Reentrant and Nonreentrant Mechanisms Contribute to Arrhythmogenesis During Early Myocardial Ischemia: Results Using Three-Dimensional Mapping

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The present study assessed the mechanisms responsible for the initiation and maintenance of premature ventricular complexes (PVCs) and ventricular tachycardia (VT) during early ischemia using a unique computerized mapping system capable of recording simultaneously from 232 individual intramural sites. In the chloralose-anesthetized cat, during normal sinus rhythm prior to ischemia, ventricular activation was rapid with a total activation time of 25 ± 2 msec. Five minutes after occlusion of the left anterior descending (LAD) coronary artery, activation was delayed during sinus rhythm (64 ± 6 msec) (p<0.001 vs. control) and was characterized by slow conduction in the same plane and block in both the same plane and in the endocardial-to-epicardial direction. In 76% of cases (16 of 21), initiation of single PVCs and the first beat of VT occurred through intramural reentry. In all but one case, initiation occurred in the subendocardium, adjacent to the site of delayed subendocardial and midmyocardial activation of the preceding sinus beat. The activation time of the sinus beat preceding the PVC or VT was significantly prolonged (149 ±7 msec, p<0.001 vs. sinus beats during ischemia not followed by a PVC or VT) with most of the delayed activity occurring in the subendocardium and midmyocardium, a finding that would not have been apparent by epicardial mapping alone. The length of the reentrant pathway ranged from 1.8-3.0 cm. Marked delay was a necessary, but not a sufficient, condition for reentry to occur since, in some cases, delays as large as 220 msec was found without initiation of reentry or the occurrence of nonreentrant PVCs or VT. Maintenance of VT by intramural reentry arose in either the subendocardium or the subepicardium and was primarily dependent on the continued presence of marked transmural delay (159 ±8 msec). In contrast, in 24% of cases (5 of 21), initiation of the first beat of VT arose in either the subendocardium or subepicardium by a mechanism other than reentry as evidenced by the lack of intervening electrical activity between the end of the preceding sinus beat and the initiation of the ectopic beat. The preceding sinus beat was characterized by delay (129 ± 12 msec) comparable to that of sinus beats preceding reentrant ectopic beats (p = NS), but the marked delay was distant from the site of nonreentrant initiation. Ventricular tachycardia could be initiated by one mechanism (reentrant or nonreentrant) and maintained or terminated by another mechanism. Both mechanisms could also occur during the initiation of the same beat and during the same tachycardia. Thus, the initiation and maintenance of VT during early ischemia is due to both intramural reentry and nonreentrant mechanisms. Therapeutic interventions designed to inhibit the malignant arrhythmias associated with early ischemia and, hence, sudden death in man will likely require demonstration of efficacy against not only the reentrant but also nonreentrant mechanisms. (Circulation Research 1987;61:352-371)

The precise mechanisms responsible for the malignant ventricular arrhythmias during early myocardial ischemia remain speculative. Reentry has long been postulated as a major mechanism, but there has been very little direct evidence. Extracellular electrograms recorded from the ischemic region early after myocardial ischemia demonstrate delay and fractionation,1-3 suggesting that slow conduction occurs during sinus rhythm. Continuous electrical activity has been recorded from epicardial electrograms in the ischemic region between sinus beats and premature ventricular complexes (PVCs),2 indicating that reentry may contribute. However, these studies do not provide definitive proof since the reentrant pathways were not delineated. These previous studies were limited by a relatively small number of recording sites and/or a limited area of recording that in most cases was confined to the epicardial surface. Janse et al4 evaluated the mechanisms responsible for arrhythmias in the isolated ischemic porcine and canine heart using 60 epicardial or intramural electrode...
recording sites. Although these authors demonstrated no evidence for reentry on the epicardial surface in the initiation of ventricular tachycardia (VT), they did, in some cases, demonstrate epicardial reentry in the maintenance of VT. They also presented one example of reentry involving activation of intramural sites, suggesting that intramural processes participate in the development of arrhythmias. Furthermore, since ectopic activity appears to arise in the subendocardium, this would also suggest that intramural processes may contribute substantially to arrhythmogenesis during early myocardial ischemia. Because this study was limited by the mapping of only a portion of the relatively large porcine heart, it could not exclude reentry at sites remote from those in which recorded activity was obtained. Based on these findings, non-reentrant mechanisms, possibly due to "currents of injury" flowing from ischemic to nonischemic tissue, were postulated as the major mechanism contributing to arrhythmias in the ischemic heart. However, to assess definitively which mechanisms are operative requires the ability to map simultaneously from multiple intramural sites throughout the entire heart with a large data storage capacity and with enhanced resolution. The computerized three-dimensional cardiac mapping system we developed and built in our laboratory overcomes many of the limitations of previous systems and can record simultaneously and continuously from 232 bipolar intramural sites from the entire feline heart. In particular, two major questions were posed. First, what is the role of intramural electrical activity in the initiation and maintenance of ventricular tachycardia during early ischemia? Second, in what way do nonreentrant mechanisms contribute to arrhythmogenesis in the ischemic heart?

**Materials and Methods**

**Animal Preparation and Protocol**

Seven adult cats (average weight, 3.7 kg) were anesthetized with ketamine HCl (12.5 mg/kg) and \( \alpha \)-chloralose (75 mg/kg), intubated, and artificially ventilated with a Harvard respirator. Muscle relaxation was maintained by decamethonium bromide (0.25 mg/kg i.v.). Catheters were inserted in the femoral artery and vein. A Gould Brush Model 260 recorder (Gould Inc., Instruments Division, Cleveland, Ohio) was used to monitor a lead II surface ECG and systemic arterial pressure. Body temperature was controlled an infrared lamp. Left thoracotomy was performed by excision of ribs 2-5. A pericardial cradle was constructed, and the left anterior descending (LAD) coronary artery was isolated at its bifurcation. A Gould Brush Model 260 recorder (Gould Inc., Instruments Division, Cleveland, Ohio) was used to monitor a lead II surface ECG and systemic arterial pressure. Body temperature was maintained at 37° C via a thermostatic esophageal probe controlling an infrared lamp. Left thoracotomy was performed by excision of ribs 2-5. A pericardial cradle was constructed, and the left anterior descending (LAD) coronary artery was isolated at its bifurcation.

**Electrode Localization**

After termination of the experiment, each plunge electrode was removed and replaced by a labelled pin as described previously. The heart was removed and placed in formalin for at least 24 hours. After fixation, a detailed epicardial map was made by placing clear cellophane over the surface of the fixed heart and tracing the location of the labelled pins in relation to each other and to anatomical landmarks. To facilitate sectioning, the pins were replaced by small color-coded plastic brush bristles. The heart was then cut transversely into slices approximately 5-7 mm thick. The outline of each slice was traced carefully to show the exact insertion site and direction of each electrode as well as the site of the most distal bipole pair. The tracings were then enlarged for later three-dimensional isochronic map construction as described below.

**Mapping System**

Details regarding the cardiac mapping system used in the present study have been reported previously and will be summarized only briefly here. Electrical activity from multiple intramyocardial sites was recorded from plunge electrodes as shown in Figure 1. Intramural recordings were obtained from plunge electrodes that were fabricated using 50-\( \mu \)m diameter, Teflon-insulated tungsten wire contained within a 21-gauge, stainless steel, straight needle. All electrodes have an interpole spacing of 500 \( \mu \)m. The left ventricular plunge electrodes contained 8 bipolar pairs each separated by 500 \( \mu \)m. The septal electrodes contained 4 bipolar pairs each separated by 2.5 mm. The right ventricular electrodes consisted of 2 bipolar pairs separated by 500 \( \mu \)m. The most proximal of the electrode pairs was located 500 \( \mu \)m from the epicardial surface. The large plunge electrodes, previously used...
in our study of chronic canine myocardial infarction, allowed assessment of septal activation as deep as 8 mm below the epicardial surface.

Bipolar electrogram data from each of the 232 sites were individually amplified, filtered from 40–500 Hz, and converted from analog to digital at a 2 kHz sampling rate to yield true simultaneous data acquisition without multiplexing. The digital data were then stored on a Sangamo Weston Sabre IV high-density recorder (Fairchild Weston Systems, Inc., Sarasota, Fla.) in 12 parallel bits (dynamic range of ± 50 mV with least significant bit resolution of 25 µV). The data were later analyzed off-line using a PDP 11/34A computer system (Digital Equipment Corporation, Maynard, Mass.) with interactive high-resolution color graphics.

Construction of individual isochronic maps was performed as follows: initially, the tape containing the electrogram data was played back, and the surface lead II tracing also stored on the digital tape was reviewed to locate the depolarizations of interest, such as a premature ventricular complex or a run of ventricular tachycardia. Individual electrograms from each electrode site occurring within the selected window were automatically calibrated and displayed, 8 at a time, on a high-resolution Barco color monitor. Computer-derived activation times were assigned, based on a peak criterion. The computer-chosen activation time of each electrogram was reviewed and manually overridden if required. Because signals obtained from the ischemic zone were of low amplitude, an amplitude threshold of 0.25 mV was considered to indicate activation of tissue by the depolarizing wavefront. The basis for this level of activity being consistent with depolarization of the tissue is the previous observation that activity of lower amplitude was not accompanied by activation of immediately adjacent electrode sites. Furthermore, the use of this criterion of 0.25 mV did not influence the construction of the three-dimensional isochronic maps.

Conduction block between two electrodes was defined by any of three criteria: 1) intervening electrodes exhibited no activation, 2) large temporal gaps occurred between two electrodes but adjacent electrodes in a less direct spatial path exhibited sequential activation, and 3) recordings from electrode sites distal to a block demonstrated low-voltage electrotonic activity preceded or followed closely by a larger amplitude electrogram. There is a slight chance that the low-voltage electrotonic activity that is preceded or followed by a discrete activation represented propagated activity in a small region of myocardium subtended within the 500-µm interbipole spacing; however, this did not influence the construction of the three-dimensional isochronic maps.

Following extensive review of all electrograms, activation times were printed out for all sites and were then assigned to their respective intramyocardial locations as indicated by the detailed three-dimensional localization described above. Isochrone maps were then hand-drawn to yield a three-dimensional topographical contour map of cardiac activation.

**Data Analysis and Statistics**

The direction of the three-dimensional activation wavefront is described by the following: "transverse activation" is conduction that proceeds in an endocardial-to-epicardial direction; "longitudinal activation" is conduction to adjacent regions (side-to-side) in the same intramural plane (e.g., endocardium or epicardium). This may involve activation that proceeds apically, basally, clockwise, or counterclockwise, or in any other intermediate direction perpendicular to the endocardial-to-epicardial direction. Longitudinal and transverse activation are not defined in reference to fiber orientation.

Total activation time for each beat was determined by taking the difference in the activation times between the earliest and latest sites of activity. Conduction velocity was determined when isochrones were parallel by dividing the distance between two recording sites along the direction of the activation wavefront by the difference in their activation times. The ischemic zone,
after LAD coronary occlusion, was not demarcated by dye or microspheres. However, the region of ischemia was defined as those regions in which the transmural recordings exhibited a marked decrease in amplitude and an increase in duration of the bipolar electrogram since this correlates well with the regional decrease in myocardial blood flow.\textsuperscript{7} All data are presented as mean ± SEM. Statistical analyses were performed by the Student’s t test for paired or unpaired data as appropriate. Differences of \( p < 0.05 \) were considered significant.

### Results

**Assessment of Plunge Electrode Insertion on Hemodynamics and Transmural Activation Time**

Insertion of 50 plunge electrodes into the canine heart in vivo resulted in no significant alteration in hemodynamic parameters (heart rate, mean arterial blood pressure, mean left ventricular pressure, cardiac output, and stroke work), when assessed prior to and 5, 30, 60, and 180 minutes after electrode insertion.\textsuperscript{8} In the 7 animals evaluated in the present study, insertion of 37 plunge electrodes did not result in any significant change in heart rate (182 ± 11 vs. 180 ± 9 min\(^{-1}\)) or mean arterial blood pressure (105 ± 9 vs. 105 ± 8 mm Hg) when assessed prior to and 30 minutes after electrode insertion. Furthermore, in 4 of the 7 animals, mean left atrial pressure was determined prior to and 30 minutes after plunge electrode insertion. While 2 of the animals had mean left atrial pressures in the control state of 3 mm Hg, 1 animal had a mean left atrial pressure of 1.0 ± 1.2 vs. 1.5 ± 1.2 mm Hg.)

Also, insertion of 50 plunge electrodes into the canine heart did not affect epicardial activation time measured using surface button electrodes prior to and after plunge electrode insertion.\textsuperscript{9} In the present study, alteration of the electrocardiogram occurred in 1 animal in which insertion of a plunge electrode into the high anterior septum led to a right bundle-branch block pattern that did not resolve with removal of the electrode. Three-dimensional mapping confirmed a right bundle-branch block with activation of the right ventricular wall (18 sites). Times were assessed before and after insertion of the remaining 34 plunge electrodes in 4 animals in which the electrocardiogram did not change with plunge electrode insertion. The activation times of the 3 widespread electrodes did not change significantly after insertion of the remaining 34 electrodes.

**Incidence of Arrhythmias**

Occlusion of the LAD coronary artery was performed in 6 cats in which activations were not altered by electrode insertion. None of the animals developed ventricular fibrillation. Four developed ventricular tachycardia. One developed only PVCs and 1 developed no ventricular ectopy. Complete detailed three-dimensional mapping was performed on 59 beats of ventricular tachycardia (11 runs) and 13 single PVCs and couplets and on 84 sinus beats (9 control and 75 during ischemia) for a total of 156 beats determined on the basis of over 36,000 individual measurements of activation time.

**Activation Sequences During Sinus Rhythm**

Sinus rhythm in the control preischemic state was characterized by rapid conduction that initiated in the septum and spread throughout the heart with a total activation time of 25 ± 2 msec (\( n = 6 \)). Activation spread from subendocardium to epicardium. A representative three-dimensional isochronous map of a normal sinus beat in the control state prior to ischemia is illustrated in Figure 2A. Activation began in the septum (beats \( \text{NS}_{\text{control}} \), level III, *), with rapid activation to both the apex and base and from endocardium to epicardium. By 20 msec, most of the heart had depolarized except for the posterior left ventricular wall and a portion of the right ventricle. Ventricular activation was complete by 30 msec with a total activation time of 29 msec, equivalent to the duration of the QRS. Activation maps of sinus beats prior to ischemia were superimposable for each animal with activation times varying no greater than 2 msec.

Within minutes after ischemia, electrograms during sinus rhythm fractionated into multiple components, with a decrease in amplitude and an increase in duration (see Figures 3 and 5). However, activation times were not difficult to assign since the degree of fractionation was markedly less than previous studies due to the small interpole distance (500 \( \mu \)m). After ischemia and during sinus rhythm, there was progressive conduction delay. Total activation time increased to 64 ± 6 msec at 5 minutes after coronary occlusion (\( n = 6 \)) (\( p < 0.001 \) vs. control sinus beats). Delay, which could often vary considerably from beat-to-beat, was due to both slow conduction and block. Slow conduction occurred primarily in the longitudinal, or side-to-side direction, rather than in a transverse or endocardial-to-epicardial direction. Unidirectional block, either transmurally or nontransmurally, also occurred in the longitudinal direction during sinus rhythm with marked activation delay distal to the area of block. Conduction block could occur consistently from beat-to-beat, with a 2:1 pattern of periodicity, or with a more erratic occurrence with no consistent repetitive pattern. Conduction block also occurred in the transverse direction, both in an endocardial-to-epicardial direction and in the reverse epicardial-to-endocardial direction. As a result of block in both longitudinal and transverse directions, delayed activation was almost always found in the subendocardial and midmyocardial regions.
Examples of three-dimensional activation sequences of 2 consecutive sinus beats 5 minutes after ischemia are illustrated in Figure 2B. The surface electrocardiogram shows a loss in height of the R wave and ST segment depression. In the first sinus beat during ischemia (NS$_2$), conduction started from the site of initiation in the septum (NS$_1$, level III, *) and spread rapidly to both apex and base. Activation posteriorly in the nonischemic zone was comparable to the preischemic control. However, unlike conduction during control sinus rhythm where longitudinal conduction was very rapid and most subendocardial regions lay within the 10 msec isochrone (Figure 2A), sinus rhythm 5 minutes after ischemia was characterized by slow longitudinal conduction. In addition, there were areas of conduction block, as indicated by the blackened areas, where electrodes demonstrated no activation and thickened lines where large temporal gaps between two electrode sites occurred, while the adjacent electrodes in a less direct spatial path demonstrated sequential activation. In levels II and III, the depolarizing wave-front spread slowly both clockwise and counterclockwise (relative to the base-apex direction) to activate the subendocardium in the anterior left ventricle by 60 msec. In level I, nontransmural longitudinal conduction block occurred in both clockwise and counterclockwise directions. The block was functional in nature since its presence and degree varied from beat to beat. Late activation in level I occurred from both directions around the areas of nontransmural block and from late epicardial activation from level II. Transverse activation in this region in level I was slow and occurred in an epicardial-to-endocardial direction. The latest activation for this beat occurred in the subendocardium 81 msec after initiation (NS$_1$, level I, 90-msec isochrone). In the apical slice at level IV, longitudinal conduction was slow, and, unlike the control state, transverse conduction proceeded from endocardium to midmyocardium with block in the midmyocardium at two sites. Conduction continued slowly around the areas of block with delayed activation of the epicardium and late activation from the epicardium to the...
initiation of Arrhythmias by Intramural Reentry

In 76% of cases (16 of 21), PVCs and runs of ventricular tachycardia (VT) were initiated through intramural reentry with the initiation occurring adjacent to the site of very delayed subendocardial or midmyocardial activation. The length of the reentrant pathway varied from 1.8–3.0 cm. The total activation time of sinus beats preceding PVCs or runs of VT initiated by intramural reentry was 149±7 msec, p<0.001 vs. total activation time of sinus beats 5 minutes after ischemia not followed by either PVCs or VT. An example of the initiation of a PVC by intramural reentry 5 minutes after ischemia is shown in Figure 4. For comparison, this example is from the same animal as in Figures 2 and 3. The activation sequence of the preceding sinus beat (NS) is shown on the left with the initiation at the asterisk (level III). The activation wavefront proceeded with slow longitudinal conduction both clockwise and counterclockwise, encountering transmural block (level III), nontransmural block (levels I and II) longitudinally, and transverse block (level IV). In the most basal section (level I), the wavefront propagated in both a clockwise and a counterclockwise direction, with slow activation around an area of nontransmural block (70-msec isochrone), epicardial-to-midmyocardial activation, and very late activation of the subendocardium (190-msec isochrone) around the area of midmyocardial block. This delay in subendocardial activation allowed recovery proximal to the longitudinal block, with initiation of the PVC in the adjacent subendocardium shown on the right by reentry 40 msec later at the 230-msec isochrone (PVC, level I, *). The conduction velocity was calculated as 0.09 m/sec from the 160 to the 190-msec isochrone during the sinus beat. The distance from the end of the 190-msec isochrone to the initiation of the PVC at the asterisk was 3.5 mm, which would require a similar conduction velocity of 0.09 m/sec. Thus, the 40-msec "gap" was entirely explained on the basis of continued slow conduction from the 190- to the 230-msec isochrone. In contrast to the second sinus beat shown in Figure 2B, which did not initiate a PVC, initiation of the PVC was dependent on late midmyocardial-to-subendocardial activation, which did not show decrement and which led to activation of the adjacent subendocardium (Figure 4, PVC, *). Although the conduction velocity of the very delayed activation was similar for these two sinus beats, the pathway of delayed activation differed. This is shown in more detail in Figure 5. On the top is a blowup of the isochronic map of the most basal sections (level I) of the sinus beat and PVC shown in Figure 4. Below are selected bipolar electrograms from subendocardial sites A and C and subendocardial-to-subepicardial electrograms for the electrode shown at B. The nontransmural longitudinal block at the level of the subendocardium between A and C is quite apparent since the spread of the activation from these sites failed to activate the subendocardium at B as evidenced by the lack of early activation in the subendocardium at B (L). Late activation in the region of site B conducted from the subepicardium to the midmyocardium (67–72 msec) but was blocked in the midmyocardium. Conduction then moved around this block to activate the subendocardium at 188 msec. The wave-
Figure 3. Diagrammatic representation of development of transverse conduction block after LAD coronary occlusion. In the upper part of the figure are expanded drawings of isochronic maps of the most apical sites outlined by a dotted line in Figure 2 for the control preischemic sinus beat shown on the left and the first sinus beat 5 minutes after coronary occlusion (NS) shown on the right. On the top portion of the figure is the location of the plunge-needle electrode containing 8 bipolar pairs. Arrows denote spread of the activation wavefront. In the lower part of the figure, bipolar electrogram recordings from the 8 intramural sites from the actual electrode are shown. Isochronic maps and bipolar electrograms are both oriented with subendocardium on top, and subepicardium on the bottom. Signals are autocalibrated, and amplitude calibration scale is displayed to the left of each electrogram. A 248 msec time window is shown for each recording. Vertical cursor marks the activation point on each electrogram and its activation time (relative to initial activation for each beat). Numbers on the left of each tracing (17–24) indicate channel number from which recording was obtained.
FIGURE 4. Three-dimensional isochronic maps of a sinus beat (NS) followed by premature ventricular complex (PVC) 5 minutes after occlusion of LAD coronary artery. Initiation of the PVC occurs by intramural reentry shown by the dark arrow from NS to PVC. Additional details are as described in Figure 2 legend.

front then continued just basal to an area previously activated (80-msec isochrone) and activated an adjacent subendocardial site (*) at 228 msec to initiate the PVC. This process is termed "intramural reentry."

After initiation of the PVC (Figure 4), the depolarizing wavefront spread rapidly to the base, and conducted slowly both clockwise and counterclockwise, encountering transmural block (level I) and nontransmural block (levels II and III). There was a greater degree of transverse block in level IV with centrifugal activation of the midmyocardium and epicardium in a counterclockwise direction. The terminal activation in
level III at the 330-msec isochrone resulted from fusion of two epicardial activations from levels II and IV, 94 msec after the initiation of the PVC, but did not propagate further. Thus, the relatively rapid activation of the PVC led to fusion of the wavefront and termination of the arrhythmia.

It is interesting to note that the mechanism responsible for initiation of the PVC in Figures 4 and 5 by a process of intramural reentry would have escaped detection by epicardial mapping alone since the major area of delay was in the midmyocardium and subendocardium. Mapping of the epicardium alone would have demonstrated terminal epicardial activation of the sinus beat at 70 msec (NS, level I, arrow, Figure 4) and initiation of the PVC at the epicardial surface at 240 msec (PVC, level I, arrow, Figure 4) with no intervening epicardial activations, suggesting a nonreentrant mechanism arising in the nonischemic region.

An example of a sinus beat followed by a 3-beat run of VT that is initiated by intramural reentry 4 minutes after ischemia is shown in Figure 6. Initiation of the last sinus beat (NS) occurred in the septum (level III, *) and spread rapidly to the apex and base, and clockwise and counterclockwise, encountering varying degrees of block. There was longitudinal block that was transmural in levels II and III and nontransmural in levels I and IV. Transverse block occurred in level V. Spread of the depolarizing wavefront was delayed because of slow longitudinal conduction in levels I and III. Activation then spread apically from the 70-msec isochrone in level II to the 130-msec isochrone in level III, and to the 180-msec isochrone in level IV, encountering tissue that was not depolarized previously because of longitudinal block in levels III and IV. Despite the small volume of tissue that is activated late (180-msec isochrone), the wavefront continued apically and activated an adjacent subendocardial site (T, level V, 210-msec isochrone, *) to initiate the first beat of the tachycardia by intramural reentry. Once again, the conduction velocity of the very delayed terminal activation of the sinus beat (0.11 m/sec, from the 130-msec isochrone, level III, to the 180-msec isochrone, level IV) was the same as the conduction velocity from the end of the sinus beat to the initiation of the first beat of ventricular tachycardia (0.12 m/sec, from the 180-msec isochrone, level IV, to the 210-msec isochrone, beat T, level V). Thus, the activation wavefront was continuous. In this case and in other examples analyzed, the site of initiation of the first beat of ventricular tachycardia occurred at a subendocardial site in the ischemic zone. However, because of transverse or endocardial-to-epicardial block, epicardial breakthrough did not occur at this site but rather at an adjacent site in the nonischemic zone, where transverse block did not occur (T, level V, 240-msec isochrone). Thus, the finding that epicardial breakthrough occurs in the nonischemic zone does not imply that the ectopic impulse arose in the nonischemic zone. Mapping of the epicardial surface alone would have failed to detect the marked subendocardial delay, and the mechanism would not have been attributed to reentry.

Although the initiation of PVCs and runs of VT by intramural reentry usually occurred in the subendocardium, adjacent to an area of very delayed subendocardial or midmyocardial activation, it occurred on the epicardial surface on only one occasion.

**Maintenance of Ventricular Tachycardia**

Maintenance of VT was usually due to intramural reentry. When a run of ventricular tachycardia was initiated by intramural reentry, maintenance usually involved a similar or an adjacent pathway. For example, the sites of marked delay during sinus rhythm that initiated the tachycardia were often the sites of continued delay that played a pivotal role in the maintenance of the intramural reentry circuit. The extent of conduction delay in the preceding reentrant beat (159 ± 8 msec) was one of the major determinants as to whether VT continued to propagate. Without marked delay, reentry could not occur since there was not adequate time for adjacent tissue to recover excitability to allow reactivation and initiation of the next beat of the tachycardia. This is illustrated in Figure 7A where the lead II surface ECG of a sinus beat and a single PVC 5 minutes after ischemia is shown. This example is identical to that shown in Figure 4, in which the PVC was initiated by intramural reentry. Figure 7B shows a sinus beat followed by an 8-beat run of ventricular tachycardia 4 minutes after ischemia in which the first beat of the tachycardia was initiated by intramural reentry in the same manner as the PVC shown in Figure 7A. Below each beat is shown the total activation time for each beat in milliseconds. The single PVC in Figure 7A was initiated by intramural reentry, but the ectopic beat conducted with an activation time of only 94 msec, which was insufficient time for depolarized tissue to recover its excitability to continue and initiate a sustained tachycardia. In contrast, the initial beat of the run of ventricular tachycardia in Figure 7B conducted with an activation time of 164 msec, which was long enough for adjacent tissue to recover its excitability and maintain the VT by a process of intramural reentry. Furthermore, all subsequent beats of the tachycardia exhibited a comparable or greater degree of activation delay as the tachycardia continues to propagate. However, the initiation of the second beat of the VT (T2) and all subsequent beats of the tachycardia to T4 occurred at a site just 5 mm apical to the site of initiation of the first beat. Figure 8 shows the three-dimensional isochronic maps of the third and fourth beats of the tachycardia. The third beat was initiated at a subendocardial site in level II (*). It could not propagate counterclockwise in levels I and II because of transmural longitudinal block. These sites of block were the area of terminal activation from the previous beat and the block was likely due to the wavefront encountering refractory tissue. The activation wavefront moved counterclockwise slowly, but when it reached the high anterior wall, very marked delay occurred. This region, which was an area of marked delay and block during the terminal sinus beat, continued to demonstrate very slow conduction around an area of nontransmural
FIGURE 5. Actual intramural electrogram recordings indicating initiation of PVC by intramural reentry (shown below). On the top portion of the figure are the most basal slices from Figure 4 for both the normal sinus beat (NS) and the PVC. The recording labelled A is taken from subendocardium from the point labelled A on the isochronic map for the normal sinus beat. Recordings labelled B are 8 transmural recordings from subendocardium (SUBENDO) to subepicardium (SUBEPI) shown by the dotted line at point B from SUBENDO to SUBEPI. Point C indicates the subendocardial recording from point C, also on the isochronic map for the normal sinus beat. Arrow indicates the point of initiation of reentry. See Figure 2 legend for additional details.
block. The latest epicardial activations in levels I and II were 130 and 140 msec, respectively. Although these led to late epicardial activation in level III (200-msec isochrone), this part of the wavefront did not propagate further and was not part of the reentrant pathway leading to initiation of T4. Rather, it was the slow, reverse epicardial-to-endocardial activation in level II (170-msec isochrone) that then led to activation of the same subendocardium site at which T3 was initiated (T3, level II, *), completing the reentrant pathway.

Again, mapping the epicardial surface alone would have indicated that reentry was not present since the latest epicardial activation T3 (level III, 200-msec isochrone) was very distant from the first epicardial breakthrough site of T4 (level II, site E), in reality, the reentrant pathway was moving intramurally. The conduction velocity of the terminal activation of T3 (0.17 m/sec, from the 130-msec isochrone, level I to the 170-msec isochrone, level II) was similar to that from the 170 to the 200-msec isochrone (T3, level II, *) (0.16 m/sec).

Figure 6. Three-dimensional isochronic maps of a sinus beat (NS) followed by a three-beat run of ventricular tachycardia (T1, T2, T3), 4 minutes after occlusion of LAD coronary artery. In this case, initiation of the tachycardia occurs by intramural reentry as shown by the arrows from level IV to V. See Figure 2 legend for additional details.
Initiation of Arrhythmias by Nonreentrant Mechanisms

Although reentry is the predominant mechanism responsible for both initiation and maintenance of VT, a nonreentrant mechanism was found to initiate VT in 24% of cases (5 of 21). This was based on the finding that the marked delay from the preceding beat occurred at sites distant from the initiation of the nonreentrant beat, and despite the presence of multiple intermediate electrode recording sites, there was no intervening electrical activity. Nonreentrant initiation of VT occurred in the subepicardium and in the subendocardium at the border of the nonischemic zone. The activation delay of the sinus beats preceding nonreentrant initiation (129 ± 12 msec) was not significantly different from the delay of sinus beats preceding initiation of PVCs or VT due to reentry. However, the marked delay occurred at sites distant from the initiation of nonreentrant activity. In contrast, maintenance of VT by a nonreentrant mechanism was always initiated in the subepicardium. The activation delay of ectopic beats maintaining the nonreentrant ventricular tachycardia (136 ± 7 msec) did not differ significantly from those maintaining reentrant tachycardia, but again, the marked delay was distant from the site of nonreentrant initiation of the subsequent nonreentrant beat.

The isochronic maps of a sinus beat and the first 2 beats of a 3-beat run of VT 5 minutes after ischemia are shown in Figure 9. After the initiation of the sinus beat (NS) in the septum (level III, *), the wavefront moved apically and basally as well as clockwise and counterclockwise, encountering various degrees of transmural and nontransmural block. Very slow conduction occurred in levels III and V and merged at the site of latest activation (level IV, 150-msec isochrone) at a site near the apex. However, initiation of the tachycardia (T₁) occurred 80 msec later at a distant subendocardial site in the base (T₂, level I, *). There was no intervening activity between the termination of one beat and the initiation of another despite electrode being located at multiple intermediate sites. Furthermore, after a total activation time for the first ectopic beat of only 98 msec with the latest activation at a site in level III (320-msec isochrone), the second beat of the tachycardia (T₂) was initiated at a distant site but in the base in the subepicardium (T₂, level I, *). Again, no intervening depolarizations were found. The third beat (T₃) was initiated (by a nonreentrant mechanism) at the same subepicardial site as T₂, 243 msec after the initiation of T₁.

Thus, VT can be initiated and maintained by either intramural reentry or nonreentrant mechanisms. Several runs of VT were initiated and maintained by the same mechanism, whether reentrant or nonreentrant. However, the situation was even more complex in that both mechanisms could be present not only in the same run of tachycardia but also in the same beat. A continuous surface lead II ECG tracing from an animal after 6 minutes of ischemia is shown in Figure 10. For each beat, detailed three-dimensional mapping was performed to determine its mechanism and site of initiation. The first single PVC-labelled R₄ was initi-
FIGURE 8. Three-dimensional isochronic maps representing the transition between the third ($T_3$) and fourth ($T_4$) beats of the ventricular tachycardia shown in Figure 7. 4 minutes after coronary occlusion. Arrows indicate sites of intramural reentry. Area designated with an $E$ on the level II map of $T_3$ indicates the area of earliest epicardial activation in the normal zone.
FIGURE 9. Three-dimensional isochronic maps representing a sinus beat followed by the first 2 beats of a 3-beat run of ventricular tachycardia (T₁,T₂), 5 minutes after occlusion of the LAD coronary artery. Maps indicate a nonreentrant mechanism for initiation and maintenance of ventricular tachycardia. T₁ initiated in the subendocardium (*, level I) and T₂ is initiated in the subepicardium (*, level I), both by a nonreentrant mechanism. See Figure 2 legend for additional details.
Figure 10. Multiple mechanisms of initiation and maintenance of ventricular tachycardia. A continuous surface ECG tracing 5 minutes after occlusion of the LAD coronary artery. Each sinus and premature beat has been mapped three-dimensionally and the mechanism (R, reentrant; NR, nonreentrant) of initiation for each ectopic beat is listed below each beat. R, refers to intramural reentry occurring in the apical region, and R, refers to intramural reentry occurring along a different pathway in the base. Note that a tachycardia can be initiated by one mechanism but maintained or terminated by another. In addition, the initial beat of the third run of ventricular tachycardia (VT,) is initiated both by intramural reentry and a nonreentrant mechanism resulting in a “fusion beat.”

The 3 tachycardias shown in Figure 10 were each maintained by a nonreentrant mechanism, arising from the same subepicardial site (see Figure 9, T,, level I, *). Furthermore, this site never initiated a tachycardia, but it maintained the tachycardias in which the first beats were initiated by either a nonreentrant, reentrant, or a combination of both reentrant and nonreentrant mechanisms. In the 3 tachycardias shown in Figure 10, T, was initiated by the subepicardial site between 156 and 174 msec after that site had been activated during T, (see Figure 12). However, for VT, and VT, T, and all subsequent beats of the tachycardia, except the last beats, were initiated from this same site with a coupling interval of 205–222 msec (Figure 12). In the case of VT, this focus suddenly ceased after T,, but a subsequent beat (T,) was initiated much later in the apex through the mechanism of intramural reentry. In the case of VT, the last beat of the tachycardia (T,) was initiated from the same epicardial site but with a longer coupling interval of 281 msec prior to termination of the tachycardia. For VT,, which was only a 3-beat run of ventricular tachycardia, T, and T, were initiated at the same apical site but with a longer coupling interval of 210 msec in level V by intramural reentry. Simultaneously there was a nonreentrant initiation at a subepicardial site in level I (diamond) with no intervening activity seen at multiple adjacent electrode sites. Thus, both mechanisms can interact and compete, even resulting in a “fusion” beat.

Discussion

The results of the present study demonstrate for the first time that the initiation, as well as the maintenance, of VT during early myocardial ischemia can be mediated by intramural reentry. Previous studies have suggested reentry as a possible mechanism based on several indirect findings, including the presence of fractionated electrograms and continuous electrical activity between the basic and premature beat. However, proof requires the delineation of the reentrant pathway. Using detailed simultaneous mapping from 232 intramural sites in the feline heart, the complex movement of the activation wavefront was delineated three-dimensionally. The results demonstrated that the
FIGURE 11. Three-dimensional isochronic maps of the first beat ($T_1$) of third run of ventricular tachycardia ($VT_3$) shown in Figure 10 and its preceding sinus beat (NS) 5 minutes after occlusion of LAD coronary artery. The first beat of the tachycardia is initiated simultaneously by intramural reentry occurring in apex (asterisk) indicated by arrows and by a nonreentrant mechanism occurring in basal subepicardium ($T_1$, level 1, *). See Figure 2 legend for additional details.
very delayed activation of the last sinus beat occurred in the subendocardium and midmyocardium adjacent to the initial site of activation of the premature beat, and that the activation of this adjacent subendocardial site in initiating the premature beat occurred with the same conduction velocity of the wavefront as seen during the delayed activation of the sinus beat. The question of whether initiation of the premature beat occurred by means of continuous cell-to-cell spread of depolarization was secondary to electrotonic activity that induced triggered activity via early or delayed after-depolarizations could not be answered definitively. However, because the slowed conduction velocity was remarkably consistent from the end of the sinus beat to the initiation of the premature beat and because the markedly delayed activation of the preceding sinus beat could be characterized by bipolar electrograms with amplitudes of nearly 2 mV (Figure 5), the delayed activation wavefront was sufficient to depolarize the adjacent regions directly to initiate the premature beat by a purely reentrant mechanism.

Although the finding of markedly delayed activity in the subendocardium and midmyocardium differs from previous studies that demonstrated predominantly epicardial conduction delay, the present findings are not inconsistent. First, a moderate degree of conduction delay was found in the subepicardium. Second, based on differences in action potential characteristics and activation times between closely adjacent cells, a subendocardial border zone may exist between superficial and deep subendocardial cells during ischemia and may account for the findings of marked subendocardial and midmyocardial delay in the present study. Third, markedly delayed activation in the subendocardium and midmyocardium, which were found in an overwhelming majority of instances involving reentrant and nonreentrant ectopic beats, has been noted by others during both myocardial ischemia and several days after myocardial infarction. This accounts for the occasional finding of intramural reentry in these situations. The reason for the increased prevalence of intramural reentry noted in the present study probably relates to the resolution of the mapping system used, which allowed for the delineation of small regions of marked intramural delay. The limited number of intramural recording sites in the large canine and porcine hearts in these previous studies limited the delineation of the delayed intramural activation that occurs in very localized regions but which contributes significantly to the occurrence of intramural reentry. Even mapping from 60 intramural sites in the relatively large canine and porcine heart leaves a very large portion of the heart without adequate recordings. In the present study, recordings were obtained from 232 individual intramural sites from the left ventricle, right ventricle, and septum of the feline heart. Since the feline heart is approximately one-twelfth the mass of the canine heart, our procedures provided a three-dimensional resolution (to resolve very small reentrant pathways and to leave no portion of the heart unmapped) comparable to obtaining recordings from nearly 2,800 sites in the canine heart. The feline preparation is also useful because of the similarity of the coronary artery anatomy to that of man, as well as the reproducible arrhythmias that occur during myocardial ischemia.

Our findings also differ in some respects from those of Janse et al., who demonstrated evidence of reentry on the epicardial surface during the maintenance of VT but failed to demonstrate reentry during the initiation of VT. The intramural location of the reentrant pathways and the small path length attest to the need for enhanced resolution and complete three-dimensional mapping to define the movement of the complex three-dimensional activation wavefront and to delineate the reentrant pathway.

The basis for the genesis of reentry in the initiation of ventricular tachycardia is the slow conduction and
block present even during normal sinus rhythm early after ischemia. Unidirectional block during sinus rhythm occurs in both a longitudinal or side-to-side direction and in a transverse or endocardial-to-epicardial direction. The nature of this unidirectional block is unknown but likely involves nonuniform recovery of excitability. Although early ischemia is characterized by a decrease in the refractory period in the ischemic zone, marked differences in the refractory periods occur even between adjacent regions and between the endocardium and epicardium. Since conduction block can occur when the gradient of recovery of excitability becomes marked, this dispersion of recovery may account for both the longitudinal and transverse block. This conclusion is supported by the finding that the development of conduction block occurred in the wake of recently activated tissue (see Figures 4 and 8). It was surprising that, despite similar morphologies of the surface ECG during sinus rhythm after ischemia, marked differences in conduction delay and block were present from beat to beat. Although disparities in the recovery of excitability appear likely as the mechanisms contributing to unidirectional block, other possibilities exist. For example, differences in propagation of the activation wavefront in relation to fiber orientation can lead to differences in conduction velocity, wavefront voltage, and block. Likewise, recurrent discontinuities in axial resistance can also lead to decremental conduction, block, and the development of a reentrant circuit. Because fiber orientation was not assessed in the present study, comment cannot be made on its precise role in the development of unidirectional block and thereby the development of the reentrant pathway.

The extent and location of slow conduction and block could vary markedly between consecutive sinus beats; and when activation becomes substantially delayed, reentry can occur. Slow conduction around an area of nontransmural, unidirectional longitudinal block could lead to delayed activation distal to the block. If conduction was delayed long enough to allow recovery of tissue proximal to the block, reentry could occur. The same was true for transverse block where slow conduction around an area of transverse block could lead to delayed activation. If the wavefront was delayed markedly by conducting through adjacent subendocardium and midmyocardium that was not activated by the initial wavefront, it could reexcite tissue proximal to the block and initiate reentry. Although delay was necessary for reentry to develop, it was not a sufficient condition since delay as long as 220 msec was not associated with reentry. Therefore, other factors such as the refractory properties of the adjacent tissue, the conduction velocity of the activation wavefront, and the precise pathway also contribute.

In addition to intramural reentry, a nonreentrant mechanism also contributes to initiation and maintenance of VT. This conclusion was based on the finding that the marked intramural delay from the preceding beat occurred at a site distant from the initiation of the nonreentrant beat, despite multiple intervening electrodes. The possibility that reentry occurred between recording sites and was not detected is unlikely because of the high resolution of the system used. Although the smallest reentrant pathway delineated during early ischemia in the present study was 1.8 cm in length, delineation of reentrant pathways as small as 10 mm in length has been possible during ventricular fibrillation after reperfusion, using 232 intramural recording sites in the feline heart. Thus, the resolution of the three-dimensional mapping system is sufficient to delineate very small reentrant circuits. Some studies have suggested that reentrant circuits can be present in a volume of tissue as small as 0.3–0.5 cm³. Yet, in the present findings, reentrant pathways as small as 1.8 cm can be viewed as circular pathways with circumferences of 1.8 cm and diameters of approximately 0.6 cm. Thus, the smallest volume of tissue subtending this reentrant loop is on the order of 0.2–0.3 cm³, which is consistent with the studies cited above. Microreentry or reflection, involving a small number of adjacent myocytes could not be ruled out, but it was unlikely since the electrograms from the sites of nonreentrant activation failed to demonstrate any evidence of delayed activity or adjacent inexcitable segments. The mechanism underlying this nonreentrant activity is unknown. Abnormal automaticity is unlikely since it is suppressed by elevations of extracellular K⁺ that occur during ischemia. Furthermore, the idioventricular rate is unchanged during early ischemia. Janse and Pogwizd and Con have proposed that “injury currents” flowing between ischemic and normal tissue initiate premature beats including VT. Using isovoltic mapping, these investigators demonstrated a maximum current source of 2 μA/mm² in the nonischemic region that may be adequate to initiate a premature depolarization. Another possible mechanism is triggered activity that is induced by either early or delayed afterdepolarizations. Although early afterdepolarizations have been noted in the myocardium of ischemic papillary muscle, delayed afterdepolarizations have not been demonstrated in ischemic myocardium. However, they occur in states of increased intracellular calcium that may occur during ischemia in vivo. Recent studies have demonstrated that lysophosphoglycerides, which accumulate in ischemic myocardium, particularly in the extracellular and interstitial space, are capable of inducing delayed afterdepolarizations and triggered rhythms in vitro. The delayed afterdepolarizations induced by lysophosphoglycerides occur in vitro despite increased extracellular K⁺ and a decrease in pH. The nonreentrant maintenance of VT that occurred in the subepicardium was particularly interesting in that it possessed many of the features of a triggered rhythm associated with delayed afterdepolarizations. It never initiated a tachycardia but always began after a premature beat, whether reentrant or nonreentrant from another site. A decreased coupling interval of the first premature beat led to a decreased coupling interval of the subsequent tachycardia. In one case, the tachycardia actually slowed prior to termination. Although
none of these features alone is unique to triggered rhythms associated with delayed afterdepolarizations, the similarity is intriguing. The finding that both reentrant and nonreentrant mechanisms occur in the same tachycardia suggests that these mechanisms can interact. However, the finding that both mechanisms can occur in the same beat demonstrates that they can compete and, at times, lead to fusion of a premature beat. Thus, ventricular tachycardia can be initiated, maintained, and terminated by either mechanism.

Although the present results demonstrate both longitudinal and transverse unidirectional block, slow conduction, and delayed activation distal to the block, these findings do not fulfill the last of the required criteria for reentry initially proposed by Mines since the reentrant pathway was not interrupted resulting in abolition of the arrhythmia. However, the problems inherent in physically interrupting the reentrant pathway in the present study include the following: 1) the location of the reentrant pathway was not known de novo and can only be determined by multiple simultaneous transmural recordings and subsequent detailed analysis; 2) since the pathway spreads as a three-dimensional wavefront through both subendocardial and midmyocardial regions, ablating the exact pathway involved would be difficult, if not impossible; 3) since conduction through a specific reentrant pathway was not always confined to a discrete region, but at times involved adjacent regions, ablating a certain area might only shift the reentrant pathway to adjacent regions and thereby not abolish the reentrant circuit; and 4) during ischemia, several reentrant pathways are involved. Thus, ablating a site in one reentrant pathway might only shift the reentrant pathway to an alternate site, thus failing to abolish the arrhythmia. In addition, the presence of both reentrant and nonreentrant mechanisms at the same time and in the same run of VT or even within the same premature beat probably precludes abolition of the arrhythmia by ablation of a particular site.

In conclusion, both reentrant and nonreentrant mechanisms contribute to the development of premature beats and VT during early ischemia. The influence of either or both mechanisms in the genesis of ventricular fibrillation remains to be clarified. However, it is clear that the efficacy of pharmacologic interventions in the setting of acute ischemia will require approaches to interrupt both mechanisms.

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