Reentrant Ventricular Arrhythmias in the Late Myocardial Infarction Period in the Dog

13. Correlation of Activation and Refractory Maps

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SUMMARY. Isochronal maps of ventricular activation were analyzed in dogs 3–5 days after ligation of the left anterior descending coronary artery utilizing a 64-channel multiplexer. Isochronal maps of the effective refractory period were determined from 62 epicardial sites and correlated with the activation maps. The ischemia occurring in the surviving epicardial layer prolonged refractoriness in a spatially nonuniform manner. The resulting pattern of refractoriness on the epicardial surface resembled concentric rings of isor refractoriness which increased in duration from the normal zone to the center of the ischemic zone. The formation of an arc of functional unidirectional conduction block occurred along the gradient of refractoriness and the exact location of the arc depended on the S1-S2 interval. When a short S1-S2 failed to induce reentry, fewer adjacent sites with sufficiently disparate refractoriness formed a smaller arc of block. A subsequent S3 encountered further nonuniformly shortened refractoriness (normal areas had shortened refractoriness greater than ischemic areas) and the arc of block was lengthened. This required a longer time for the wavefront to circulate around the arc. When it then reached the distal side of the arc, refractoriness had expired proximal to the arc and reentry occurred. Similarly, nonuniform shortening of refractoriness explained why one reentrant beat may or may not produce successive reentrant beats. Therefore, the spatial pattern of refractoriness forms the substrate for the arc of unidirectional conduction block that is fundamental to the development of ventricular reentry in this experimental model. (*Circ Res* 57: 432–442, 1985)

RECENT isochronal activation studies (Mehra et al., 1983; El-Sherif et al., 1983) have shown that ventricular arrhythmias induced by programmed electrical stimulation in dogs, 3–5 days postinfarction are due to reentrant circuits which satisfy Mines’ criteria for reentry (Mines, 1914). These circuits are located in the thin surviving epicardial layer overlying the infarction. The activation pattern for initiating reentry begins when a premature beat encounters a functional arc of unidirectional conduction block. The premature activation divides into two wavefronts and conducts around each end of the arc of block. The two wavefronts coalesce distal to the arc of block and break through the arc of block, thereby reentering previously excited tissue. The basic presupposition has been that the arc of block is due to disparate refractoriness of adjacent sites. This study will characterize the distribution of refractoriness in these hearts and show that refractoriness does explain the formation of the arc of block and the basis for the variations in initiation and spontaneous termination of reentrant beats.

**Methods**

In mongrel dogs weighing 15–20 kg, the left anterior descending coronary artery was ligated distal to the anterior septal branch. Details of the surgical technique have been described previously (El-Sherif et al., 1977). After 3–5 days, each dog was reanesthetized with sodium pentobarbital, 30 mg/kg, i.v., and ventilated with room air through an endotracheal tube using a Harvard positive pressure respirator. Supplemental doses of anesthetic and saline were administered through a catheter in the cephalic vein. Electrocardiographic lead II and aortic blood pressure were continuously monitored on an Electronics for Medicine DR 10 recorder. The heart was exposed by reopening the left thoracotomy. A bipolar plunge electrode [two hooked 0.005-inch (diameter) enamel-coated stainless steel wires] was put into the basal right ventricle with a 21-gauge hypodermic needle. Programmed electrical stimulation was performed with a Bloom DTU-101 digital stimulator. When sinus slowing was required, a Grass S88 stimulator was used to stimulate the left and right vagosympathetic trunks simultaneously (0.5-msec square wave pulses at a frequency of 20 Hz, 1–10 V) through two Teflon-coated silver wires, 0.010 inch in diameter.

The heart was paced from the basal right ventricle at twice diastolic threshold for eight basic beats (S1–S1 = 380 msec). Subsequently, a premature stimulus, S2, was initiated at coupling intervals (S1–S2) of 260 msec or less in steps of 10 msec. When an S3 produced a premature beat followed by a spontaneous ventricular beat, we studied all the S1–S2 intervals that gave rise to any ventricular arrhythmias. If S3 failed to initiate any spontaneous beats, S2 was given at intervals of 230 msec or less following an S1–S2 interval that exceeded the effective refractory period of the pacing site by 10–20 msec. Similarly, when S3 produced a premature beat followed by a spontaneous ventricular beat, those S2–S3 intervals were studied that gave rise to any ventricular arrhythmias.
When spontaneous ventricular beats could be reproducibly initiated by specific programmed stimulation (which varied from one experiment to the other), a sock electrode was placed on the ventricle. This electrode was comprised of the foot of a nylon stocking with 62 individually sewn bipolar silver electrodes (using 0.005 inch in diameter, Teflon-coated silver wire) at an interpolar distance of 1–2 mm.

Bipolar electrode recordings were obtained and used to construct epicardial isochronal activation maps. A higher density of electrode pairs (6–10 mm between pairs) covered the border and infarction zones. A greater interelectrode pair distance covered the remaining epicardial surface. Intramural recordings were obtained with specially designed 21-gauge needles (Kassel and Gallagher, 1977). Details of the recording techniques, the multiplexer recording system, and the methods for constructing epicardial isochronal activation maps have been previously reported (El-Sherif et al., 1982 and Mehra et al., 1983).

Once the activation maps showed complete epicardial bridging between the first spontaneous ventricular beat and the premature beat that initiated it, the effective refractory period was determined at each of the 62 electrode sites. This was done in 15 dogs using the following technique. Through each pole of each bipolar pair, monopolar cathodal stimulation was achieved while the anode was located at a distance in the thoracic muscle. Monopolar cathodal stimulation was done to avoid the complex strength-interval relations that characterize both monopolar anodal and bipolar stimulation (van Dam et al., 1956; Brooks et al., 1960; Hoffman and Cranefield, 1960). The threshold current required to capture the ventricle from each pole was determined and then doubled. Sites requiring more than 10 mA for threshold stimulation were considered inexcitable. After eight basic beats at a cycle length of 380 msec, the maximum S1-S2 interval that failed to evoke a propagated ventricular response to S2 at twice threshold current was taken as the effective refractory period (ERP) of S1. If the ERP differed between each pole of the bipolar pair, the smaller of the two was taken as the ERP of that particular site in order to construct an isorefractory map.

The ERP for S2 was determined by using an S3. The S1-S2 stimulation interval used at each site was then selected to be the same as the measured interval of activation recorded at each site during the initiation of the arrhythmia from the right ventricular pacing site. This method takes into account any delay in S1-S2 activation of a site that occurred after a short S1-S2 interval, and describes the state of refractoriness following S2 that S3 will encounter. Similarly, the ERP of S2 was determined using an S4; the S2-S3 and S2-S4 stimulation intervals were selected to be the same interval as the activation records showed them to be during the initiation of the arrhythmia.

After termination of the electrophysiological study, the anatomy at specific recording sites was determined by inserting short needles through the sock and into the heart at each site. After removing the sock and examining the surface, we cut the heart transversely into 0.5-cm-thick sections and stained them with nitroblue tetrazolium.

**FIGURE 1. Isochronal maps of activation and refractoriness in a normal heart.** Activation occurred following stimulation from the base of the right ventricle near the region of pulmonary outflow (square wave). The top left and right borders represent the right and left atrioventricular junctions. The two curvilinear surfaces on the right and left are contiguous, and extend from the posterior base to the apex of the heart. Isochronal lines are drawn at 20-msec intervals. S1 is the map of activation of the eighth paced basic beat at a cycle length of 380 msec. S2 is the map of a premature beat initiated 160 msec after S1. RP1 is the isorefractory map of the effective refractory periods of S1. The isochronal refractory lines are drawn at 20-msec intervals. RP1 is the isorefractory map of S2. The lead II electrocardiogram is shown at the top of the figure.
FIGURE 2. Isochronal maps of epicardial activation and refactoriness in an infarcted heart. Part A: activation map of S\textsubscript{i} initiated from the right ventricle (square wave), that followed an S\textsubscript{i} by 230 msec. The arc of conduction block is represented by a thick solid line. The dashed arrows represent the general direction of activation around each end of the arc of block. The broken circle surrounding the number 280 designates the area and isochrone of earliest reentrant activation. Part B: activation map of S\textsubscript{i} that followed S\textsubscript{i} by 160 msec. The arc of block has a larger radius than seen in part A. Similarly, the dashed arrows represent the direction of activation around the arc of block. The broken circle around the number 220 designates the area of earliest reentrant activation. Part C: isorefractory map of the effective refractory period of S\textsubscript{i}. The dashed line encloses the approximate region of the infarction. Part D: superimposition of the arcs of block determined in parts A (solid line) and B (dashed line). The refractory period of specific sites are represented by filled circles and were so represented in parts A–C. Notice that the arc of block always occurred between sites of short and longer refactoriness. T is a time calibration with excursions from baseline every 100 msec. II is lead II electrocardiogram. V\textsubscript{1} is the first spontaneous reentrant beat.

(Nachlas and Shnitka, 1963). The juxtaposition of infarcted and noninfarcted areas was then noted.

Five dogs that had not been subjected to prior coronary artery ligation were studied in a manner identical to those with ligations. As a result of stimulation from the right ventricular base, activation patterns were determined during S\textsubscript{i}, during S\textsubscript{2} at the minimum S\textsubscript{i}–S\textsubscript{2} and during S\textsubscript{3} at the minimum S\textsubscript{2}–S\textsubscript{3} interval following the minimum S\textsubscript{i}–S\textsubscript{2} interval. The ERP of S\textsubscript{i} and S\textsubscript{2} were then measured at each recording site, as described above.

**Results**

**Normal Hearts**

In the normal hearts studied, no arcs of functional conduction block occurred during S\textsubscript{i}, S\textsubscript{2}, or S\textsubscript{3}. Figure 1 shows that, in a normal heart, after basic ventricular stimulation at a cycle length of 380 msec, S\textsubscript{i} activated the epicardial surface completely within 80 msec. The isochrones of activation presented here, and subsequently, are in 20-msec intervals and depict the pattern of activation. At the shortest S\textsubscript{i}–S\textsubscript{2} interval of 160 msec, S\textsubscript{2} activated the epicardium within 100 msec. At the shortest S\textsubscript{2}–S\textsubscript{3} interval after the above S\textsubscript{i}–S\textsubscript{2} interval, S\textsubscript{3} conducted more slowly and the total epicardial activation time was within 120 msec. Neither S\textsubscript{2} nor S\textsubscript{3} resulted in an unstimulated beat, nor did an arc of functional conduction block arise. The refractory periods were distributed uniformly, as shown by the fact that the effective refractory period following S\textsubscript{i} (RP\textsubscript{i}) spanned 30 msec (160–190 msec) and the effective refractory period of S\textsubscript{2} (RP\textsubscript{i}) spanned 30 msec (110–140) after an S\textsubscript{i}–S\textsubscript{2} of 160 msec. In all normal hearts, no arc of block occurred, and the dispersion of effective refractoriness was 30 ± 10 msec.
Infarcted Hearts

The conduction of a premature beat, S₂, in a heart in which the coronary artery had been ligated is quite different and is shown in Figure 2. As the S₁-S₂ interval was decreased from 260 msec in 10-msec increments, an unstimulated beat occurred following an S₁-S₂ interval of 230 msec; the activation map is shown in Figure 2A. The pattern of activation following S₂ showed the development of a functional arc of conduction block (thick line), around both ends of which conduction proceeded. The arc of conduction block is drawn between adjacent sites which are separated in activation time by two or more isochrones. Conduction slowed as it traveled around the arc, with the two wavefronts coalescing at 120 msec and then proceeding in an apical-to-basal direction. Slowly conducted activation reentered previously excited tissue proximal to the arc of conduction block 280 msec after S₂. As the S₁-S₂ interval was further shortened, nonstimulated beats continued to appear with varying morphology.

The pattern of activation following the shortest S₁-S₂, 160 msec, is shown in Figure 2B. The site of stimulation was unchanged, but the pattern of activation changed significantly. The arc of conduction block had a larger diameter because the S₂ failed to penetrate as far into the ischemic region. After the two wavefronts coalesced at 120 msec, the slow conduction was in a lateral-to-septal direction, still somewhat apical-to-basal. The activation reentered previously stimulated ventricle at sites extending basally along the septum 220 msec after S₁.

To study the relationship of the arc of block to effective refractoriness, we determined the ERP of each site and constructed an isorefractory map (Fig. 2C). Similar to the isochronal activation maps, the ERP arc delineated in increments of 20 msec beginning with the shortest ERP. The ERP of 180 and 160 msec were located in normal tissue and left ventricular epicardium, while the longest ERP of 320 msec was located in the center of the infarcted region. The dispersion of refractoriness was 160 msec with...
concentric rings of refractoriness producing a graded increase in ERP going from the border zone toward the center of the infarction. Therefore, a long-coupled S2 of 230 msec could penetrate further into the ischemic epicardium before it encountered refractory tissue than could a more closely coupled S2 of 160 msec. The direct dependence of the arc of block on the ERP is further shown in Figure 2D in which the arc of block from Figure 2, A and B, are superimposed, and the specific sites that were used to draw the activation and refractory maps are labeled with their respective ERP. Notice that the arc of conduction block occurs between adjacent sites of short and long refractoriness with the area of longer refractoriness being distal to the arc of block. At an S1-S2 of 230 msec, sites with ERP of 210-240 msec were excited before conduction block occurred. The slowing of conduction in the epicardium overlying the infarct permitted the excitatory wavefront to activate sites distal to the arc of block after the expiration of their ERP. At an S1-S2 of 160 msec, those sites with ERP of 210-240 msec now provided a barrier to conduction, whereas sites with ERP of 160-190 msec were excited before conduction block occurred.

The configuration of the arc of block and the reentrant pathway in a ventricle showing a window of reentry, i.e., a range of S1-S2 intervals producing spontaneous reentrant beats, may appear also as two separate pathways. In Figure 3, results are presented from a heart in which the infarction produced an epicardial area at the apex (stippled area) that was inexcitable when paced directly. The activation pattern produced at the long end of the window of refractoriness (S1-S2 = 250 msec) is depicted in Figure 3A. The activation proceeded around both ends of the arc of block and coalesced at 100 msec and slowly conducted to reenter in the mid-septal area 280 msec after S2. Except for a small branching in the anterolateral left ventricle, the arc and circuit were uncomplicated. On the short side of the window of reentry, the pattern was changed, as shown in Figure 3B. An S1-S2 of 170 msec produced similar conduction around the basal left ventricular end of the arc of block with the small branch of the arc extending further toward the base. The more important change occurred at the septal aspect of the arc of block. The arc branched and isolated an area in which slow conduction could proceed. Reentrant excitation emerged from this new conduction route 240 msec after S2, before the reentrant loop could be completed in the anterolateral limb. The ERP were determined at 59 recording sites (excluding the three inexcitable sites at the apex), and Figure 3C presents the data in an isorefractory map. The pattern is concentric rings of increasing refractoriness.
from normal myocardium to the center of the infarction. The $S_2$ at longer $S_1$-$S_2$ intervals was able to penetrate beyond the refractoriness barriers that blocked the $S_2$ at the shorter $S_1$-$S_2$ intervals. Figure 3D depicts specific electrode sites used for both recording and stimulation. The ERP of each site is noted and the arcs of block from Figure 3, A and B, are superimposed. The shifts in the configurations of the arcs of block are consistent with the specific ERP. Each arc of block showed longer ERP distal to the arc and shorter ERP proximal to the arc. At an $S_1$-$S_2$ of 250 msec, sites with an ERP of up to 250 msec were activated before conduction block occurred. However, at an $S_1$-$S_2$ of 170 msec, most of these sites were distal to the arc of conduction block.

$S_2$ Fails But $S_3$ Succeeds

In some hearts, an $S_2$ was unable to initiate a reentrant beat, whereas an $S_3$ could. The differences in the patterns of refractoriness encountered by $S_2$ and $S_3$ are shown for one such example in Figure 4. An $S_2$ of 180 msec after $S_1$ failed to initiate a spontaneous beat, but $S_3$, 140 msec after $S_2$, gave rise to a spontaneous reentrant beat, $V_i$, as shown in the ECG of Figure 4. The activation pattern of $S_2$ at 180 msec is shown. An arc of conduction block was encountered by the $S_2$, and activation proceeded clockwise via the left ventricular free wall and counterclockwise from the right ventricle, across the anteroseptal left ventricle and coalesced with the clockwise wavefront after 100 msec. The wavefront then blocked, and epicardial activation terminated 120 msec after it was initiated by $S_2$. The ERP was determined at each recording site and the results are shown as $R_P$. The ERP for specific sites on both sides of the arc of block are depicted below $R_P$ in part A. The activation conducted until it encountered areas that were still refractory.

The arc of conduction block occurred where the difference in refractoriness of adjacent sites was 20 msec, or greater. Stated in another way, conduction block occurred in regions where the gradient for refractoriness was most marked. During $S_2$, the arc of block was not continuous to the apex.

The difference in refractory periods of adjacent sites in the apical region where the arc was discontinuous during $S_2$ was less than 20 msec, as shown more clearly in Figure 5A. Between sites a and c, sites b and c, and sites e and d, the difference in ERP was 10 msec. Consequently, activation conducted directly through the region. In contrast are the results during an $S_3$ initiated 140 msec after $S_2$, shown in Figure 4.

The most significant change encountered by $S_3$ is that the arc of block that was discontinuous during $S_2$ became continuous to the apex. As a consequence, the activation that proceeded counterclockwise around the arc of block could not conduct anteriorly, but only posteriorly, coalescing more basally 100 msec after activation had been initiated. Because activation had not occurred in the anteroseptal region, conduction then proceeded toward the apex through this area and reentered the ventricle. The isoreflectory map created by $S_2$ and encountered by $S_3$ is shown in Figure 4 as $R_P$. The ERP of the specific sites surrounding the arc of block are shown in Figure 4B. The ERP at the apex where the arc of block became continuous are shown in Figure 5B.

The difference in refractoriness between a and c became 20 msec, and the difference between b and c became 30 msec. As a result of this increased difference of refractoriness, conduction block of $S_3$ occurred, going in the direction of a and b to c. Consequently, the wavefront of activation arrived at site c 120 msec later. The increased difference of refractoriness was due to the non-uniform shortening of ERP due to $S_3$. The ERP at sites a and b shortened by 30 and 40 msec, respectively, whereas

![Figure 5](http://circres.ahajournals.org/)

**FIGURE 5.** Enlargement of a portion of Figure 4. Part A: depiction of the arc of block during $S_2$ and specific sites near the apex are designated with their respective $R_p$ refractory periods. The arc was not continuous to the apex, nor was there a refractoriness disparity greater than 10 msec between adjacent sites in this gap. Part B: depiction of the arc of block during $S_3$ and the same specific sites near the apex are designated with their respective $R_p$ refractory periods. During $S_3$, the arc was continuous to the apex and the refractoriness barrier was increased between critical sites (a and c, b and c).
FIGURE 6. Isochronal activation of V₁, the spontaneous reentrant beat that was initiated as a result of the programmed electrical stimulation shown in Figure 4. Reentrant activation was first initiated at site b. The lettered sites correspond to those designated in Figure 5. The lead II electrogram is presented, along with the electrogram recordings from sites b, c, and f. The arrows in records b and f designate the time of expiration of the effective refractory period. Notice that site b recovered before site f and was reactivated first.

the ERP at site c shortened by only 20 msec. As a result, the arc of block was extended and site c was protected from being activated until 180 msec after the initiation of S₃. Similarly, the difference in ERP between sites e and d increased to 20 msec, and the apicolateral aspect of the arc of block was extended more basally. Generally, the ERP of normal sites proximal to the arc of block shortened to a greater extent than the ERP of ischemic sites distal to the arc of block.

The pattern of refractoriness between adjacent sites can similarly explain the point(s) where reentry is initiated. When S₃ arrived at site c, after 180 msec, the site that would be reexcited proximal to the arc of block must have recovered from its refractoriness. Figure 6 presents the activation pattern for the reentrant beat, V₁, and electrograms from sites b, c, and f. The ERP of S₃ at sites b and f were determined and are indicated by the arrows on the respective electrograms. The ERP of site b was shorter than that of site f, and thus it was available to be reactivated first during the 200-msec isochrone, by activation proceeding from site c. When the refractoriness expired at site f, it was then reactivated, shown here during the 220-msec isochrone. The subsequent pattern of activation was rapid, with the clockwise and counterclockwise wavefronts colliding at the base during the 280-msec isochrone. Therefore, the refractoriness left in the wake of S₃ determined the site at which reentrant activity was initiated.

Termination of Reentry

Changes in the pattern of refractoriness can account in part for the inability to sustain multiple reentrant beats, as shown in Figure 7, where S₃ was required to initiate a reentrant beat, V₁. The arc of block that developed during S₃ corresponded to the region on the left ventricle where the isochrones of refractoriness following S₂ were most dense. The conduction of S₃ proceeded around the ends of the arc of block, coalesced, and reentered to initiate V₁ after 240 msec. The conduction of V₁ then proceeded in both clockwise and counterclockwise directions and coalesced at the isochrone of 320 msec, just 100–120 msec after reentry had been initiated. The pattern of refractoriness following S₃ is depicted as RP₃ and explains, in part, why no V₂ followed V₁. As a consequence of the shortened S₂–S₃ interval of 130 msec (compared to the S₁–S₂ of 170 msec), the ERP in the normal epicardial areas shortened by 10–20 msec. However, the areas in the core of the infarction remained at 200 msec. As a result, the density of isochrones in the ischemic region increased. V₁ conducted over a shorter interval of time.
FIGURE 7. Influence of refractoriness on termination of reentrant activation following an $S_3$ that initiated reentrant activation. $V_1$. $V_2$: The isochronal activation of a reentrant beat that failed to initiate further reentry. $RP_2$: The isorefractory map of $S_3$ depicting the refractoriness encountered by $S_3$. $RP_3$: The isorefractory map of $S_3$ depicting the refractoriness encountered by $V_2$. The lead II electrocardiogram is shown.

(80–100 msec) through areas in which the ERP was shortened, and at the time of the 320 msec isochrone, the propagated wavefront could not penetrate the more concentrated gradient of refractoriness and reentry was terminated.

Transmural Refractoriness

To determine the pattern of refractoriness in a transmural direction from specific epicardial sites, needle electrodes were used with interpolar distances spaced 2 mm apart. In four different hearts, 20 intramyocardial sites were studied that were below epicardial sites located proximal and distal to the arc of block. At all such sites, ERP 2 mm below the epicardial surface were either the same or longer in duration than the epicardial ERP. At a depth of 4 mm below the epicardium proximal to the arc, the tissue similarly had the same or longer ERP than at the surface, or it was inexcitable. At the same depth (4 mm) distal to the arc, the tissue was inexcitable. Therefore, the epicardial ERP consistently was the shortest ERP transmurally. As a consequence, premature beats initiating reentry would conduct in the superficial epicardial layer but would block at the deeper, more refractory regions.

Discussion

Correlation of Activation and Refractory Maps

The main finding of this study is that, in the surviving epicardial muscle overlying a 3- to 5-day-old infarct in the canine heart, the pattern of refractoriness resembles concentric rings of isorefractoriness which increase in duration from the normal zone and peripheral aspects of the ischemic zone to the center of the ischemic zone. This pattern of refractoriness provides an adequate substrate by which to explain the formation of an arc of functional unidirectional conduction block, a necessary prerequisite for reentrant excitation in the canine ventricle. As a result of unidirectional block, a premature beat is forced to conduct around the arc of block, and when the conduction time is sufficiently long, the regions distal to the arc of block will reexcite sites proximal to the arc.
Fundamental to the electrophysiology of the canine heart 3–5 days postinfarction is the anatomical character of the infarct (Mehra et al., 1983). The thin layer of surviving epicardium provides a functionally two-dimensional model in which to study reentry. The determination of the effective refractory periods intramyocardially showed that the shortest ERP at a site are at the epicardial surface, whereas longer ERP and inexcitable tissue lie beneath the surface. Therefore, it is this superficial layer that functionally supports the unidirectional block and slow conduction of premature beats initiating reentry.

The dependence of the morphology of the arc of block on the pattern of refractoriness is further supported by the shifts in the arc when a range of S1–S2 intervals induce reentry, as shown in Figures 2 and 3. Fewer premature beats were able to penetrate to areas of longer refractoriness before blocking than earlier premature beats were able to penetrate. This could result in slight shifts in the slowly conducted wavefront causing reentry, or in the emergence of a different reentrant pathway.

One of the questions this study answers is why an S2 fails to initiate a reentrant beat but an S3 succeeds. As shown in the example of Figure 4, the arc of conduction block encountered by S2 can be too short to provide the necessary distance around which the slow conduction must proceed. The wavefronts coalesced and were blocked. Due to the nonuniform shortening of refractory periods in the wake of S2, S3 encountered an arc of block which provided a sufficiently long barrier around which conduction had to occur and the additional availability of an area in which slow conduction could occur; the result was reentrant excitation.

This study also demonstrated that the pattern of refractoriness can explain why an induced reentrant rhythm terminates and does not become sustained. Due to the observation that consecutive shortened cycles cause a non-uniform shortening of refractory periods, as shown in Figure 7, the gradient of refractoriness that is encountered by a circulating wavefront can increase during successive cycles and provide a sufficient barrier to cause conduction block. This occurrence of block is further enhanced when the conduction time around the circuit is not increased.

The measurement of successive refractory periods of spontaneous beats occurring during a sustained reentrant rhythm is not possible, because the maximal interval of inexcitability (ERP) of these beats would be masked by the next arising spontaneous beat. Therefore, one can only extrapolate that the persistence of a sustained reentrant ventricular tachycardia is due to the fact that there is not an increased gradient in refractoriness following the first and subsequent reentrant beats. The reentrant rhythm will remain sustained until a slight increase in refractoriness occurs before the wavefront enters the region of slow conduction, or as it is emerging from the area of slow conduction. An alternative view would be that a slight decrease in conduction time would occur, independent of refractoriness, and excitation would arrive at the respective sites before refractoriness had expired.

Role of Dispersion and Spatial Distribution of Refractoriness

The model of Moe et al. (1964) showed that a random distribution of refractory periods with a sufficiently large dispersion of refractoriness could provide a substrate for reentrant arrhythmias. It followed then that the magnitude of the dispersion of refractoriness could be the basic indicator of risk for reentrant excitation (Han and Moe, 1964; Sasy-niuk and Mendez, 1971). An increase in the dispersion following coronary artery ligation has been considered crucial to the development of reentrant rhythms in the ischemic heart (Levites et al., 1975; Batsford et al., 1978). However, the present study has shown that the spatial distribution of the refractoriness must also be considered. In isolated rabbit atrium, Allessie et al. (1976) showed that, although a critical dispersion of refractoriness was necessary for reentrant activation, the dimension of the area in which refractoriness was prolonged was likewise critical to reentry. Boineau et al. (1980) confirmed the findings of Allessie by showing that it was the unique pattern in which refractory periods were distributed that resulted in reentrant excitation in the in vivo canine atrium, rather than the degree of refractory period inhomogeneity. The activation maps reported here are similar to the activation patterns reported by Boineau et al. They showed that the nonuniform distribution of refractory periods was likewise characterized by adjacent regions of short and long durations. A premature atrial beat initiated from the area of shortest refractoriness blocked between these areas, conducted around the area of prolonged refractoriness, coalesced, and reentered the area of initiation. As in the studies of Boineau et al. (1980), Allessie et al. (1976), and Kuo et al. (1983), we have shown that reentrant excitation was initiated by a premature beat originating in the region of shortest refractory period and conducted toward areas having longer refractory periods.

Measurements of the Recovery of Excitability

In the past, several techniques have been utilized to estimate the time at which excitability is recovered at local sites. Monophasic action potentials recorded from a suction electrode (Sarachek et al., 1972; Kuo et al., 1983) or an electrogram recorded from close bipolar electrodes (Martins et al., 1983) have been used. However, neither of these techniques are able to measure when excitability extends beyond the duration of the action potential or the Q-T interval of the electrogram, i.e., postrepolarization refracto-
Unidirectional Block and Refractoriness

In this study, the extra stimulus technique of Krayer et al. (1951) was used to determine directly the reexcitability of each site, as defined by the effective refractory period (the longest $S_1$-$S_2$ interval that fails to initiate a response to $S_2$ when the current of stimulation is two times late diastolic threshold). Refractory period measurements done by Allessie et al. (1976) used the interval obtained at 4 times threshold current, while Boineau et al. (1980) used the interval obtained at 1.1 times threshold current. Michelson et al. (1980) studied refractoriness in ischemic myocardium 3–8 days after occlusion and reperfusion. Their study compared strength-interval relationships at selected ischemic and normal sites, and they pointed out the difficulties inherent in choosing a standardized threshold current for the definition of a refractory period. The use of too high a current creates problems due to the recruitment of less refractory, less ischemic fibers at some distance from the stimulating electrode. Choosing too low a suprathreshold current results in the choice of an interval that would change significantly with only slight changes in current. Because there is no final conclusion about which electrical parameters best describe the refractoriness properties of the cells during in vivo conduction, twice diastolic threshold was used in the present study, and has been used routinely in other electrophysiological studies (Denes et al., 1974; Harumi et al., 1974; Levites et al., 1975).

Allessie et al. (1978) determined in isolated atrial strips that a refractoriness gradient of 11–16 msec was sufficient to cause conduction block. In the study reported here, and in previous reports (Mehra et al., 1983; El-Sherif et al., 1983; El-Sherif et al., 1984), we have arbitrarily represented conduction block to occur between adjacent sites separated by 40 msec or more of activation time. The end points of the arc of block occur between sites having only a 40-msec difference in activation time and may be located in an area where only a 10- to 20-msec difference in effective refractoriness exists between the sites. Consequently, these areas of the arc may be the least exactly represented portions of the arc. However, there is no such question in the middle portions of the arc, and it is in these areas that the arc of functional conduction block most clearly corresponds to the area where isochrones of refractoriness are crowded together, designating a steep gradient of refractoriness. Although the experimental protocol did not address the issue of the minimum gradient necessary for conduction block to occur, it was observed that conduction block did occur when the difference in effective refractory period between adjacent sites increased from 10 to 20 msec (see Figs. 4 and 5).

Anisotropic Conduction

Spach et al. (1981, 1982) have shown that, in normal cardiac tissue, conduction in a direction parallel to the myocardial fiber orientation is more rapid but has a low safety factor for conduction, whereas conduction in a direction perpendicular to the fiber orientation is slower but has a high safety factor for conduction. They have shown this anisotropic conduction in small isolated preparations of atrial muscle and ventricular papillary muscle, and it can set the stage for reentrant excitation. Ursell et al. (1985) have shown that small (less than 1 cm²) isolated preparations of ischemic epicardium conduct more slowly transverse to fiber direction than parallel to fiber orientation. However, the importance of anisotropic conduction in vivo in the normal or ischemic heart is yet undetermined. In a preliminary study, we have studied the role of nonuniform refractoriness and anisotropic conduction in the ischemic heart (El-Sherif et al., 1985). The activation during an $S_2$ that initiated a reentrant beat was studied during epicardial stimulation from at least two sites, one parallel and one perpendicular to the fiber orientation of the ischemic epicardial layer. Stimulation from either site resulted in an arc of conduction block that occurred along the gradient of refractoriness. Although a possible contribution of fiber orientation to nonuniform refractoriness could not be ruled out, the correlation between the arc of block and the isochrones of refractoriness was compelling.

Conclusion

Ischemia, 3–5 days postinfarction, causes a lengthening of effective refractory period resulting in a nonuniform spatial distribution of refractoriness in the ventricular epicardium characterized by contiguous zones with steep gradients of refractoriness between them. This forms the substrate for the development of an arc of functional unidirectional conduction block. The further nonuniform shortening of refractoriness due to repetitive short cycle length explains why the initiation of reentrant activation may require more than one stimulated premature beat, and why one reentrant beat does not necessarily produce successive reentrant beats.

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