Ciaccio, Edward J. Premature excitation and onset of reentrant ventricular tachycardia. *Am J Physiol Heart Circ Physiol* 283: H1703–H1712, 2002. First published May 30, 2002; 10.1152/ajpheart.00310.2002.—It was hypothesized that quantitative sinus rhythm electrogram measurements could be used to predict conduction events that result from premature stimulation and reentrant ventricular tachycardia inducibility. Sinus rhythm activation and electrogram-duration maps were constructed from bipolar electrograms acquired at 196–312 sites in the epicardial border zone of 43 canine hearts (25 with and 18 without reentrant ventricular tachycardia inducible by premature stimulation). From these maps, lines of electrical discontinuity, where blocks would occur during premature excitation, were estimated. The mean error in distance between the estimated and actual block lines of premature excitation was 0.97 ± 0.49 cm. Based on the quantitative characteristics of the activation and electrogram-duration maps and the longest block line that formed during premature excitation, it was possible to predict whether reentry would occur (sensitivity, 94.7%; specificity, 79.6%). In reentry experiments, the breakthrough-point location along the unidirectional arc of the block that initiated reentry was also predictable (mean error, 0.79 ± 0.19 cm). Sinus rhythm measurements are useful to predict conduction events that result from premature stimulation and reentry inducibility.

**Activation; reentry; sinus rhythm**

The precise relationship between the pattern of electrical activation that occurs during sinus rhythm vs. the pattern of activation during premature excitation in the infarct border zone is incompletely understood (14). Properties of nonuniform anisotropic conduction can account for some of the observed phenomena that lead to induction of reentrant ventricular tachycardia following premature stimulation; for example, the tendency of the long axis of the central common pathway, or isthmus, of figure-8 reentrant circuits to often align approximately in parallel to muscle fibers (14). However, in a canine infarct-model study in which reentry in the epicardial border zone was induced by programmed stimulation, the long axis of the isthmus was not always aligned with muscle-fiber orientation and was actually oriented transversely in ~15% of experiments (2). It is likely, therefore, that other factors besides anisotropy are important in governing the formation of functional arcs of conduction block at the onset of reentrant ventricular tachycardia.

Recent work suggests that electrical discontinuities present in the infarct border zone may be of great importance in determining the pattern of activation during reentry. For example, it was determined in a canine reentry-model study that the location where the isthmus of the reentrant circuit formed was uniquely marked by disruption of the gap junctional distribution that extended the full thickness of the border zone layer (7). In the study, it was proposed that the arcs of conduction block that bound the reentry isthmus coincide with edges of the area of full-thickness gap junctional disruption at segments aligned approximately in parallel with muscle fibers (7). The combined effect of an electrical discontinuity in gap junctional properties and the transverse orientation of any oncoming wave front at these locations was anticipated to block electrical conduction during reentry (7).

In another study using the same canine infarct model, it was shown that areas of the border zone with rapid conduction during reentrant ventricular tachycardia tend to have a short sinus rhythm electrogram duration (3), which is therefore likely to be reflective of the degree of abnormality of the substrate. Furthermore, boundaries between areas with large differences in electrogram duration during sinus rhythm, where discontinuities in electrical properties were anticipated to occur, were coincident with the positions of arcs of functional conduction block present during reentrant ventricular tachycardia (3). Hence, areas of rapid activation and areas of electrical discontinuity during sinus rhythm (which can be detected and localized by measurement of sinus rhythm electrograms) are presumably important factors governing the setup, initiation, and localization of reentrant circuits in the infarct border zone. It was hypothesized for the present study that areas of the border zone with less abnormality and areas of electrical discontinuity as detected and localized by sinus rhythm electrogram measurement could be used to predict the electrical activation pat-
tern during premature excitation and reentry inducibility. As in previous studies, sinus rhythm electrograms were used for measurement, because in these signals it is relatively simple to quantify the interval of local activity and the starting points of isoelectric intervals compared with signals obtained during ventricular pacing or tachycardia.

METHODS

These procedures were used to extract data during canine postinfarction experiments and to measure characteristics of the activation pattern in the infarct border zone during sinus rhythm, premature excitation, and ventricular tachycardia.

Data collection and mapping. A myocardial infarct was created by ligation of the left anterior descending coronary artery (LAD) in situ in experiments on 43 canine hearts. Four or five days later, canines were anesthetized with pentobarbital sodium (30 mg/kg), the chest was opened, and positive-pressure ventilation was applied. A bipolar electrode multianarray was then sutured onto the anterior surface of the canine heart for recording and stimulation. Bipolar electrograms were recorded from 196 to 312 sites in the epicardial border zone of the anterior left ventricle at an average spatial resolution of 4–5 mm and were amplified 100–1,000× by a computer software auto-gaining procedure. The signal-pass band applied before digitization of the signals had high- and low-pass corner frequencies of 2 and 500 Hz, respectively. Attempts to induce reentry were made in these hearts by premature electrical stimulation (4). Stimulating electrodes embedded in the recording multielectrode arrays enabled pacing from constant locations at the LAD and lateral, base, and center regions of the anterior epicardial surface. Programmed stimulation proceeded using 10 S1 stimuli followed by a single S2 premature stimulus. The premature coupling intervals were successively shortened on subsequent stimulus trains until reentry was induced or block occurred. For consistency between experiments, the electrode multianarray was placed on the heart with the same edge always positioned along the LAD margin. For simplicity, the region of the ventricle where recording sites in the multianarray were located was considered to be coincident to a first approximation with the entire infarct border zone.

For the present study to investigate the relationship between sinus rhythm electrogram characteristics and the activation pattern during premature excitation, 25 experiments in which long runs (>10 beats) of monomorphic reentrant ventricular tachycardia could be repetitively induced by premature stimulation and 18 experiments lacking reentry inducibility were used retrospectively. These data were used previously to study the relationship between sinus rhythm electrogram characteristics and the activation pattern during reentrant ventricular tachycardia (3). For simplicity, experiments in which only short runs (<10 beats) of tachycardia were inducible, which would be more complex to characterize quantitatively, were not included in this study.

Activation maps of sinus rhythm, pacing, and reentry (when it occurred) were made by automatically marking activation times of electrogram signals at the point of the sharpest slope along the largest peak deflection and printing the times for all sites on a computerized map grid (4). On visual inspection of the resulting activation map, where context with respect to neighboring recording sites suggested that the activation time at a particular site lacked continuity, the electrogram was marked at the sharpest slope of any electrogram deflection (when present) that more closely coincided with the activation times of neighboring sites. This set of rules was applied to ensure consistency in the activation-marking procedure. The locations of arcs of conduction block were drawn on the map grid between sites in which activation differed by >40 ms and where wave fronts on opposite sides of the arcs moved in different directions according to the maps (4). Arcs were drawn using a spline-interpolation function to 0.1 mm precision, which was beyond the resolution of the electrode multianarray but consistent from one activation map to the next. With the use of the same computerized electrode grids that were used for activation mapping, sinus rhythm electrogram duration maps (i.e., activation duration) were then constructed as described previously (3). The sinus rhythm electrogram duration was measured for each recorded signal during a single arbitrary cardiac cycle at the beginning of the experiment before any pacing of the heart. It is defined as the time interval from beginning to end of the contiguous series of electrogram deflections that includes the time of local activation (3). Contiguous deflections are those in which there is no isoelectric segment >5 ms in length between successive deflections. The electrogram duration was used as a distinct measure of the electrical activity in the border zone.

Localization of electrical discontinuity lines. From the sinus rhythm activation maps, the locations and shapes of lines of electrical discontinuity (where arcs of conduction block would be expected to form during premature excitation) were predicted. Points where the difference in activation time between adjacent sites (vertical, horizontal, or diagonal directions) was >10 ms were delimited on the computerized mapping grid by closed circles (see Fig. 1A). The 10-ms threshold was selected based on the observation made during initial mapping procedures that long, continuous arcs of conduction-block formation during premature excitation tended to occur along areas with differences in sinus rhythm activation time on the order of 10 ms between adjacent sites. Because the precision of activation marking in our studies was ~1–2 ms (4), the built-in redundancy (i.e., measurement of the difference at all adjacent sites in the vertical, horizontal, or diagonal directions) helped ensure detection of pertinent areas. Areas where the resulting points were <1 cm apart on the grid were considered to be contiguous, and spline interpolation was used to form a curved line from the points as described elsewhere (2). This curved line was used as an estimate of the location of the longest (primary) arc of conduction block expected to form during premature excitation. For simplicity, statistics were only computed for the longest arc of conduction block expected to form during premature excitation.

Once the estimated location of the longest block line that was expected to form during premature excitation was established, parameters were quantified using the computerized electrode grid for measurements. The actual locations of arcs of conduction block formation during premature excitation were determined from activation maps (actual arcs of block separated by <1 cm were considered contiguous for measurement purposes). The longest actual vs. estimated arcs of block of premature excitation were then compared by computing the surface area enclosed by the outer boundaries and dividing by the actual arc length to normalize the measurement (Fig. 1F; surface area between arcs denoted by grid region). The symmetry of the longest actual arc of conduction block to form during premature excitation with respect to stimulus site position was also determined mathematically. The distances $d_1$ and $d_2$ from the stimulus site to either
Fig. 1. Activation and electrogram duration maps for an experiment in which long runs of monomorphic reentry were inducible by premature stimulation from the base. Sinus rhythm (SR) cycle length was 414 ms. Ventricular tachycardia was repetitively inducible by pacing the heart using 10 S1 stimuli with a coupling interval of 300 ms and 1 premature stimulus 145 ms later (see RESULTS). A: sinus rhythm activation map. ● Locations between adjacent sites where activation time difference was ≥10 ms; blue lines, spline interpolations of predicted locations of conduction block during premature excitation. B: sinus rhythm electrogram duration map for the cycle shown in A; scale relates gray color and electrogram duration. Center of blue arrow indicates estimated breakthrough point (area with shortest electrogram duration along the longest block line anticipated to occur during premature excitation). C: when paced at a coupling interval of 350 ms, conduction was most rapid in the direction denoted by arrows. LAD, left anterior descending artery; LAT, lateral. D: during S1 pacing from the base, the longest estimated and actual arcs of block partially coincided. E: during premature excitation from the base, the longest estimated and actual arcs of block mostly overlapped, and the estimated vs. actual breakthrough locations for initiation of reentry were also in close correspondence (center of blue and black arrows, respectively). F: quantitative methods used for comparative calculations: outer bounds of the surface area between estimated and actual arcs of block (grid region), distance between estimated and actual breakthrough points (short line between ●, enlarged in inset), and symmetry of the ends of the arcs of block to the stimulus-site location (gray lines). G: block lines that bound the isthmus of the reentrant circuit partially align with those expected to form during premature excitation. H: short actual arc of block that formed adjacent to the stimulus site approximately overlapped a short estimated block line from A (blue line), and slow conduction occurred at the location of the other short estimated block line. I: after premature stimulation from the center, the impulse was interrupted in coincidence with a large segment of the longest estimated block line of premature excitation. Red symbols indicate pacing.
endpoint of the actual block line were measured as shown in Fig. 1B, and symmetry was then computed as

\[
symmetry = \frac{(d_1 - d_2)(d_1 + d_2)}{d_1 + d_2} \times 100\%
\]

From this equation, if \(d_1 = d_2\), the ends of the arc of block would be perfectly symmetric with respect to stimulus-site position; i.e., symmetry would be 100%. The symmetry would be \(<100\%\) and positive when \(d_1 > d_2\) and \(> -100\%\) and negative when \(d_2 > d_1\). The absolute value of symmetry for each experiment was then used to compute the mean symmetry for the 25 reentry experiments. Also, the location along the predicted premature arc of conduction block where electrogram duration on either side had the shortest mean value was estimated to be the breakthrough point that would result in initiation of reentry. It was hypothesized for this measurement that at the point of lowest mean electrogram duration across the arc, the characteristics of electrical conduction would be closest to normal myocardial tissue and therefore less subject to conduction block compared with other areas where conduction was anticipated to be more abnormal. For all reentry experiments, the \(x\)-\(y\) (Euclidean) distances between actual and estimated breakthrough points on the computerized grid were then tabulated. For these measurements, the standard error was calculated to show the variation from the mean.

Several additional measurements were made to determine whether reentry inducibility could be predicted based on the activation characteristics of premature excitation. Mean parameters of sinus rhythm activity associated with the estimated line of block, the breakthrough point, and the entire border zone were determined for each experiment as described in Table 1, and the measurements were then pooled from all experiments for statistical purposes. Scatter plots were constructed using the parameters described in Table 1, and optimal linear thresholds along one and two dimensions were calculated using a linear discriminant function to predict whether reentry would be inducible. Scatter plots with predictive accuracy >80% are discussed in RESULTS. The sensitivity (proportion of experiments with reentry inducibility that were correctly identified) and specificity (proportion of experiments without inducible reentry that were correctly identified) were also computed. Significant linear correlation between parameters \((P < 0.001)\) was then determined using a commercial computer program (SigmaStat, Jandel Scientific).

### RESULTS

In Fig. 1, electrogram maps are shown for an experiment in which reentry was inducible from the basal margin of the grid. In this experiment, the sinus rhythm cycle length was 414 ms, and ventricular tachycardia with a cycle length of 176 ms was repetitively inducible by pacing the heart using 10 S1 stimuli with a coupling interval of 300 ms and a single premature stimulus 145 ms later. The sinus rhythm activation map is shown in Fig. 1A. The locations between adjacent sites where the activation time difference was \(>10\) ms are delimited (closed circles superimposed on the computerized mapping grid). Based on the positions of the points, curved lines were drawn by spline interpolation, which were the predicted locations of conduction block during premature excitation (Fig. 1A, blue lines). The sinus rhythm electrogram-duration map for the cycle shown in Fig. 1A is shown in Fig. 1B with the gray scale denoting the relationship between gray color and the electrogram duration (in ms). The estimated breakthrough point, located at the area with the shortest electrogram duration along the longest block line anticipated to occur during premature excitation, is denoted by the center of the blue arrow (Fig. 1B). Smaller differences in activation time tended to occur across the estimated breakthrough point where electrogram duration was shortest (Figs. 1, A and B). When paced from the center of the epicardial border zone at a coupling interval of 350 ms (Fig. 1C), conduction was most rapid in the direction denoted by arrows. Based on anisotropic considerations in which the activation wave front proceeds most rapidly in parallel with the long axis of normal myocardial cells (14), the arrows therefore approximate muscle-fiber orientation in the border zone (i.e., coursing from LAD to apex). Because the multielectrode grid was positioned with the same side overlapping the LAD of the heart in all experiments (see METHODS), muscle-fiber orientation was approximately the same for all maps constructed for this study.

The effect of rapid programmed electrical stimulation was then assessed. During S1 pacing from the base (Fig. 1D), the longest estimated and actual arcs of block partially coincided. During premature excitation from the base (Fig. 1E), the longest estimated and actual arcs of conduction block mostly overlapped, and the estimated vs. actual breakthrough locations for initiation of reentry were also in close correspondence (center of blue and black arrows, respectively). After premature stimulation, conduction proceeded rapidly from the stimulus site at the base to quickly impinge on the line of discontinuity as a cohesive, approximately linear wave front. The direction of the oncoming wave front to the long line of electrical discontinuity was approximately normal; i.e., activation all along the top, horizontal portion of the line occurred approx-

### Table 1. Quantitative parameters of premature excitation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Association</th>
<th>Description</th>
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<tbody>
<tr>
<td>LB₁</td>
<td>PE long line of block</td>
<td>Actual length</td>
</tr>
<tr>
<td>LB₂</td>
<td>PE long line of block</td>
<td>SR activation time difference across its length</td>
</tr>
<tr>
<td>BZ</td>
<td>Entire border zone</td>
<td>SR activation time difference between adjacent sites</td>
</tr>
<tr>
<td>BZED</td>
<td>Entire border zone</td>
<td>SR electrogram duration</td>
</tr>
<tr>
<td>BP</td>
<td>PE breakthrough point</td>
<td>Activation time difference across breakthrough point during PE</td>
</tr>
<tr>
<td>BF₁</td>
<td>PE breakthrough point</td>
<td>Time from S2 to arrival at breakthrough point during PE</td>
</tr>
</tbody>
</table>

LB, line of block; BZ, infarct border zone; BP, breakthrough point; PE, premature excitation cycle; SR, sinus rhythm cycle. See text for further descriptions of variables.

AJP-Heart Circ Physiol • VOL 283 • OCTOBER 2002 • www.ajpheart.org
imately at time 40 ms and activation along most of the bottom, vertical portion of the line occurred approximately at time 80 ms (Fig. 1E). Illustrated in Fig. 1F are some of the quantitative methods used for comparative calculations: the outer bounds of the surface area between estimated and actual arcs of block (grid region), the distance between estimated and actual breakthrough points (short line between closed circles symbols, enlarged in inset), and the symmetry of the ends of the arcs of block to the stimulus-site location (gray lines). It can be observed from the reentry-activation map that the block lines that bound the isthmus of the reentrant circuit partially align with those expected to form during premature excitation in this experiment (Fig. 1G). After premature stimulation from the lateral side (Fig. 1H), the short actual arc of block that formed adjacent to the stimulus site approximately overlapped a short estimated block line from Fig. 1A (shown in blue), and slow conduction occurred at the location of the other short estimated block line (note 20–40-ms isochrones, which are bunched on the map of Fig. 1H near the stimulus site). After premature stimulation from the center, the impulse was interrupted in coincidence with a large segment of the longest estimated block line of premature excitation (Fig. 1I). However, near the basal margin, arrival of the activation wave front was delayed, which resulted in coalescence of individual wave fronts there rather than reentry. After premature stimulation from the lateral side, the short actual arc of block that formed adjacent to the stimulus site approximately overlapped a short estimated block line from Fig. 1A (shown in blue), and slow conduction occurred at the location of the other short estimated block line (note 20–40-ms isochrones, which are bunched on the map of Fig. 1H near the stimulus site). After premature stimulation from the center, the impulse was interrupted in coincidence with a large segment of the longest estimated block line of premature excitation (Fig. 1I). However, near the basal margin, arrival of the activation wave front was delayed, which resulted in coalescence of individual wave fronts there rather than reentry.
than block of a single propagating wave front. As in Fig. 1, in other experiments where secondary lines of electrical discontinuity were detected, block did not actually occur there if the primary arc of block shielded the secondary arc from impact of the activating wave front in the normal direction.

In Fig. 2, the results of sinus rhythm electrogram measurements for the 25 experiments with inducible reentry are shown. The estimated vs. actual longest block lines to form during a premature stimulation cycle that resulted in initiation of reentry are shown, respectively, by blue and black curved lines. The coupling interval of this premature stimulation cycle ranged from 135 ms (Fig. 2Q) to 220 ms (Fig. 2E). During any given experiment, the coupling interval of premature stimulation that resulted in reentry onset changed by no more than 10–20 ms between episodes of induction, and reentry could only be induced by stimulation at the site location, which is denoted by the red pacing symbol for each of the experiments of Fig. 2. Premature excitation resulted in tachycardia when the stimulation site was located at the LAD margin in 13 experiments, at the basal margin in 6 experiments, at center in 5 experiments, and at the lateral margin in 1 experiment. The LAD and basal stimulus-site locations appear in relatively close proximity in the two-dimensional activation maps of Fig. 2. To distinguish them, for maps constructed using the 196-electrode array (Fig. 2, A–J), examples of pacing locations at the basal and LAD margins are denoted in B and D, respectively. For maps that were constructed using the 312-electrode array (Fig. 2, K–Y), examples of pacing locations at the basal and LAD margins are denoted in K and L, respectively. For all reentry experiments, the site at which a premature stimulus resulted in reentry was in an area where sinus rhythm activation was rapid.

The estimated and actual breakthrough points (centers of blue and black arrows, respectively) are also shown in Fig. 2. In each case, the difference in sinus rhythm activation time was relatively short at the estimated breakthrough point (not shown). The details for the experiment of Fig. 1 are depicted in Fig. 2F. In two experiments (Fig. 2, K and L), two reentry morphologies were inducible via premature stimulation, and the location of the second isthmus is shown in red. In one experiment (Fig. 2Y), breakthrough occurred across two arcs of block, and dual isthmuses were present during the same reentry morphology. In each part of Fig. 2, there is often a close correspondence between the estimated and actual arcs of conduction block and the breakthrough points. For each experiment, there tended to be a delay of ~20–60 ms between arrival of the wave front on the opposite side of the unidirectional block line and onset of reentry, which suggests that conduction velocity tended to slow dramatically at this point (~0.1–0.2 m/s). From the experiments of Fig. 2, the absolute mean degree of symmetry from the location of the site at which a premature stimulus resulted in reentry to the ends of the arcs of block generated by that stimulus was 82 ± 3%. The mean difference in location between the longest estimated vs. actual arc of block to form during premature excitation was 0.97 ± 0.49 cm, and the mean distance between the estimated and actual breakthrough points was 0.79 ± 0.19 cm. The longest estimated and actual arcs of conduction block had mean lengths of 6.53 ± 0.51 and 6.14 ± 0.53 cm, respectively, for reentry experiments, and 2.21 ± 0.34 and 2.31 ± 0.34 cm.
respectively, for experiments in which reentry was not inducible. Therefore, in experiments with reentry inducibility, the mean length of the long arc of block formation during premature excitation was approximately threefold that of experiments lacking inducibility. For comparative purposes, the arcs of conduction block that formed during reentry are also shown in Fig. 2 and are denoted as dotted gray lines with a gray arrow indicating activation direction during the diastolic interval of reentry.

Scatter plots of the electrogram parameters described in Table 1 that could be used for classification (with an accuracy >80%) of the 43 experiments into those with vs. those lacking reentry inducibility are shown in Fig. 3. A plot of the mean difference in sinus rhythm activation time across the location of the estimated arc of block vs. the length of that arc was useful to predict reentry inducibility with an accuracy of 95.3% (Fig. 3A, solid line). This scatter plot also indicates that reentry induction was most likely to occur when the estimated arc length of premature excitation was relatively long (>3.5 cm, dotted line), and arc length alone could be used to predict inducibility of reentry (accuracy, 86.0%). A plot of mean difference in sinus rhythm activation vs. electrogram duration throughout the border zone also was predictive of reentry inducibility (Fig. 3B; accuracy, 81.4%). The difference in activation time from the proximal to distal sides of the actual breakthrough point vs. the time from premature stimulus to arrival of the wave front at the proximal side of the actual breakthrough point was useful to predict reentry inducibility with an accuracy of 88.4% (Fig. 3C, solid line); furthermore, the difference in activation time from the proximal to distal sides of the actual breakthrough point with a threshold of 68 ms was also predictive of reentry (accuracy, 81.4%; dotted line). With the use of the two-dimensional linear discriminant functions shown in Fig. 3, the mean sensitivity of these parameters for classification of experiments into those in which reentry would be inducible vs. those lacking reentry was 94.7%, and the mean specificity was 79.6%.

In this series of experiments, there was no significant linear correlation of the electrogram parameters to the sinus rhythm-cycle length or to the premature stimulation-coupling interval that resulted in reentry induction. Linear regression relationships that were significant ($P < 0.001$) are shown in Table 2 and can be stated as follows: when the mean site-to-site difference in sinus rhythm activation time throughout the border zone is large, the length of the arc of conduction block estimated to form during premature excitation tends to be long (Table 2, Eq. 1), and there will be a relatively large mean difference in sinus rhythm activation time across the arc location (Table 2, Eq. 2). When this arc of block is long, the time interval for the activation wave front to propagate from the premature stimulation site to the breakthrough point is prolonged (Table 2, Eq. 3), which in turn is related to an increased difference in activation time on opposing sides of the breakthrough point during the premature excitation cycle (Table 2, Eq. 4). A long estimated arc of conduction block and a large difference in activation time on opposing sides of the predicted breakthrough point during the premature excitation cycle are highly predictive that reentry will actually occur (Fig. 3, A and C). In summary, the equations of Table 2 state that induction of reentry is directly related to the status of the border zone during sinus rhythm (as can be determined by quantification of electrogram shape) and to the resulting pattern of activation during premature excitation. When there is a high degree of electrical abnormality throughout the infarct border zone as measured by a large mean difference in sinus rhythm activation time from site to site, the probability is increased that block will occur along a long continuous portion of this tissue when the infarct border zone is excited prematurely. The resulting long arc of conduction block delays the arrival time of the activation wave front to the opposite side of the arc. If this delay is sufficiently long so that there is recovery of excitability in the initially activated region, breakthrough across the arc of block will likely occur to initiate reentry.

**DISCUSSION**

In this study, it was shown that sinus rhythm measurements can be useful to predict functional lines of conduction block that form during premature excitation. Furthermore, from these measurements it is possible to predict whether reentry will occur and the location of the breakthrough point in the case of inducible reentry. These findings are now discussed in detail.

**Detection of electrical discontinuity from sinus rhythm measurement.** In the two-dimensional canine model used for this study application, arcs of conduction block tended to be functional; i.e., the occurrence depended on transient electrical properties including the time for recovery of excitability during a particular activation cycle, the wave-front orientation, and the quantity of current available for activation (4, 14). However, the actual locations where functional arcs of block form during both premature excitation and reentry tended to be constrained to localized regions of the infarct border zone in the canine hearts (4) and could also possess similar properties of constancy in patients (11), although the exact correlation between reentry in canine and human hearts is presently uncertain due in part to differences in infarct ages. In a previous study of the relationship between sinus rhythm activity and

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**Table 2. Significant regression relationships of premature excitation parameters**

<table>
<thead>
<tr>
<th>Eq. No.</th>
<th>Regression Equation</th>
<th>$r^2$</th>
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<tbody>
<tr>
<td>1</td>
<td>$LB_i = 1.1BZ_w + 0.78$</td>
<td>0.26</td>
</tr>
<tr>
<td>2</td>
<td>$LB_d = 7.7BZ_w - 40$</td>
<td>0.38</td>
</tr>
<tr>
<td>3</td>
<td>$BP_{sd} = 5.4LB_i + 91$</td>
<td>0.58</td>
</tr>
<tr>
<td>4</td>
<td>$BP_d = 0.66BP_{sd} - 1.9$</td>
<td>0.49</td>
</tr>
</tbody>
</table>

See text and Table 1 for descriptions of variables.
reentrant circuits in the canine heart, it was shown that the location and orientation of the isthmus long axis and its exit position are identifiable as a unique area with a large and relatively uniform gradient in sinus rhythm activation time (3). Because a segment of the longest block line that formed during premature excitation tended to align perpendicular to the exit of the reentrant circuit isthmus (see Figs. 1 and 2), that segment was in consonance with the location and direction where the aforementioned gradient of sinus rhythm activation was large. Where the electrical discontinuity is large, a markedly increased effective axial resistivity would be expected to occur (13). Areas with large effective axial resistivity are most vulnerable to conduction block when transient electrical properties satisfy certain conditions (13). Hence, boundary lines that separate points with large differences in sinus rhythm activation time are likely to be coincident with lines of electrical discontinuity where the magnitude of the effective axial resistivity is large. This suggests that electrogram measurements can be used to detect areas of electrical discontinuity in the border-zone substrate, which relates to the pattern of activation during premature excitation and reentrant ventricular tachycardia. This could potentially be very useful to characterize the state of the heart at the border zone without the need for invasive histological study.

Correlation of electrical discontinuities to full-thickness gap junctional disruption. The estimated locations of arcs of conduction block that formed during premature excitation tended to be concave in shape with respect to stimulus-site position and in a few experiments formed an approximately closed contour (Fig. 2, C, D, N, S, and X). These demarcations may represent edges of the region of full-thickness gap junctional dissociation, which have been shown to coincide with the boundaries of the isthmus of the reentrant circuit (7). Along such edges where the magnitude of electrical discontinuity is great (i.e., where there is an abrupt spatial transition), the magnitude of the effective axial resistivity is also large (13). Hence, formation of any block line there during premature excitation from a particular stimulus site position would be anticipated to be less susceptible to transient electrical properties and therefore highly reproducible during repetitive episodes as was observed. However, whenever two lines of electrical discontinuity were in proximity, block of the activation wave front along one line during the premature excitation cycle, followed by bifurcation of the wave front and propagation around the arc tended to prevent block from occurring at the secondary line of discontinuity. This was likely due to the combined effects of 1) the delay in arrival at the secondary location with a resulting increased time for recovery of excitability there, along with 2) coalescence of distinct wave fronts arriving there from several directions rather than arrival of a coherent oncoming wave front in a direction normal to the discontinuity.

Although regions of full-thickness gap junctional disruption tend to coincide with the location where the isthmus of the reentrant circuit forms (7), other canine studies provide evidence that the magnitude of the transition across any and all lines of electrical discontinuity and their proximity are also important determinants of isthmus shape. For example, it has been observed elsewhere (3) that during an experiment in which only short runs of monomorphic tachycardia were inducible, arcs of conduction block bounding the isthmus of the reentry circuit shifted from one discontinuity to the other, which caused the isthmus to narrow and resulted in termination of tachycardia within a few cardiac cycles. In another canine infarct study of the dynamics of long runs of reentrant ventricular tachycardia (1), short segments of the arcs of block bounding the reentry isthmus were observed to undergo gradual shifts in location from one cardiac cycle to the next; at these segments, any electrical discontinuity would be anticipated to be weaker in magnitude or nonexistent, so that minute changes in transient electrical properties could result in moderate changes in block-line location.

Position of stimulus site that initiates reentry. In Fig. 1A, it can be observed that activation of the border zone proceeded inward from all margins (LAD, base, apex, and lateral) but was most rapid from the base. This may suggest that the underlying substrate at the rapid location was potentially less abnormal than other areas of the border zone. Because healthy epicardial tissue is less refractory to premature stimulation (14), a premature impulse that originates from the basal margin for the experiment of Fig. 1 would be expected to most rapidly propagate inward at the infarct border zone as a large, cohesive wave front compared with stimulus sites positioned elsewhere in the border zone, which is essentially what was observed (compare Fig. 1, E, H, and I). For reentry induction, it is essential that rapid and approximately simultaneous arrival of the premature impulse at all points along one side of a long line of electrical discontinuity occur (i.e., the oncoming wave front is propagating approximately normal to the line) so that nearly simultaneous conduction block along the entire line will result. This event would then be followed by wave front bifurcation with the distinct wave fronts propagating around the block line so formed. The tissues on the opposite side of the block line would then activate, and if it were of sufficient length so that a satisfactory delay were introduced, breakthrough would be expected to occur at a point where the effective axial resistivity was lowest (13). Thus low effective axial resistivity is probably associated with the short mean sinus rhythm electrogram duration that was observed to occur on either side of the breakthrough point leading to reentry. Induction of reentry, therefore, would be anticipated when the premature stimulation site was located within a region with relatively rapid impulse conduction and positioned so as to be approximately equidistant (symmetric) with respect to the ends of the longest line of electrical discontinuity. The outcome in this case would be a relatively rapid arrival of the wave front along all points on one side of the discontinuity line. As expected, in the series of reentry experiments of this
study, the premature stimulation-site location was coincident with an area of rapid sinus rhythm activation (e.g., Fig. 1) and approximately symmetric with respect to the ends of the longest line of electrical discontinuity (Figs. 1 and 2). Elsewhere in the border zone where propagation of the activation wave front during sinus rhythm was slow and/or discontinuous, any premature impulse that originated from those regions propagated less rapidly and cohesively so as to preclude a nearly synchronous arrival normal to any long line of electrical discontinuity. The result in this latter case was wave-front termination and sinus capture as when pacing from the lateral and center regions of border zone for the experiment shown in Fig. 1, H and I.

**Combined factors leading to reentry induction.** According to the results of this study, a relatively long, continuous unidirectional arc of conduction block must form as the result of premature stimulation for initiation of reentry. After formation of the arc, the wave front then bifurcates and proceeds around it, traveling more slowly in the direction transverse to muscle fibers (14, 6); 2) across any highly fractionated regions where there is dispersal of cells and zig-zag conduction (6); 3) at lines of electrical discontinuity where the effective axial resistivity is high (13); and 4) within the area where the isthmus of the reentrant circuit forms, because gap junctional interconnections have been disrupted and tend to conduct slowly when excited prematurely (7). Increased magnitude of any of these factors acts to impede conduction and therefore to delay the arrival of the wave front on the trailing side of the unidirectional arc at the point where it will potentially reenter the previously excited area. If the delay in its arrival is insufficient for recovery of excitability on the leading side of the unidirectional arc, reentry will not occur. Therefore, for reentry, the isthmus long axis would most commonly be expected to align in parallel with muscle-fiber direction with the long block line forming during premature excitation aligning approximately perpendicular to it and hence transverse to the muscle fibers. This would tend to maximize slow propagation of the premature wave front, because it would then proceed primarily in the direction transverse to fiber orientation before its arrival at the isthmus formation area (point 1 above; see Fig. 2). Also, presence of a greater density, surface area, and/or increased severity of abnormal cells (up to some limiting value, after which conduction proceeds too slowly or not at all) would be expected to increase the likelihood of reentry by increasing points 2–4, which would also slow propagation of the premature wave front. If points 2–4 were sufficiently great to provide the necessary delay for breakthrough at the end of the premature excitation cycle, the reentry isthmus long axis could conceivably be aligned nearly transverse to muscle fibers [i.e., negligible contribution of point 1, nonuniform anisotropic conduction (14, 6), for reentry induction] as has been observed in ~15% of canine infarct experiments with monomorphic reentrant circuits (2). These same points 1–4 also act to slow conduction when the premature stimulation site is within the area where the isthmus actually forms (center stimulation as in Fig. 2, A, E, J, R, and U), except that the delay due to point 4 occurs immediately after application of the premature stimulus pulse rather than at the end of the premature excitation cycle.

When the activating wave front arrives on the opposite side of the unidirectional arc, breakthrough will occur at the point where recovery of excitability is first achieved, which will most likely be the place where the substrate properties are closest to normal epicardial tissue (14). Normal epicardial tissue is characterized by relatively rapid impulse conduction (~1 m/s), and the electrogram deflection is narrow compared with abnormal epicardium (14). Hence, as anticipated, the point of shortest electrogram duration, which is on the order of 15–25 ms in this study, was indicative of the breakthrough point as can be observed in Fig. 1B. As described elsewhere (2), more rapid conduction during tachycardia tended to occur at all of the patchwork areas having relatively short sinus rhythm-electrogram duration, which supports the hypothesis that these areas activate more normally than do other areas of the infarct border zone. Breakthrough across the arc of unidirectional block was often significantly delayed on arrival of the activation wave front (by ~20–60 ms), which suggests that very slow conduction occurred as the wave front impinged on the block line on an order that would be below the spatial resolution of the mapping system used for data acquisition (4- to 5-mm distance between recording sites). Other investigators (9) have observed ultraslow conduction in myocardial tissue (conduction velocity of 1–2 cm/s), which could account for the substantial delay that was observed to occur between arrival of the wave front on the opposite side of the unidirectional block and onset of reentry.

Although the sinus rhythm electrogram duration tended to be short within the area where the isthmus of the reentrant circuit formed (Fig. 1B), conduction there tended to be relatively slow during premature excitation (Fig. 1E), which was paradoxical to the behavior of other areas of the border zone just described. However, two unique tissue properties at this area of the border zone likely influence electrogram shape. First, the surviving tissue tends to be thinnest at the region where the isthmus forms (14, 10), so that little or no asynchronous activation of underlying tissue would be anticipated to occur that could act to expand the electrogram deflection. Second, although disruption of gap junctional interconnections is prevalent throughout the area where the isthmus forms, this disruption tends to be relatively uniform from cell to cell (7). Therefore, the properties of electrical interconnection of the epicardial substrate in this region of the border zone are relatively constant, so that presence of conduction inhomogeneities that could also act to expand the electrogram deflection would be expected to be negligible.

**Clinical correlates.** Although clinical ventricular tachycardias can originate from intramural reentry and focal mechanisms (8), both contact (12) and noncontact (11) studies suggest that substantial numbers of tachycardias are caused by reentrant circuits that
are mostly or entirely constrained to the endocardial surface. Patients with unstable tachycardias and multiple clinical tachycardia morphologies are common, but these are the most difficult to treat using catheter ablation. Stevenson’s group found that single catheter-ablation lesions in human ventricular tachycardia were useful to prevent recurrence of unstable tachycardias and multiple tachycardia morphologies (12). In their study, lesion placement was guided initially by sinus rhythm electrogram measurements (identification of low-voltage regions). This was followed by induction of ventricular tachycardia and final positioning of the catheter using the tachycardia recordings to determine locations where pacing resulted in entrainment with concealed fusion. If ablation of infarct-related tachycardia could be guided by delineation of the arrhythmogenic region based on sinus rhythm electrograms alone, it would be of clinical relevance, because hemodynamic stability would be maintained with successful ablation of unstable and multiple-morphology tachycardias (12).

In the canine infarct study described herein, dual-reentry morphologies were inducible in 2 of 25 experiments. In the dual-reentry morphology experiments, the functional arcs of block of each morphology mostly coincided [both those forming during premature excitation and those forming during reentry (Fig. 2, K and L)]. This result suggests that a single ablation lesion may prevent recurrence of dual morphologies in canine model experiments as in clinical studies (5, 12), and therefore that the methodology has potential clinical application. This may be particularly relevant because areas of lesion tend to be extensive when each of multiple-reentry morphologies are separately ablated during clinical therapy, which is not desirable because the risk of complications, including damage to functioning myocardium, may increase (12). Moreover, for any type of tachycardia, targeting reentrant circuits by ablating the location of the estimated breakthrough point at the end of the premature excitation cycle would have the added benefit of reducing lesion size and thereby also diminishing the possibility of significant structural damage to the heart, compared with the conventional approach of ablating across the entire width of the reentrant circuit isthmus. Finally, estimation of the stimulus-site location most likely to result in reentry induction, based on symmetry of the ends of the long functional arc of block estimated to form during premature excitation, would be useful when the reentry circuit is complex and induction of the tachycardia morphology is necessary to accurately map the pathway.

**Study limitations.** Reentrant ventricular tachycardia in postinfarction human hearts tends to be more complex and involve more layers than the two-dimensional canine heart model of reentry in the epicardium that was used for this study (5, 8, 12). Therefore, application of the methodology described herein to clinical tachycardias may potentially yield significantly different results. Electrogram duration measurements were made using an arbitrary amplitude threshold to delineate the contiguous time interval associated with local activation. Use of a different threshold could alter the precise locations of regions with differing electrogram duration. Corroborating histological analyses would be useful in future studies to correlate electrical activity as measured by quantification of electrogram shape to presence of abnormal cellular coupling.

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**REFERENCES**


