Reentrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

9. Electrophysiologic-Anatomic Correlation of Reentrant Circuits

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SUMMARY We studied isochronal maps of ventricular activation during ventricular arrhythmias induced by programmed premature stimulation in dogs 3–5 days after ligation of the left anterior descending coronary artery. The entire epicardial surface and selective intramural sites were recorded using a computerized multiplexing technique. The electrophysiologic data were correlated with the anatomic characteristics of the infarction. In nine of 17 dogs (55%), the induced ventricular rhythm was due to reentrant activation in the surviving epicardial layer overlying the infarction. The irregular epicardial layer (up to 4 mm thick) had grossly intact myocardial fibers on microscopic examination but showed abnormal electrophysiologic characteristics. The stimulated premature beat that initiated reentry produced a continuous arc of functional conduction block within the surviving epicardial layer. The activation wave front circulated slowly around both ends of the arc of block, rejoined on the distal side of the arc before breaking through the arc to reactivate an area proximal to the block. This resulted in splitting of the initial single arc of block into two arcs. Reentrant activation continued as two synchronous circuits that traveled clockwise around one arc and counterclockwise around the other. Reentry spontaneously terminated when the leading edge of both reentrant circuits encountered refractory tissue, resulting in the coalescence of the two arcs of block into one.

The present study may increase the understanding of the electrophysiologic mechanism of some ventricular repetitive responses and tachyarrhythmias induced by programmed premature stimulation in the clinical laboratory.

IN OUR recent study on isochronal mapping of induced ventricular arrhythmias in dogs during the late myocardial infarction period,1 we showed that a reentrant circuit located on the epicardium is responsible for the induced arrhythmias. The reentrant circuit consisted of a functional arc of conduction block around which the activation wave front advanced in a circular manner at slow and irregular speed. In that study, however, epicardial recordings were obtained from a grid of electrodes placed on the infarction and border zones and complete ventricular activation was not mapped. To determine the overall ventricular activation pattern during induced ventricular arrhythmias in dogs 3–5 days after ligation of the left anterior descending coronary artery, we recorded from electrodes spread over the entire epicardial surface and from selective intramural sites using a computerized multiplexing technique. The electrophysiologic observations were then correlated with the anatomic characteristics of the infarction.

Methods

In 17 mongrel dogs that weighed 15–20 kg, the anterior descending coronary artery was ligated just distal to the anterior septal branch. Details of the surgical technique have been described.2 Three to 5 days after coronary artery occlusion, the dogs were reanesthetized with sodium pentobarbital, 30 mg/kg i.v., and ventilated with a positive-pressure respirator. A left lateral thoracotomy was then performed and the pericardium was used to cradle the heart. Electrocardiographic leads I and II and femoral blood pressure were continuously monitored on an Electronics for Medicine DR10 electrophysiologic recorder. A bipolar hook electrode was introduced in the base of the right ventricle for stimulation. Both regular pacing and premature stimulation were performed using a programmable digital stimulator (model DTU-101 MVA, Bloom Associates, Ltd.). The stimulator delivered rectangular pulses of variable duration (usually 2–5 msec) at twice diastolic threshold with an accuracy up to 1-msec interval. To slow the sinus rhythm, stimulation of the right or left vagosympathetic trunk was accomplished by delivery of 0.5-msec square-wave pulses 1–10 V intensity at a frequency of 10–20 Hz, through two silver wires (0.012 inch in diameter).3 In all experiments, multiple responses could be induced by programmed premature stimulation. During regular pacing (S1, S2 at cycle lengths of 350–450 msec) one (S1) or two (S1, S2) successive premature beats were introduced at cycle lengths of 180–280 msec. The coupling interval of S2 was gradually shortened until a ventricular arrhythmia was initiated or until effective refractoriness of the right ventricular myocardium was reached. In the latter situation, S2 was introduced at an interval 2–5 msec longer than the effective refractory period, and then an S1 was introduced at gradually shorter coupling intervals until one or more nonstimulated beats occurred. The stimulation protocol varied from one experiment to the other, as detailed in the Results section.
Once a reproducible arrhythmia was established, a nylon sock with 62 individually sewn bipolar electrodes was slipped onto the ventricle for epicardial mapping and positioned with respect to epicardial landmarks. The electrodes were made of Teflon-coated silver wire (0.005 inch in diameter). The bipolar electrodes had an interpolar distance of 1–2 mm. Socks of two types of electrode configurations were constructed. In the first design, all the electrodes were uniformly distributed, with approximately 1.2 cm between each bipolar electrode pair. We soon realized that with this sock, many of the electrograms were relatively redundant as reentry was localized in and around the infarction zone. A second sock was constructed that had a higher density of electrodes (approximately 8 mm between electrode pairs) covering the area of the infarction and the border zones and a lower density (approximately 1.5 cm) on the remaining surface of the heart. The sock’s electrodes were connected to the amplifiers that interfaced with the 64-channel computerized data acquisition system. Of the 64 channels, one was used for surface ECG, one for timer pulses and the remaining 62 for bipolar cardiac electrograms. Data were acquired into the computer system, processed and printed. Isochronal maps of epicardial excitation were then constructed manually. In cases where the density of epicardial electrodes was insufficient, a patch electrode with 48 (8 × 6) bipolar recording sites was positioned on the area of interest. The 4 × 5-cm patch electrode was made of stiff paper with an interelectrode distance of 5 mm. The two poles of each bipolar electrode were 1–2 mm apart. The patch electrode was slipped underneath the sock and multiple responses were initiated to map the area of interest. In nine experiments, intramural needles were introduced in the border and ischemic zones to determine excitation characteristics within the myocardium. The needles were 1 cm long with up to 10 recording sites (five bipoles) along its length. After the introduction of the needles, about 10 minutes were allowed for recovery of the injury potential and then the multiple responses were mapped for intramyocardial excitation. Similar use of sock, patch and needle electrodes has been described.

After termination of the electrophysiologic study, the anatomic locations of intramura l recording sites were determined and correlated with epicardial recording sites by inserting short, clipped needles at selective sites. The anatomy of the infarction was first determined by gross examination. The heart was then cut transversely at 0.5-cm intervals and the sections were stained using the nitroblue tetrazolium (NBT) microscopic enzyme-mapping procedure. NBT results in an intense blue staining reaction in undamaged regions of the heart, while areas of ischemic injury appear as clearly delineated pale zones. A tridimensional outline of the infarction was then constructed and correlated with the recorded electrograms. For histologic examination, tissue blocks were fixed in acetate-buffered neutral 10% formalin, embedded in paraffin, and cut 5–7 μ thick. The sections were stained with hematoxylin-eosin.

The Mapping System

The complete system is shown in figure 1. It consists of 64 high-input impedance differential amplifiers with a filter setting of 0.03–500 Hz. The bipolar electrograms are individually amplified and then connected to sample-and-hold circuits. The analog data are then multiplexed by a 64-channel multiplexer. After passing through a programmable gain amplifier (PGA), the data are digitized by a 12-bit A/D converter. The sampling rate per channel is 1000 samples/sec, resulting in a total throughput rate of 64,000 samples/sec. The control unit of the system allows gain selection up to 5000 with the help of a selector switch that alters the gain of the PGA. In this system, the gain of all channels is the same and can only be changed simultaneously. The control unit also provides the electrical isolation. Its memory permits a continuous stream of data to be acquired by the Direct Memory Access Interface (DR11B) of the PDP 11/34 computer (Digital Equipment Corp.). Double buffering is used to store the data in memory, which are then dumped onto a magtape (Kennedy 9300). All the system software is stored on 5-megabyte RL01 disks. Two disk drives interface with the PDP 11/34 computer. Other system peripherals include a terminal (Tektronix 4010) for system communication and a printer/plotter (Versatec 111A) to obtain a hard copy of the processed electrograms.

Software

System software is configured under the RT-11 operating system. The data acquisition routines permit us to acquire all 64 channels of data for a selective duration. Approximately 120 seconds of data can be recorded on 1200 feet of magtape. Single or multiple segments of data in a repetitive sequence can be acquired. A single segment indicates a continuous run of data for as long as 30 seconds, whereas during multiple-segment recordings, these sequential runs of data are acquired automatically with at least 1 second of no recording. To verify that all channels are recording satisfactory electrograms, the data can be quickly reviewed by acquiring data into the computer and printing all 64 scalar leads on the printer/plotter. This usual

![Mapping System Diagram](image-url)

**Figure 1.** The computerized mapping system, consisting of 64 individual amplifiers, the data from which are multiplexed, digitized by the analog-to-digital (AID) converter and stored on digital magnetic tape interfaced with the PDP 11/34 computer. System communication through the terminal permits storing and processing of selective segments of data on the magnetic disk as well as plotting of data on the printer plotter.
ly takes less than 1 minute for a 3-second recording. To process the data, the reference ECG lead of a selected run is displayed on the terminal and a time window of data to be analyzed is chosen. The specified data are then read from the magtape. Activation times for individual electrograms were determined using previously established criteria. The data from all 64 channels are then plotted along with activation times. Unless otherwise specified, all isochrone maps were constructed manually at 20-msec intervals.

Results

In 15 dogs, two to seven nonstimulated responses could be initiated by programmed premature stimulation (S₂S₃ stimulation in four experiments and S₃S₄S₅ stimulation in 11 experiments). In two dogs, longer runs (10–30 beats) of monomorphic ventricular tachycardia were induced. The rate of induced ventricular rhythms was 230–430 beats/min. In nine of 17 dogs (55%), all induced ventricular rhythms were due to reentrant activation in the surviving epicardial layer overlying the infarction. This includes one of the two dogs that showed longer runs of ventricular tachycardia. In five of the remaining eight dogs, the first nonstimulated beat was the result of an epicardial reentrant circuit. During subsequent impulses, arcs of functional conduction block and areas of slow conduction were found on the epicardial surface of the infarction. However, neither epicardial recordings nor selected intramural recordings identified the overall ventricular activation pattern. Often, when additional intramural needles were introduced to further study the ventricular activation pattern, the multiple responses became nonreproducible. These arrhythmias could have been reentrant or focal in origin. The results from experiments in which isochronal mapping successfully identified the reentrant pathway will be presented here.

Isochronal maps from one of the experiments in which reentrant activation was localized in the epicardial layer overlying the infarction are shown in figure 2. The figure examines in detail the mechanism of induction of reentrant activation by programmed premature stimulation. In this experiment, pacing was applied to the base of the right ventricle at a basic cycle length (S₁S₂) of 400 msec. Two premature stimuli (S₂ and S₃) were introduced at coupling intervals of 240 and 215 msec, respectively, and resulted in a reproducible run of three nonstimulated beats. Time zero represents the earliest activation observed on the epicardial surface. A latency period of 10–20 msec from the stimulus to earliest epicardial activation was routinely observed. During S₃, the entire epicardial surface was activated within 80 msec (four isochrones) with the last isochrone located on the apical part of the infarct. During the first premature beat (S₂) in panel B, the activation wave front showed significant slowing (crowded isochrones) before conduction block occurred (represented by the heavy solid line).

The arc of conduction block was functional in nature, as it did not exist during S₁ stimulation. Both the zone of conduction delay and the arc of conduction block were localized within the visible epicardial border of the infarction. The activation wave front traveled around the two ends of the arc of block and from the noninfarcted epicardial surface of the left ventricle, coalesced on the distal side of the arc and advanced in the direction from the lateral to the septal borders of the infarction. The entire epicardial surface was activated within 120 msec (compared to 80 msec during S₁) and the last part to be activated was an area in the central zone of the infarction. The second premature beat (S₃) shown in panel C was associated with a significant change in the configuration of the arc of functional conduction block. The block occurred close to the septal border of the infarction and extended further on the superior border; both changes resulted in lengthening of the arc of block. The extension of the arc of block closer to the septal border of the infarction occurred because the block occurred proximal to the zones that were showing conduction delay during S₃ stimulation. Hence, during S₃, more “depressed” myocardial sites were included within the distal border of the arc of block.

The activation front traveled around both ends of the arc of block, coalesced and then advanced slowly across the central zone of the epicardial surface of the infarction. The slow activation front reached a site along the distal border of the arc of block 200 msec from the onset of right ventricular activation. By this time, the functional refractoriness had expired at an area on the proximal side of the arc of block and consequently reactivation of this area occurred and initiated the first reentrant beat. Conduction velocity improved when the wave front reached the normal myocardium. The reactivation of an area on the proximal side of the arc of block was associated with splitting of the arc of block into two separate arcs. Epicardial activation during the first reentrant beat (panel D) continued in the form of two simultaneous circulating wave fronts, a clockwise circuit around the upper arc and a counterclockwise circuit around the lower arc. The two circuits combined into a wave front that conducted slowly between the two arcs of block and then activated the normal myocardium, thereby initiating the second reentrant beat. Epicardial activation during the second reentrant beat (panel E) continued in the form of two circulating wave fronts that coalesced and were forced to conduct slowly along a circuitous pathway bordered on each side by the two arcs of functional conduction block. Once again, the third reentrant beat started by activation of a site on the proximal side of the arcs of block and activation advanced as two circulating wavefronts. However, both wave fronts encountered refractory tissue close to the lateral border of the arcs of block and failed to advance. This resulted in fusion of the two arcs of block into one arc and interruption of the reentrant process.

Although the geometry of the arcs of functional conduction block varied to some extent during the three reentrant beats, the QRS morphology of these beats was basically similar. This is reflected by an approximately similar distribution pattern of the isochronal lines on the epicardial surface outside the central zone of the infarction. Also, the QRS duration of those
complexes (80–90 msec) reflects activation of the normal myocardium. The slow activation wave in the central portion of the infarction that bridged the diastolic interval between reentrant beats was not discernible in surface leads.

Figure 3 illustrates selected simultaneous electrograms from critical sites on the epicardial maps in figure 2 and demonstrates the nature of both slow conduction and conduction block necessary for successful reentry. Electrograms recorded along the arcs of functional conduction block as well as the central zone of slow conduction are shown. The electrograms depict

A.

![Diagram A](image)

B.

![Diagram B](image)

C.

![Diagram C](image)

D.

![Diagram D](image)

E.

![Diagram E](image)

F.

![Diagram F](image)
the presence of diastolic bridging between the last stimulated beat (S,) and the first reentrant beat (V,) as well as between successive reentrant beats. Some electrograms recorded along the distal side of the arcs of functional conduction block showed two separate potentials. The first, a low-amplitude slow potential simultaneous with the activation potential on the proximal side of the arcs of block, represented a distant field or electrotonic potential.1 The second was a sharp multiphasic deflection that represented delayed myocardial activation at the electrode site. The figure shows that conduction block between sites proximal and distal to the arcs of block is functional in nature and cycle length–dependent since it was not present during the S1 beat.

The results of another experiment in which intramural needle recordings were obtained are shown in figures 4 and 5. In this experiment, two nonstimulated beats were reproducibly induced by an S1S2S3 stimulation protocol (S1, 380 msec; S2, 215 msec and S3, 190 msec). Figure 4 illustrates the isochronal maps of the sinus beat, S1S2S3 stimulated beats and the two nonstimulated responses. Isochronal lines were drawn at 10-msec intervals in panel A and at 20-msec intervals in panels B to F. During the sinus beat two separate areas of early epicardial activation were seen on the right and left ventricular surfaces. The two wave fronts collided on the anterior and posterior surfaces of the heart. The entire epicardial surface was activated within 40 msec and the last part to be activated was the central area of the infarction. The isochronal activation maps during the initiation, perpetuation and termination of the reentrant process were basically similar to those described in figure 2. During S1, the entire epicardial surface was activated within 60 msec with no evidence of conduction delay or block. S2 induced a functional arc of conduction block within the septal border of the infarction. The activation wave front advanced around both ends of the arc of block to reach the distal side of the arc of block 120 msec from the onset of right ventricular activation. S3, on the other hand, resulted in a longer, more convoluted arc of conduction block due to extension of the area of block within the superior zone of the infarction. The activation wave front advanced around both ends of the arc of block, traversing a circuitous longer pathway at a slower speed before reaching the distal border of the arc of block 180 msec from the onset of right ventricular activation.

Reactivation of an area proximal to the arc of block initiated the first reentrant beat. It also resulted in splitting of the arc of block into two separate arcs. Epicardial activation during the first reentrant beat was in the form of two synchronous circuits around the two arcs of block. A transverse extension of one of the arcs of block significantly narrowed the excitable pathway between the two arcs and markedly reduced conduction velocity. During the second reentrant beat, this extension completely bridged the two arcs of block, resulting in termination of the reentrant process. The conduction velocity around the two arcs was relatively fast during the second reentrant beat compared with the first. The area between the two arcs could have been completely refractory due to the shorter transit time around the arcs of block. The difference in the speed of epicardial conduction during the two reentrant beats was also reflected in the duration of the surface QRS complexes. The first reentrant beat had a wide notched QRS of approximately 110 msec duration, compared with 70 msec for the second reentrant QRS. The noninfarcted epicardial surface was activated within 120 msec (six isochrones) during the first reentrant beat compared to 80 msec (4 isochrones) during the second beat. This analysis, however, does not take into consideration the contribution of septal and intramyocardial activations, which may influence the overall QRS vector, or the possibility that QRS durations may have been different in other surface leads with different vectorial orientation.

Figure 5 illustrates epicardial and intramural recordings obtained from needle electrodes introduced at three different sites during the induced reentrant rhythm shown in figure 4. As depicted on the isochronal maps in figure 4, site A was located in the normal zone to the right of the septal border of the infarction. Sites B and C were located within the infarct zone approximately 7 and 10 mm distant from site A, respectively. Figure 4 shows that sites B and C were just distal to the functional arcs of conduction block during S1 and S2 stimulated beats. At each site, the most proximal needle electrode recorded from the superficial 1-mm epicardial layer. This electrogram was synchronous with the recording obtained from the epicardial sock electrode in the immediate vicinity. Four of the intramural recordings were obtained from levels 2, 4, 6 and 8 mm below the epicardial surface. Recordings at the 6-mm level are not shown. Electrograms at site A show almost simultaneous activation of epicardial...
dial and intramural sites. The polarity of the electrograms from each of the sites is not the same because the bipoles of each pair were not connected with the same polarity. On the other hand, at sites B and C, electrical potentials denoting myocardial activation were only recorded up to 2 mm below the epicardial surface. Intramural recordings at the 4-, 6- and 8-mm levels below the surface revealed broad low-amplitude deflections consistent with a cavity potential. During the S1 stimulated beat, the electrograms at the epicardial and the 2-mm level at sites A and B were recorded within 10 msec.

On the other hand, during S2 and S3 beats the epicardial and the 2-mm intramural electrograms at B showed two separate deflections. The first, a low-amplitude slow potential (arrows) simultaneous with the sharp potential recorded at site A, represented a distant field or electrotonic potential. The second was a sharp multiphasic deflection and represented delayed myocardial activation at site B. After S2 and S3, activation at B occurred 80 and 120 msec, respectively, after activation at A. The conduction block between sites A and B was also functional in nature and cycle length-dependent. The electrograms at site C were simultaneous with or slightly delayed compared to those at B. However, the electrotonic potentials seen at site B
were not discernible at site C. Also, the electrograms at site C were notched and of longer duration than those at site B. The epicardial and the 2-mm intramural sites at A were reexcited within 40 msec of the delayed activation that followed S₃ stimulation at sites B and C. This initiated the first reentrant beat.

Figure 6 was obtained from the same experiment shown in figures 4 and 5 and illustrates the anatomic characteristics of the infarction. The heart was sectioned transversely into 5-mm-thick slices and the sections were stained using NBT. The right side of the figure shows a composite drawing made from gross examination of each of the slices. It illustrates a relatively large anteroseptal infarction. The infarction extended up to the endocardial surface but it did not involve the right ventricular myocardium or the right ventricles.

**Figure 4.** Isochronal maps of epicardial activation in another dog. Panel A shows excitation during a sinus beat and panels B through F during S₁, S₂, S₃, and two nonstimulated beats, respectively. The initiation, perpetuation and termination of reentrant activation were similar to those in figure 2. See text for details.
Figure 5. Intramural bipolar recordings from sites A, B and C during the reentrant rhythm shown in figure 3. At each site the most proximal needle electrode recorded from the superficial 1-mm epicardial layer (EPI) and the remaining electrograms were obtained from 2, 4 and 8 mm below the surface. The arrows point to electrotonic potentials synchronous with excitation at A. See text for details. S = stimulus artifact.

half of the septum. Although no attempt was made to identify the Purkinje network, previous studies have shown that a sheet of few cell layers of Purkinje fibers survives the infarction. A layer of surviving epicardium overlay portions of the infarcted tissue in all the sections. The surviving epicardial layer was characteristically wedge-shaped, especially on the septal border of the infarction. A surviving subendocardial myocardial wedge was less frequently observed. Figure 6 also contains a photograph of the stained section at the level where intramural needles A and C were inserted. The position of the needles is marked by arrows. Intramural recordings at A were obtained from the normal myocardium immediately to the right of the septal extension of the infarction. The recordings revealed muscle potentials at the epicardial and all intramural sites (fig. 5). On the other hand, recordings at site C were obtained from the paraseptal region of the left ventricle. At this site, a 2.5-mm-thick layer of surviving myocardium was overlying a dense core of necrotic myocardium that extended up to the endocardial surface.

The epicardial and the intramural electrode at the 2-mm level recorded muscle potentials. Deeper intramural electrode recordings from necrotic myocardium showed low-amplitude, broad, cavity potentials. As shown in figure 4, site C was located immediately to the left of the arc of functional conduction block during premature stimulation. The arc of functional conduction block corresponded to the site where a rapid transition occurred in the thickness of the wedge-shaped, surviving epicardial layer (fig. 6). In other experiments, arcs of functional conduction block developed as deep as 15 mm inside the visible epicardial border of the infarction. In experiments in which the position of the arc of block was correlated with the anatomy of the infarction, the block developed in surviving epicardial layers 1.5–4 mm thick.

We did not try to systematically correlate the sites of functional conduction block with the microscopic characteristics of the epicardial layer in all experiments. However, in five experiments in which microscopic sections from sites of functional conduction block were studied, a sheet of structurally intact myocardium of 60–150 cell layers was observed. Figures 7 and 8 show microscopic sections obtained from a different experiment and illustrate the surviving epicardial layer overlaying the infarction from a section where the arc of functional conduction block was located. Figure 7 is low-magnification photomicrograph of a 4.5 × 7.5-mm myocardial slice. The demarcation between the surviving epicardial layer and necrotic myocardium is highlighted by the dark line. In this section, the surviving epicardial layer tapered in thickness irregularly from 2 mm (approximately 100 cell layers) at the edge of the section to a central area, where the necrotic zone extended to the epicardial surface. In this experiment, the arc of conduction block was approximately located at the 1.5–2-mm-thick zone (marked by an arrow). Figure 8 is a higher-magnification photomicrograph that shows the sharp demarcation between intact myocardial fibers at the top and infarcted muscle at the bottom. The surviving myocardial fibers were structurally intact with clearly visible myofibrils and nuclei. In other experiments, the normal-appearing epicardial layer showed mild leukocytic infiltration, mainly near the epicardial surface, and in some areas wavy fibers and small zone of necrosis were observed.
On the other hand, the infarction zone was made of myocardial fibers showing a wide variety of tissue damage, ranging from massive necrosis with dense cellular infiltration to focal necrosis and cellular reaction in the less damaged part of the tissue.

In experiments in which reentrant activation occurred in the surviving epicardial layer overlaying the infarction, conduction delays and conduction block consistently developed along the tangential axis. On the other hand, conduction across the sagittal axis (i.e., endocardial-epicardial axis) of the thin epicardial layer was usually synchronous or only showed slight dispersion (less than 40 msec) (fig. 5). In some experiments, intramural recordings obtained close to the border of the infarction showed functional intramyocardial block along the endocardial-epicardial axis, as shown in figure 9. A cross-section of the heart around the border zone of the infarct shows a wedge-shaped thin layer of surviving myocardium was overlaying the infarction zone. Intramural needle electrodes were inserted at 6-mm intervals in the normal zone (A), along the border zone (B) and in the infarction zone (C). A possibly reentrant ventricular beat (V) was induced by a single premature impulse (S₂). During the basic stimulated beat (S₁), myocardial potentials were recorded at the epicardial and intramural sites at A and B. However, at site C, activation potentials were recorded from the epicardial and the 2-mm intramural site and cavity potentials were obtained from deeper intramural sites. During S₂, functional conduction block occurred in a tangential direction between site A on one side and sites B and C on the other side. Further, a functional intramyocardial block occurred at site B between the 4- and 2-mm intramural levels, respectively. In this and in seven other experiments in the present study, the epicardial map did not complete the reentrant pathway. In none of these experiments could the gap of epicardial excitation be completely bridged by intramural extension. The number of intramural recordings obtained in these experiments was limited and adequate tridimensional mapping could not be obtained. As mentioned earlier, the introduction of more intramural needles at crucial sites was frequently associated with a change in the ventricular activation pattern. In some of these experiments, functional intramyocardial conduction delays and conduction block at the border of the infarction may have contributed to reentry.

Discussion

Electrophysiologic Determinants of Reentrant Circuits

The present study confirms our recent observations on the electrophysiologic determinants of reentrant ac-
FIGURE 8. Border between normal (top) and necrotic (bottom) myocardium from the same infarction shown in figure 7. Nuclei are absent from the necrotic muscle cells. An inflammatory response is seen throughout the necrotic muscle and phagocytic (Ph) removal of necrotic cells has begun in some areas. Hematoxylin-eosin stain; magnification × 150.

tivation in canine 3–5-day-old ischemic ventricular myocardium. The length of the arc of functional conduction block, which defines the length of the reentrant circuit, and the degree of slow conduction are crucial factors for the creation of a reentrant circuit. A premature beat that successfully initiates reentry results in a longer arc of conduction block and slower conduction compared to one that fails to induce reentry. The slower activation wave front travels around a longer and more circuitous route, providing sufficient time for refractoriness along a site on the proximal side of unidirectional block to expire. Reexcitation of this site completes the reentrant circuit. This study also reemphasizes the functional nature of the obstacle (the arc of conduction block) around which a reentrant circuit is formed. This is illustrated by the fact that in the same area of the myocardium, activation can proceed at a relatively fast speed during slow heart rates. Both the zone of conduction block and the slow conduction around it are probably created by areas of myocardium with abnormally prolonged refractoriness when these areas are challenged to conduct at cycle lengths shorter than the time necessary for full recovery of excitability. However, as refractory periods were not mea-
sured, the role of changes in excitability resulting in slow conduction and block cannot be ruled out.

This study helps to explain why two or more successive premature beats may succeed in initiating reentry when a single premature beat fails. A single premature beat \((S_2)\) that fails to initiate reentry results in a shorter arc of functional conduction block and a lesser degree of slow conduction, which does not allow enough time for refractoriness to expire along the proximal side of the arc of block. Under these circumstances, a second premature beat \((S_3)\) is forced to conduct in myocardial sites that have not fully recovered their excitability. Such areas were usually located close to the border of the infarction as well as in the central part of the epicardial surface of the infarction. An \(S_3\) results in a longer and more circuitous arc of functional conduction block and much slower conduction, particularly in the central part of the epicardial surface of the infarction. The transit time of the activation front around the arc of block will thus be prolonged, allowing sites on the proximal side of the arc of block to recover excitability. Excitation of these sites will complete the reentrant circuit (fig. 10). Besides the length of the arc of block and the degree of slow conduction around the arc, a third factor comes into play when reentrant activation is initiated by more than one premature beat. The arc of functional conduction block may move closer to the “normal” myocardial zone during the second premature beat \((S_3)\) compared with the first premature beat \((S_2)\) (fig. 2). This is probably because of differential shortening of refractoriness in predominantly normal as compared to ischemic sites. Besides the inclusion of more “depressed” myocardial sites on the distal site of the arc of block, the slow activation front now reexcites “normal” myocardium, which probably has “shorter” refractoriness. The combination of all three factors facilitates reentry after \(S_3\) because the difference in activation times across the arc of block would be greater than the refractory period of some sites proximal to block.

The present study has emphasized an important characteristic of reentrant activation in this ischemic canine model: that reentrant activation consistently occurred in the form of two wave fronts traveling around two arcs of functional conduction block. The beat that initiates reentry results in a continuous arc of conduction block. The activation front circulates slowly around both ends of the arc of block and rejoins on the other side of the arc of block before breaking through the arc to reactivate an area proximal to the block. This results in splitting of the initial single arc of block into two arcs. Reentrant activation continues as two synchronous circulating wave fronts, a clockwise circuit around one arc and a counterclockwise circuit around the other arc. A narrow zone of slow conduction occurs between the two arcs. Because the surviving myo-

**Figure 9.** Intramural needle recordings (A to C) showing intramyocardial conduction block after premature stimulation \((S_2)\). (right) A cross section of heart around the border zone of the infarction (hatched area). \(S_2\) resulted in a functional conduction block in the surviving epicardial layer between sites \(A\) and \(B\)–\(C\) and an intramyocardial block at \(B\) between the 2- and 4-mm recordings. See text for details.
two arcs of block into one single arc and termination of reentrant activation. Conduction block always occurred in areas of very slow conduction within the central region of the epicardial surface of the infarction. The fusion did not occur in the area where the initial arc split, probably because here the wave front traveled from zones with longer refractory period to ones with shorter refractoriness.

The presence of two synchronous reentrant circuits was shown by Janse et al. during ventricular tachycardias that followed acute regional myocardial ischemia in isolated porcine and canine hearts. More recently, Wit et al. in a preliminary report, described a similar activation pattern during induced ventricular rhythms in a canine ischemic model similar to the one used in this study and in our recent report. However, the presence of two synchronous reentrant circuits around two separate arcs of block is not essential to maintain reentrant activation. Reentrant activation could be maintained in the in vivo heart by one reentrant circuit around a single arc of block when the second arc of block is contiguous with the atrioventricular annulus so that the second circuit is aborted. This could be seen in some examples of induced atrial flutter in the in vivo canine heart. A similar situation is seen when reentrant activation activation is initiated in vitro in isolated pieces of cardiac tissue. Analysis of the reentrant activation induced in small pieces of rabbit atrial tissue by Allessie et al. revealed that in addition to the main circulating wave front around a single arc of block, a second arc of block sometimes joined the cut edge of the preparation.

**Anatomic Substrate of Reentrant Circuits**

After left anterior descending coronary artery ligation, blood flow is reduced more in the subendocardium and resistance to flow in the infarcted tissue causes a redistribution of flow in the epicardial layers. Combined with the enlargement of collateral vessels, this results in sufficient flow to the epicardium that it usually survives. Although the geometry of the infarction varied in different experiments, our pathologic studies consistently revealed a layer of surviving epicardial tissue overlaying the core of necrotic myocardium. The epicardial layer varied in thickness from a few cells to a few millimeters (up to 200 cell layers), as verified histologically. The surviving epicardial layer was generally wedge-shaped, with more depth at the border than at the central portion of the infarction. Although the surviving epicardial layer looked grossly intact on microscopic examination, this layer has a reduced myocardial blood flow. Our previous in vitro recordings from the surviving "ischemic" epicardial layer showed cells with variable degrees of partial depolarization (resting potentials from -84 to -50 mV), reduced action potential amplitude and decreased upstroke velocity. Full recovery of responsiveness frequently outlasted the action potential duration reflecting the presence of postrepolarization refractoriness. In these cells, premature stimuli could elicit graded responses over a wide range of coupling...
intervals. Slowed conduction, Wenckebach periodicity, and 2:1 and higher degrees of conduction block could be easily induced by fast pacing or premature stimulation. The present study showed that both the arcs of functional conduction block and the slow activation fronts of reentrant circuit developed in the surviving electrophysiologically abnormal epicardial layer overlaying the infarction. Conduction across the sagittal axis of the epicardial layer was usually synchronous or showed only slight delays compared to conduction in the tangential direction. The variation of conduction velocity in the different directions may be a result of the geometry of activation as well as the intrinsic properties of the tissue.17 Thus, a majority of reentrant circuits in the present study could be viewed to have essentially a two-dimensional configuration. In the remaining experiments, gaps in the activation wave front of varying duration could not be accounted for by epicardial excitation. If these beats were reentrant, a variable degree of intramyocardial or subendothelial extension of the reentrant circuit i.e., “a tridimensional configuration,” cannot be excluded.

The electrophysiologic-anatomic correlation of reentrant activation shown in this study may only pertain to infarctions with this particular anatomy. In the present canine model, programmed premature stimulation usually induced nonsustained rather than sustained tachycardias (the latter is defined as 10 or more beats). Both nonsustained and sustained tachycardias could be localized to the thin epicardial layer in the present study as well as in our recently published report.1 On the other hand, other experimental infarctions, particularly those induced by coronary occlusion and reperfusion as well as several human infarcts, may have a complex anatomy, with bundles of surviving myocardium intermingled with infarcted tissue. In these hearts, a complex tridimensional configuration of the reentrant pathway could be more common. For instance, induced sustained tachycardias in dogs after coronary occlusion and reperfusion could not be attributed to an epicardial reentrant circuit.10 Further, a majority of surgically correctable clinical “reentrant” tachycardia seem to be localized to the endocardial or subendothelial zones.18 Nevertheless, the electrophysiologic determinants of reentrant activation in these hearts would probably not differ significantly from those in the present study.

Of particular interest is our observation that the arcs of functional conduction block did not exactly follow the visible epicardial border of the infarction but were usually located up to 15 mm inside that border. This usually corresponded anatomically to areas where the wedge-shaped epicardial layer tapered to 1.5 to 4 mm. However, we did not try to correlate exactly the sites of the arc of functional conduction block and slow conduction with the number of underlying surviving cell layers. The possibility of having relatively more electrophysiologically depressed myocardial cells in thin epicardial layers compared to cells in thicker layers cannot be excluded. That is, the contribution of the geometrical characteristics of the epicardial layer (taking from the border zone to the central zone) in localizing the site of conduction block and slow conduction could not be evaluated independently of a possibly graded electrophysiologic characteristic of the involved tissue.19 The exact relationship between thickness of tissue and conduction block awaits further investigation.

In the present study, the resolution of intramural activation was limited. The bundle branch–Purkinje activation was not frequently recorded by the intramural needles, although a few cell layers of Purkinje fibers survive on the endocardial side of the infarction.3 The exact role of the surviving endocardial layer in reentrant beats is not known. For the beats where the complete reentrant circuit could be localized to the surviving epicardial layer, the endocardium probably had an insignificant role. Although it can be argued that a reentrant circuit existed on the endocardium similar to the one on the epicardium, this is unlikely because reentry ceased as soon as the epicardial circuit was blocked. In the experiments in which the complete reentrant circuit could not be mapped on the epicardium, intramural and/or endocardial activation may have played an important role.

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References

Physical Training Increases Ventricular Fibrillation
Thresholds of Isolated Rat Hearts During Normoxia, Hypoxia and Regional Ischemia

TIMOTHY D. NOAKES, M.D., LOUISE HIGGINSON, AND LIONEL H. OPIE, M.D.

SUMMARY The effect of exercise training on cardiovascular mortality is controversial. The purpose of this study was to determine the effect of a period of treadmill training on the ventricular fibrillation threshold of the isolated rat heart. Trained hearts had higher threshold values during standard, control perfusion conditions, and when exposed to hypoxia, hypoxia plus isoproterenol infusion, or when subjected to coronary artery ligation. Myocardial metabolic studies failed to define the mechanism for the effect of running training. However, in coronary ligated hearts, the content of the arrhythmogenic substance 3',5'-cyclic adenosine monophosphate (cyclic AMP) was reduced in the ischemic zone of hearts from trained rats. Cyclic AMP levels were also lower in trained hearts during control perfusions. We conclude that running training increases the resistance of the heart to ventricular fibrillation by mechanisms that are largely unknown, although they may involve cyclic AMP.

THE RELATION between exercise and ischemic heart disease remains controversial. Although even extreme exercise, such as marathon running, does not give total protection against coronary atherosclerosis or sudden cardiac death,1,2 there is strong epidemiologic evidence for an association between high levels of physical activity either at work3 or in leisure time4-7 and a reduced incidence of coronary heart disease and, in particular, sudden death. Paffenbarger and Hale8,9 high energy output at work provided greater protection against sudden death than against death occurring 6 hours after the onset of symptoms. Similarly, in studies of British civil servants, not only were the overall coronary mortality rates lower in those who reported vigorous leisure time activity, but sudden death mortality and mortality from the first and subsequent heart attack were also lower.4,5,7 These findings are compatible with a specific, training-related protection against rapidly fatal heart attack. Indeed, Paffenbarger10 postulated that part of the myocardial adaptation to training may be a stabilization of cardiac rhythm, perhaps conferring a reduced risk of the development of that chain of events proceeding from ectopic ventricular activity to fibrillation and death.

Additional epidemiologic studies are required to settle these controversial issues; but further information can be obtained from animal models designed to investigate the effects of exercise training on the myocardial obesity, abnormal glucose tolerance or high blood cholesterol.

Another possibility is that exercise training specifically protects against sudden coronary death. Thus, in the longshoreman studies reported by Paffenbarger and Hale,8,9 high energy output at work provided greater protection against sudden death than against death occurring 6 hours after the onset of symptoms. Similarly, in studies of British civil servants, not only were the overall coronary mortality rates lower in those who reported vigorous leisure time activity, but sudden death mortality and mortality from the first and subsequent heart attack were also lower.4,5,7 These findings are compatible with a specific, training-related protection against rapidly fatal heart attack. Indeed, Paffenbarger10 postulated that part of the myocardial adaptation to training may be a stabilization of cardiac rhythm, perhaps conferring a reduced risk of the development of that chain of events proceeding from ectopic ventricular activity to fibrillation and death.

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Reentrant ventricular arrhythmias in the late myocardial infarction period. 9. Electrophysiologic-anatomic correlation of reentrant circuits.

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