the distal limbus (Figure 7D, waveform 4). The abrupt change in the waveform at position 3 (Figure 7D) in the crista provides the explanation for the return of successful propagation across the C-L junction to the limbus. When the premature interval was shortened from 150 to 145 msec, fast longitudinal conduction (large biphasic waveforms) abruptly shifted to a slow form of longitudinal conduction due to the onset of dissociated microscopic longitudinal conduction (multiphasic or fractionated waveforms). Due to the longer time now required for the impulse to conduct from the site of origin in the upper lateral crista to the level of the C-L junction, there was sufficient time for excitability to return in the crista along the C-L junction. Specifically, when the premature interval was decreased by 5 msec (150 to 145 msec), the time between the last normal depolarization waveform and that of the premature depolarization at the level of the C-L junction (Figure 7D, waveform 3) increased from 156 to 180 msec, a time interval that was longer than the longest refractory period of 175 msec in the medial zone of the crista along the C-L junction. Thus, the mechanism of the seemingly paradoxical return of conducted impulses that occurred with continued reduction of the premature interval was that of anisotropic discontinuous propagation producing dissociated microscopic longitudinal conduction superimposed on the anisotropic distribution of the refractory periods of the crista.

Just as markedly different events occurred throughout the preparation when premature impulses originated at two sites only 1–2 mm apart in the upper crista, different conduction events occurred throughout the preparation when premature impulses
originated at closely apposed sites located on different sides of the C-L junction. Premature stimuli applied to the crista at the lower border of the C-L junction reproduced the events shown in Figure 3B2 for another preparation. That is, conduction block occurred only in the medial zone of the upper crista while propagation continued across the C-L junction to the limbus and to all other areas of the preparation, even with the earliest propagated response at a premature interval of 162 msec. (This sequence is not shown because of its similarity to that of Figure 3B2.)

When the site of origin of the premature impulse was on the limbus side of the C-L junction only 1.3 mm from the above stimulus site, quite different conduction events occurred throughout the preparation. Figure 8A shows the waveforms and the pattern of normal excitation spread from this site at a cycle length of 700 msec. At a premature interval of 170 msec (Figure 8B), propagation continued throughout the preparation except that conduction failure occurred in the upper medial crista (waveform 2, arrow), where the refractory periods were longer than 175 msec. Further reduction of the premature interval to 155 msec resulted in propagation failure to the entire crista and pectinates (conduction block across the C-L junction), indicated by the solid arrows superimposed on the waveforms in Figure 8C. Note that the conduction block was due to the refractory period on the crista side of the C-L junction (162 msec) being longer than the premature interval of 155 msec at the stimulus site on the limbus side of the junction (Figure 8C). Although propagation failed to cross the C-L junction, stable conduction continued to the distal part of the limbus and then to the anterior atrial septum. From theexcitation spread along the lower atrial septum, entered the lowermost part of the crista, and then continued in a superior direction in the lower crista. This resulted in marked delay in excitation in the crista at the level of the C-L junction (Figure 8C, waveform 3) and in the upper pectinates (waveform 1), while simultaneously there was reappearance of (delayed) conducted impulses in the upper medial crista (waveform 2).

The considerable delays in excitation in the crista at the level of the C-L junction and in the upper pectinates, as well as the reappearance of conduction in the medial zone of the upper crista, were accounted for by the considerable time required for the impulse to traverse a different and much longer pathway. Because of this, the impulse arrived at each site in the crista and pectinates well beyond the local refractory periods. Consequently, when the impulse propagating in the lower crista reached the C-L junction, it continued across the C-L junction and initiated reentry in the limbus (Figure 8C, waveform 4). We interpreted the seemingly complex changes with sudden delays in local excitation of the crista at the level of the C-L junction, the reappearance of conduction in the upper medial crista, and reentry in the limbus to be accounted for by several interactions. The major factor was the discontinuity of repolarization at the C-L junction, which was made possible electrically by the discontinuity of axial resistance at the junction; that is, the refractory period decreased 15 msec in going from the crista to limbus side of the C-L junction. Therefore, the location of the site of origin of the premature impulses was critical in relation to the repolarization discontinuity, although the stimulus sites were only 1.3 mm apart. For example, the complex sequential events could not be produced

FIGURE 8. Effects of progressively earlier premature impulses originating in the limbus near a repolarization discontinuity at the crista-limbus junction. The extracellular waveforms are shown for the same recording sites as in the previous figure. Panel A shows the normal sequence at a cycle length of 700 msec. Panels B and C show the patterns of excitation spread and associated waveforms at progressively shorter premature intervals (170 and 155 msec). The "T" symbols on the patterns of excitation spread indicate the approximate areas where block occurred. The solid arrows on some of the premature waveforms indicate sites where no excitation occurred.
by premature impulses arising on the crista side of the C-L junction. Another requirement was the presence of an additional pathway between the limbus and crista (i.e., the anterior and lower atrial septum) so that the impulse could reach the crista after block occurred at the C-L junction.

**Stepwise Development of Reentrant Circus Movement**

Multiple extrasystoles frequently followed early premature impulses that originated in the lateral zone of the crista. Therefore, we stimulated the lateral crista at a constant cycle length of 300 msec and used nine to 12 electrodes to monitor progressively earlier premature impulses. The results consistently demonstrated a reentrant circuit that involved the lateral crista and pectinates. Because there were multiple events that were complex, and each event interacted with the others to produce reentry, we simplified as much as possible by creating small preparations consisting of segments of the crista and adjoining pectinates.

Figure 9 illustrates the typical effects (n=5) found with progressively earlier premature stimuli in an upper crista and pectinate preparation by showing patterns of excitation spread and five extracellular waveforms recorded at the following locations (Figure 9A): the lateral crista inferior to the stimulus site (C1 and C2), proximal upper and lower pectinate muscle bundles (P1 and P3, respectively), and the junction of the upper and lower pectinates (P2). In this section we divide the lower pectinate bundle into proximal (near the crista) and distal (near the junction) parts. There was no repolarization discon-
Continuity at the pectinate junction, but in the lower area of the lateral crista the refractory period was 7 msec shorter than at the stimulus site, consistent with the decrease in the refractory period in an inferior direction shown in Figure 3A.

Normal beats resulted in fast longitudinal conduction in the lateral crista, as well as in the upper and lower pectinate bundles (Figure 9A). Initial activation at the pectinate junction (P2) occurred from the impulse in the upper pectinate, that is, waveform P2 preceded waveform P3 in the lower pectinate (Figure 9A). Note that the waveform at the pectinate junction (Figure 9A, P2) contained late multiple small deflections, which occurred after the deflection at P3 proximally in the lower pectinate. The origin of these small deflections was transverse propagation in the lower pectinate at the junction; however, as best we could determine, the small deflections represented interaction of impulses conducted from the upper pectinate across the junction with those arriving from the lower pectinate.

At a premature interval of 182 msec (Figure 9B), the following events occurred: 1) In the proximal portion of the lower pectinate 7 mm from the stimulus site, unidirectional decremental conduction to block occurred along the long axis of the fibers, an anisotropic discontinuous propagation phenomenon. That is, along the long axis of the fibers there was a progressive decrease in the amplitude of the extracellular waveform with increasing distance from the stimulus site, and a positive uniphasic deflection (P3, first arrow) occurred at the site of propagation failure in the proximal segment of the lower pectinate (Figure 9B, 182). Consequently, there was no conduction distally to the pectinate junction via this route. 2) Stable propagation continued in the upper pectinate, and when the impulse arrived at the pectinate junction, excitation extended across the junction to the distal lower pectinate, which had not been excited due to block in its proximal segment. Note that the premature waveform (Figure 9B, 182) at the junction (P3) was quite different from the normal waveform (Figure 9A), which raises the question as to why the junctional site (P3) was not activated in a similar way as with the normal beat. The marked difference in waveform shapes and the delay of conduction of the premature impulse across the junction were similar to our earlier demonstration of localized conduction changes of premature impulses at such a junction, rather than the shape change at the junction (P3) being due to the block in the proximal lower pectinate (P3). The initial deflection of the premature impulse at P3 was due to excitation of the upper bundle at the junction, and the second deflection occurred after considerable delay (27 msec) in transmission of the impulse across the junction to the lower pectinate. 3) Excitation due to the second deflection at the junction initiated retrograde conduction in the lower pectinate as evidenced by the second uniphasic positive deflection indicative of decrement to block of that impulse in the proximal segment of the lower pectinate (Figure 9B, 182, second arrow in P3). Not that this positive deflection represented a very small area of reentry from which the reentrant impulse did not spread.

Reduction of the premature interval to 175 msec (Figure 9B) caused a decrease in the distance over which longitudinal decrement to block occurred inferiorly from the stimulus site in the lateral crista, that is, longitudinal conduction did not reach position P3 (no initial depolarization at P3). However, propagation continued in the upper pectinate (P4) and when the premature impulse reached the pectinate junction (P4), the delay across the junction increased to 33 msec. The increased delay across the junction resulted in enhanced retrograde conduction in the distal lower pectinate (which had not been excited due to proximal block in the lower lateral crista). This can be seen by the change from decrement to block (small uniphasic deflection) at position P3 in the proximal lower pectinate at a premature interval of 182 msec to the prominent deflection of stable propagation at a premature interval of 175 msec. In the lateral crista, this resulted in an increase in the area of reentry, which still remained localized (without repetitive activity) due to decrement to block of the reentrant impulse at position C3 (Figure 9B, 175, solid arrow in C3). Further shortening of the premature interval to 170 msec produced greater delay of impulse transmission across the pectinate junction (now 48 msec).

The greater delay in initiating activation of the distal lower pectinate at the junction, in turn, enhanced retrograde conduction to the crista as can be seen by the change from decrement to block at position C3 in the lateral crista (premature interval 175 msec) to a prominent biphasic deflection (premature interval 170 msec). When the premature interval was reduced another 2 msec to 168 msec, the unidirectional longitudinal decrement to block in the lateral crista occurred closer to the site of origin of the premature impulse (Figure 9B, 168, solid arrow in C3). In the upper pectinate the effective conduction velocity also decreased as can be seen by the associated decrease in the amplitude of the extracellular waveform at P4, and the localized delay across the pectinate junction increased markedly to 62 msec. However, the localized delay continued to have the opposite effect in the proximal lower pectinate and lower lateral crista. That is, the effective conduction velocity of the retrograde impulse continued to increase, as can be seen by the decrease in the time difference between the second deflection in the waveform at position P2 and the deflections at P3, and C3 in Figure 9B (as well as the increase in amplitude of the waveform at P3) for the premature intervals of 170 and 168 msec. Stable conduction of the reentrant impulse in the lateral crista now continued superiorly to position C1, where the upper pectinate attached to the crista; from this area the reentrant
impulse propagated again into the upper pectinate to establish continued circus movement (one to six repetitive beats).

**Interpretation of multiple events leading to reentry.** Note the marked asymmetry of events in the proximal and distal parts of the reentrant circuit in relation to the pectinate junction (an anisotropic structural discontinuity), which was located in the middle of the circuit. That is, progressively earlier premature stimuli resulted in a progressive reduction in effective conduction velocity proximal to the pectinate junction, consistent with the leading circle concept. However, the enhanced velocity in the distal part of the circuit with increasing prematurity would not be expected by the leading circle concept. The event accounting for the opposite changes in effective conduction velocity in the proximal and distal parts of the circuit was the marked delay of conduction localized to the pectinate junction. The localized delay provided time for increasing excitability to return in the distal lower pectinate (an area that did not undergo initial premature excitation due to decremental block proximally). Note that associated with the progressive delay in conduction across the junction (Figure 9B, P2), the second small deflection (due to excitation of the distal lower pectinate) shifted in time with the deflections in the distal part of the reentrant pathway, which comprised the proximal lower pectinate and lower lateral crista.

Thus, the stepwise development of the reentrant circus movement shown in Figure 9 required a variety of localized events at multiple sites within the circus “pathway” to initiate reentry. 1) Initial decrement to block occurred along the long axis of the fibers in the direction of shorter action potentials, an anisotropic discontinuous propagation phenomenon, which initially set the stage for reentry. 2) There were marked nonuniformities and discontinuities of conduction velocity of the premature impulse throughout the reentrant circuit, and these corresponded to specific structures with respect to sites of block and localized conduction delay. 3) The longer refractory periods in the superior portion of the lateral crista had the effect of “blocking” reentrant propagation of moderately early retrograde conducted reentrant impulses from the lower pectinate. This created “concealed” reentry by confining initial reentry to a localized area in the lateral crista without continued circus movement. 4) Very short premature intervals caused a marked increase in localized delay of impulse transmission across the pectinate junction in the middle of the reentrant circuit, which, in turn, allowed time for more complete repolarization to occur in the superior portion of the lateral crista. Consequently, with marked delay in the return of the impulse (now propagating with enhanced velocity) to the lower lateral crista, stable retrograde propagation of the returning premature impulses could continue as circus movement with conduction into the upper pectinate.

**Discussion**

**Protective Effects of Inhomogeneities of Repolarization**

These results provide a new and different perspective concerning the long-held idea that the spatial dispersion of repolarization is of primary importance because it enhances reentry. Our results show that there is an opposite role, likely of equal importance. That is, normally the overall pattern of repolarization in the right atrium provides a fundamental protective mechanism to ensure synchronous atrial contractions by preventing reentrant repetitive activity following the most commonly occurring “premature” impulses, that is, those that initiate atrial excitation when the sinus node pacemaker rate abruptly increases. The major protective effect was related to the longest atrial action potentials occurring in the sinus node area with a continued decrease in action potential duration with increasing distance from the sinus node area. We found that premature impulses arising from the sinus node area (including the earliest propagated response that we could initiate in this region) extended throughout the right atrium without failure, which can be accounted for by the impulse continually entering tissue of equal or enhanced excitability. Thereby, the multiple regional differences in action potential duration have a major, albeit indirect, effect on the safety of propagation of premature impulses that conduct from the sinus node area to the A-V node.

**Interaction of Repolarization and Anisotropic Discontinuous Propagation in Causing Reentry**

In contrast to the protective role of the naturally occurring spatial pattern of atrial repolarization for premature impulses arising in the sinus node area, conduction block and reentry occurred frequently when the premature impulse originated at sites distal to the sinus node area. From these distal sites, early premature impulses blocked as propagation entered regions containing action potentials longer than those at the site of origin. In “Results,” an interpretation of the interactive roles of repolarization and anisotropic discontinuous propagation has been presented with each experiment and thus will not be repeated here. However, the major feature was that early premature impulses initiated multiple events within very small areas of specific structures, and the different events interacted to make reentry possible.

The details of the multiple events within small areas were amazingly complex compared with the picture we have been able to obtain from isochrone maps of atrial reentry. For example, the events leading to reentry were considerably more complicated than those thought to occur with the leading circle concept, which emphasizes the absence of an “anatomical obstacle.” We found all events to occur in discrete anatomical structures (prominent
atrial bundles), and muscle bundle junctions (localized discontinuities of axial resistance) were highly important in creating localized conduction delays in a reentrant circuit. For example, repolarization discontinuities occurred at muscle bundle junctions, and these sites were important in generating one-way block. The multiple events at localized sites interacted to produce different types of reentry at different macroscopic size scales (25 mm² to several cm²). In each case, however, neither repolarization inhomogeneities (leading circle concept) nor anisotropic discontinuous propagation was the only factor involved. Thus, reentry occurred as a result of a combined repolarization-anisotropic discontinuous propagation "mechanism."  

Our results provide a basis for a long known but poorly understood feature required of a premature impulse to produce reentry. Allessie et al30 originally emphasized that slight shifts in the position of the stimulus electrode will determine whether or not reentry occurs after a premature impulse. The anisotropic distribution of repolarization in some bundles accounted for this phenomenon for stimulus site changes over distances as small as 1 mm along an axis transverse to the longitudinal axis of the fibers. Our results also show that many sites where muscle bundles join one another have associated repolarization discontinuities. At these locations, shifts of the premature stimulus site within 200 µm accounted for initiating block in one direction while conduction continued in another direction, the requisite for reentry. Thus, the critical nature of the premature stimulus site was related to locations where the steepest repolarization gradients occurred. In turn, the steepest repolarization gradients were found within anisotropic bundles in the direction of high axial resistance (across rather than along the fibers) and at the junctions of two bundles (a localized increase in axial resistance). We conclude, therefore, that the critical effect of small shifts in the site of origin of premature impulses was due to spatial differences in cellular repolarization properties15 combined with anisotropic structural complexities.

Conclusion: An Electrophysiological Model of the Right Atrium

The idea of an atrial specialized conduction system,22-23 introduced in the early 1960s,22 is still the most widely used framework for the electrophysiological organization of the atrium. The results presented here and in the accompanying paper15 provide a new and different perspective concerning the question of a model of the atrium that includes multiple regional differences in repolarization15 and complex multidimensional propagation events at a microscopic8-10 and macroscopic15 size scale. At a minimum level of complexity, our results suggest the following:

1) Depolarization. Regional and directional differences in conduction velocity and Vmax are determined by interactions between a) the kinetics of the depolarizing currents (primarily sodium current) and b) the passive anisotropic properties of atrial bundles at a microscopic level.6-10 Both of these factors regulate the safety of propagating impulses8,9; the kinetics of the depolarizing current are the primary determinant, but the kinetics of the ionic channels are markedly influenced from site to site by differences in electrical load (differences in downstream membrane capacitance to be discharged8) due to anisotropic structural complexities.7,9

2) Repolarization. There are many regional differences in the cellular properties of the atrium that result in associated differences in action potential shape and duration, and the repolarization differences are linked to multiple regional differences in the contractile properties of atrial myocytes. The multiple regional differences are organized spatially with the longest action potentials in the sinus node area, where rate and rhythm changes usually originate, and with an associated decrease in the duration of atrial action potentials with increasing distance from the sinus node area.

3) Electrophysiological consequences. The functional effects of the overall spatial pattern of repolarization are quite different depending on the site of origin of the most common intervention, a premature impulse. The major functional effect is to enhance conduction of early impulses entering atrial muscle from the sinus node following responses of the normal pacemaker to interventions that require abrupt changes in rate and rhythm. Conversely, when the cycle length decreases abruptly due to impulses that originate abnormally at sites distal to the sinus node area, there is a great propensity for conduction disturbances that lead to reentry. The propagation events that lead to reentry, however, involve a combined "mechanism" due to a) the spatial pattern of repolarization and b) discontinuities of anisotropic propagation at a microscopic9 and macroscopic15 size scale.

This scheme has the utility of providing a simplifying feature that should be helpful in developing more realistic electrophysiological models of the atrium: complex interactions that determine propagation (depolarization) are considered separate from the complex interactions that determine the spatial differences in the repolarization shape of the action potential. Depolarization interactions primarily involve the net sarcolemmal membrane current and anisotropic structural complexities8,9-10 while repolarization interactions primarily involve passive and active ionic transport mechanisms9,15 that regulate contractility.15

References


**KEY WORDS** • repolarization inhomogeneities • anisotropic discontinuous propagation • repolarization discontinuities • anisotropic repolarization patterns • atrial reentry • concealed reentry

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*Sparse et al A Repolarization-Anisotropic Propagation Mechanism 1631*
Interaction of inhomogeneities of repolarization with anisotropic propagation in dog atria. A mechanism for both preventing and initiating reentry.

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