Model of Bipolar Electrogram Fractionation and Conduction Block Associated With Activation Wavefront Direction at Infarct Border Zone Lateral Isthmus Boundaries

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Background—Improved understanding of the mechanisms underlying infarct border zone electrogram fractionation may be helpful to identify arrhythmogenic regions in the postinfarction heart. We describe the generation of electrogram fractionation from changes in activation wavefront curvature in experimental canine infarction.

Methods and Results—A model was developed to estimate the extracellular signal shape that would be generated by wavefront propagation parallel to versus perpendicular to the lateral boundary (LB) of the reentrant ventricular tachycardia (VT) isthmus or diastolic pathway. LBs are defined as locations where functional block forms during VT, and elsewhere they have been shown to coincide with sharp thin-to-thick transitions in infarct border zone thickness. To test the model, bipolar electrograms were acquired from infarct border zone sites in 10 canine heart experiments 3 to 5 days after experimental infarction. Activation maps were constructed during sinus rhythm and during VT. The characteristics of model-generated versus actual electrograms were compared. Quantitatively expressed VT fractionation (7.6±1.2 deflections; 16.3±8.9-ms intervals) was similar to model-generated values with wavefront propagation perpendicular to the LB (9.4±2.4 deflections; 14.4±5.2-ms intervals). Fractionation during sinus rhythm (5.9±1.8 deflections; 9.2±4.4-ms intervals) was similar to model-generated fractionation with wavefront propagation parallel to the LB (6.7±3.1 deflections; 7.1±3.8-ms intervals). VT and sinus rhythm fractionation sites were adjacent to LBs ≈80% of the time.

Conclusions—The results suggest that in a subacute canine infarct model, the LBs are a source of activation wavefront discontinuity and electrogram fractionation, with the degree of fractionation being dependent on activation rate and wavefront orientation with respect to the LB. (Circ Arrhythm Electrophysiol. 2014;7:152-163.)

Key Words: cardiac electrophysiology ▪ electrical conductivity ▪ electrophysiologic techniques, cardiac ▪ infarction ▪ tachycardia, ventricular

Ventricular tachycardia (VT) caused by a reentrant circuit is a life-threatening arrhythmia after myocardial infarction.1 Canine and swine models of experimental infarction can be useful to study the electrophysiological characteristics of this arrhythmia.2–4 In a canine infarction model, the VT reentrant circuit often resides in the infarct border zone (IBZ), which is the thin region of surviving myocardium between the infarct rim and the epicardial surface.2,5,6 For the canine infarction model, the IBZ is thinnest at the reentrant circuit isthmus location.2,5,6 Away from the isthmus, IBZ thickness increases sharply, and it has been shown previously that points of sharpest thin-to-thick IBZ transition coincide with locations where functional block is present during reentrant VT. These locations where functional block forms during VT are defined as lateral isthmus boundaries (LB). The LBs are distinctive from the isthmus entrance and exit, through which the activation wavefront propagates during VT.

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In previous work, we described a geometry-to-propagation model in subacute canine infarction, which was based on IBZ geometric relationships.2 The IBZ thickness was measured by MRI7 and histology.8 It was predicted that at sharp thin-to-thick transition sites, which occurred along the LBs, curvature of the outward-directed propagating activation wavefront would be convex (ie, curved outward so that the conducting volume being electrically activated would be greater than the volume previously activated). At the LBs, wavefront convexity can attain a critical degree of curvature so that there is difficulty in providing sufficient electric charge to the larger volume of tissue distal to the activating wavefront, resulting in slow electrical conduction or functional block. It was also predicted that propagation across isthmus edges would be possible at segments of the boundary.
canine experiments, ventricular pacing (V-Pace) was performed from the isthmus region at the same cycle length as VT during normal sinus rhythm. These recordings were also marked and mapped for activation time and used for further analysis.

**Fractionation Model Equations**

Alterations in the geometry of the conducting medium result in wavefront curvature changes, which can cause slow conduction and block in isolated cardiac muscle. Alterations from smaller to larger volume in the direction of electric wavefront propagation results in a change from high to low impedance, with the current flow at the transition being insufficient to depolarize the distal, thicker segment of tissue. On the basis of this phenomenon, we have shown that conduction velocity in the IBZ, symbolized as theta (θ), can be approximated as follows:

$$\theta \approx \theta_0 \pm \frac{D}{T} \cdot \Delta T$$

where \(\theta_0\) is the conduction velocity when there is no curvature along the leading edge of the activation wavefront (ie, when the wavefront is rectilinear), \(D\) is the diffusion coefficient, which is the current flow and because of the cell membrane voltage gradient \(0.05-0.2 \text{ mm}^2/\text{ms in ventricular myocardium}\), \(c\) is the spatial resolution, or space step, in units of millimeters, \(T\) is IBZ thickness, where the thickness direction, perpendicular to the epicardial surface, is defined to be the Z axis, and \(\Delta T\) is the IBZ thickness change over 1 space step as the leading edge of the wavefront propagates in the X-Y plane. When the thickness transition is thin-to-thick, the wavefront leading edge becomes convex, that is, it is curved outward so that the conducting volume being activated is greater than the volume previously activated, and the sign in Equation 1 is negative, resulting in wavefront slowing. Conversely, when the thickness transition is thick-to-thin, the wavefront leading edge becomes concave, that is, curved inward so that the conducting volume being activated is less than the volume previously activated, which results in wavefront acceleration, symbolized by a positive sign in Equation 1.

The influence of thin-to-thick versus thick-to-thin wavefront propagation on the conduction velocity will differ, even when the absolute magnitude of the last term in Equation 1 is identical. Suppose that \(\theta_0=0.4 \text{ mm/ms in the IBZ, and let the diffusion coefficient } D=0.1 \text{ mm}^2/\text{ms, and the spatial resolution } c=1 \text{ mm. Thus, } D/c=0.1 \text{ mm/ms and is a constant. Furthermore, suppose the thickness region is } \approx 100 \mu\text{m in thickness and at the immediately adjacent outer circuit pathway the thickness is } \approx 500 \mu\text{m, in accord with previous observations, then }\Delta T/T=400/100=4, \text{ and the magnitude of the term on the right-hand side of Equation 1 is 0.4. In the thin-to-thick direction, this is the critical degree of curvature resulting in a conduction velocity } 0=0.4-(0.1 \times 4)=0 \text{ mm/ms (ie, there is conduction block). Values of }\Delta T/T>4 \text{ also lead to conduction block, whereas values of }\Delta T/T\leq 4 \text{ will result in slowed conduction. Figure 1 shows graphs of the relationship when the absolute value of the right-hand term is }\leq 0.4. The time to traverse a 1-mm distance when \(0=0.4 \text{ mm/ms, which occurs when the right-hand side of Equation 1 is zero, is } 2.5 \text{ ms (left-most point in each graph). When the right-hand term of Equation 1 has a value of } -0.39, \text{ so that } 0=0.4-0.39=0.01 \text{ mm/ms, the time to traverse the 1-mm distance shortens from 2.5 ms to } \approx 1 \text{ mm/0.79 mm/ms}=1.3 \text{ ms (right-hand side of Figure 1B). Therefore, as also can be seen in panel C by superimposing the traces of panels A and B, large absolute changes in conduction time occur not when } D/c \times \Delta T/T \rightarrow +0, \text{ but only when } D/c \times \Delta T/T \rightarrow -0, \text{ which is along the portion of the trace in panel C noted by an asterisk (\*). Supposing that } D/c \text{ is a constant, this portion of the curve will be realized when } T \text{ is small and }\Delta T/T \text{ is large, that is, when wavefront propagation is in the outward direction at the edge of the thinnest portion of the border zone, where it transitions to sharply thicker border zone, which occurs at the LBs.}
and variable propagation outward from them (denoted as short arrows on 1 side). At points along the LB with a more gradual slope, the convex, outwardly propagating wavefront will travel more rapidly because \( \Delta t \) in Equation 1 will be of lesser magnitude. At points along the LB with a sharper slope, the wavefront will travel more slowly because \( \Delta t \) in Equation 1 will be of greater magnitude. Depending on the variability in thickness transition along the LB, and the resulting dramatic differences in slow conduction velocity according to the region of the trace with asterisk in Figure 1C, discontinuity in the wavefront propagation can occur, leading to the possibility of electrogram fractionation. Individual wavefronts along faster edges of the LB will not propagate and merge into the pathways of slower portions of the wavefront because of the sharp thin-to-thick transition between them (Figure 2B).

During normal sinus rhythm, propagation in the same direction across the LB would be expected to result in wavefront discontinuity although to a lesser extent because of the longer cardiac cycle. Propagation in the opposite direction, from thick-to-thin, would not result in wavefront discontinuity, according to the trace of Figure 1B because only small changes in increased conduction velocity would occur. If the activation wavefront propagates in parallel to the LBs during sinus rhythm, wavefront discontinuity and the possibility of electrogram fractionation can occur as illustrated in Figure 2C. The wavefront blocks at points of sharp thin-to-thick transition along the LB edges, as denoted by vertical straight lines. At these points, the wavefront becomes discontinuous and must travel around, as shown by curved arrows. The propagating wavefront would not be expected to become highly discontinuous, however, because there is no impediment to propagation along the centerline.

To estimate electrogram fractionation based on the geometric changes in the conducting medium, the extracellular voltage \( \phi_e \) caused by activation wavefront propagation can be described using the following equation, as illustrated in Figure 3A:

\[
\phi_e(P, t_o) = \frac{4\pi \sigma (a+b)^2}{2\pi}\left[\sum_{i,j} \frac{\partial \sigma}{\partial x} \frac{\partial \phi}{\partial x} + \frac{\partial \sigma}{\partial y} \frac{\partial \phi}{\partial y}\right] \left[(a+b)^2 + d^2\right]^{1/2} (2a \cdot dx \cdot dy)
\]

(2)

where \( P \) is the observation point at time \( t_o \), the extracellular voltage is \( \phi_e \), the intracellular and extracellular conductivity are \( \sigma_e \) and \( \sigma_i \), respectively, \( \partial \sigma_e / \partial x \) and \( \partial \sigma_i / \partial y \) are proportional to the transmembrane current per unit volume \( I_{m} \), and \( \partial \) denotes the partial differential. About dimensions, \( a \) is the distance from the epicardial surface to the midpoint of the IBZ along the \( Z \) axis (thickness) direction, \( b \) is the distance between the point of observation and the epicardial surface, \( d \) is the distance in the \( XY \) plane from the source of activation to the observation point, \( dx \) and \( dy \) are unit distances equal to the spatial resolution of the grid, and activation wavefront propagation is in the \( XY \) coordinate plane. In Equation 2, the summation is taken for all grid squares \( j \) and the denominator is the distance \( r \) between the observation point \( \phi_e(P, t_o) \) and a point on the wavefront leading edge:

\[
r = \sqrt{(a+b)^2 + d^2}
\]

(3)

As a first approximation, suppose that the change in intracellular potential, and the intracellular conductivity, are uniform throughout the IBZ, and that the recording electrode is at the heart surface so that \( b=0 \). Equation 2 can then be approximated as follows:

\[
\phi_e(P, t_o) = \frac{k1}{(a+b)^2} \left[\sum_{j} \frac{d^2}{\partial d^2}\right]^{1/2}
\]

(4)

where \( k1 \) is a constant, the summation is over all grid points \( j \) that are activating at time \( t_o \) (denoted as unit squares of dimension \( dx \) dy in Figure 3A) and

\[
d = \sqrt{x^2 + y^2}
\]

(5)

with \( x \) and \( y \) being the distances from source to recording electrode along the \( X \) and \( Y \) axes. To simplify the equation further, suppose \( \alpha = c \delta \) (that is, half the IBZ thickness at the observation point is much less

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**Figure 1.** Relationship between time for propagation across a 1-mm distance and activation wavefront curvature in the infarct border zone. The ordinate axis shows the time to travel a 1-mm distance and the abscissa is the right-hand term of Equation 1. The right-hand term is shown ranging from 0 (rectilinear wavefront) to 0.39. A. The right-hand term is noted with negative sign (convex wavefront curvature causing deceleration); B. It is noted for positive sign (concave wavefront curvature causing acceleration); C. Both are graphed for comparison.

On the basis of these traces of Figure 1, it can be demonstrated that the geometry of the IBZ conducting medium influences functional block line formation during reentrant VT. This is shown in schematized form in Figure 2A. The IBZ is the region between infarct (green) and epicardial surface, and XYZ coordinate axes are noted. The IBZ is thinnest above the rectangular portion of the infarct at center, noted at 1 location by the short vertical dashed line. Entrance and exit points along the LBs are noted. At points of sharp thin-to-thick transitions along the LBs, however, at the downward ramp, the more gradual transition prevents wavefront curvature from becoming critically convex so that propagation proceeds although slowing occurs (right-hand term of Equation 1 is negative but with magnitude <0). The wavefront then bifurcates, travels along the outer pathway of the reentrant circuit as two distinct wavefronts, and then coalesce at the isthmus entrance, forming double-loop reentry.

Figure 2B shows how conduction velocity can change when there is variable steepness along the LBs. Colors from red to blue denote early-to-late activation time during 1 VT cycle. The more gradual thickness transition at the LBs when compared with panel A enables very slow
than the distance from activation to observation point), and let $k2$ be a constant that prevents the denominator from approaching zero, then

$$
\phi_e (P, t_0) = \sum_j \frac{k1}{k2 + \sqrt{x_j^2 + y_j^2}}
$$

with the summation, as in Equation 4, being over all grid squares $j$ that are activating at time $t_0$. For calculations, activation at each grid square was considered to be a point source located at the center of the square. Equation 6 was used to calculate the simulated value of the extracellular potential for parallel and perpendicular propagation along a LB, with conduction velocity varying in the range shown in Figure 1. The space step was 1 mm, and the time step (or time resolution, equivalent to digital sampling rate) was 1 ms, consistent with actual sampling rates used in clinical recording systems. The activation wavefront was presumed to propagate in only 1 direction: from thin-to-thick in the direction perpendicular to the LB in 1 simulation, and in parallel with the LB for the other simulation. The bipolar electrode was oriented as adjacent diagonally oriented grid squares with respect to the LB, which would be the average orientation by random chance. Each electrode was considered to be a point located at the center of each grid square, so that interelectrode distance between the bipoles, based on the Pythagorean theorem, was $\sqrt{1^2 + 1^2} = 1.414$ mm. Ten distinct sharp transitions with randomly changing slope, separated by 1-mm distances along the LB, were used for simulation (examples of eight transitions are schematized in Figure 2B). The magnitude of each transition was a random value ranging from 100 to 490 μm in thickness for a 1-mm distance (maximum ΔT/T = 3.9, corresponding to a minimum conduction velocity = 0.01 mm/ms), which is in accord with previous observations. Ten point sources were used, one at each of the 10 sharp transitions, so that the summation in Equation 6 was over 10 values. The configuration is shown...
in Figure 3B. The wavefront leading edge, consisting of 10 discrete points, is discontinuous after passage across thin-to-thick IBZ transitions. The wavefront propagates toward and across the diagonally oriented bipolar electrode. Because the bipolar extracellular signal was calculated, Equation 6 was implemented as follows:

\[
\phi(B,t) = \sum_{j} \frac{k_1}{k_2 + \sqrt{x_{j,n}^2 + y_{j,n}^2}} - \frac{k_1}{k_2 + \sqrt{x_{j,n}^2 + y_{j,n}^2}}
\]  

where \( p \) and \( n \) represent the positive and negative electrode, respectively, \( j \) is one of ten discontinuous points on the leading edge of the wavefront that activates at time \( t \), and \( \phi(B,t) \), the bipolar extracellular potential, is calculated for all time \( t = 1 \) to 175 ms in 1 ms steps to form the electrogram. The electrogram amplitude \( \phi \) was normalized by scaling \( k_1 \) so that a biphasic electrogram deflection would exhibit a 2 mV peak-to-peak amplitude when acquired from a bipolar electrode oriented diagonal to a uniformly propagating wavefront.

**Measurements Used to Test the Model**

The degree of overlap of the arcs of conduction block forming during VT versus V-Pace was determined by overlapping activation maps on the computerized grid. Portions of the two block lines were considered overlapped if they were located between the same recording sites and had the same orientation. The percentage of the total VT block line length that was overlapped by V-Pace block lines was tabulated.

The number of fractionated electrogram sites immediately adjacent to VT block line locations (within 1 recording site), versus those without such an association, was tabulated. The number of sinus rhythm versus VT and V-Pace fractionation sites that coincided was determined (whether or not they were adjacent to a block line location). The characteristics of fractionated electrograms were tabulated for a 175-ms interval in terms of the number of deflections, the deflection duration, and number of zero-crossings across a spline interpolation average with 100-ms intervals between interpolation points. The analysis interval was selected as 175 ms because this is approximately the average VT cycle length in the canine model. These measurements were made using 20 recordings each for VT, V-Pace, and sinus rhythm. The 20 recordings were composed of two electrograms from each of the 10 experiments. The pair of recording sites analyzed from each experiment was spatially distinct and selected at random. The same measurements were made for 20 model-generated electrograms (parallel and perpendicular to the LB). Although fractionated electrograms have low amplitude peaks, the tallest of these peaks in each fractionation sequence was used as a reference for detection of distinct electrogram deflections. For each fractionated electrogram (actual or model generated), deflections were counted as distinct if the positive- or negative-going peak of the deflection extended to \( \pm 20\% \) of the absolute height of the tallest deflection, with height being referenced to the local spline interpolation average level.

All electrogram data were normally distributed and expressed as mean±SD. To a first approximation, each electrogram was considered to be a random vector uncorrelated to other electrograms. This approximation was previously shown to be satisfactory in the sense that the correlation matrix is sparse, using the same type of bipolar canine postinfarction data as was acquired in the current study.21 Statistical comparisons were, therefore, made between mean electrogram parameters using the unpaired t test (SigmaPlot version 9, 2004). Correction was done using the Bonferroni method for comparisons of five measurements having different parameters and data type, so that the significance level was taken as \( P<0.05/5 \) (ie, \( P<0.01 \)). To check for electrogram correlation between recording sites, the SD in electrogram morphology over 10 sites in a single experiment was compared with the SD in the data pooled from all experiments. Similar values in SD would suggest a similar lack of correlation in electrogram morphology between sites in a single experiment with respect to the lack of correlation when comparing electrograms from different experiments. The \( F \) test was used for comparisons (MedCalc version 11.6, 2011; MedCalc Software bvba, Ostend, Belgium).

**Results**

Examples of actual fractionated electrograms acquired from the LBs during monomorphic VT are provided in Figure 4A. Continuous electrogram deflections without an isoelectric interval extend for much of the 175-ms duration of each trace. The signal peaks tend to be similar in size and there is no predominant peak.

Examples of electrograms synthesized with minimal or no propagation disturbance imparted are shown in Figure 4B. The inset at left shows the configuration, with the diagonally oriented bipolar electrode being denoted as two solid circles, activation wavefronts shown as vertical lines, and propagation direction given by arrows. When a single rectilinear wavefront crosses a diagonally oriented bipolar electrode, the result is the top trace in panel B, a typical biphasic electrogram shape. The time instances 1 and 2 from the inset are shown along the model-generated electrogram. The biphasic amplitude of the deflection is 2 mV as noted by the scale.
Examples of actual fractionated electrograms acquired during normal sinus rhythm are shown in Figure 5A. These electrograms were acquired from LBs while the wavefront propagation direction was approximately parallel to the LB. Examples of electrograms synthesized when the activation wavefront travels in parallel to the LB are shown in Figure 5B. In these model-derived VT electrograms, based on the scale at right, individual deflections are <1 mV in amplitude. The VT activation map corresponding to the traces of Figure 5A, and functional block line locations during this VT, are given on the left-hand side of Figure 5C. The earliest activation is in red, and latest is in blue color. A sinus rhythm activation map for this canine experiment is shown at right side of Figure 5C. The locations of VT functional block are overlaid on the sinus rhythm activation map as dotted lines. The recording sites from which the actual sinus rhythm electrograms of panel A were obtained are denoted by squares in the sinus rhythm activation map of panel C. The wavefront propagation direction during sinus rhythm, as shown by arrows, is in parallel with the LBs. The sinus rhythm electrograms of recording sites 44 and 45 were acquired from the location where the isthmus entrance would be present during VT, whereas the sinus rhythm electrogram of recording site 75 was acquired from the location where the isthmus exit would be present during VT.

Figure 6 shows IBZ activation maps with activation times from early (red) to late (blue). The activation map during monomorphic VT with double-loop reentrant circuit is shown in panel A. V-Pace at the same cycle length is shown in panel B, with functional block forming around the stimulus site. Although there is some smoothing of the isochrones by the automated mapping program, at each line of block there is a difference of ≥40 ms in the activation time on either side, and the wavefront curves around the sides of the block line as it propagates outward. In the V-pace map of panel B, the functional block lines tend to form near the edges of the isthmus boundary location. The overlap of the functional block lines forming during VT (panel A) and during V-Pace (panel B) are shown in Figure 6C, with the lines forming during V-Pace delineated in gray. The good coincidence in the overlap suggests that the location where functional block can form around the isthmus during reentrant VT can be detected by V-Pace from the isthmus area at a cycle length comparable with the VT cycle length.

In Figure 7, a monomorphic VT activation map is shown in panel A, and panel B shows selected electrogram tracings recorded during sinus rhythm, and during the same monomorphic VT as shown in A. Examples of electrogram recordings, from channels 71 to 80, are shown in panel B for both VT and sinus rhythm. Vertical bars mark the extent of electrogram fractionation, when it occurs. Their locations on the electrode grid of panel A are marked by channel numbers from 71 to 80 for reference to the traces in panel B. Sites of fractionation during sinus rhythm (pink circles) and during VT (light blue circles) are shown in panel A. Electrogram fractionation is more widespread in VT when compared with sinus rhythm. During both sinus rhythm and during VT, many fractionated sites are adjacent to LBs, in accord with our fractionation model. However, fractionation is not present at all LB sites, and some sinus rhythm and VT fractionation sites do

at right. Similarly, when discontinuous rectilinear wavefronts pass the bipolar electrode at different times, the result is a double potential (middle and lower trace in panel B). The middle trace in Figure 4B is based on two discontinuous wavefronts of equal length (the configuration is at left). The lower trace in Figure 4B is based on three discontinuous wavefronts, a long central wavefront and short peripheral wavefronts (see configuration at left).

Examples of electrograms synthesized with a significant propagation disturbance imparted as a highly variable thin-to-thick LB transition are shown in Figure 4C. The largest peaks are of similar size and there is no predominant peak. There are also some broad deflections. The duration of the synthetic fractionation extends along much of the 175-ms interval shown. In the bottom trace of panel C, peaks that extend above a threshold level and that would be separately counted as distinct peaks for quantitatively characterizing the degree of fractionation are noted by asterisks, with the average electrogram level as determined from spline interpolation being used as a reference for determining the height of the peaks in the normal direction, shown as a dashed line (see Methods section of this article). Based on the scale at right, the maximum change in electrogram amplitude is <1 mV in amplitude.
not overlap, as would be expected according to the model, because genesis of fractionation requires significant spatial variation in the thin-to-thick IBZ transition at the LBs, and it also depends on wavefront orientation with respect to the LBs.

Summary Statistics
For all experiments, 67.7% of VT functional block lines, as determined from activation mapping, were coincident with V-Pace functional block lines. Table 1 shows details of the overlap association for individual fractionated electrogram recording sites. The overlap of V-Pace versus VT fractionation sites was 77.3%, whereas the overlap of sinus rhythm fractionation sites with both VT and V-Pace fractionation sites was about one third. Electrogram fractionation site characteristics are noted in Table 2. During reentrant VT for all experiments, there was an average of 18.8±7.2 fractionated electrogram sites per 196 total sites (Table 2). A mean of 15.2±7.7 (80.9%) of those fractionated sites were adjacent to VT block line locations at the LBs. During sinus rhythm, there was an average of 14.8±6.1 fractionated electrogram sites. A mean of 11.3±6.8 (76.4%) of those sinus rhythm fractionated sites were adjacent to VT block line locations at the LBs. In the middle column, data for V-Pace are shown and is intermediate to the results of VT and sinus rhythm. Overall, therefore, most recording sites where electrograms are fractionated are in proximity to the locations where functional block lines form at the LBs.

The morphological characteristics for actual and model-derived fractionated electrograms are provided in Table 3. The mean number of deflections, time between deflections, and number of zero-crossings seem to be similar for VT, V-Pace, and the perpendicular propagation model. The morphological characteristics of sinus rhythm seem to be similar to the parallel propagation model values. Statistical comparisons of these numbers are provided in Table 4. All possible comparisons are shown, with measurements that were expected to be similar shown at top in the table (only 3/12 of these comparisons showed a significant difference as noted by asterisks) and measurements expected to be dissimilar shown at bottom in the table (13/15 of these comparisons showed a significant difference). The respective values for sinus rhythm and the parallel propagation model are, therefore, mostly similar to...
each other and dissimilar to the values for VT, V-Pace, and the perpendicular model. This suggests that wavefront propagation tends to be outward across the LBs during VT and V-Pace but in parallel with the LBs during sinus rhythm, leading to differing statistical properties of fractionated electrograms during VT and V-Pace versus sinus rhythm.

The time between electrogram deflections pooled from all experiments was 9.24±4.35 ms during sinus rhythm (Table 3) which compared with a value of 12.19±4.18 ms measured for a single experiment. During VT, the time between electrogram deflections pooled from all experiments was 16.32±8.86 (Table 3) which compared with a value of 16.15±5.24 ms for a single experiment. For both sinus rhythm and VT, there were no significant differences between the mean and SD in pooled versus single experiment results (P>0.05), thus suggesting that electrogram morphology is uncorrelated between recording sites.

**Discussion**

**Summary**

A model was developed to describe the genesis of local electrogram fractionation during reentrant VT and during sinus rhythm and its dependency on activation wavefront orientation with respect to sharp transitions in IBZ thickness at the LBs. It was hypothesized that heterogeneity in the thin-to-thick transition at the LBs could cause activation wavefront curvature at each point to approach critical convexity with varying degree, so that propagation across these regions would be slow and discontinuous according to the range of parameters given in Figure 1A. The wavefront discontinuity results from variability in ΔT/T and, therefore, in the convexity of wavefront curvature approaching the critical value. The statistical characteristics of VT and V-Pace fractionated electrograms have properties similar to model-derived fractionation with wavefront propagation perpendicular to the LB, suggesting that this orientation predominates in the genesis of VT fractionation, and V-Pace fractionation when the pace site is located within the isthmus region. The statistical characteristics of sinus rhythm fractionated electrograms have properties more similar to model-derived fractionation with wavefront propagation parallel to the LB, suggesting that this orientation may predominate during the genesis of sinus rhythm fractionation.

**Competing Models of Electrogram Fractionation**

Although this study suggests that wavefront curvature can generate discontinuous conduction that leads to electrogram fractionation, it does not prove that this is the actual...
mechanism, even for sites overlapping the LB. Other models of fractionation have been proposed, described for both ventricles and atria of animals, as well as in clinical studies, which may be responsible for at least some of the fractionation observed in this study. One of the earliest models showed that fractionated electrograms are present in canine IBZ in healed infarcts where there is wide separation of individual myocardial fibers, which can be distorted in orientation. Slow and inhomogeneous activation resulting in electrogram fractionation can be caused by convolution in the wavefront pathway, with individual deflections representing depolarization of a distinct myocyte bundle, and the reduction in fractionated electrogram amplitude resulting from the sparsity of viable muscle fibers. In an earlier study as in the present study, electrogram fractionation was detected during sinus rhythm and during VT although differences in fractionation criteria altered the measured fractionation interval. Fractionation can also be caused by wavefront discontinuities and alterations in propagation direction caused by presence of local fibrosis of sufficient density. Electrical heterogeneity can play a role in the complexity of electrogram deflections, as suggested by a gradual increase in electrogram fractionation as electrogram voltage decreases. Systolic interval shortening

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**Table 1. Fractionation Recording Site Association**

<table>
<thead>
<tr>
<th>Description</th>
<th>Overlap, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT/VP fractionation</td>
<td>77.3</td>
</tr>
<tr>
<td>VT/SR fractionation</td>
<td>31.3</td>
</tr>
<tr>
<td>VP/SR fractionation</td>
<td>34.4</td>
</tr>
</tbody>
</table>

SR indicates normal sinus rhythm; VP, ventricular pacing during sinus rhythm; and VT, reentrant ventricular tachycardia.

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**Table 2. Fractionated Site Characteristics**

<table>
<thead>
<tr>
<th>Description</th>
<th>VT</th>
<th>VP</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractionated electrogram sites</td>
<td>18.8±7.2</td>
<td>15.7±9.8</td>
<td>14.8±6.1</td>
</tr>
<tr>
<td>Frac sites associated with LB</td>
<td>15.2±7.7</td>
<td>12.6±8.9</td>
<td>11.3±6.8</td>
</tr>
<tr>
<td></td>
<td>(80.9%)</td>
<td>(80.3%)</td>
<td>(76.4%)</td>
</tr>
</tbody>
</table>

Frac indicates fractionated electrogram; LB, lateral boundary; SR, normal sinus rhythm; VP, ventricular pacing during sinus rhythm; and VT, reentrant ventricular tachycardia.

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**Figure 7.** A reentrant ventricular tachycardia (VT) activation map is shown at top, with the location of functional block lines being denoted by curved black lines. The earliest activation is in red, and latest is in blue color as in Figures 5 and 6. Isochrones and activation times at individual recording sites are noted, and arrows show the direction of wavefront propagation during reentrant VT. The locations of fractionated electrogram sites for those recordings acquired during VT are marked with light blue circles and for sinus rhythm (SR) the sites are noted by pink circles. Examples of fractionated electrogram recordings from this experiment are shown in B for SR and VT.
after either drift or acceleration of a moving vortex can manifest as electrogram fractionation because of the change in source location. All these other mechanisms are likely responsible for some electrogram fractionation observed in our current study, particularly for recording sites away from LB regions. Because these experiments were done in 3- to 5-day-old canine infarction, it is unlikely that a finalized form of fibrosis played a major role in the genesis of the observed fractionation. In contrast, interstitial inflammation, swelling, and islands of electrophysiologically abnormal areas would be present. Although thinning and convolution of surviving strands of myocardial fibers can result in fractionation, this mechanism would likely only be valid for any fractionation observed within the isthmus location itself, where the IBZ is thinnest and thus the surviving strands are fewest. Furthermore, the findings of a recent clinical study suggest that fibrosis is not coincident with the location of fractionated atrial electrograms. Regardless of the mechanism that causes the discontinuous conduction leading to fractionation, it is actually the lack of spatiotemporal resolution in the electrogram recordings that results in a fractionated electrogram appearance.

New Fractionation Model

In several previous acute canine postinfarction studies that used MRI and histological analysis to determine the IBZ geometry, sharp and variable thin-to-thick transitions were shown to occur only at the LBs. On the basis of the new model, which was developed from this observation, fractionated electrograms form at IBZ locations where the parameters of Equation 1 cause the slope of the trace in Figure 1A to be steep (noted with asterisk in Figure 1C). The steep region of the curve will be manifested at portions of the IBZ with smallest thickness $T$ extending sharply to thicker regions, so that $\Delta T$ is large, and therefore $T/\Delta T$ is maximally large. Only at the LBs, where the thinnest border zone changes rapidly to thicker border zone, do these conditions occur. As we have shown elsewhere LBs are not necessarily oriented in the muscle fiber direction and can even be perpendicular to this direction.

Point locations were used to define the leading edge of the activation wavefront. The multiple point sources caused a jagged synthesized electrogram shape because the distance between each source and the observation point changes by a discrete value during each time step. Whereas, when the activation wavefront leading edge is modeled as a continuous surface, the change in source location would not be as abrupt from 1 time step to the next, which would result in a more continuous electrogram shape. Likewise, the use of point electrodes in this study rather than electrodes with finite surface area increased the jaggedness of the fractionated electrogram morphology because passage of the wavefront across the electrode occurs more abruptly.

Our observations were made in canine hearts with coronary occlusion and may not be directly applicable to electrogram fractionation in all clinical cases of postinfarction VT. The model is not representative of structural heterogeneities caused by fibrosis and tissue remodeling that can also be present in clinical postinfarction scars. The mathematical formulation used only represents changes in IBZ thickness and wavefront curvature. Although thickness changes are present in scars causing clinical reentrant VT, other structural heterogeneities that alter the ratio of source current to load may also be present, including tissue expansion, bifurcation, uncoupling of muscle fibers, and sharp wavefront curvature around excitable fibrotic scar tissue, which can result in similar effects to those we have attributed to the LBs. Although the geometry of our model was, therefore, idealized, it nevertheless serves as an initial platform to estimate locations where fractionation can occur and is in partial agreement with actual canine data (Tables 1–4).

Our findings also suggest that quantitative analysis of sinus rhythm electrogram recordings can be useful in detecting arrhythmogenic regions, as is also possible using noncontact mapping data. However, fewer fractionated electrogram sites can be detected during sinus rhythm because of, in part, the slower activation rate and because wavefront propagation may sometimes be oriented in the direction thick-to-thin across the LBs, which would not result in a discontinuous wavefront (Figure 1).

<table>
<thead>
<tr>
<th>Top</th>
<th>Fractionation Type</th>
<th>No. of Deflections</th>
<th>Time Between Deflections, ms</th>
<th>No. of Zero-Crossings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT: perpendicular model</td>
<td>0.0038*</td>
<td>0.3982</td>
<td>0.0002*</td>
<td></td>
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<tr>
<td>VP: perpendicular model</td>
<td>0.0012*</td>
<td>0.9799</td>
<td>0.0163</td>
<td></td>
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<tr>
<td>SR: parallel model</td>
<td>0.2772</td>
<td>0.1039</td>
<td>0.3190</td>
<td></td>
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<tr>
<td>VT to VP</td>
<td>0.4173</td>
<td>0.3997</td>
<td>0.4161</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Bottom</th>
<th>Fractionation Type</th>
<th>No. of Deflections</th>
<th>Time Between Deflections, ms</th>
<th>No. of Zero-Crossings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT: parallel model</td>
<td>0.2481</td>
<td>0.0001*</td>
<td>0.0001*</td>
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<tr>
<td>VP: parallel model</td>
<td>0.4917</td>
<td>0.0001*</td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>SR: perpendicular model</td>
<td>0.0001*</td>
<td>0.0016*</td>
<td>0.0001*</td>
<td></td>
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<tr>
<td>VT to SR</td>
<td>0.0007*</td>
<td>0.0027*</td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>VP to SR</td>
<td>0.0086*</td>
<td>0.0010*</td>
<td>0.0001*</td>
<td></td>
</tr>
</tbody>
</table>

N=20 for each group. Measurements expected to be similar, so that no significant differences would be anticipated to occur, are shown in top panel. Measurements expected to be dissimilar, with the expectation of significant difference, are shown in bottom panel. SR indicates normal sinus rhythm; VP, ventricular pacing during sinus rhythm; and VT, reentrant ventricular tachycardia.

*Significance (P<0.01).
Conclusions
A model was developed, which indicates that at transitions from thinnest to thicker IBZ, spatial variations in the geometry of the conducting medium cause localized differences in activation waveform velocity, which can result in electrogram fractionation. Specifically, when \( \Delta T/T \approx 0.4 \), which is most likely to occur at the LBs, convex waveform curvature and slow conduction can occur, which when variable cause discontinuous conduction and electrogram fractionation, with the amplitudes of the individual deflections being <1 mV (Figures 4 and 5). In part, because of changes in wavefront orientation during sinus rhythm, and also because of the rate dependence of critical curvature,\(^\text{19}\) very slow conduction and block are more likely during the shorter cycle lengths of reentrant VT, and during V-pacing when the stimulation site is within the reentry isthmus location. The activation wavefront can propagate in parallel to LBs during sinus rhythm, leading to fractionation which is of a shorter duration because of the more normal speed of the central portion of the wavefront (Figure 2C). We compared actual fractionation with model-generated fractionation based on a statistical analysis. Because thin-to-thick IBZ transitions are not necessarily oriented transverse to the muscle fiber axis,\(^\text{2,16,28}\) this model can account, in part, for the observation that functional block, with its associated fractionation, can occur off-axis to muscle fibers or even transverse to muscle fibers.\(^\text{16}\) The model can possibly be used to predict actual fractionated electrogram morphology that would be generated by a particular LB geometry, but would require evaluation of Equation 2 without approximation, and knowledge of the precise orientation and geometry of each bipolar electrode, as well as the wavefront leading edge at all time epochs.

Limitations
For simplicity, wavefront propagation was considered to be constrained to travel in directions either perpendicular or parallel to LBs by our model. Propagation along an intermediate angle will likely result in intermediate fractionation properties. To reduce complexity, we did not consider zigzag conduction, intramural conduction, or transmural conduction, the subject of future research. The number of experiments in which fractionation was measured in this study, 10, is limited. Confirmation with a larger pool of experiments should be done.

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Dr Peters acknowledges funding from the British Heart Foundation (RG/10/11/28457 and Centre of Research Excellence), the Imperial ElectroCardioMaths Programme, and the National Institute for Health Research (UK) Biomedical Research Centre.

Disclosures
None.

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**CLINICAL PERSPECTIVE**

During clinical electrophysiological study in patients with ventricular tachycardia caused by a reentrant circuit, catheter mapping can be used to detect and target arrhythmogenic zones for radiofrequency ablation. The optimal region to ablate would be a line positioned between the lateral isthmus boundaries, where the electric impulse is the most constrained. This would minimize lesion size and maximize effectiveness to prevent reinduction of the reentrant circuit. On the basis of the model presented in this study, the optimal ablation target could be determined as follows. Recording at the distal ablation electrode from a region with low amplitude electrograms (<1 mV) would suggest that the catheter resides over the thinnest infarct border zone, where the volume of substrate contributing to form the extracellular signal is smallest. The lateral boundaries of the reentry circuit isthmus (diastolic region) would be detected as lines of fractionated electrograms at opposite edges of this region. Ablation across these lines of fractionated electrograms would be expected to interrupt the circuit across the isthmus location. The typical lesion length, based on previous canine and clinical studies in which the dimensions of the reentrant circuit isthmus were determined, would be ≈1 to 2.5 cm. From the findings of this study, it would be possible to detect the optimal ablation target during sinus rhythm, V-Pace, or ventricular tachycardia although the best delineation of the lateral boundaries would likely be done during V-Pace or during ventricular tachycardia because fractionated electrograms are more likely to be present during these rhythms.
Model of Bipolar Electrogram Fractionation and Conduction Block Associated With Activation Wavefront Direction at Infarct Border Zone Lateral Isthmus Boundaries
Edward J. Ciaccio, Hiroshi Ashikaga, James Coromilas, Bruce Hopenfeld, Daniel O. Cervantes, Andrew L. Wit, Nicholas S. Peters, Elliot R. McVeigh and Hasan Garan

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