

Role of activation signatures in re-entrant ventricular tachycardia circuits

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Abstract

Introduction: Development of a rapid means to verify the ventricular tachycardia (VT) isthmus location from heart surface electrogram recordings would be a helpful tool for the electrophysiologist.

Method: Myocardial infarction was induced in 22 canines by left anterior descending coronary artery ligation under general anesthesia. After 3–5 days, VT was inducible via programmed electrical stimulation at the anterior left ventricular epicardial surface. Bipolar VT electrograms were acquired from 196 to 312 recording sites using a multielectrode array. Electrograms were marked for activation time, and activation maps were constructed. The activation signal, or signature, is defined as the cumulative number of recording sites that have activated per millisecond, and it was utilized to segment each circuit into inner and outer circuit pathways, and as an estimate of best ablation lesion location to prevent VT.

Results: VT circuit components were differentiable by activation signals as: inner pathway (mean: 0.30 sites activating/ms) and outer pathway (mean: 2.68 sites activating/ms). These variables were linearly related ($p < .001$). Activation signal characteristics were dependent in part upon the isthmus exit site. The inner circuit pathway determined by the activation signal overlapped and often extended beyond the activation map isthmus location for each circuit. The best lesion location estimated by the activation signal would likely block an electrical impulse traveling through the isthmus, to prevent VT in all circuits.

Conclusions: The activation signal algorithm, simple to implement for real-time computer display, approximates the VT isthmus location and shape as determined from activation marking, and best ablation lesion location to prevent reinduction.

KEYWORDS

activation, circuit, electrogram, mapping, ventricular tachycardia

Abbreviations: iv, intravenous; LAD, left anterior descending coronary artery; VT, ventricular tachycardia.

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1 | INTRODUCTION

Ventricular tachycardia (VT) caused by a re-entrant circuit is a major health problem.¹ In recent years, catheter ablation therapy utilized for blocking the VT circuit pathway has advanced.² Yet, VT isthmus location and the best ablation lesion site are not always readily ascertained,³ sometimes due to bystander areas⁴ and activation pattern complexity. The VT isthmus (aka central common pathway) is defined as the junction of two or more loops of the driving electric circuit.⁵ At this meeting place, the electrical impulse is constrained, thereby enabling a short ablation lesion to block the pathway with minimal damage to the heart.⁶ The relationship between the area encompassing the isthmus, versus the periphery of the border zone, is uncertain.⁷ Improving the quantitative understanding of this

association would enhance knowledge regarding VT circuit componentry.

In this study, a canine postinfarction model is utilized to measure the quantitative aspects of electrical wavefront activation in the epicardial border zone during VT.⁸ Double-loop re-entrant circuits driving VT are common in this model, as in postinfarction patients.⁹ It is known that conduction velocity tends to be slow within the confines of the VT isthmus, as compared with the periphery of the re-entrant circuit,^{10–12} in part due to remodeling of molecular-level properties such as ion channels and gap junctions.^{13,14} Our hypothesis is that differences in the activation time between neighboring heart surface electrogram recording sites in a multiarray can be helpful to discern VT isthmus location and to suggest ablation targets when the source is a double-loop (figure-of-eight) re-entrant circuit.

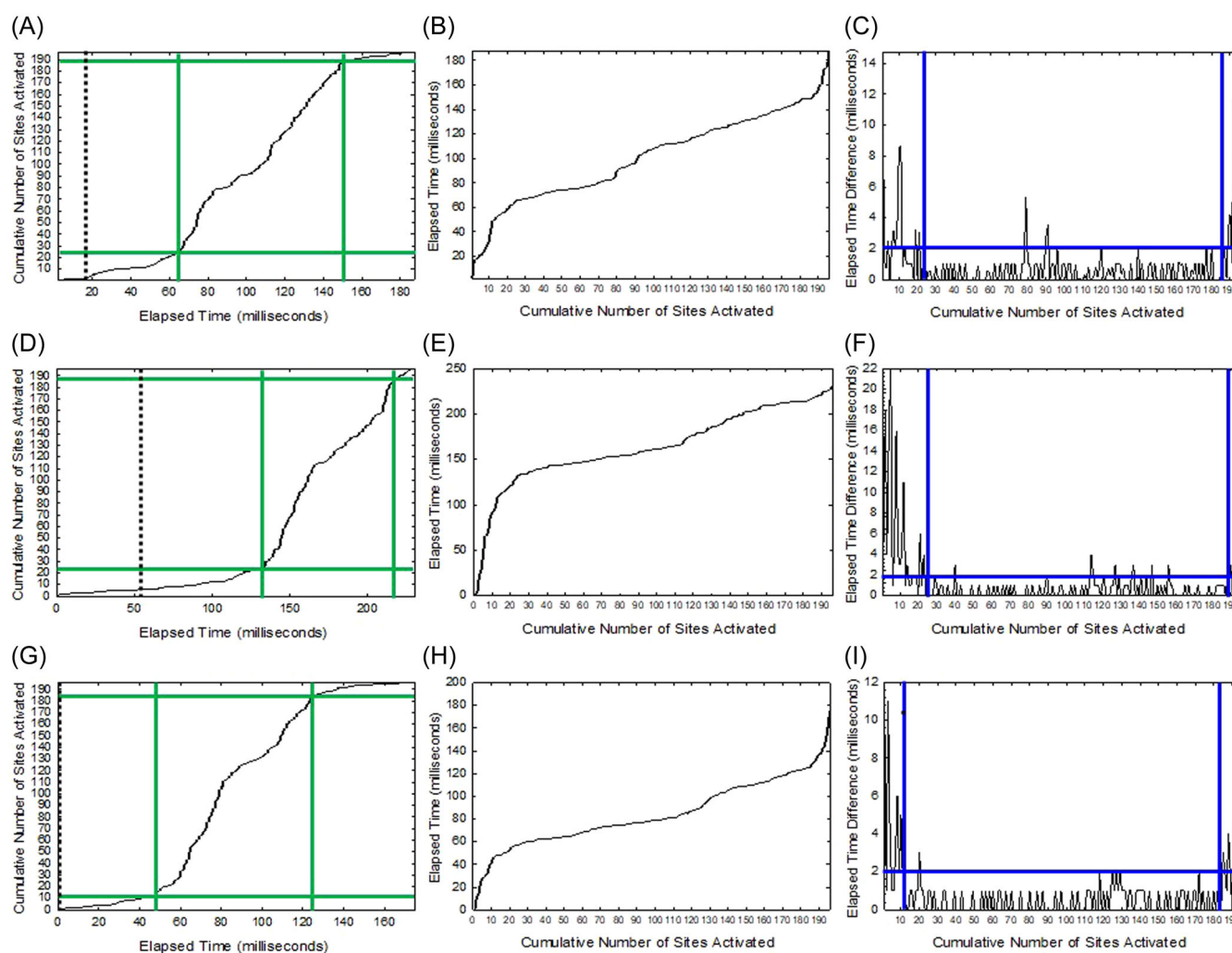


FIGURE 1 Method to determine endpoints of the activation signal for three canine experiments (shown as three separate rows). The corresponding activation maps for the VT morphologies are illustrated in Figure 2. The VT activation signals are noted in the left panels of this figure. The VT activation signals with axes reversed are shown in the center panels (B, E, and H). The derivatives of the traces in the center panels are shown in the right panels, C, F, and I. The boundary between inner and outer pathways (blue vertical lines) was computed using a threshold of 2 ms (blue horizontal line) for spikes in elapsed time difference from the right-hand panels. These boundaries were then shown on the activation signal (green horizontal lines) to obtain the elapsed time boundaries between inner and outer pathways (green vertical lines) and the best ablation lesion (mid-segment, shown as a black vertical dotted line) in panels A, D, and G. VT, ventricular tachycardia.

2 | METHOD

Experiments proceeded in 22 mongrel canines, with permission of the Institutional Animal Care and Use Committee at Columbia University Medical Center. After administration of 15–30 mg/kg of pentobarbital intravenously (iv), the chest was opened and the left anterior descending coronary artery (LAD) was ligated 1 cm from its base, causing myocardial infarction in the subepicardium.^{5,15} At 3–5 days after the administration of pentobarbital (15–30 mg/kg, iv), the chest was reopened and a 196–312 bipolar multielectrode array was positioned over the anterior epicardial left ventricle and sutured in place. The location of the multiarray approximately overlapped the entire epicardial border zone. Programmed electrical stimulation from the left ventricle was utilized to induce VT. The stimulus train consisted of 10 S1 intervals sufficient to capture activation of the heart (approximately 300–400 ms coupling interval), followed by a single premature S2 stimulus with a typical coupling interval of 150–180 ms. In all canines, monomorphic VT was reproducibly inducible using this procedure, and in four of the experiments, two different VT morphologies were inducible, depending on stimulus site

location and the S1–S2 coupling interval, for a total of 26 VT circuit morphologies overall.

During VT, bipolar electrograms were acquired from 196 to 312 recording sites at a 1–2 kHz sampling rate and 8-to-12-bit voltage resolution.¹⁶ The electrode bipoles are spaced 1 mm apart, and bipolar electrodes are positioned approximately 4 mm apart. Using an in-house developed computer program, electrograms were marked for the sharpest slope associated with the largest deflection for several cardiac cycles after induction and stabilization of the VT. Stabilization occurred within the first 10 beats of VT in all experiments. The activation marks were then mapped on a two-dimensional computerized grid. The activation times were manually corrected as needed, based on their association with nearby activation times. When electrogram fractionation occurred, the time of the sharpest deflectional slope most similar to the activation time at nearby recording locations was used as the local activation time. From the activation markings, isochrones were automatically drawn at 20 ms intervals on the computerized grid, with colors showing different time epochs on the activation maps. The presence of conduction block on the grid was defined to occur at boundaries

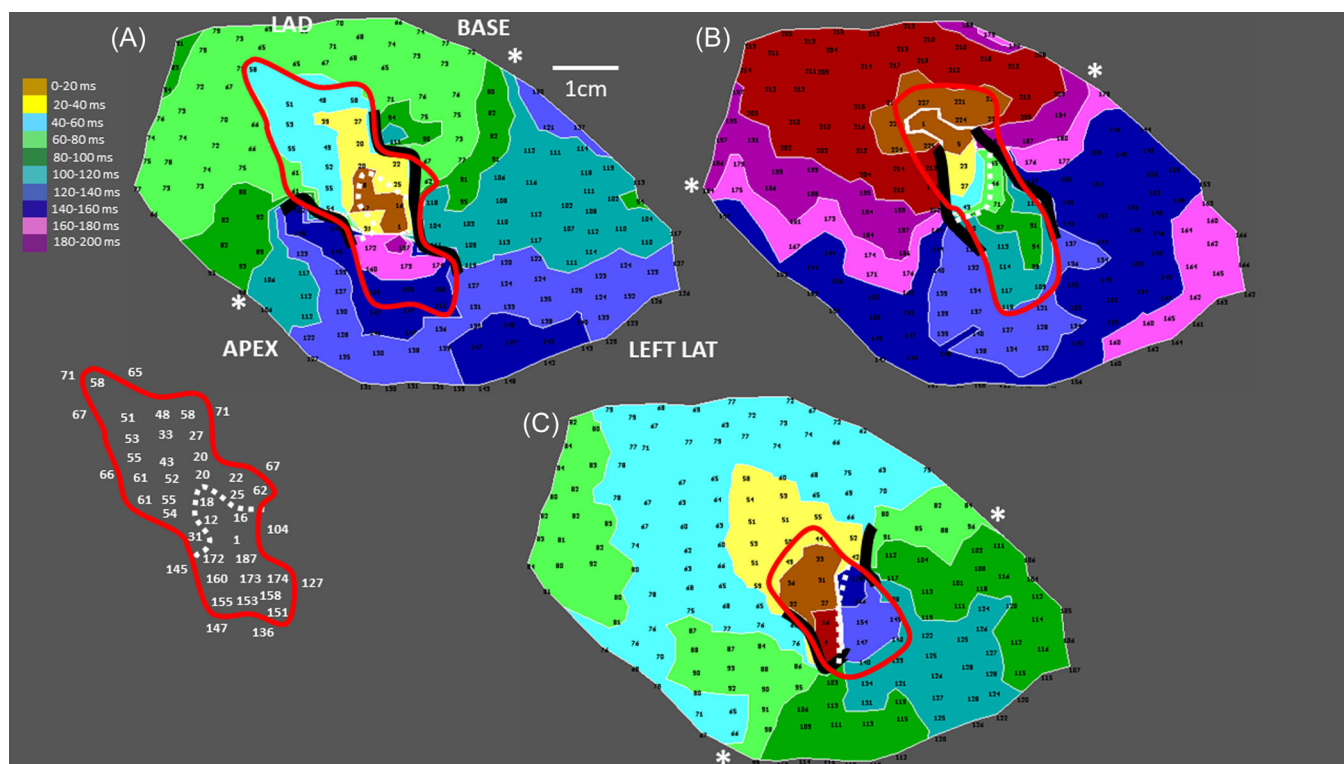


FIGURE 2 Examples of double-loop VT circuit morphologies when the isthmus exit orientation is approximately aligned with the longitudinal to muscle fiber bundle axis in the epicardial border zone. The maps/experiments of panels A, B, and C, correspond to the top, middle, and bottom rows in Figure 1, respectively. Functional block bounding the VT isthmus laterally is delineated as thick black lines. Early activation is shown in red or brown. Latest activation is dark blue or violet in color. Isochrones are 20 ms apart, and they are noted by different colors (shown by the key in panel A), separated by thin white lines. Activation time at each site during the cycle is shown by printed numbers, with an enlargement shown in the inset below for panel A. Asterisks denote areas of slowing in the periphery of the infarct border zone. Anatomical landmarks are noted in panel A. The inner circuit pathway calculated from the activation signal is encompassed by a curved red line. The white dashed line shows where a suggested ablation lesion should be, which is based on the activation signal graph, inner pathway mid-segment. LEFT LAT, left lateral boundary; VT, ventricular tachycardia.

separating locations with activation times differing by >40 ms, and in which the activation waves on either side traveled in differing directions.^{8,17}

The activation signal, or signature, was defined as the cumulative number of electrogram recording sites that had activated each unit millisecond time epoch, and it was computed over one representative cycle of VT after the arrhythmia had stabilized, for each of 26 circuit morphologies. The activation signal was plotted as the number of recording sites cumulatively activated (ordinate or y-axis) versus the elapsed time during the VT cardiac cycle (abscissa or x-axis). It provides a description of the characteristics of electrical activation over the surface area of the multiarray, and it is a signal in the sense that it has one independent and one dependent variable. The onset of the cardiac cycle was defined as the time of earliest activation on the map during the prototypical cycle. Based on prior knowledge that conduction velocity tends to be slower within the VT isthmus as compared with the periphery of the infarct border zone,^{11,12,14} the

activation signal was segmented into two components using its slope. The portion of the trace with the shallowest slope was considered to represent the inner pathway of the VT circuit. The portion of the trace with the sharpest slope was considered to represent the outer pathway of the VT circuit, where electrical activation tends to be more rapid. The segmentation was done by maximizing the difference in activation signal slope between the different segments.

The process of graphing and segmenting the VT activation signal is shown in Figure 1 for three different canine experiments in which the 196-electrode grid was used. In the top row is a result of one experiment. The activation signal is plotted on the left as a thin black trace (panel A). It is plotted as a cumulative number of the 196 recording sites activated, versus elapsed time in the VT cycle in milliseconds. For the first 63 ms of elapsed time in the VT cycle, there is evident a gradual upstroke in the activation signal. At 64–150 ms in elapsed time, there is a sharper upstroke in the activation signal. Then, from about 150 ms to the end of the cycle (the VT cycle length),

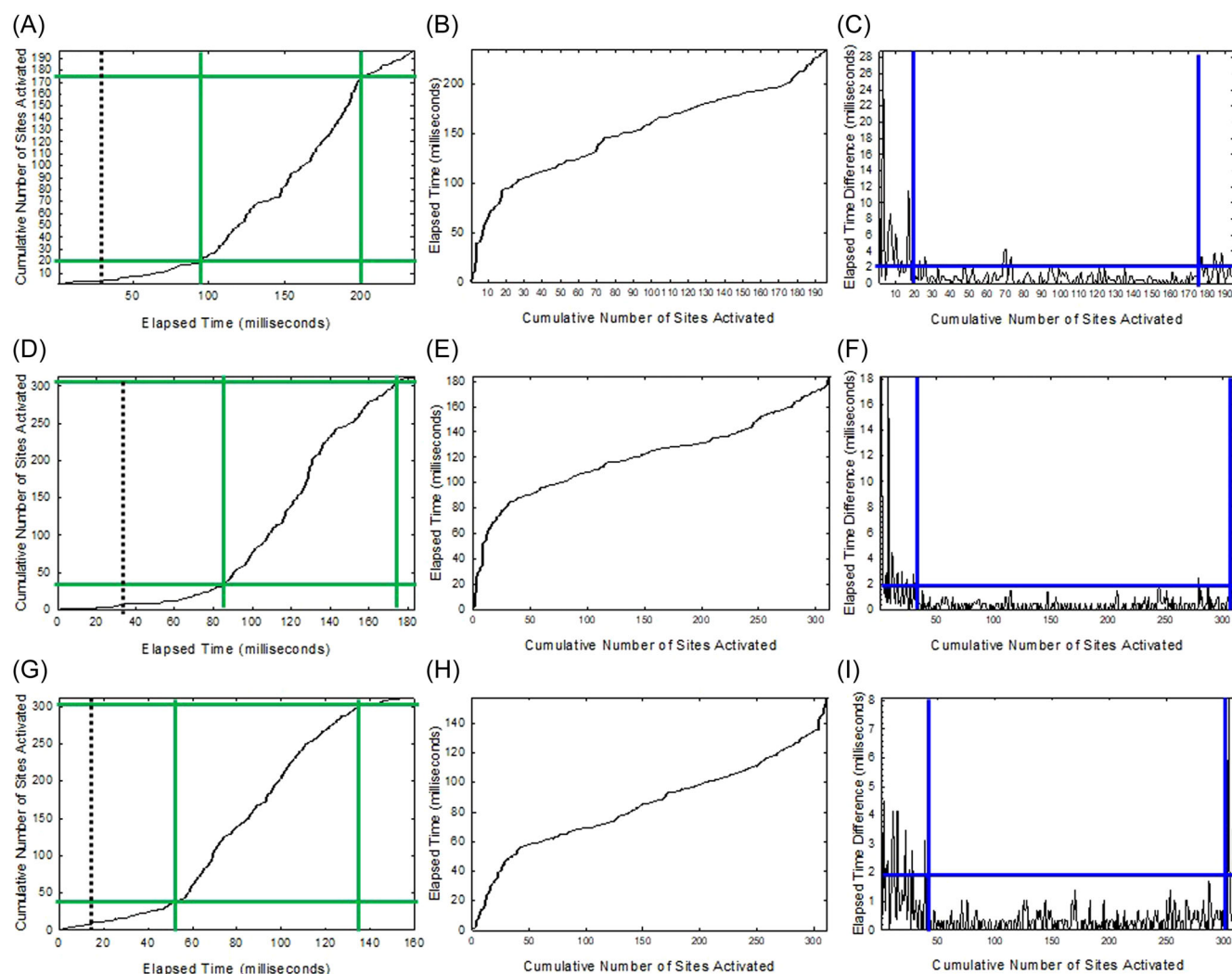


FIGURE 3 Activation signals for three canine postinfarction experiments with the corresponding activation maps noted in Figure 4. In panels A, D, and G, the outer pathway with rapid conduction resides between the vertical green lines, and in each case, there is an approximately linear increase in the cumulative number of sites activated versus the elapsed time in the VT cycle. VT, ventricular tachycardia. In panels B, E, and H, the activation signal axes are reversed, with derivatives in C, F, I.

there is a more gradual increase in recording sites activated per elapsed time. We surmised from this activation signal graph, panel A, that areas of shallower activation slope, up to 63 ms in elapsed time and after 150 ms in elapsed time, would approximately correspond to the VT re-entrant circuit isthmus where conduction tends to be slower, and defined more succinctly, this would represent the inner circuit pathway. To quantitate, we first reversed the axes of panel A, as shown in panel B, with other parameters the same. Then, the difference in elapsed time per site activated (first derivative) in the trace of panel B was plotted in panel C. Using a threshold elapsed time difference of 2 ms (horizontal blue line in panel C), areas with greater versus less elapsed time difference as demonstrated by vertical spikes in the graph, with no more than 10 ms between spikes, were determined and are shown as the two vertical blue lines. The lines bound the recording sites activating within the inner circuit pathway (segments outside the vertical blue lines) versus the outer pathway (the segment between the vertical lines). The vertical lines in panel C occur at 24 and 186 cumulative sites activated. Using these values to draw the green horizontal lines in panel A, their vertical interception with the trace demonstrates the precise, quantitatively derived boundary between inner and outer pathways in terms of elapsed time in the VT cycle (panel A).

The same was done for two other example experiments, as shown in the second and third rows of Figure 1. The left panel is the activation signal, the center panels show the trace with axes reversed, and the right

panels are the derivative of the middle panel. The same threshold of 2 ms elapsed time difference is used to determine the cumulative recording sites activated to demarcate the boundary between inner and outer pathways (panels F and I), which are then used to show the inner/outer circuit pathway boundaries in terms of the elapsed time in the VT cycle (vertical green lines, panels D and G). This method, an algorithm simply implemented with a few lines of computer code, was used to define the boundaries of inner versus outer circuit pathways for all experiments and VT morphologies.

Once the boundaries were ascertained numerically, a curved line was positioned on the computerized activation map to encompass all those recording sites that activated during the inner pathway segment. A further line was drawn at the mid-time of the inner pathway segment as an estimation of the target area for radiofrequency ablation. For all experiments and all VT morphologies (26 in total), the mean number of recording sites activating per millisecond was plotted for outer versus inner pathways to determine correlative relationships (SigmaPlot for Windows ver. 13; Systat Software).

3 | RESULTS

In Figure 2, activation maps are depicted for the corresponding activation signals of the experiments depicted in Figure 1. In the VT activation maps of Figure 2, the isthmus is approximately aligned

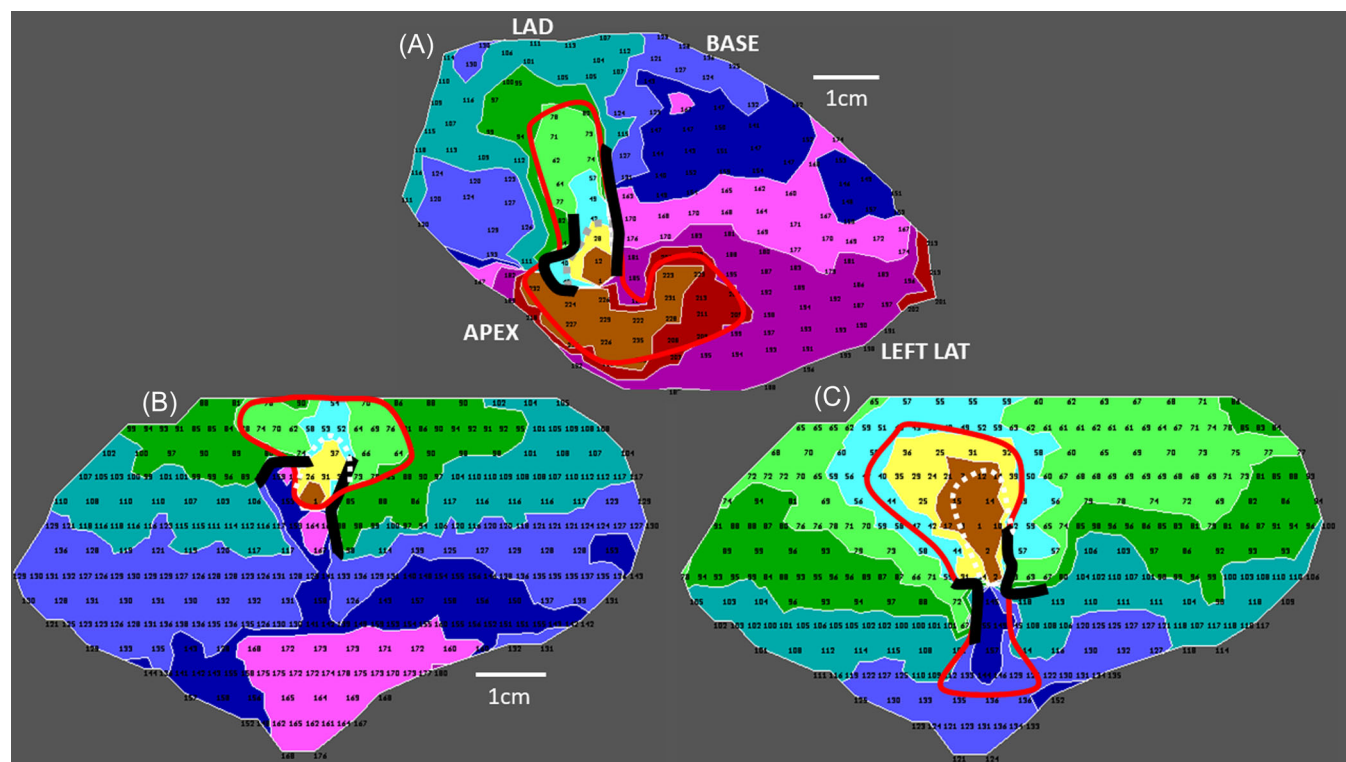


FIGURE 4 Examples of double-loop re-entrant circuits with the isthmus exit pointing approximately toward the LAD margin. The experiments of panels A, B, and C correspond to the top, middle, and bottom rows of the quantitative results shown in Figure 3. In each map, activation of the periphery is relatively uniform, as reflected in the activation signal (see legend for Figure 3). LAD, left anterior descending coronary artery; LEFT LAT, left lateral boundary.

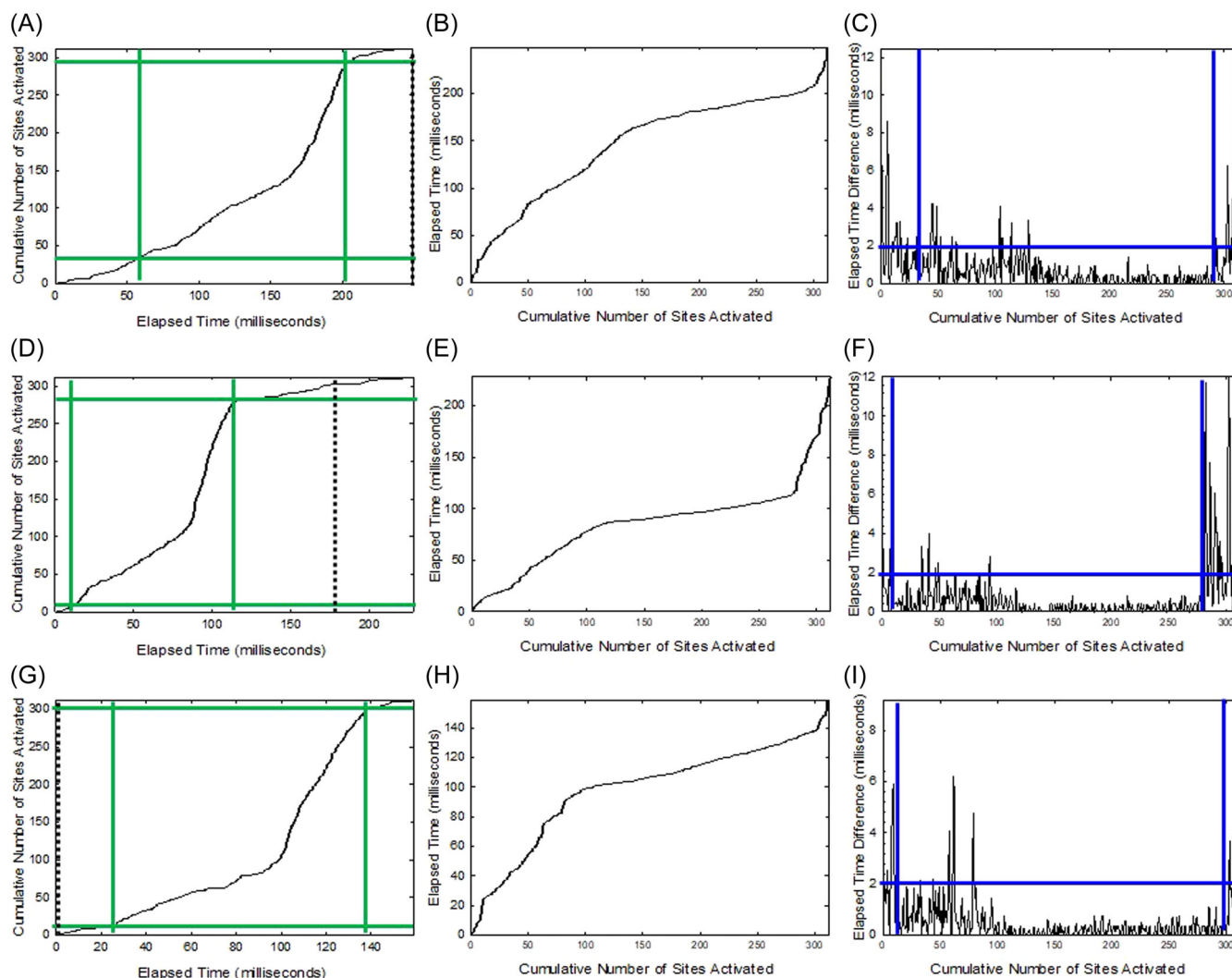


FIGURE 5 Activation signals for experiments with the corresponding VT activation maps are noted in Figure 6. The outer pathways, depicted as occurring between the vertical green lines, panels A, D, and G, include an initial slower activating component (lesser slope), which follows around the circuit at the exit boundary of the inner pathway (Figure 6). The sharper upward slope along the distal portion of the outer pathway may be the result of the additional delay provided by the more slowly activating proximal portion, enabling additional time for recovery of excitability, which causes rapid activation. VT, ventricular tachycardia. In panels B, E, and H, the activation signal axes are reversed, with derivatives in panels C, F, and I.

longitudinally with respect to muscle fiber axis along the epicardial border zone, 23° to the left of vertical for this configuration.¹⁸ Isochrones are separated by 20 ms and are denoted by thin white lines. Early activation is colored in red, brown, and yellow, and latest activation by dark blue and violet. A color key is depicted at left for activation time in panel A and is similar for the other panels. Conduction block laterally bounding the VT isthmus, noted as thick black lines, was functional, as determined by its presence during VT but not during the normal sinus rhythm.¹⁹ The inner circuit pathway determined by the activation signal graphs of Figure 1 is bordered by the thin red line on each activation map. The thin red lines separate activation at the sites of the inner versus outer pathways, as derived from the left-hand panels of Figure 1. For example, from Figure 1A, the relatively slow conducting inner pathway activates from 150 to 63 ms

in the prototypical VT cycle, the area enclosed by the red line in Figure 2A. In the inset below the panel, activation times at proximate sites are shown enlarged. Within the inner pathway, the activation times are all within the range determined in Figure 1A. Furthermore, the suggested ablation lesion is at 19 ms in Figure 1A, shown as a dashed line in Figure 2A and its inset. In Figure 2B,C, the corresponding activation signals are graphed in Figure 1D,G, respectively. The confines within the red lines so determined in Figure 2 overlap the VT isthmuses ascertained by activation mapping, plus they encompass additional areas preceding and following along the circuit pathway. If the mid-time for each inner pathway segment shown as a delineating dashed line in Figure 2 were used as a guide for ablation lesioning, in each case it would likely impede passage of the electrical impulse through the VT isthmus, though verification was not done in this study.

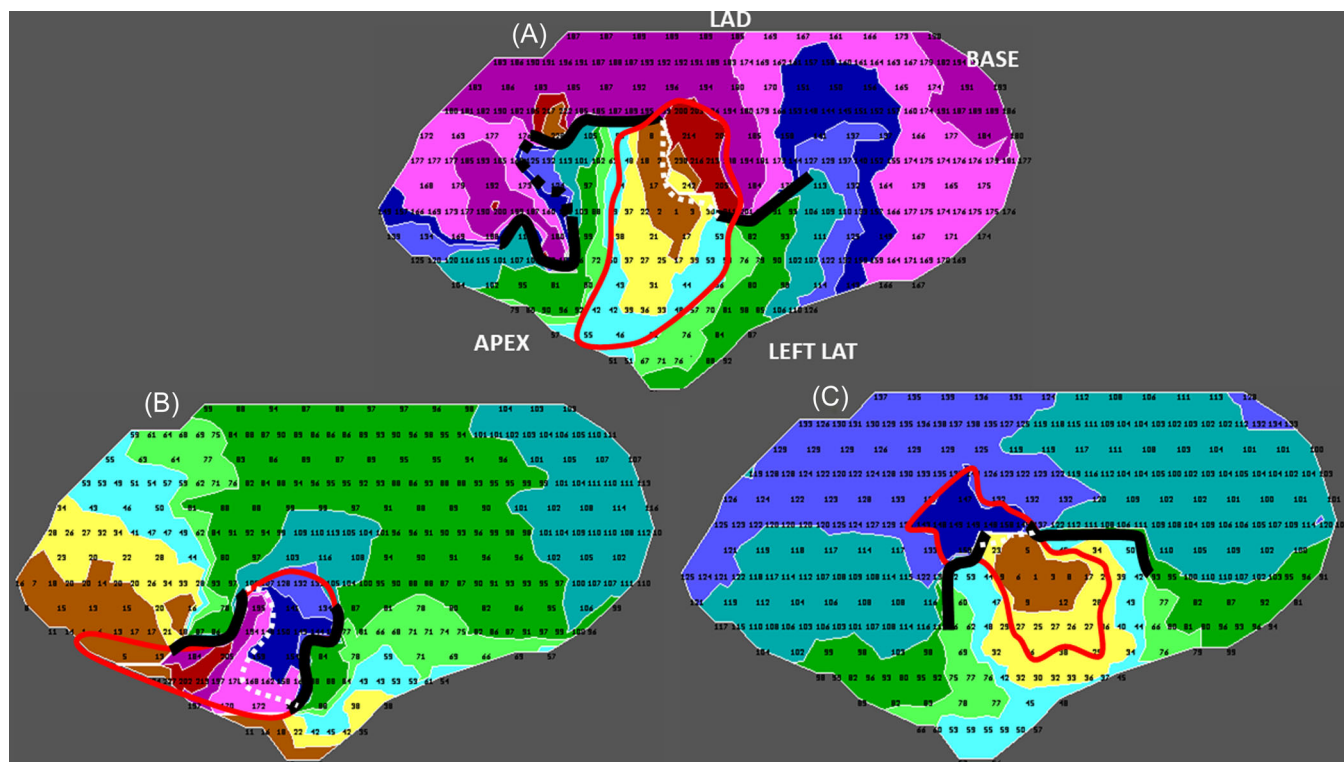


FIGURE 6 Examples of activation maps when the isthmus exit is oriented toward the apex or left lateral anatomical landmarks, corresponding to the activation signals in Figure 5. Functional conduction block is delineated with curved black lines, and the VT isthmus is mostly overlapped by the inner pathway, so designated with the red line. There is significant slowing following activation wave propagation distal to the exit boundary of the inner pathway. LAD, left anterior descending coronary artery; LEFT LAT, left lateral boundary; VT, ventricular tachycardia.

In Figures 3 and 4 are depicted activation signals and maps, respectively, for examples in which activation at the isthmus exit during VT is directed toward the LAD margin. In Figure 3, for each activation signal trace, panels A, D, and G, the sharpest slope, which defines the outer pathway segment, is mostly uniform, and it is similar in magnitude for the three experiments shown. The inner pathway segment has a shallower slope, it is located at the beginning and the ending segment of the activation signal. The shallower slope means that fewer sites cumulatively activate per unit time in each panel. In Figure 4, the inner pathway border demarcated with a red curved line overlaps the isthmus determined by activation mapping, plus additional portions of the circuit, as derived from the activation signals of Figure 3. The mid-time point is delineated by a white dotted line in each case, and an ablation lesion there would likely block the electrical impulse from passing through the isthmus region, effectively ending/preventing VT with this circuit configuration.

Examples of VT activation maps in which the isthmus exit points toward the apex or toward the left lateral margin are provided in Figures 5 and 6. In the activation signal graphs, Figure 5, there is a unique signature. The segment with sharp slope is comprised of two subsegments—which are distinguished as a shallower and a sharper slope. The segment with the sharpest slope indicates very rapid activation, perhaps due to the additional delay and recovery of electrical excitability afforded by propagation through the slower region after exit

from the inner pathway. The region with shallower slope corresponds to the slower activating regions beyond the isthmus exit in the corresponding panels of Figure 6.

In Figures 7 and 8, examples are shown when the isthmus exit points approximately transversely to the muscle fiber axis. Due to a large degree of transverse propagation in the outer circuit pathway thereby resulting, the slope of the activation signal is relatively shallow for the outer pathway segment (Figure 7A,D,G) compared to the results shown in Figures 1, 3, and 5, same panels. The VT isthmus determined via activation mapping is overlapped by the inner pathway calculated from the activation signal (Figure 8).

3.1 | Summary statistics

For all VT morphologies, the inner pathways had a mean of 0.30 sites activating per millisecond, versus 2.68 sites activating per millisecond at the outer pathways. These variables were linearly related ($p < .001$). In Table 1, the range in the number of recording sites activating per millisecond is shown for inner (0.11–0.49) versus outer (1.13–5.45) circuit pathways. Thus, the quickness of outer pathway activation is approximately an order of magnitude greater than the inner pathway. The second row of Table 1 depicts the range in total number of sites activated in inner (4–60) versus outer (132–293)

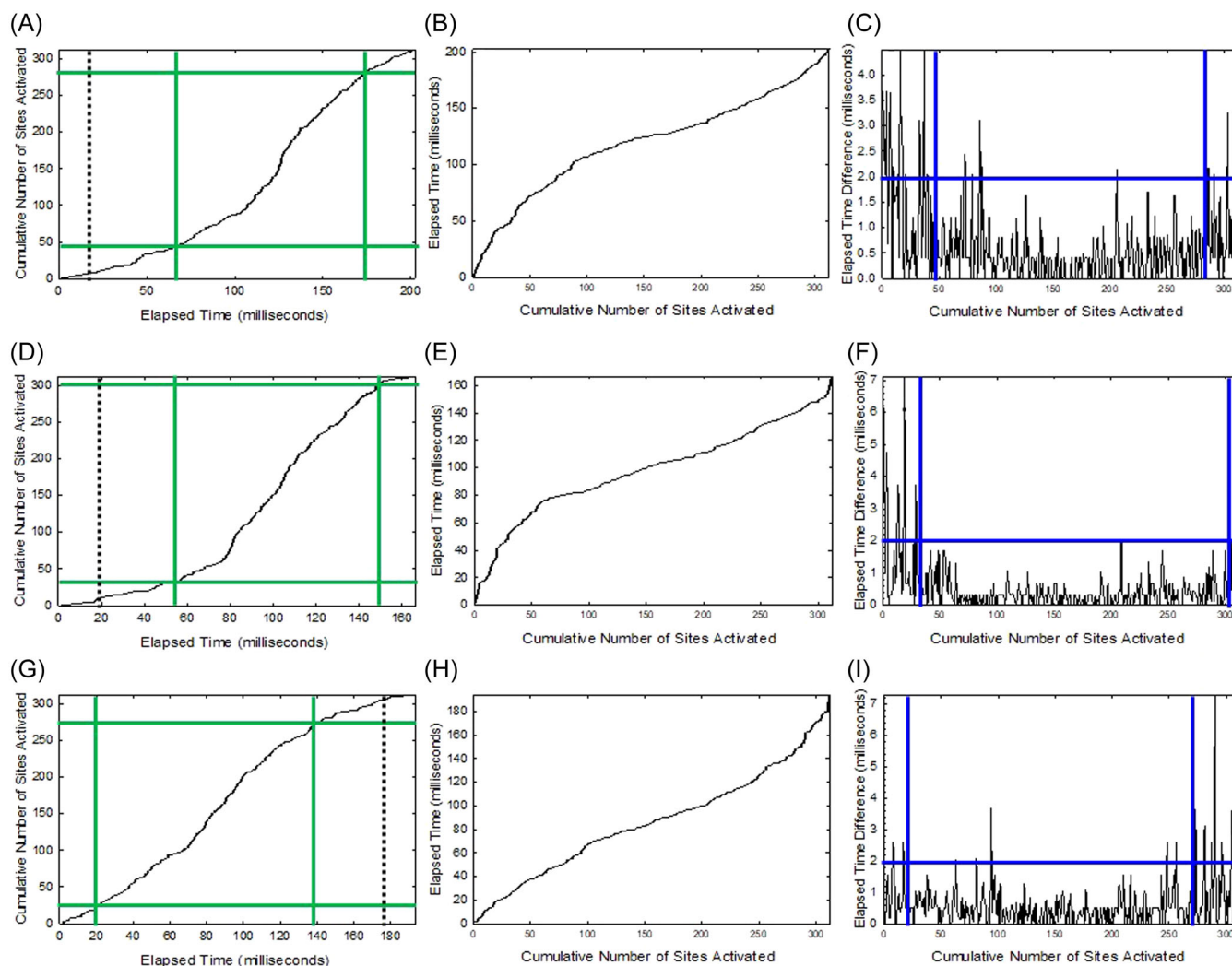


FIGURE 7 The activation signal graphs in rows top, middle, and bottom, correspond to panels A, B, and C, for the activation maps of the three experiments in Figure 8. Here, with the isthmus exit orientation approximately in line with the transverse to muscle fiber bundles (Figure 8), there is a lesser degree of differentiability between inner and outer pathways, that is, the slopes differ less markedly (panels A, D, and G) as compared to isthmus configurations shown in prior examples. This is likely the result of slower, more transverse activation wavefront propagation in the outer pathway.

circuit pathways. In the third row, the range in elapsed time for inner (15–150 ms) versus outer (32–162 ms) pathways to activate is shown. Hence, inner versus outer pathways activate over similar time periods, even though there are often many more sites activating in the outer pathway and it typically consists of a much larger circuit area as compared with the inner pathway.

4 | DISCUSSION

4.1 | Summary

In the study, activation signals were defined as the cumulative number of recording sites activated per millisecond during a representative VT cycle, and this measure was utilized for the quantitative analysis of re-entrant circuits in canine postinfarction experiments. After marking and mapping

VT activation, the isthmus was localized, and propagation throughout the double-loop circuit during VT was evident. The inner circuit pathway was characterized as a region with the shallowest activation signal slope, and its location on the computerized VT activation map showed overlap with the VT isthmus determined by activation mapping, but often included additional portions of the circuit in both the proximal and distal directions. The outer pathway corresponded to that portion of the activation signal with the sharpest slope as determined quantitatively. The slope of the outer pathway activation signal segment depended in part upon the location and direction of the VT isthmus exit.

4.2 | Circuit segmentation and properties

The activation signal was utilized to segment circuit pathway components. The inner pathway consists of relatively slow-moving electrical

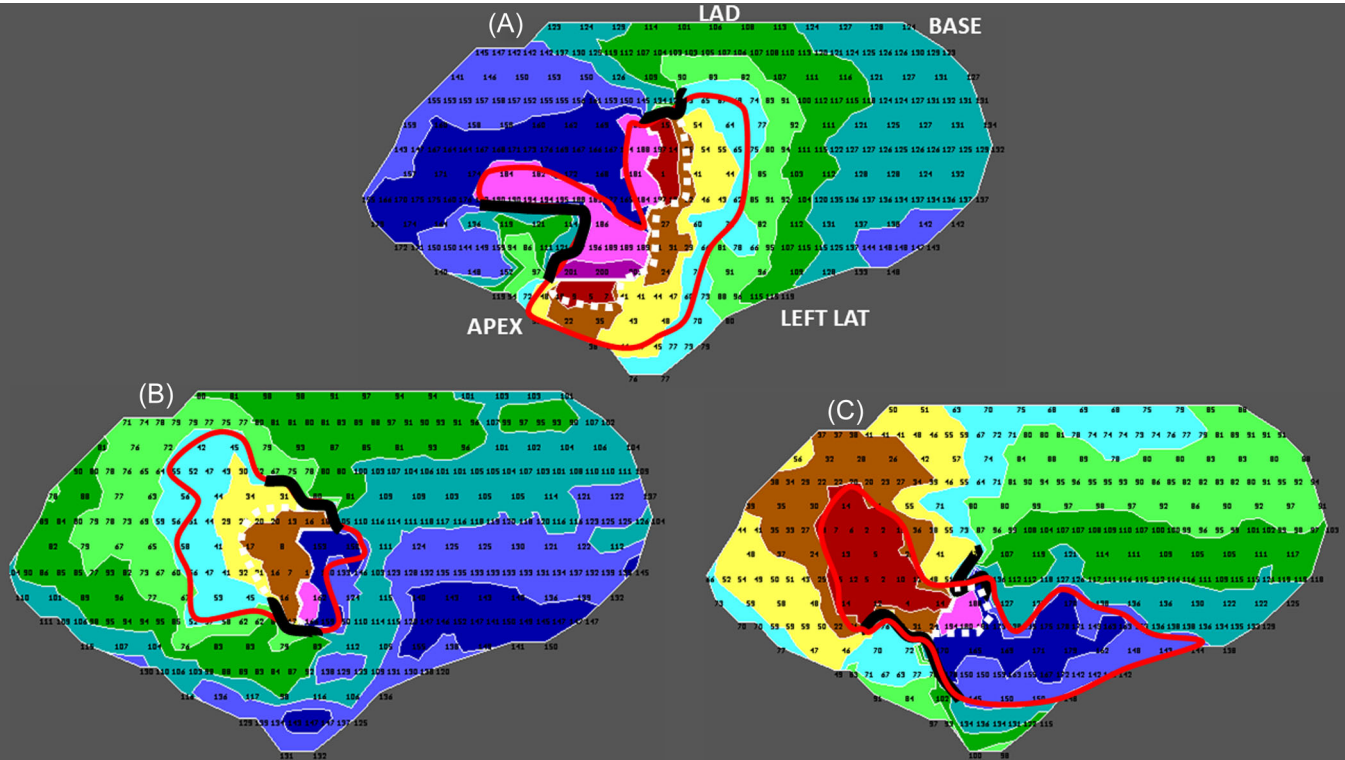


FIGURE 8 The activation maps show the isthmus exit pointing approximately transverse to muscle fiber bundle axis at the surface of the epicardial border zone. This likely results in slower activation at the periphery of the circuit. Hence, the periphery (outer pathway) would be expected to activate at a lesser rate as compared with other isthmus exit configurations. LAD, left anterior descending coronary artery; LEFT LAT, left lateral boundary.

TABLE 1 Ranges in activation signal parameters.

Quantity	Range—inner pathway		Range—outer pathway	
Sites activating per ms	0.11	0.49	1.13	5.45
Total sites	4	60	132	293
Elapsed time (ms)	15	150	32	162

activity.^{11,12} This is evident not only in the activation maps (Figures 2, 4, 6, and 8) but also in the activation signals (Figures 1, 3, 5, and 7) and their statistics (Table 1). The activation signal is in part dependent on the total number of recording sites per pathway. There are lesser number of sites in the inner pathway (Table 1); thus, there will be a lesser accumulation of sites that have activated per time epoch. Contrarily, the outer circuit pathway often comprises a large surface area²⁰ and it extends to the periphery of the border zone; thus, it is composed of many electrogram recording sites (Table 1), which results in a relatively sharp slope in the activation signal. The outer pathway can also be characterized as having a relatively rapid conduction velocity, the presence of an extended activation wavefront, and perhaps multiple activation wavefronts, all of which enable the activation of a greater surface area, and greater number of recording sites, per unit time, causing an increase in the slope of the activation signal. The morphology of the activation signal, or signature, may also

depend in part on isthmus orientation. Similar signatures (Figures 1, 3, 5, and 7) were found when the isthmus exit orientation was directed at a similar angle with respect to the vertical in the map (Figures 2, 4, 6, and 8, respectively). The slopes of each segment in the activation signal were relatively uniform for similar morphologies of isthmus exit direction (Figures 1, 3, 5, and 7). This may be due to a difference in molecular-level properties at the inner versus outer pathways.^{13,14}

4.3 | Clinical correlates

Activation mapping is important to define VT circuit boundaries.²¹ However, these boundaries are not always apparent due to bystander regions,²² nonuniform conduction, and additional late activating regions (the latter of which is evident, e.g., in Figure 4B). The activation signal provides a signature of VT circuit properties unique to each circuit morphology, and it is readily and easily computed and assessed, so that it can be used to validate and verify the result of activation mapping. An algorithm to render the inner versus outer signal pathway of the VT circuit in real time, and the reputed line for making a catheter ablation lesion to interrupt the circuit, can be written with a few lines of computer code without the need for considering the two-dimensional heart surface relationships. Isthmus exit location also affects the activation signal, and it might be useful to verify and

validate the isthmus orientation characteristics. Based on the study, it could be possible to detect the inner circuit pathway and best ablation lesion location using a large roving multipolar catheter, although this assertion should be tested and confirmed in future studies.

This technique may add to the armamentum of the clinical electrophysiologist to complement current methods of substrate mapping.²³ An example is in the detection of slow uniform propagation associated with late activation during sinus rhythm, which is aligned with the VT isthmus long-axis and can be utilized for its localization. The last sinus rhythm activation point is typically in proximity to the VT isthmus entrance. This was shown initially in canine and noncontact clinical postinfarction studies.^{24–26} In more recent contact clinical studies, slowing during sinus rhythm associated with VT isthmus location is noted and referred to as isochronal crowding.^{22,27,28} If VT can be induced, even for one or a few cycles, use of the approach described herein could supplement or even eliminate the need for any activation mapping, which requires two-dimensional and sometimes ponderous interpretation.

4.4 | Limitations

The experiments utilized for this study were done with a canine postinfarction model, which exhibits some but not all properties of re-entrant VT in the clinical setting.²⁹ Similar properties include the possibility of repeatedly inducing monomorphic VT caused by a re-entrant circuit, often with a double-loop circuit configuration, induction by a premature coupling interval S1–S2, the possibility to entrain the tachycardia, the presence of an isthmus and circuit in the infarct border zone, anisotropic conduction, and remodeling of molecular-level properties. Yet, the model differs from human ischemic VT in that it is analyzed at 3–5 days after infarction, before the substantial occurrence of fibrosis. The circuit is epicardial in postinfarction canine hearts, but it is more often endocardial, sometimes with a mid-myocardial component, in clinical postinfarction cases. The lateral isthmus boundaries are often formed mostly by functional conduction block in canine postinfarction.⁹ However, they may have a significant anatomical component in clinical postinfarction.³⁰ Thus, the quantitative results found in this study require verification in the clinical electrophysiology lab.

Much of the putative isthmus site in the presented maps would likely have been derived based on activation mapping alone without computer analysis of activation density plotting. More complex arrhythmia circuits may prove a more challenging setting to validate this model. The use of a static fixed multielectrode array as described herein allows for reliable activation temporal plot density, but this may be more difficult to implement in clinical VT ablation, with more dynamic mapping catheter interaction with the substrate, and issues of electrogram sampling. The suggested ablation line noted in this study is helpful for visualizing propagation, but its utility is yet to be verified.

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DATA AVAILABILITY STATEMENT

The data that support the findings will be available in Columbia University Data Science at <https://datascience.columbia.edu/> following an embargo from the date of publication to allow for commercialization of research findings.

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