Slow Ventricular Activation
in Acute Myocardial Infarction

A Source of Re-entrant Premature Ventricular Contractions

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SUMMARY
The evolution of premature ventricular contractions (PVCs) in acute myocardial infarction was studied by recording bipolar potentials from the left ventricle before and after coronary artery occlusion in dogs. The potentials were recorded from 154 locations in the left ventricular wall as well as at the endocardial and epicardial surfaces. Desynchronization and marked slowing of previously uniform activation was noted and resembled abbreviated, local fibrillation. The dissociation of excitation was either simple, characterized by fragmentation into single delayed spikes, or complex, characterized by numerous spikes. Sustained, desynchronized activity, confined to local myocardial areas, was observed up to 215 msec after the onset of activation. These local areas of sustained excitation functioned as a source of re-entrant activity and were associated with PVCs. Histochemical stains of myocardium indicated a relationship between the inhomogeneous distribution of ischemia (stain) and the desynchronization of the electrical activity.

Additional Indexing Words:
Acute myocardial infarction
Ventricular fibrillation
Ischemic heart disease
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Localized fibrillation
Sudden death
Re-entry
Arrhythmias

This study was performed to examine the theory that slow ventricular activation is a mechanism which produces premature ventricular contractions in acute myocardial infarction and leads to ventricular fibrillation. Slow desynchronized activation in ischemic myocardium which lasts longer than the refractory period of adjacent normally excited tissue, or greater than 200 msec, has not previously been demonstrated in the intact heart after coronary artery occlusion.

Methods
Twenty normal dogs ranging in weight from 13 kg to 18 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg body wt. After intubation, a left lateral thoracotomy was performed and the heart was cradled in the pericardium to expose the left ventricle. A branch of the anterior descending coronary artery was exposed and a snare was placed around it. The vessel was occluded for 10 to 15 sec to determine the resultant area of cyanosis and was then released. Subsequently, 11 intramural, multipoint electrodes were placed in regions both within and outside the boundaries of the cyanotic zone (Fig. 1). One reference electrode was placed in the right ventricle, distant to the region affected by the occlusion. After recording control bipolar electrograms from the eleven electrodes and the reference electrode, the coronary artery was occluded and potentials were monitored intermittently for 3-6 hr. In eight dogs, after a variable period of ischemia, the occlusion was released and the electrograms were again recorded at intervals until stabilization of the observed electrophysiologic transients or ventricular fibrillation occurred.

Control bipolar electrograms were recorded from 14 bipolar contacts located 1 mm apart on each of the 11 electrodes. Thus potentials could be recorded from a total of 154 intramyocardial locations. The electrodes were coupled directly to a set of field effect transistor (FET) buffer amplifiers with an input impedance of $10^{11}$ ohms and unity gain. The signals were subsequently amplified and recorded on magnetic tape at a speed of 7.5 in/sec. The frequency response of the system was from 0.1 Hz to 2.5 kHz. The lead II ECG was also recorded. After occlusion of the coronary artery, a selector switch was used to sample or display all of the electrodes in quick succession.

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Recording Methods. Fourteen bipolar potentials were recorded between 15 consecutive terminals on each of 11 needle electrodes; thus a total of 154 points (11 x 14) were recorded from the epicardium, endocardium, and intramurally in each experimental animal. The 11 LV needle electrodes were inserted perpendicular to the wall adjacent to the occluded vessel. The RV electrode was used as a time-reference control and was not affected by occlusion. A blow-up of one needle is shown and one of the 14 bipolar leads at the epicardium (EPI) is indicated. After coronary occlusion, the 154 points were consecutively scanned using a special switching network and a cathode ray tube (CRT) display. Six different bipolar electrograms were viewed or recorded simultaneously. Progressive changes or transients were recorded on analog magnetic tape. An oscillograph was used to display data immediately or later.

At the end of each study, the dogs were sacrificed and blocks of tissue containing the electrodes were excised and immediately quick-frozen with powdered dry ice. Histochemical staining techniques, according to the method of Nachlas et al., were performed and correlations were made between the electrical events and the histological sections.

Results

Although premature ventricular beats occurred during the period of occlusion, ventricular tachycardia or ventricular fibrillation rarely occurred. However, after releasing the occlusion, the frequency of premature beats and the occurrence of ventricular tachyarrhythmias were markedly increased as previously noted by Harris and Rojas. Subsequent to the acute occlusion of the vessel, changes were noted in the electrograms recorded from the zone of ischemia and at its boundaries. These changes in the bipolar complexes progressed over time and were characterized by asynchronous, fragmented activation. No changes were observed in electrodes in distant regions of the left ventricle or in the control right ventricular electrogram. Figure 2 demonstrates the two types of asynchronous excitation noted in this study. In A, the more simple degree of desynchronization is illustrated. The major bipolar complex is followed by a second spike at 44 msec. This spike indicates a uniformly
delayed region of activation recorded by this bipolar pair of electrodes. In B, the complex is fragmented into multiple asynchronous spikes indicating a marked desynchronization of activation within this region. The latter electrogram suggests a more complex degree of disorganization of the previously uniform wavefront. In C, a normal complex is presented for comparison.

**Evolution of Desynchronized Excitation**

In normally activated myocardium, the bipolar potential appears as a rapid deflection of 4 to 10 msec duration, as shown in figure 2C. The normal potential represents the synchronized activation of the tissue within this specific local area. The progressive, desynchronization after experimental coronary occlusion in one of the dogs is illustrated in figure 3. Control and postocclusion bipolar electrograms were recorded from electrodes placed in the left ventricular wall together with an RV bipolar reference. Note the amplitude and duration of the control potentials and the resultant decrease in amplitude, marked increase in duration, and the fragmentation of the complexes into multiple components following occlusion. This sequence of desynchronization was characteristic of specific regions of the affected myocardium in all of the dogs in this study. In some electrodes only widening of the complexes with a decrease in amplitude was noted.

**Evolution of a Spike of Delayed Excitation**

The development of a spike of delayed excitation is shown in figure 4. Coincident with the loss of amplitude of the primary deflection, a second delayed spike developed (arrow) which occurred 40 msec later. This process of fragmentation began as a subtle late slur in the third complex. The

![Figure 2](image)

**Figure 2**

Two Types of Desynchronized Activation. Simple desynchronization as shown in A was most often characterized by single delayed spikes; occasionally two widely-spaced delayed spikes as shown in figure 8B and 9 were noted. In A, the delayed activity occurred 44 msec after the initial deflection. A complex form of desynchronization is shown in B and is characterized by multiple spikes. The electrogram indicates prolonged and nonuniform activation within the area. In C, a normal electrogram is shown for comparison. Note the greater amplitude and shorter total duration of the complex characteristic of a uniform synchronous wavefront.

![Figure 3](image)

**Figure 3**

Progressive Desynchronization Subsequent to Coronary Occlusion. A bipolar reference electrogram (Bi Ref) recorded from the normal right ventricle is shown here. Below, bipolar intramural electrograms (BIP) recorded from an area of left ventricular ischemia are demonstrated. These signals were recorded simultaneously during the control period and at 30, 60, and 180 min subsequent to coronary artery occlusion. Note the progressive decrease in amplitude of the bipolar potential with increased duration and fragmentation of the complex. Also note that the reference electrogram in the RV remains stable throughout the period of occlusion.
delayed spike progressively increased in amplitude coincident with a decrease in the amplitude of the primary, initial deflection. Note that there was alternation in the amplitude of the delayed spike beginning with the fourth beat. This relationship between the amplitudes of the primary and delayed deflections suggests that in the cycles exhibiting fragmentation some of the fibers which normally activated during the primary complex did not excite initially but fired synchronously 40 msec later resulting in the second spike. The combined amplitudes of the two spikes (initial and delayed complexes) was much less than the total amplitude of the complex before fragmentation. This indicates that a sizable amount of the tissue recorded by this electrode was inexcitable, and that a small amount excited after a uniform delay of 40 msec.

Cyclic Variation of Delayed Activation

Figure 5 demonstrates a progressive delay of a late spike. In addition to progressive delay of the spike, there was an increase in its amplitude in the third cycle coincident with a decrease in the amplitude of the earlier nondelayed component.

Figure 6 demonstrates alternation of a late deflection. Bipolar potentials recorded from two adjacent electrode terminals are shown below the bipolar reference electrogram recorded from the right ventricle. Note the presence of a delayed spike, occurring 70 msec after the initial complex in the first and third cycles, which is absent in the second and fourth cycles. The sequence of events suggests that the area of delay was blocked completely (not excited) every other beat since there was no change in the amplitude of the primary spike which would be expected to occur if normal excitation alternated with cycles of delayed excitation.

Figure 4

Evolution of Delayed Activation. The top electrogram is the bipolar reference potential (Bi Ref) recorded from the right ventricle. The lower electrogram (BIP) was recorded from an area of left ventricular ischemia. A series of nine cardiac cycles (beats) are shown. Note that with progressive loss in amplitude of the primary spike which indicates initial activation of the region, a delayed spike of activity (arrow) develops and becomes more prominent in amplitude. There is a definite correlation between the decrease in amplitude of the primary spike and the increase in amplitude of the secondary one.

Figure 5

Progressive Delay of Spike. This figure illustrates an enlargement and expanded time base recorded at a later time but from the same electrode as shown in figure 4. Note the progressive delay of the fragment over three cycles. This type of dissociation into an initial deflection and a smaller delayed fragment was frequently noted in these studies. Note the slight decrease in the amplitude of the primary complex which occurred simultaneously with a slight increase in amplitude of the delayed spike in the third cycle. This sequence, as well as the evolution of the delay shown in figure 4, suggests a uniform time-dependent delay in the excitability of some fibers with each cycle.

Figure 6

Alternation of Delayed Activation. A bipolar reference electrogram (Bi Ref) from the right ventricle is indicated above. Bipolar intramural potentials (BIP) recorded from two adjacent pairs of electrodes are shown below. Note the delayed fragment in the first and third cycles.
Spatial-Temporal Relationship Between Simple and Complex Desynchronization and Normal Activation

Figure 7 illustrates a marked prolongation of complex activity recorded from a bipolar electrode 90 minutes after acute coronary occlusion. The fragments were spread out over a period of 215 msec, and this activity exceeded the durations of local, bipolar T waves recorded from neighboring electrodes.

In figure 8 (several seconds later) the selector was switched to display simultaneous activity recorded from three electrodes sites (A, B, and C) located at different points in this same dog's left ventricle. The approximate locations of these three points and the bipolar signals recorded from these regions are illustrated in the schematic diagram of the ischemic left ventricular wall. The rapid single deflection of short duration in the top tracing indicates a relatively narrow, homogeneous distribution of activation. The center tracing demonstrates two delayed spikes of activation occurring at 150 and 255 msec respectively after the initial complex. These delayed deflections represent regions not initially depolarized during the first spike, as shown by the previous examples in figures 4 and 5 which demonstrate the evolution of such activity. The lower tracing demonstrates marked desynchronization of activation of an adjacent zone which lasted for 215 msec. This is a record from the same electrode site as was shown previously in figure 7. Note in comparing the complex in figure 7 with that in 8C that there are some differences in the duration and form of the activity recorded at different times from this area. These electrograms suggest a

**Figure 7**

Slow-Desynchronized Activation in Ischemic Myocardium. *Note the prolonged duration of complex, fragmented activity. This electrogram was recorded between two terminals one mm apart. This prolonged activity appeared to be the source of delayed spikes in adjacent areas (fig. 8).*
complex dissociation with asynchronous firing of minute fiber clusters. It would appear that this region of prolonged, disorganized activity is the source of the late fragments in the middle tracing (B) of figure 8.

Propagation of Delayed Activity—Origin of the Premature Ventricular Beat

Figure 9 illustrates two examples of delayed activity which resulted in premature ventricular beats. The example in figure 9A demonstrates the evolution of a PVC in the same dog that exhibited the markedly prolonged local activity in figures 7 and 8. In A, the lower tracing illustrates the bipolar potential recorded from an intramural electrode located in an ischemic area; the top tracing is a bipolar reference electrogram recorded from the right ventricle. In the first cycle in A, there was a single rapid spike. However, in the second cycle the initial spike was followed by a second spike of delayed activation at 270 msec. In the third cycle the initial complex was followed by two delayed spikes, one at 150 and the other at 270 msec. In the
fourth cycle the initial complex was followed by a large spike at 290 msec. These data suggest block of the activity delayed by 270 msec (in the second and third cycles) but propagation from this area when delayed by 290 msec due to further recovery of excitability (decreased refractoriness) in the rest of the myocardium. Propagation of the delayed activity in the fourth cycle is indicated by the presence of a premature complex in the distant reference electrode. In B, a similar sequence of events was recorded from another dog during a period of ischemia. These two examples are representative of an association between locally delayed excitation and the occurrence of PVCs which was observed in most animals after coronary occlusion.

**Correlation Between Histochemical Tissue Stains and Electrical Activity**

The sensitivity of ischemic myocardial injury to certain histochemical stains allowed correlation of the histologic (biochemical) changes with the electrical events occurring in these regions. From the work of previous investigators it has been shown that differential uptake of the histochemical stain reflects variation in dehydrogenase activity, which can be correlated with changes in mitochondrial swelling using high power light and electron microscopy.1,3 Under low power magnification these variations in density of uptake appear as variations in hue with the normal areas being darkest and the most severely affected areas staining the lightest. Figure 10A shows an area of ischemic tissue completely surrounded by normal staining myocardium. The fibers in this area demonstrate a greater degree of injury than the surrounding fibers and the injury appears relatively homogeneous for the cluster. This represents the biochemical-structural correlate of the simple type of desynchronization, i.e., the single or uniformly delayed spike of activity which was recorded from this area and is shown in figure 2A.

Figure 10B shows markedly inhomogeneous staining of a region of myocardium which is predominantly ischemic but which has islands of densely staining fibers dispersed throughout. Electrical activity recorded from this area (fig. 2B) demonstrated an equally inhomogeneous pattern of activation corresponding to the complex type of desynchronization.

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Discussion

Both clinical observation and experimental studies have established that premature beats falling during the ventricular vulnerable period may produce ventricular fibrillation in patients with ischemic heart disease. Therefore, appreciation of the mechanisms of PVCs in acute myocardial infarction is an important first step in understanding the more complex problem of ventricular fibrillation.

Two theories which have been proposed to explain the genesis of PVCs in ischemia are 1) formation of ectopic ventricular impulses, presumably due to automatic firing of Purkinje tissue which has the capacity for diastolic depolarization and 2) re-entry. In vitro, microelectrode studies have shown that ventricular Purkinje fibers undergo diastolic depolarization and fire automatically due to a variety of stresses including hypoxia.4,5

Several models of re-entry have been postulated to explain PVCs in infarction. Common to each of these concepts is a hypothetical region of depressed conduction in which the impulse is delayed for a duration longer than the refractory period of adjacent tissue. Thus, the recovered myocardium is prematurely re-excited or re-entered by the impulse as it emerges from the region of delay. Recent studies by Wit, Hoffman, and Cranefield,6,7 using a Y loop model of a Purkinje-muscle junction with depressed conduction in one of the Purkinje limbs
of the loop, have demonstrated a specific form of re-entry. Although they used an isolated and geometrically simple network, their studies demonstrated a theoretically possible pathway of re-entry.

In the intact heart, Han has shown re-entrant beats and multiple repetitive contractions following artificially stimulated premature beats in dogs with experimental ischemia. Also, as suggested by the previous studies of Han and Moe, re-entrant activity occurs following premature beats, if the ventricular tissue receiving the premature wavefront possesses an abnormal degree of inhomogeneous recovery during the relative refractory period. Their excellent studies explain re-entry in a setting of inhomogeneously distributed myocardial refactoriness and recovery. However, this concept assumes an initiating premature beat just as the experimental observations of Han demonstrating re-entry depend on the delivery of a premature stimulus to the preparation. Our studies differ from these in that premature beats were not used to evoke re-entry. We were primarily concerned with the spontaneous development of PVCs as a natural consequence of the single intervention of coronary occlusion.

Durrer et al. have demonstrated slow-desynchronized ventricular conduction during experimental myocardial infarction in the intact dog heart. They have also suggested this as a mechanism of PVCs in myocardial infarction.

Thus, from studies on isolated tissue preparations, there is good evidence that re-entry can occur under rather specific experimental conditions. Also, studies in the intact heart indicate that re-entrant extrasystoles do occur in response to artificially stimulated premature beats and that slow-desynchronized ventricular conduction can occur secondary to acute myocardial infarction. Clearly indicated were direct observations in the intact heart of transient electrophysiologic events leading to the spontaneous evolution of PVCs secondary to coronary occlusion. Since these events could occur anywhere within the ventricular myocardium, as well as at the epicardial and endocardial surfaces, methods were needed for recording these events within the total three dimensional volume of ischemic tissue and its boundaries. In this study, the use of multiple needle electrodes, where each needle contained 14 bipolar points, provided a total of 154 separate locations for observing the ischemic muscle. Since these 154 points were connected to a network which allowed rapid switching, monitoring, and recording of these locations, it was possible to record events that developed over a wide area within the three dimensional volume of myocardium.

Interpretation of Fragmented Bipolar Potentials

Normal activation produced tall, rapid complexes in the extracellular bipolar electrodes separated by a 1 mm distance. The amplitudes varied between 15 to 40 mV and the duration between 4 to 10 msec during the control periods. During ischemia, the complexes were progressively reduced in amplitude and increased in duration. The increased duration was commonly associated with complex fragmentation or splintering of the previously smooth waveforms. Since an interelectrode distance of 1 mm was used in this study, the recorded deflections represent the depolarization of many cells within the local area. Thus, the shattering and prolongation of the bipolar complexes were interpreted to mean that the cells in this region were asynchronously activated. With progressive desynchronization, there was less summation of potential at any one instant and thus the amplitude was concurrently diminished with time after coronary occlusion. It follows that the pathway of excitation was complex and possibly circuitous rather than uniform. The basic mechanism of this nonuniformity is outside the scope of this study. However, the correlation between the degree of electrophysiologic complexity and the inhomogeneous binding of the biochemical stain by the tissue is evidence that the myocardium was depressed in a nonuniform manner.

In Figure 11, a possible relationship between the electrophysiologic and anatomic (or biochemical) nonuniformity is schematically presented. If the nonuniformity were coarse, involving varying degrees of depression of different cell clusters, the activity would be prolonged and the pathway might resemble that illustrated in A. If the functional nonuniformity were geometrically "finer grained" as in B, then a greater duration of activity would be expected in the depressed area because of the longer effective pathway. Delayed excitation, persisting in ischemic myocardial areas for periods longer than 200 msec, would act as a source of re-entrant activity which could spread prematurely into surrounding areas undergoing recovery by this time and give rise to PVCs (figures 8 and 9).

A possible mechanism of myocardial re-entry which is consistent with the data obtained in this study is illustrated in figure 12. The evolution of a
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Figure 11

Suggested Mechanism of Complex Desynchronization and Slow Propagation. In this schematic figure the white areas represent severely depressed (unexcitable) myocardium. The stipled areas represent less severely depressed, nonhomogeneously excitable myocardium. The area of wavey lines represents normally excited myocardium in the absolute refractory period. In A, the more coarsely distributed nonhomogeneity results in fewer spikes of larger amplitude, and a shorter duration of the activity than in B. In B, the more finely distributed nonhomogeneity of depressed excitability results in more complex and effectively longer pathways. The greater degree of asynchronous excitation in B results in a larger number of spikes of smaller amplitude, and a markedly prolonged duration of the circuinus activity confined to this region. The activity is confined by the absolute refractory state of the surrounding myocardium which has previously been excited by the normally propagated wavefront through this region. In this example there is interplay between the duration of persistent desynchronized activity and the duration of the recovery period of the surrounding myocardium, a factor which determines whether re-entrant PVCs are generated or not.

delayed spike and also a PVC are schematically illustrated. The geometric relationships shown in this figure are used only to indicate the degree of myocardial delay (time) and not the pathway of the activity. Slowing of activation is postulated to occur as depicted in figure 11 and not as unidirectional spread as shown here. In figure 12, three areas representing different states of myocardial excitability (X, Y, and Z) are shown. Area X represents electrically normal myocardium, Y represents an area of markedly inhomogeneous excitability, Z represents an area of uniformly depressed excitability (at 25 msec). As the initial wavefront passing through area X encounters area Y, the velocity of propagation of that segment of the wavefront is decreased as a result of the marked desynchronization. If this slow activity persists for 50 msec and area Z becomes excitable at this time, the impulse will activate area Z, resulting in the single delayed spike. The activity will be confined to area Z because area X is still refractory from the normal wavefront. If the configuration of area Y is such that the desynchronized activity persists for 200 msec or longer, as in figure 10B, then recovery will allow re-entry of the activity into area X resulting in a propagated premature beat. The area of slow conduction, as represented in this figure by region Y, is the same area that generates the electrograms illustrated in figures 7 and 8C and is depicted schematically in figure 11. In figure 12, area X corresponds to normal myocardium, area Z which represents an area of homogeneously depressed excitability, corresponds to the lightly-stained area illustrated in 10A. Area Y, which
Figure 12
Suggested Mechanism of Delayed Spike or PVC. X, Y and Z are three geometrically defined regions with the functional characteristics indicated by the code on the right at the center of the figure (NE = normal excitability; IDE = inhomogeneously depressed excitability; ARP = absolute refractory period; HDE = homogeneously depressed excitability). In A, the late fragment results from the delayed excitation of Z, a region of homogeneously depressed excitability which is time dependent. The source of the activity which fires Z late is region Y, which still contains activity at 50 msec because of its inhomogeneously distributed, depressed excitability. There is no propagation of the delayed activity because of the absolute refractory state of the surrounding "normal" myocardium (X). In B, the characteristics of region Y result in a longer duration of complex activation to 250 msec. Since this duration is longer than the ARP of the surrounding myocardium, propagated reexcitation (PVC) results.
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represents an area of inhomogeneously depressed excitability, corresponds to myocardium which exhibits the staining characteristics of figure 10B. For a delayed spike to occur as shown in figure 12A, either direct continuity or an excitable pathway must be present between regions having the functional characteristics of Y and Z. Spatial continuity between areas exhibiting the staining characteristics of both A and B in figure 10 was a common finding in this study.

Demonstration of re-entry as an actual mechanism, as opposed to a theoretical concept, to explain PVCs in acute myocardial infarction requires data in the following areas: 1) demonstration in the intact heart of a region of slow conduction of sufficient duration to delay a component of ventricular activation beyond the refractory period of the surrounding normal myocardium; 2) demonstration that the region of slow conduction, if present, actually is the source of re-entrant activity. The latter, or the actual demonstration of re-entry, requires the simultaneous recording of potentials in the region of delay and the region of re-entry as well as a precise representation of the pathway of the impulse between the two regions. Ischemically-induced re-entry was not proven by this study because the precise pathway of the impulse emerging from a region of depressed conduction and spreading to the surrounding myocardium was not demonstrated. However, short of this proof this study demonstrates 1) that coronary occlusion results in localized areas of delayed and sustained myocardial activation; 2) that these delays may exceed 200 msec, which approaches or exceeds the absolute refractory period durations of adjacent, normally excited tissue; and 3) that the occurrence and actual timing of PVCs correlate with the presence and duration of the delayed activation.

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