SUMMARY. We evaluated the contribution of intramural electrical events in initiation and maintenance of ventricular tachycardia in 15 dogs 3-8 days after either permanent (n = 2) or transient (n = 13) coronary artery occlusion. Seven of the dogs (47%) demonstrated eight distinct monomorphic ventricular tachycardia patterns which were mapped by means of a recently designed computerized system capable of simultaneously detecting, storing, and assessing information from 232 individual cardiac sites. Using both epicardial and intramural electrodes, we found definitive evidence for intramural reentry in seven of the eight monomorphic tachycardias analyzed. Furthermore, five of these animals (71%) demonstrated microreentry, in which small epicardial conduction loops exited intermittently into nonrefractory subendocardium to initiate succeeding beats, while, in the remaining two dogs, ventricular tachycardia was due to macroreentry, during which the broad subendocardial wavefronts depolarizing the ventricle constituted the proximal (fast) reentry limbs. Detailed anatomical analysis of the resultant infarcts demonstrated the thin surviving epicardial tissue rim to be the site of conduction delay necessary for reentry, whereas "preferred pathways" of exit into the subendocardial plane occurred at the infarct borders and were of variable configuration. Successful interruption of these rhythms should accompany interference with the process of exit into nonrefractory subendocardial tissue.

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MALIGNANT ventricular arrhythmias frequently occur during the recovery phase of acute myocardial infarction (Moss, 1980) and contribute to the enhanced risk of sudden cardiac death in the weeks to months that follow the initial event (Moss et al., 1977; Moss, 1980). Therapeutic interventions to prevent or treat these lethal arrhythmias are currently empirical, nonspecific, and consequently often unsuccessful in reducing the risk of sudden cardiac death. Previous investigators have utilized a canine model wherein either permanent (El-Sherif et al., 1977) or transient coronary artery occlusion followed by reperfusion (Karagueuzian et al., 1979; Michelson et al., 1980) results in a high proportion of animals that are susceptible to induction of ventricular tachycardia with programmed electrical stimulation using protocols analogous to those employed clinically in patients with evolving myocardial infarction. Likewise, detailed pathological examination of these experimental infarcts demonstrates marked similarity to infarcts in patients with documented ventricular tachycardia and subsequent sudden cardiac death, in that both exhibit interdigitation of necrotic and apparently viable myocardial tissue (Ursell and Fenoglio, 1982). Although the time course of the anatomic and electrophysiological derangements is accelerated in experimental compared to human infarction, the sequence of infarct evolution is comparable, suggesting that the pathophysiological basis of arrhythmogenesis probably is analogous.

Several lines of evidence indicate that reentry is a likely mechanism for sustained ventricular tachycardia during evolving myocardial infarction. Induction of ventricular tachycardia by premature extrastimuli and the presence of continuous diastolic electrical activity recorded from regions bordering the infarct during the tachycardia (El-Sherif et al., 1977) suggest, albeit indirectly, a reentrant process. Furthermore, recent evidence utilizing epicardial mapping from multiple sites both in vivo (El-Sherif et al., 1981; Wit et al., 1982; Mehra et al., 1983; Cardinal et al., 1984) and in vitro (Richards et al., 1984), indicates that reentrant circuits overlying the infarct are the source of some, but not all, ventricular tachycardias. These studies have emphasized that reentry is initiated by functional conduction block occurring within the surviving epicardial tissue rim overlying the infarct, and that induction is related to the prematurity of the paced extrasystole. Although these findings have contributed substantially to our understanding of the genesis of ventricular tachycardia, there are several critical observations which indicate that "epicardial reentry" is not fully responsible for the ventricular tachycardias seen either clinically or experimentally. For example,
since only epicardial or extremely limited intramural activation information is monitored in these studies, it is left implicit that the remaining, noninfarcted ventricle activates passively from the epicardium. Likewise, results from clinical epicardial and endocardial mapping studies clearly demonstrate that earliest activation occurs in the endocardium during ventricular tachycardia (Horowitz et al., 1980), and successful surgical interruption of these tachycardias occurs after ablation of endocardial regions (Wittig and Boineau, 1975; Josephson et al., 1979a). Epicardial reentry circuits in experimental animals are consistently associated with "large gaps" in the sequence of activation, despite extremely detailed and extensive epicardial recordings (Wit et al., 1982; Mehra et al., 1983; Cardinal et al., 1984). In addition, reentry has not been demonstrated in many of the sustained tachycardias. Experimental studies sometimes employ interventions to facilitate mapping which may artifactually alter the arrhythmogenic substrate, including cardiopulmonary bypass, ventriculotomy, pharmacological maneuvers to enhance arrhythmogenesis, and interference with the autonomic innervation of the heart. Finally, several fundamental observations, such as beat-to-beat variation in morphology of the QRS complex during the initial beats of a monomorphic tachycardia, have not been adequately explained. Thus, although disturbances in epicardial conduction contribute to the genesis of ventricular arrhythmias during evolving infarction, this likely constitutes only one element predisposing the heart to ventricular tachycardia.

The present investigation was performed to elucidate the role of epicardial and intramural activation in the genesis of monomorphic ventricular tachycardia. Specifically, two major questions were posed. First, what are the contributions of subendocardial and intramyocardial regions in the initiation and maintenance of monomorphic ventricular tachycardia? Second, what are the anatomic and electrophysiological substrates during evolving infarction that are responsible for monomorphic ventricular tachycardia, as well as what aspects might be potentially amenable to therapeutic manipulation?

Methods

Animal Preparation

Fifteen adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg intravenously), intubated, and artificially ventilated with a Harvard respirator. After antibiotic prophylaxis (300,000 U penicillin, intramuscularly), a limited sterile thoracotomy was performed through the 4th left intercostal space, a pericardial cradle was constructed, and the left anterior descending coronary artery was isolated immediately proximal to the first large diagonal branch. A snare consisting of polyethylene tubing (PE 190) was gradually lowered onto a suture surrounding the artery, and partial occlusion was maintained for 20 minutes, followed by complete occlusion (Harris, 1950). In 13 animals, the snare was released after 2 hours of total occlusion and the myocardium was reperfused, whereas in the remaining two dogs, the artery was permanently ligated. Lidocaine hydrochloride (2 mg/kg) was administered intravenously immediately before coronary occlusion and, in the reperfused group, again just prior to reperfusion. The chest then was closed in layers, and the residual pneumothorax was evacuated through a small thoracostomy tube. A sterile cannula was placed into the left external jugular vein and exteriorized through a posterior cervical incision, and the animals were returned to their cages for recovery.

Programmed Electrical Stimulation

Three to 8 days after myocardial infarction, the animals were reanesthetized (sodium pentobarbital, 30 mg/kg, intravenously) and, by the cardiac activation mapping system described below, were studied electrophysiologically. The lead II electrocardiogram and femoral arterial blood pressure were monitored in all dogs by a Gould (model 260) six-channel recorder, whereas five dogs had more extensive hemodynamic evaluation. The dogs were ventilated, the left chest reopened, and a pericardial cradle was constructed. A sock electrode array, consisting of 24–32 epicardial button electrodes fitted into a nylon mesh (details below), was placed around the heart and sewn gently to the atrioventricular groove (Fig. 1). Bipolar endocardial hook electrodes which were constructed from Teflon-coated stainless steel wires (diameter = 0.33 mm) were then inserted into peri-infarct pacing sites through an introducing needle, and programmed electrical stimulation was performed, utilizing a Bloom model DU-101 programmable stimulator (Bloom Associates).

Pacing was performed with pulse width = 2 msec and at twice diastolic threshold current (0.5–5.0 mA). The protocol was similar to that used clinically (Josephson et al., 1978a), in that a train of eight paced beats (S1's) at basic cycle lengths = 300, 250, or 220 msec was delivered, after which double premature stimuli (S2 and S3) were introduced at varying coupling intervals. The S2-S3 interval was lowered by 2-msec decrements until noncapture of S3 resulted, at which time the S1-S2 coupling interval was narrowed. This sequence was repeated until either the heart became refractory to the S2 stimulus, ventricular fibrillation ensued (followed by DC cardioversion), or

![Figure 1](https://example.com/figure1.png)
Mapping System and Data Analysis

Details regarding the recently designed cardiac mapping system employed in the present study have been reported (Witkowski and Corr, 1984) and will be only briefly summarized. Electrical activity from multiple surface and intramycocardial locations was collected from arrayed electrodes as depicted in Figure 1. Epicardial electrodes were constructed from cylindrical Teflon buttons, pierced by two double-stranded stainless steel wires with soldered interfaces separated by 0.6 mm (Witkowski and Corr, 1984). These were held tightly onto the epicardial surface by a nylon mesh sock (Harrison et al., 1980), which maintained the button positions throughout each experiment. Intramural recordings were obtained from plunge electrodes which were fabricated from 50 µm in diameter Teflon-insulated tungsten wire contained within a 21-gauge straight needle, having an interpole spacing of 0.5 mm and an interpair distance of 2.5 mm (Witkowski and Corr, 1984). The most proximal of the four electrode pairs was located 500 µm from a small phenolic collar which rested on the epicardial surface. This design ensured that the endocardial-most electrode pair, located 8 mm from the epicardium, would lie within the left ventricular wall except in regions of extreme wall thinning, such as in the very center of a transmural infarct. For assessment of right ventricular activation, only the three epicardial-most pairs were consistently within the ventricular myocardium, so that the distal (endocardial-most) pair in these regions was ignored during electrogram analysis.

Two hundred thirty-two bipolar electrograms obtained during each cardiac activation were amplified, filtered from 40–500 Hz, sampled at a 2-kHz rate, and individually converted from analog to digital on 232 channels to yield true simultaneous data acquisition on all channels. Digital data were then stored in 12 parallel bits on a Sangamo-Weston Sabre IV high-density recorder, and subsequently analyzed off-line using a PDP 11-34 (Digital Equipment Corporation) computer system equipped with interactive high-resolution color graphics.

Map construction was performed in several automated steps to facilitate rapid and accurate analysis of the three-dimensional data. Initially, the electrocardiogram was scanned, and a time window was chosen to focus on depolarizations of interest, such as the initiating beats of ventricular tachycardia (Witkowski and Corr, 1984). Individual electrograms from each electrode site occurring within the critical window were automatically calibrated, displayed on a high-resolution Barco color monitor, and computer-generated activation times were derived, based on peak criteria (Durrer and Van Der Tweel, 1954; Gallagher et al., 1978). During review of each electrogram, the computer-chosen activation time was manually overridden in case of an overt error in analysis. Since signals from infarcted and peri-infarcted zones were often of low amplitude and poorly defined in configuration, an amplitude threshold of 0.25 mV was arbitrarily considered to indicate tissue activation by a depolarizing wavefront. This arbitrary cut-off was based on the observation that activity of lower amplitude was not consistently accompanied by activation of immediately adjacent electrodes to result in reasonable activation sequences. Conduction block between two electrodes was defined by any of three criteria: (1) intervening electrodes demonstrated no activation, (2) electrode recordings distal to a block demonstrated low-voltage electrotonic activity followed closely by a larger amplitude electrogram (Wit et al., 1982; Mehra et al., 1983), and (3) large temporal gaps between two electrodes occurred while adjacent electrodes in a less direct spatial path connecting them demonstrated sequential interval activation. For analysis of transmural conduction patterns, plunge electrodes which recorded activation...
at every electrode pair transmurally were considered to activate "antegrade" if the direction of activation was endocardium to epicardium, and "retrograde" if this pattern was reversed.

Following electrogram review, computer-generated and hand-drawn isochronal maps were obtained based on activation times, and then converted to the three-dimensional representations presented below. Epicardial maps were drawn, using activations derived from both surface electrodes and the most proximal plunge bipoles, located immediately beneath the epicardium. Subendocardial maps were derived from the distal plunge bipoles situated 8 mm below the epicardial surface in the left ventricle and 5.5 mm deep at right ventricular sites. The minimum speed of conduction along the mapped reentrant pathways was determined by direct measurements of interelectrode dimensions from the heart in question, as viewed from the epicardial surface. Path lengths were divided by the differences in activation times between the appropriate electrodes to yield conduction velocities in each limb of the reentrant loop.

Anatomical Studies

Anatomical studies were performed to delineate the relation of specific activation pathways to the three-dimensional topography of the infarcts. The morphological analyses were undertaken in four dogs without prior detailed knowledge of the electrophysiology underlying the arrhythmias. Intact, excised hearts, in which the surface and intramural positions of the epicardial and plunge electrodes were marked with stickpins, were fixed for several days in 10% sodium phosphate-buffered formalin. A large transmural block comprising most of the anterior free wall of the left ventricle and containing the electrode sites of interest was removed from the heart and cut transversely into 4–7 transmural blocks measuring up to 6 x 2 x 2 cm. The epicardial location of each pin was diagrammed carefully, the pins were removed, the left lateral transmural cut surface was marked with India ink, and the blocks were processed conventionally for light microscopy. Each block was sectioned subserially in its face and intramural positions of the epicardial and plunge bipoles, located immediately beneath the epicardium. Subendocardial maps were derived from the distal plunge bipoles situated 8 mm below the epicardial surface in the left ventricle and 5.5 mm deep at right ventricular sites. The minimum speed of conduction along the mapped reentrant pathways was determined by direct measurements of interelectrode dimensions from the heart in question, as viewed from the epicardial surface. Path lengths were divided by the differences in activation times between the appropriate electrodes to yield conduction velocities in each limb of the reentrant loop.

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Infarct topography was reconstructed in three dimensions, and the precise epicardial surface and intramural locations of each electrode were determined by examining the subserial sections in an apical-to-basal sequence. Anatomically precise drawings of selected sections (40–50 per heart) were made with the use of an optical drawing tube attached to a conventional light microscope equipped with a 2X objective lens. With this system, a pen placed on paper at the side of the microscope is optically superimposed on the microscopic field of vision, thereby permitting accurate tracings of the structural elements of the section. For each section drawn, the outlines of the epicardial fibroadipose tissue, including coronary arteries, the myocardium, the borders delineating infarct from viable tissue, and the epicardial and transmural positions of each electrode, were traced. The tracings were drawn at a magnification of approximately 20X which permitted resolution of individual cardiac myocytes.

Results

Inducibility

Fifteen dogs survived either transient (n = 13) or permanent (n = 2) coronary artery occlusion and underwent detailed electrophysiological study with three-dimensional activation analysis between the 3rd and 8th postoperative day. In seven dogs (47%) monomorphic ventricular tachycardia (VT) was reproducibly elicited by the pacing protocol described previously, including the two animals with permanent coronary ligation (100%) and five of 13 with transient left atrial descending coronary artery (LAD) occlusion (38%). In these seven animals, eight distinct VT morphologies were evaluated in detail, and the tachycardia cycle lengths, durations, and modes of termination are summarized in Table 1. The cycle length of the ventricular tachycardias varied between 155 and 240 msec, and there was no correlation between the presence or absence of reperfusion and the cycle length of the tachycardia. The tachycardias were terminated by rapid burst pacing (cycle length, 90–140 msec) when the arrhythmia exceeded 10–15 seconds in duration, although spontaneous termination did occur, as did degeneration of ventricular fibrillation in two animals. In the latter two cases (dogs 2 and 3), attempted overdrive pacing during VT was unsuccessful and fibrillation ensued only after >30 seconds of monomorphic VT. Since activation analysis of these arrhythmias was concentrated on the early

Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Reperfusion</th>
<th>Cycle length (msec)</th>
<th>Duration of VT (sec)</th>
<th>Mode of VT termination</th>
<th>Mechanism</th>
<th>Initial polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>+</td>
<td>240</td>
<td>&gt;10</td>
<td>Burst paced</td>
<td>Microreentry</td>
<td>+</td>
</tr>
<tr>
<td>2+</td>
<td>+</td>
<td>155</td>
<td>&gt;10</td>
<td>VF</td>
<td>Microreentry</td>
<td>+</td>
</tr>
<tr>
<td>3+</td>
<td>+</td>
<td>160</td>
<td>&gt;10</td>
<td>VF</td>
<td>Microreentry</td>
<td>+</td>
</tr>
<tr>
<td>4–</td>
<td>-</td>
<td>160</td>
<td>&gt;10</td>
<td>Burst paced</td>
<td>Microreentry</td>
<td>–</td>
</tr>
<tr>
<td>5A</td>
<td>–</td>
<td>240</td>
<td>2</td>
<td>Spontaneous</td>
<td>Macroreentry</td>
<td>–</td>
</tr>
<tr>
<td>5B</td>
<td>+</td>
<td>185</td>
<td>&gt;10</td>
<td>Burst paced</td>
<td>Microreentry</td>
<td>+</td>
</tr>
<tr>
<td>6+</td>
<td>+</td>
<td>160</td>
<td>&gt;10</td>
<td>Burst paced</td>
<td>Macroreentry</td>
<td>+</td>
</tr>
<tr>
<td>7+</td>
<td>+</td>
<td>155</td>
<td>&gt;10</td>
<td>Burst paced</td>
<td>Microreentry</td>
<td>+</td>
</tr>
</tbody>
</table>

VT = ventricular tachycardia; VF = ventricular fibrillation; + or — indicates the presence or absence of each index in the respective animal.
beats of VT prior to a sustained drop in coronary perfusion pressure and associated ischemia, the mechanism responsible for induction of the tachycardia was attributed to the prior infarction, rather than to acute ischemia.

Validation of the plunge Electrode Procedures

Five dogs, three with monomorphic and two with polymorphic ventricular tachycardia, underwent hemodynamic assessment during the electrophysiological studies, using the full complement of needle electrodes. There were no significant alterations in heart rate, mean arterial blood pressure, mean left atrial pressure, mean left ventricular pressure, cardiac output, or stroke work, when assessed prior to and 5, 30, and 60 minutes after plunge needle insertion (Fig. 2). Furthermore, two of these five animals were studied for longer than 3 hours, and no hemodynamic deterioration occurred during either experiment.

Although there were often transient 5- to 10-minute periods following plunge insertion during which episodic multiform ventricular ectopic beats occurred, these always subsided by the time programmed stimulation was begun. Likewise, there were no instances, in any of the dogs studied, of failure to elicit monomorphic ventricular tachycardia subsequent to placement of the plunge electrodes in dogs that demonstrated this phenomenon prior to plunge needle insertion. Alternatively, there were no instances in which conversion to monomorphic ventricular tachycardia occurred in animals in which only polymorphic ventricular tachycardias was present before placement of the plunge electrodes. Figure 3 demonstrates the epicardial patterns and activation times of epicardial electrodes during normal sinus rhythm and with pacing in a dog which later demonstrated monomorphic VT. The activation times at the epicardial electrode sites are shown both immediately before insertion of the plunge electrodes, and 60 minutes later, for each map. Linear regression analysis of the two groups of activation times (Fig. 3), reveals a high correlation and a slope near 1. In the entire group of dogs studied, average values for linear regression slopes were 0.94 ± 0.03 (SEM) during sinus rhythm and 0.95 ± 0.03 with ventricular pacing, while correlation coefficients averaged 0.94 (sinus rhythm) and 0.97 (pacing).

Mechanisms of Ventricular Tachycardia

Two distinct variants of reentry were observed in the initiating beats of monomorphic ventricular tachycardia. In five animals with monomorphic ventricular tachycardia (71%), a microreentrant mechanism was present, in which an independently circulating epicardial reentrant loop intermittently exited down to the subendocardium after recovery of excitability and initiated broad wavefronts of conduction which resulted in complete ventricular depolarization. In the remaining two animals, maintenance of the tachycardia was attributable to macroreentry, wherein a fast limb of the reentry loop was subendocardial in origin, and a slow limb was epicardial. The fast subendocardial limb in the macroreentrant tachycardias was part of a broad wavefront which depolarized the entire ventricle, such that the reentry loop itself did not activate, independent of ventricular depolarization, but rather constituted a part of the overall activation sequence.

Microreentry

An example of the activation sequences during initiation of monomorphic ventricular tachycardia by a process of microreentry is illustrated in Figures
Effects on conduction of plunge needle insertion. Epicardial maps in normal sinus rhythm (NSR) and with endocardial pacing from the right ventricle (*\textsuperscript{1}) are shown for infarct dog 2. Numbers represent activation times of surface electrodes before and 1 hour after insertion of 50 plunge needles and are referenced to the earliest epicardial activation. The corresponding plots are linear regression analyses of activation times in each case. \( m = \) least squares slope; \( r = \) correlation coefficient.

4 through 8, in a dog (dog 2) with a previous infarct associated with coronary occlusion and reperfusion. The electrocardiogram in Figure 4 illustrates a run of ventricular tachycardia initiated by a train of extrastimuli (S\textsubscript{1}'s) followed by two premature extrastimuli (S\textsubscript{2} and S\textsubscript{3}). The first four extrasystoles of the run (T\textsubscript{1} through T\textsubscript{4}) are polymorphic, whereas the subsequent beats are of uniform morphology, occurring at a coupling interval at 155 msec. The activation maps in Figure 4 represent isochronal activation patterns in both the epicardial (upper) and subendocardial (lower) planes during the transition between the last premature paced beat (S\textsubscript{2}, left side) and the first nonpaced extrasystole (T\textsubscript{1}, right side) of this tachycardia. The origin of S\textsubscript{3} is the endocardial pacing site, activation reaching the subendocardium (*) Fig. 4) at a time defined as 0 msec. From this point, depolarization proceeds in two wavefronts (arrows) radially in the subendocardial plane around a large area of conduction block, ultimately activating the left lateral border of this zone within 120 msec. Synchronous with conduction in the subendocardial plane, depolarization also proceeds upward through ventricular muscle to the epicardium, as was documented by multiple plunge electrodes located within the left and right ventric-
FIGURE 4. S₃-T₁ transition (dog 2). Epicardial and subendocardial isochronal activation maps illustrating transitions between the last premature beat of a pacing train (S₃) and the first nonpaced extrasystole (T₁). Cardiac chambers and landmarks are described in the lower left map. Each * within shaded areas corresponds to electrodes demonstrating conduction block within the given activation planes. On the electrocardiogram, vertical lines and numbers correspond to times of earliest subendocardial activation for each depolarization sequence illustrated, while asterisks represent the sites of subendocardial exit. See text for details.

In the epicardium directly overlying the large region of subendocardial conduction block, however, activation cannot originate from immediately subjacent tissue. Thus, on the epicardial plane, the activation wavefront invades this zone from the area adjacent to the endocardial pacing site, but, during S₃, blocks in a front (heavy line; S₃, Fig. 4) located on the septal border of the zone. This block is functional in nature, as has been well demonstrated in previous studies (Wit et al., 1982; Mehra et al., 1983), and results in the conduction wavefront circulating around the basal and apical portions of this epicardial border zone. The wavefront ultimately enters this zone, overlying the silent subendocardium and mid-myocardium, but conduction is slow (crowded isochrones, S₃ epicardium) within this area, allowing for tissue proximal to the epicardial conduction block to recover excitability. This culminates in reentry into this region, not only on the epicardial surface (broken arrows, S₃ epicardium), but also retrogradely, from epicardium to the subendocardium after recovery of excitability (large arrow, Fig. 4). This reentry into the subendocardium occurs 139 msec after the initial S₃ activation at a site (**, Fig. 4) near to, but not identical with, the original pacing site, and marks the beginning of the following depolarization sequence, T₁.

The activation pattern of the first nonpaced extrasystole, T₁, is, at least in its initial phase, similar to that of S₃, and is diagrammed in Figures 4 (right half) and 5 (left half), the latter figure illustrating the transition to the second nonpaced beat, T₂. As was the case during S₃, subendocardial depolarization occurs in two broad wavefronts radially progressing around a sizable area of conduction block, whereas midmyocardial and epicardial muscle is passively activated along these fronts. On the epicardial plane, however, the delayed wavefront from the S₃ activation, which broke through and reentered retrogradely into adjacent nonrefractory subendocardium to initiate the T₁ depolarization sequence, also has conducted radially around a new line of epicardial conduction block (Fig. 5; T₁ epicardium). This new front on the epicardium was formed by the delayed depolarization during the S₃ beat, and resulted in delayed recovery of excitability. This
wavefront then enters the epicardial rim of tissue overlying the subendocardial silent zone, but due to its premature arrival, conducts even slower than during the S3 beat. Again, this allows for the zone proximal to the epicardial block to recover, and it is reexcited (dashed arrows; T1, Fig. 5) both in the epicardial plane and, via intramural pathways, in the subendocardium (**, Fig. 5). For the T1 beat, exit into the subendocardium occurred 269 msec after the initial S3 activation and coincided with the beginning of the T2 depolarization sequence. Note that in the surface electrocardiogram in Figure 5, the onset of T2 is coincident with the earliest subendocardial activation. Epicardial delay was so pronounced during the T1 beat that the epicardial rim overlying the subendocardial silent region exhibited activation well after retrograde subendocardial excitation had occurred (300 msec isochrone). The similarity in QRS morphology between T1 and T2 is due to the fact that exit into the subendocardium occurred at the same location to begin both of these depolarization sequences.

The activation sequence of the second nonpaced extrasystole, T2, is also illustrated in Figure 5. In its final stages, the activation sequence for T2 differs from that of the previous two beats (S3 and T1), and ultimately results in a distinct activation pattern characteristic of the subsequent uniform beats of the monomorphic ventricular tachycardia. After exit of the T1 depolarizing wavefront into the subendocardium (**), T2 activation on this plane once again proceeds radially around the central electrically silent zone. As in previous beats, passive transmural conduction occurs in an antegrade fashion to depolarize the midmyocardium and epicardium in most of the noninfarcted ventricle. On the epicardial plane, the conduction wave which reentered tissue proximal to the conduction block during the latter stages of the T1 beat, also circulates around the basal portion of the epicardial rim but, during T2, blocks completely and cannot enter the basal portion of this zone (four blocked electrodes; T2, Fig. 5 epicardium). This probably is a direct result of the extreme delay in epicardial activation observed during the preceding depolarization sequence (beat T1), causing this zone to be refractory at a time when the circulating wavefront has arrived for the next depolarization. Instead, the conduction wavefront enters this zone at its apical aspect (400 msec isochrone), conducting very slowly in an apical-to-basal direction. After considerable delay, this conduction wave emerges from the slowly conducting epicardial rim and reenters nonrefractory tissue both in the epicardial plane and, conducting transmurally, into the subendocardium. Exit occurs at 522 msec in the right ventricle and slightly thereafter (554 msec) at the left lateral aspect of the infarct border to initiate the T3 depolarization sequence (not shown). The sequence and timing of conduction in the epicardial zone overlying the infarct during T2 accounts for the
relatively long $T_2-T_3$ coupling interval, as well as for the change in extrasystole QRS morphology beginning with $T_3$.

The previous examples have illustrated the transition between three polymorphic extrasystoles preceding a run of monomorphic ventricular tachycardia, demonstrating that: (1) most of the ventricle depolarizes after the delayed epicardial conduction wave exits and then reenters into the subendocardium following the recovery of excitability; (2) an epicardial reentrant loop can circulate, independent of the broad wavefronts depolarizing the noninfarcted ventricle, an example of microreentry, and (3) initial polymorphism of monomorphic ventricular tachycardia is due to differing exit sites from regions of epicardial delay into nonrefractory subendocardium. The morphology of a given extrasystole is conditioned by the exit site of the preceding extrasystole. The former two principles are also characteristic of the stable monomorphic phase of this ventricular tachycardia, as shown in Figure 6, schematizing the transition between the fifth and sixth nonpaced extrasystoles ($T_5$ and $T_6$). Subendocardial $T_5$ activation commences (0 msec) at a right ventricular paraseptal location (*), followed by radial spread on this plane around the central subendocardial silent zone. Slightly later (39 msec), a second area of subendocardial activation begins on the lateral border of this zone, spreading radially in the opposite direction of the first wave, the two eventually meeting at the base of the heart. Again, transmural conduction in the normal myocardial regions is toward the epicardium, as documented by intramural electrodes. However, a broad wavefront of block occurs at the epicardial surface during $T_5$ (Fig. 6, $T_5$–epicardium) overlying the silent subendocardium and midmyocardium. Activation proceeds around this block via two separate circulating wavefronts, at the basal and apical borders of the epicardial rim. The basal circuit, activating in a clockwise fashion, exits into the epicardial rim, resulting in retrograde subendocardial activation at 133 msec (large arrow $A$, Fig. 6), initiating the $T_6$ depolarization sequence from the RV subendocardium (**). The other circulating wavefront, activating independently in a counterclockwise manner, exits into nonrefractory subendocardium (large arrow $B$, Fig. 6) slightly later (at 175 msec) at the lateral border of the subendocardial silent zone (**). Just as occurred during $T_5$, the subendocardial pattern of $T_6$ consists then of two colliding wavefronts originating from opposite ends of the infarct border. Transmural conduction proceeds in an antegrade...
FIGURE 7. Intramural electrograms (dog 2). Electrograms from four intramural plunge needles are shown for the $S_3$-T$_1$ transition illustrated in Figure 4. Dots on the map correspond to positions of epicardial and subepicardial electrodes utilized to determine the two activation sequences. A 250-msec time window is shown in each recording. Signals have been autocalibrated, and the amplitude calibration scale is displayed to the left of each electrogram. A vertical cursor marks the activation point of each electrogram and its time of activation (relative to the first subendocardial activation of $S_3$). See text for details.

Intramural activation information, such as that outlined in Figure 7, can be utilized to construct maps summarizing the directional behavior of transmural conduction. The three maps in Figure 8 represent the transmural activation sequence during normal sinus rhythm, as well as during the T$_1$ and T$_5$ beats of the ventricular tachycardia shown in Figures 4–6. Darkly shaded areas correspond to the regions of subendocardial conduction block, as in the previous diagrams, whereas each circle represents a plunge electrode position outside this zone which demonstrated transmural activation of the pattern indicated. During sinus rhythm, most of both ventricles activates antegradely, as expected. However, as the middle (T$_1$) map indicates, even though the majority of the noninfarcted ventricle activates normally from endocardium to epicardium, a discrete zone of reverse transmural activation corresponding to the pathway of transition between T$_1$ and T$_2$ is apparent (light shading). This is also the case during the T$_5$ beat, in which the two circulating epicardial loops were shown to maintain monomorphic VT (Fig. 6). In the lower map of Figure 8,
NSR

T₁

T₅

- Antegrade activation
- Retrograde activation
- Simultaneous transmural activation

FIGURE 8. Transmural activation patterns (dog 2). Directionality of transmural conduction is indicated at plunge electrode sites outside the region of subendocardial block (darkerly shaded) for a sinus beat, as well as beats T₁ and T₅ described in Figures 4-7. X’s correspond to electrodes demonstrating bidirectional subendocardial block.

The two zones of exit (shaded) again correspond to discrete regions of retrograde transmural activation, whereas the remaining noninfarcted ventricle, for the most part, activates antegradely. The remaining electrodes which do not activate antegradely during the ectopic beats are either periseptal, where no endocardium connects the ventricles, or in peri-infarct regions. However these are only isolated retrograde events (Fig. 8). Thus, transmural activation is largely antegrade, except within the discreet pathways of exit.

Macropreentry

A distinct mechanism was discovered to be important in the initial beats of ventricular tachycardia in two animals (Figs. 9 and 10). The isochronal maps in Figure 9 summarize the transition between beats S₃, (the last paced beat), T₁, and T₅ (the initial spontaneous beats of monomorphic ventricular tachycardia) in an animal 6 days after permanent coronary artery ligation (dog 5). Unlike the previous example, in Figures 4–6, this tachycardia does not exhibit the initial polymorphism often preceding monomorphic ventricular tachycardia, but instead inscribes a uniform QRS pattern from the onset of the arrhythmia. The last premature paced beat, S₃, originates at the subendocardial base of the right ventricle (*) and activates, as in the previous tachycardia, radially around a large electrically silent zone and, at the same time, transmurally to more superficial myocardial layers. Whereas the subendocardium activates completely by 80 msec, the activation front on the epicardial plane invades the zone (epicardium—S₃), reentering tissue proximal to the block after recovery of its excitability. As in the previous example, transmural conduction proceeds retrograde and exit into the subendocardium occurs at 239 msec (**), corresponding to the beginning of the T₁ depolarization sequence. As is evident from this initial transition, the first nonpaced beat need not originate at a location near the pacing site. In this case, the exit site from this epicardial region was located on the opposite side of the pacing site, producing an activation sequence for T₁ which differs markedly from that shown for S₃, a finding also reflected in the differing QRS morphologies for the two beats.

The activation pattern for beat T₁ also begins in the subendocardial plane, proceeds around the area of conduction block in the subendocardium as two wavefronts, and conducts transmurally toward the epicardium. The depolarization wavefront on the epicardial plane appears similar to that on the subendocardial plane, but encounters conduction block along a broad front. Eventually, the two merging epicardial wavefronts enter the epicardial rim overlying the subendocardial silent zone at its septal side at 320 msec. Once within this epicardial zone, conduction is again very slow until exit into the subendocardium occurs (***, at 462 msec) at a site on the opposite side into which the impulse initially reentered the epicardium. The following extrasystole, T₂, then activated in a virtually identical fashion after subendocardial reentry had occurred, consistent with the observed monomorphic QRS configuration.

Several elements are common to the first and second examples of ventricular tachycardia presented, including: (1) rapid activation of the subendocardium around a central zone of block with passive antegrade transmural conduction, (2) significant conduction delay occurring within a limited region of the epicardial border tissue, and (3) exit from electrically isolated epicardial delay zones retrograde into the subendocardium resulting in initiation of the next sequential beat of the tachycardia. However, one important difference between the two
examples is the much larger extent of conduction block and therefore size of the epicardial circuit in the latter case (Fig. 9). This suggests two potential explanations for the reentry observed in Figure 9. First, as is the case in the earlier example (Figs. 4–6), the reentry loop itself could be epicardial, activating independent of the broad wavefronts depolarizing the remaining ventricle. Alternatively, the long epicardial circuits seen with beats T1 and T2 in Figure 9 could be, in part, reflections of fast subendocardial activation transmitted to the more superficial epicardial layers. In this case, the proximal limb of the reentrant loop would actually originate in the subendocardium part of the broad wavefront depolarizing most of the ventricle. Two lines of evidence suggest that the second explanation, macroreentry, is the mechanism which is important in the ventricular tachycardia shown in Figure 9. First, from direct measurements of interelectrode distances and path lengths along the perimeter of

![FIGURE 9.](image_url)

**FIGURE 9.** $S_3-T_1-T_2$ transitions (dog 5). Epicardial and subendocardial isochronal activation maps illustrating the initiation of monomorphic VT following infarction due to coronary artery occlusion. See text for details.

![FIGURE 10.](image_url)

**FIGURE 10.** Epicardial electrograms (dog 5). Epicardial electrograms from sites on the periphery of the zone of conduction block during beat $T_1$ are shown, demonstrating centripetal conduction along the apical and basal limbs of activation. Electrograms and associated activation times are displayed relative to the first subendocardial activation during beat $S_3$. See text for details.
the epicardial conduction block illustrated in Figure 9, conduction velocities computed for the T<sub>1</sub> beat are 1.26 and 0.94 m/sec in the apical and basal limbs of the wavefront, respectively. This is much faster than 0.5 m/sec, the maximal epicardial conduction velocity determined in vivo and in vitro by several investigators (Roberts et al., 1979; Spear et al., 1983). Thus, it is unlikely that the "epicardial loops" seen in Figure 9 are truly spreading horizontally in that plane, except in the region without viable underlying subendocardial tissue, and the apparent fast epicardial conduction is due to transmitted subendocardial activation rather than tangential activation in the epicardial plane. Of course, the precise pathways of activation, and hence, conduction velocities, can only be estimated, despite the large number of electrodes located within this region, so that this argument alone might be insufficient to implicate a subendocardial component.

The other evidence implicating a macroreentrant mechanism lies in the fact that epicardial tissue immediately bordering the functional conduction block in Figure 9 is activated from noninfarcted zones showing antegrade transmural conduction, originating in the subendocardium. Electrograms recorded from several epicardial electrodes located along the proximal aspect of the reentry circuit during T<sub>1</sub> are shown in Figure 10. The map in the center illustrates the position of electrodes within the immediate vicinity of the reentrant loop. As was apparent from Figure 9, activation proceeded around the epicardial block from the left lateral infarct border and entered the epicardial zone of conduction delay at its septal margin. Unlike the example of microreentry (Figs. 4–8) in which the wavefront obtained early entrance into the epicardial rim, the timing of electrograms recorded during this beat indicates that its first access was 180° away from the earliest epicardial site, and once within the rim, it conducted slowly from the septal to lateral margin (large arrow, Fig. 10). Early access to the epicardial rim probably did not occur between electrodes, since activation within the rim was in the direction indicated. If the wavefront of conduction were circulating in the epicardial plane and exiting down to the subendocardium between successive beats, as was the case in the first ventricular tachycardia, it would be expected that conduction along the epicardial loop would exhibit centrifugal spread from the loop. However, as is clear from the electrograms in Figure 10, electrodes located on the perimeter of the loop instead show centripetal conduction, in which electrodes adjacent to the epicardial block, within the region overlying the subendocardial silent zone, are activated from "normal" tissue on the periphery. For instance, electrode A, located within a normally conducting region, activates prior to electrodes A′ and B′, which are immediately adjacent to the subepicardial block. In fact, conduction between electrodes A and B′ is blocked (B′ electrogram), and the latter electrode is activated only after the wave of conduction has spread first to electrode B, further along the "reentry loop" path. Since activation of the noninfarcted tissue on the periphery of the blocked zones occurs antegrade, from the subendocardium, it must be assumed that the proximal (fast) reentry limbs are actually subendocardial in origin. The transmural reflection of this fast conduction gives the appearance of fast conduction on the epicardial plane. Thus, the broad wavefronts of activation which depolarized the ventricles during T<sub>1</sub> participate in the reentry circuit and comprise its proximal (fast) limb.

Anatomical Correlations

Several important aspects of infarct histology and topography are summarized in Figure 11. By 3–8 days after myocardial infarction, the inflammatory and reparative processes are sufficiently advanced to permit precise delineation of the borders of the infarct. Viable cardiac myocytes were recognized easily by the presence of pink cytoplasm with cross striations and ovoid nuclei containing finely granular chromatins (panel F). Necrotic myocardium had been resorbed from the borders of the infarct, and these regions contained inflammatory cells and newly forming granulation tissue (panels A and E). The infarct core was composed of necrotic myocardium exhibiting typical advanced degenerative features (panel B). Necrotic muscle had also been resorbed along the endocardium underlying the transmural infarcts, and the endocardial borders consisted of a zone of fibro-inflammatory tissue. In numerous focal areas, endocardial necrosis was complete, and no viable muscle cells were observed (panel C). In many areas, however, a few viable muscle cells persisted in the subendocardium. These cells were loosely arranged in 1–3 discontinuous layers and appeared to be separated from each other by the local edema and inflammation (panel D). Although judged to be viable, the surviving endocardial myocytes displayed nuclear hyperchromicity and cytoplasmic eosinophilia indicative of some degree of injury.

An epicardial zone of viable myocardium was observed over each transmural infarct (Figs. 11–13). Both the epicardial and lateral borders of the infarcts were highly complex and convoluted, and were composed of extensive interdigitations with viable myocardium which created the impression of multiple "islands" of necrotic tissue when examined in two-dimensional tissue sections. In focal areas, necrosis extended fully to the epicardial fibro-adipose tissue, but these regions were small, and, when reconstructed in three-dimensions, were surrounded by interdigitating zones of viable muscle.

In order to define the precise anatomical substrate underlying the electrophysiological behavior observed during ventricular tachycardia, we examined...
in detail the areas of abnormal activity described in the examples presented above. Specifically, we focused on the anatomical correlates of epicardial delay and the "preferred pathways" of exit found to be critical in determining the perpetuation of reentrant beats. Figure 12 illustrates tracings of histological sections from the infarcted heart described in Figures 4–8 (dog 2), showing initiation of monomorphic ventricular tachycardia by a microreentrant mechanism. Selected transmural slices from base to apex and the critical electrodes located along the routes of reentry are shown. Plunge electrodes A, B, and D of Figure 12 correspond to those used to record the electrograms shown in Figure 7. During the first two interbeat transitions of this arrhythmia, epicardial conduction was delayed in the region to the left of (distal to) the line of unidirectional conduction block (Figs. 4 and 5, S2−T1 and T1−T2) and exit from this zone into the paraseptal LV initiated the subsequent depolarization sequences. In Figure 12, the area of conduction delay occurred in the region of electrodes D, E, and F (panels 4–6), located within the thin rim of surviving epicardial tissue overlying the infarct. The wavefront progressed in an apical-to-basal direction until it gained access to viable subendocardium at the periphery of the infarct. Thus, during the S3−T1 and T1−T2 transitions, electrodes A and B (Fig. 12, panels 1 and 2) were located along the "preferred pathway" of exit into nonrefractory subendocardium. The viable epicardial rim widens as it approaches the edge of the infarct, resulting in nearly simultaneous transmural activation at electrode A and true retrograde conduction at electrode B (Fig. 7).

As illustrated in Figures 6 and 8, the regions of reentry during the uniform phase of this tachycardia are distinct from those just described for the S3−T1 and T1−T2 transitions. During the T2−T6 transition (Fig. 6), two small independent circuits circulated at either edge of the intramural silent zone, exiting...
Figure 12. Selected tracings of the transmural infarct of dog 2, corresponding to electrophysiological data presented in Figures 4-8. A large transmural block containing the infarct and electrodes of interest was excised from the heart (upper diagram). Tracings are arranged in a basal-to-apical sequence, and their relative positions in the excised tissue block are shown. Critical electrode positions are depicted as channels in the tracings and are labeled A through L. Additional electrode positions are illustrated but not labeled. Infarcted myocardium is indicated in black. See text for details regarding anatomical and electrophysiological correlations.

asynchronously into the subendocardium. The anatomical regions in which this activity occurred are also shown in Figure 12. The clockwise (basal) circuit exhibited latest epicardial activity at electrode sites G and H (Fig. 12, panels 4 and 6), located at the viable rim of epicardium overlying the infarct, while the earliest subendocardial activation was situated at site I in the normal RV (Fig. 12, panel 1). Similarly, the latest epicardial electrogram in the counterclockwise (apical) circuit was recorded at electrode J (Fig. 12, panel 8), while early subendocardial activity, leading to the T$_6$ beat, occurred at electrode sites K and L (Fig. 12, panels 7 and 9). Thus, in both of these small circuits, delayed activation was localized to the thin rim of viable epicardium, whereas retrograde conduction initiating the subsequent beat occurred precisely at the infarct border—at the first access to viable subendocardium.

The correlation between infarct anatomy and electrical behavior during ventricular tachycardia was similar in the example of macroreentry presented in Figures 9 and 10 (dog 5). Figure 13 illustrates tracings of selected transmural sections from this animal. The latest epicardial activity during the S$_3$-T$_1$ transition (Fig. 9) was in the vicinity of electrode W (Fig. 13, panel 3), whereas the earliest subendocardial activation of the T$_1$ beat occurred at electrode X (Fig. 13, panel 6). Once again, late activations were recorded from epicardial tissue overlying necrotic myocardium, whereas the first access to viable subendocardium determined the site of T$_1$ initiation (**, Fig. 9). During this sequence, epicardial activation spread in a base-to-apex direction, but in the following sequence (T$_1$-T$_2$, Fig. 9), the horizontal direction of epicardial activation was apex-to-base. In this latter transition, late epicardial activation occurred again in the surviving epicardial rim (electrodes W and Y; Fig. 13, panels 3 and 4), and earliest subendocardial T$_1$ activation was located at the infarct edge (electrode Z, Fig. 13, panel 1). As is apparent from Figure 13 (panels 1-3), the epicardial border zone between electrodes W and Z becomes increasingly complex and develops extensive interdigitations of necrotic and viable tissue as it approaches the basolateral infarct edge. Thus, the wavefront traveling on the epicardial rim appears to gain access to the subendocardium within this complex border zone at the periphery of the infarct. Since transmural activation at the earliest site (electrode Z) actually progressed in an antegrade fashion, retrograde exit into the subendocardium must have preceded activation at electrode Z and presumably occurred along a convoluted oblique pathway in the highly irregular infarct border depicted in Figure 13 (panels 1-3). Thus, the "preferred pathway" from epicardium to endocardium may traverse a complex tissue channel.
which is relatively inaccessible to detection by insertion of a limited number of plunge electrodes.

**Discussion**

Results of the present study demonstrate that intramural, and, in particular, subendocardial electrical activity mediates a key role in initiation and perpetuation of reentrant ventricular tachycardias resulting from canine myocardial infarction. In all seven dogs undergoing programmed electrical stimulation and three-dimensional isochronal activation mapping, reentrant rhythms were detected and found to involve active intramural participation. Most of these rhythms (71%) were due to a micro-reentrant mechanism in which continuous circus movement at the epicardial surface was found to conduct via preferential pathways to a subendocardial exit site, from which activation of the noninfarcted ventricle emanated. In these cases, subendocardial and intramural events, although not a part of the reentry circuit per se, were critical in transmitting the rapid impulse to the ventricle. In the remaining morphologies, the subendocardium was an integral component of the macroreentry loop itself, comprising the fast proximal limb which was then reflected to the epicardial surface. In both types of reentry, slow conduction was found anatomically to correspond to the surviving epicardial tissue overlying necrotic myocardium, whereas pathways of transition between successive sequences occurred invariably at the infarct periphery, at the earliest access to viable subendocardial tissue. The configuration of these borders is highly variable so that exit may occur along either a broad front (dog 2) or a relatively narrow one (dog 5).

Previous experimental efforts directed at delineating the mechanisms responsible for ventricular tachycardia during evolving infarction have focused on the characteristics of surviving epicardial muscle. Initial studies utilized the “composite electrode,” which recorded delayed diastolic activity over a large region of surviving epicardium (El-Sherif et al., 1977; Kabell et al., 1982) and, later, involved sophisticated multi-site epicardial mapping procedures. The results of these studies indicated that reentrant loops develop entirely within the epicardial rim overlying the infarcted region (El-Sherif et al., 1981; Wit et al., 1982; Mehra et al., 1983). This concept has recently been extended by showing that interruption of activity in the epicardial loops, and termination of the tachycardias, occur when the diastolic portion of the circuit is subjected to cryothermal injury (El-Sherif et al., 1983; Gessman et al., 1983). Thus, although the importance of epicardial conduction delay during canine ventricular tachycardia has been appreciated, its precise role in overall ventricular activation has not. The computerized mapping system utilized in the present study was designed to circumvent the technical problems that have prevented adequate assessment of intramural events, in that information from multiple intramyocardial sites can be rapidly sampled, recorded, and analyzed. Furthermore, the large stor-
age capacity for data from all 232 simultaneous locations allows for analysis and comparison of multiple sequences during initiation of ventricular tachycardia.

Analysis of intramural events was also made feasible by placement of multiple plunge needles into the myocardium. Although some investigators have alluded to changes in conduction due to insertion of plunge electrodes (Mehra et al., 1983), we assessed both hemodynamic performance and epicardial conduction patterns in dogs undergoing programmed stimulation and found no alterations over the course of each experiment. Furthermore, induction of ventricular tachycardia of a given morphology was reproducible before and after plunge electrode insertion, suggesting that the reentrant pathways involved in these arrhythmias were unaffected.

Three points regarding analysis of these data impact significantly on the subsequent conclusions. First, we elected to design and utilize plunge electrodes which recorded intramural activity at fixed distances from the epicardial surface, the result being that endocardial activation per se was not always directly assessed. Although the reported survival of endocardial Purkinje cells within canine infarcts (Karaguezian et al., 1980) suggests that some conduction along this thin layer underlying the infarct could occur, the patterns of subendocardial activation observed in the present study (Figs. 4, 5, 6, and 9) in each case implicate a radial, pincer-like activation pattern around a central area of conduction block. Subendocardial zones on the far border of a block are activated last, which is inconsistent with the existence of wavefronts progressing deep to this area of block and activating the far border. The overall histological appearance of subendocardial tissue within the infarct also is consistent with subendocardial block in this region, since extensive discontinuities appear within this subendocardial zone (Fig. 11). Furthermore, the mechanism presented is derived largely from the transmural activation pattern, indicating the relationship between areas of epicardial delay and adjacent myocardium. Even if present, Purkinje conduction deep to the zone of block would not alter the basic substrate of protected delay and retrograde exit. A second important consideration is the accuracy of plunge electrode localization critical for both isochronal and anatomical analyses. By the stickpin method, every attempt was made to duplicate the precise path taken by each electrode; however, small errors could result from disparity in the angles of entry into the myocardium. We feel, however, that the resolution afforded by this method allows for precise analysis of regional electrophysiological and anatomic detail. The other factor novel to our approach was the combined use of surface epicardial buttons and immediately subepicardial plunge electrode bipoles to evaluate "epicardial" conduction. The subepicardial plunge bipole was located only 500 μm from the epicardial surface and allowed recording of detailed intramural information at the infarct borders. On the other hand, the sock array was valuable in determining the effect of plunge electrodes on conduction (Fig. 3), and provided a concentrated electrode field over areas of gross infarction at the epicardial rim where detailed transmural information was somewhat less useful. Thus, the combined use of epicardial and subepicardial bipoles within this 500-μm region maximized our ability to detect zones of delay and their relationship to adjacent tissue.

Although the mechanisms defined in the present study differ substantially from previous descriptions, our findings are not inconsistent with previous data, but rather clarify several outstanding issues. For instance, the present data account for the disparate findings of micro- (Richards et al., 1983) and macro- (Mehra et al., 1983) reentry during ventricular tachycardia, since we found that either pattern can occur, dependent upon the extent of conduction block encountered at the epicardial rim. Thus, small fronts of conduction block will result in small loops and microreentry, whereas large fronts are circumvented by wavefronts propagating from fast subendocardial activation and result in macroreentry. As would be predictable from our proposed mechanisms, zones of early epicardial activation near the QRS onset should be relatively unresponsive to interruption by ablation (Wittig and Boineau, 1975; El-Sherif et al., 1983) since they may be distant from the endocardial site of origin, whereas late regions showing diastolic activity should be consistently vulnerable to ablation (El-Sherif et al., 1983; Gessman et al., 1983). Finally, although epicardial reentry has not been clearly documented in studies evaluating infarction due to reperfusion of the coronary artery (Wit et al., 1982), we found that intramural reentry was indeed important in the five dogs studied with this lesion, and was identical to the mechanism responsible for monomorphic ventricular tachycardia in the two dogs with permanent coronary occlusion.

The implications of these mechanisms for ventricular tachycardia in patients undergoing evolving myocardial infarction depend on the degree to which the experimental preparation approximates human pathophysiology. In addition to the electrophysiological and anatomic similarities between the two types of infarction, there are several aspects of the proposed mechanisms which also coincide with current clinical observations. First, earliest activity during clinical ventricular tachycardia is endocardial when concurrent endocardial and epicardial mapping is performed intraoperatively (Horowitz et al., 1980). Second, the success of surgical techniques which involve inactivation of these early endocardial sites, including endocardial resection (Josephson et al., 1979a) and encircling endocardial ventriculotomy (Guiraudon et al., 1978), is certainly compati-
ble with the present findings. The results of endocardial ablation and isolation are difficult to explain on the basis of the previous notion of reentry confined to the epicardial surface. Third, the clinical observation that it is probable that a change in QRS morphology during clinical ventricular tachycardia is due to differing exit sites from a single reentrant loop (Josephson et al., 1979b) is entirely consistent with our proposed mechanisms, since the initial polymorphic beats of ventricular tachycardia are due to varying exit into the subendocardium from an epicardial circuit. Fourth, there is evidence for a protected reentrant loop during human ventricular tachycardia (Josephson et al., 1978b), which would again be consistent with our present observations. Despite these marked similarities between canine and human ventricular tachycardias, there might be dissimilarities as well, such as the location of human reentrant circuits, which could be septal, intramural, or endocardial.

Several critical questions remain from the observations presented. Although the data are very suggestive of the importance of intramural electrical events, the requirement for their participation in ventricular tachycardia is speculative. Only elimination of endocardial tissue from the process would definitively answer this question. Also, the role of the bundle branches and septum require direct evaluation, since clinical and experimental evidence (Spurrell et al., 1973; Klein et al., 1979; Cardinal et al., 1984) suggests that these sites may be critical under some circumstances. Several of the tachycardias analyzed in the present study originated from periseptal locations, implying that the presence of septal recordings might provide useful information about many tachycardias, particularly those arising from septal infarcts. Another question of considerable significance is the mechanism responsible for the highly malignant arrhythmias associated with nontransmural infarction, resulting in a relatively high risk of sudden death in that patient population (Cannom et al., 1976). Finally, it would seem feasible that pharmacological interruption of monomorphic ventricular tachycardia might result from agents which either increase endocardial refractoriness (and, hence, prevent exit into that plane), or, alternatively, which slow epicardial conduction such that delay might convert to block. Surgically, interruption of the reentrant path might include discreet excision of the "preferred pathways" of transmural reentry, following precise localization by mapping similar to that used in the present study.

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