The Pathophysiology of Malignant Ventricular Arrhythmias During Acute Myocardial Ischemia

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SUMMARY
In 20 anesthetized open-chest dogs, epicardial electrograms were recorded from ischemic and non-ischemic zones of the left ventricle during acute occlusion of the left anterior descending artery. The average time to onset of ventricular tachycardia during atrial pacing (150–200 beats/min) was 4 min, 18 sec. In 18 dogs, ventricular ectopic beats were induced in normal and ischemic zones after every tenth atrial stimulus. Those induced in the ischemic zone consistently caused ventricular tachycardia earlier (mean: 3 min, 22 sec) than those in the normal zone (mean: 4 min, 11 sec) (P < 0.01). This arrhythmia, whether spontaneous or induced, always followed the complex which demonstrated the greatest delay of the ischemic zone potential and increased ventricular activation time. Ventricular tachycardia was repeatedly produced by ectopic beats with late diastolic coupling. Analysis of the episodes of tachycardia leading to fibrillation revealed a progressive increase in the ventricular activation time of the successive beats, whereas in those self-terminating episodes ventricular activation time progressively decreased. These data suggest that the major determinant of malignant ventricular arrhythmias in acute ischemia may be the related abnormalities of ventricular activation rather than the coupling of the premature ectopic beats.

Additional Indexing Words:
Ventricular extrastimulus
Re-entry
Heart rate
Left anterior descending coronary artery
Intraventricular conduction
Refractory period

SINCE THE INTRODUCTION OF CORONARY CARE UNITS the importance of the treatment and abolition of ventricular extrasystoles in preventing the development of life-threatening arrhythmias and thereby reducing mortality has been shown. The demonstration of a vulnerable phase during ventricular repolarization when ectopic stimulation produced tachycardia and fibrillation heightened the awareness of the malignant properties of such ectopic beats.1,2 This concept of vulnerability has been widely accepted and has proved to be of considerable clinical value. However, several reports3–5 have indicated that this arrhythmogenic potential is not exclusively confined to those extrasystoles exhibiting the R-on-T phenomenon and that tachycardia and fibrillation may be initiated by ectopic beats occurring later in diastole.

The recording of surface electrograms from normal and ischemic areas of the canine heart during acute coronary occlusion provides clear evidence of delay and disorganization of ventricular depolarization in the ischemic zone.6 This study attempts to relate these findings to the genesis of ectopic beats during ischemia and to compare those spontaneous extrasystoles initiating an arrhythmia with those induced by programmed premature ventricular stimulation. In addition, the temporal dispersion of ventricular excitation has been studied during episodes of ventricular tachycardia which were self-terminating and compared with those which progressed to fibrillation.

Methods
Twenty adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg). After intubation, ventilation was maintained with room air using a Harvard respirator. The heart was exposed through a left thoracotomy in the fourth intercostal space and the anterior descending artery exposed below the origin of the anterior septal branch.

Two silver wires (0.012 inches diam) were inserted into the left vagosympathetic trunk through which stimuli (0.05 msec duration, 20 Hz and 1–10 volts) were delivered to slow the heart rate at the initiation of arrhythmia.7 Atrial pacing with pulses of 2 msec duration, 150–200 beats/min, and 2–10 volts was achieved by the insertion of two stainless steel wires (0.05 inches diam) into the left atrial appendage and stimulation from an S88 Grass stimulator and SIU-5 isolation unit.

Recordings from the ventricle were made by inserting two
fine teflon-coated stainless steel wires (0.003 inches diam) into the epicardium through a 25 gauge needle 1/2 inches in length. The cut ends of the wires served as close bipolar recording pairs. One pair was inserted into the high lateral aspect of the left ventricle to provide a control electrogram and two pairs into the area supplied by the left anterior descending artery.

In later experiments a different technique was used for recording ischemic zone electrograms and was designed to obtain information from as large an area as possible within the ischemic zone. A large multipolar paper electrode was made with two insulated silver wires (0.012 inches diam) which were threaded onto the surface of the paper at about 25–30 points to create multiple bipolar contacts with an interpoint distance of 2–3 mm. The two wires were connected to pin jack terminals and the subsequent recording effectively produced a “composite” electrogram from the multiple exposed bipolar contacts. This proved to be a convenient method of recording from a large ischemic area and avoided the necessity for numerous bipolar wires. The paper electrode was positioned circumferentially over the surface of the ischemic area and secured by fine 6–0 sutures at each corner. When attached in this position, the electrode covered areas of almost simultaneous activation, and during the control state, recorded an electrogram which was very similar to those from bipolar wires. The only detectable difference was a slight increase in duration seen in the composite electrogram (see fig. 1, CIZ eg). A standard electrocardiographic lead and the epicardial electrograms were continuously recorded on a Honeywell 5600 tape recorder and permanent records for analysis were subsequently registered on an oscillographic-photographic recorder at paper speeds of 100–200 mm/sec with frequency limits of 0.1–2000 Hz.

**Procedures**

Atrial Pacing

Recordings were taken before and during left anterior descending artery occlusion in sinus rhythm and during atrial pacing at 150 beats/min. If significant delays in the epicardial potentials from the ischemic zone were not apparent, higher atrial pacing rates were used — up to 200 beats/min. If arrhythmia occurred without apparent delay, alternative sites within the ischemic zone were selected for placement of the bipolar recording pairs. In each spontaneous episode of ventricular tachycardia, the coupling interval of the initiating beat was determined.

Ventricular Premature Stimulation

Investigation with programmed ventricular stimulation was undertaken only when the control occlusion had produced an arrhythmia associated with appreciable epicardial delay; with appropriate heart rate and vessel occlusion, delay of epicardial activation was achieved in all dogs. With experience it became possible to terminate many episodes of ventricular tachycardia by prompt vagal-induced slowing of the heart rate, cessation of pacing and release of occlusion, thus permitting repeated observations with a specific end point for comparative analysis. Five to ten minutes were allowed to elapse between successive occlusions and analysis of the subsequent occlusive changes was only undertaken if the electrograms had returned to their normal control pattern recorded at the beginning of the experiment. It was found that no more than five to six occlusions could be performed before abnormalities persisted after release of occlusion. Experiments were terminated by ventricular fibrillation to determine the greatest delay associated with the onset of this arrhythmia. Electrical defibrillation was not used.

Programmed stimulation was achieved with a Medical Systems Devices stimulator MK III so as to deliver an impulse (2 msec duration, 5–10 volts) to the ventricle after every tenth atrial pacing stimulus. Stimulus intensity was kept constant in each dog but varied between experiments. With each successive occlusion, the site of ventricular stimulation was altered so that the effects of premature beats induced in the nonischemic and ischemic zones could be compared. The atrial paced beat immediately preceding the extra systole was also analyzed to indicate the progressive abnormalities that occurred when the ventricles were activated along the normal atrioventricular (A-V) pathways. In five dogs, the coupling interval of the ventricular stimulus, 20% above threshold level, was adjusted in consecutive occlusions to fall in early and late diastole. Early diastole was defined as 5–10 msec after the point at which the stimulus was ineffective (i.e., within the T wave) and late diastole as 5–10 msec before the interval at which fusion complexes were produced.

**Results**

A typical example of the spontaneous changes seen after occlusion of anterior descending artery is shown in figure 1. Electrograms were recorded from the nonischemic zone or normal zone in the left ventricle (NZ eg) and from four sites within the ischemic zone (IZ eg) supplied by this vessel. As the duration of ischemia increased, the recorded potentials from the subepicardial IZ sites progressively decreased in

![Figure 1](https://circ.ahajournals.org/figure/1)

*Figure 1* Records before (control), 3, and 4 min after coronary occlusion. Recordings from standard lead II (L2), two epicardial electrograms from a nonischemic normal zone (NZ eg), two electrograms recorded from bipolar wires from ischemic zones (IZ eg), one electrogram recorded with the composite electrode from ischemic zone (CIZ eg) and one endocardial ischemic zone electrogram (IZ eg ENDO). Progressive decrease in amplitude, increase in duration and fractionation is seen in the IZ eg recordings.

*Circulation, Volume 50, December 1974*
amplitude, increased in duration, and at 4 min, had fragmented into separate components. The result of this delay was effectively to increase the total ventricular activation time, as measured from the onset of the surface QRS to the point of maximal delay of the fractionated ischemic potential. The potential recorded from the endocardial IZ site was not affected.

The degree of these ischemic abnormalities was unequal at different sites within the ischemia area; this was found in all the dogs studied and reflects the functional heterogeneity between the different recording sites. No attempt was made to localize the sites of maximum delay and limited epicardial mapping was used only to identify foci exhibiting sufficient delay for measurement analysis when this was not apparent from the initial electrode placements. Ventricular activation time measured in this way is therefore almost certainly an underestimation since it would be unlikely that the sites of greatest delay would have been consistently recorded. Nevertheless, it was found that these results were reproducible with repeated occlusions and that the delay up to and at the onset of arrhythmia was remarkably consistent, provided the control pattern had returned to normal after release.

It should be emphasized that the monitoring of close bipolar electrograms, in the present study, at multiple sites in the ischemic epicardium does not represent a new or radical departure from previous studies.\(^9\)\(^10\) Using both plunge wire bipolar or large surface multipoint bipolar electrodes we consistently showed fractionation and delay of deflections recorded in the ischemic zone. Previous work from this laboratory using these techniques has documented delays as long as 320 msec.\(^6\) Invariably the greatest degree of delay coincided with the onset of ventricular tachycardia or fibrillation.

Programmed ventricular pacing was performed in 18 dogs. Figure 2 presents the average of the results for late diastolic stimulation from all the dogs studied. The cumulative increase in ventricular activation time from the preocclusion control level, represented as zero, is plotted against time. The latter has been standardized so that the end-point represents the onset of ventricular tachycardia; thus \(\frac{1}{4}\) T, \(\frac{1}{2}\) T and \(\frac{3}{4}\) T indicate the same time point in the evolution of the arrhythmia for all dogs. It can be seen that there is no difference in the progressive increase in ventricular activation time due to incremental ischemic zone delay between the normal beats (NB) of supraventricular origin and the premature beats induced in the normal nonischemic zone (NZ, VPB) of the ventricle. However, those induced by epicardial ischemic zone pacing (IZ, VPB) show greater delay with prolongation of ventricular activation time during the last \(\frac{1}{4}\) of the occlusion period up to the onset of ventricular tachycardia. These results, when considered in real time values for the period from occlusion to onset of ventricular tachycardia, were: during supraventricular rhythm (no ventricular stimulation): mean, 4 min, 18 sec (standard deviation: \(\pm 58\) sec); normal zone, VPB: mean, 4 min, 11 sec (\(\pm 66\) sec); and ischemic zone VPB: mean: 3 min, 22 sec (\(\pm 33\) sec). Statistical analysis revealed no significant difference between the times for NB and NZ, VPB, but comparisons of IZ, VPB, with NB, and IZ, VPB, with NZ, VPB, were both significant at \(P < 0.01\) level.

In three dogs, ventricular stimulation was applied, during consecutive occlusions, to four different sites within the ischemic area. In each of these three animals, only one of the four sites was activated up to the point at which arrhythmia resulted. Pacing at each of the other three sites produced progressively wider QRS complexes until the stimulus failed to evoke a response. In all animals a site within the ischemic zone could be found at which pacing was maintained to produce an arrhythmia, but the variation within this area probably reflected the heterogeneity of recovery times.

![Figure 2](image)

The incremental delay in epicardial activation (dispersion from control) is plotted against the duration of ischemia up to the onset of arrhythmia (T). Curves are drawn for the ventricular premature beats induced in the ischemic zone (IZ, VPB), in the normal, non-ischemic zone (NZ, VPB) and for the normal supraventricular beats (NB). Dispersion of ventricular activation progressively increases in each, but IZ, VPB, exhibits a greater degree of dispersion at onset of arrhythmia.
In all dogs studied it was found that ventricular tachycardia followed an induced extrasystole, from the normal or ischemic zone, whichever exhibited the greatest activation delay. The total ventricular activation time of the arrhythmia induced by the extrasystole was always greater than that of the preceding extrasystole, which had evoked no response. In many cases it was apparent that as ischemia increased, an extrasystole would produce a short run of self-terminating ventricular tachycardia. This pattern continued until one of the extrasystoles induced a tachycardia which persisted until abolition by vagal-induced atrial slowing and release of occlusion, or until ventricular tachycardia progressed to fibrillation.

Typical changes up to the onset of arrhythmia during ischemic zone stimulation are seen in figure 3. The extrasystole and the atrial paced beat which immediately precedes it are shown at 1, 2, and 3 min after coronary artery occlusion. The lower tracing was taken 20 sec after the 3 min recording and demonstrates the onset of a brief period of arrhythmia, which spontaneously resolves. It can be seen that the CIZ electrogram of the supraventricular beat becomes progressively fragmented and delays with respect to the normal zone recording (NZ eg). Similar changes are seen in the same IZ electrogram of the extrasystole but are of greater magnitude. At 1 min the delay from stimulus to the end of premature ventricular activation or total ventricular activation measures 101 msec; at 2 min, 111 msec; and at 3 min, 136 msec. The total ventricular activation time of the induced ectopic beat that initiates the arrhythmia is 142 msec. This is not due to an increase in latency as it can be seen that the interval from stimulus to onset of the electrogram does not change as ischemia progresses.

It is interesting to note also that there is a change in morphology of the extrasystole in lead 2 until it closely resembles the supraventricular beat recorded im-

![Diagram](https://example.com/diagram.png)

**Figure 3**

The top panel shows the induced ventricular extrasystole and the preceding atrial paced beat at 1, 2, and 3 min after occlusion. The lower panel was recorded at 3 min 20 sec. CIZ eg demonstrates progressive delay with ventricular activation time increasing from 101 msec to 136 msec after 3 min, and 142 msec at onset of arrhythmia. Note change in configuration of ectopic QRS until fusion occurs. The configuration of NZ eg recording of the extrasystole changes between 2 and 3 min.
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Immediately prior to the onset of arrhythmia. The NZ eg confirms that fusion has occurred. At 1 and 2 min, the electrogram of the supraventricular beat is quite different from that of the extrasystole, whereas from 3 min on they are similar. This indicates that delay within the ischemic zone has progressed to such a degree that the normal zone is activated by the supraventricular pacemaker before the ventricular stimulus is recorded.

This sequence was repeatedly seen and suggested a causal relationship. It was apparent therefore that a ventricular extrasystole which was recorded on the surface ECG late enough to produce a fusion beat was still capable of initiating an arrhythmia. Since it appeared that the dispersion of recovery times and delay of ventricular activation of ectopic activity was responsible for the initiation of ventricular arrhythmia, the activation time of the consecutive beats of the tachycardia were also analyzed to determine if they were related to the outcome of the arrhythmia.

Figure 4 shows an example of ventricular tachycardia induced by a ventricular premature impulse delivered to the ischemic zone. Recordings from an endocardial and epicardial site within the ischemic zone are shown. Conduction delay between these two sites is indicated in msec. The delay of the induced extrasystole which initiates the arrhythmia is 124 msec, and that of the spontaneous beat that follows it 119 msec. Despite this small decrease, the arrhythmia is maintained until the delay has been considerably reduced to 59 msec. This suggested that the maintenance of the tachycardia was dependent upon a sustained level of delay. The first spontaneous beat, despite the small decrease, still exhibited sufficient delay to allow the arrhythmia to continue. In all examples of this self-terminating type of arrhythmia, the activation delay of the final beat was always less than that of the beats which had preceded it. A similar pattern was evident in those episodes of self-terminating ventricular tachycardia which arose spontaneously.

In striking contrast, the patterns of delay exhibited by those episodes of ventricular tachycardia which progressed to fibrillation showed progressive increase. An example is shown in figure 5. Ventricular tachycardia is induced by a premature stimulus delivered to the normal zone and rapidly progresses to fibrillation. Delay in activation measured from the onset of the surface QRS to the most delayed of the fragmented potentials recorded from the composite IZ electrogram is 141 msec and no arrhythmia occurred. That of the next extrasystole is 148 msec and arrhythmia is induced. It can be seen that the small inverted potential which forms the terminal component of this electrogram becomes progressively delayed until finally it cannot be identified with confidence. The over-all ventricular activation time shows a progressive increase from 183 msec to 271 msec. It is often difficult to identify the point at which tachycardia deteriorates into fibrillation and measurements of this kind rely upon clear identification of electrographic delay which can be correlated with the appropriate surface QRS complexes. Despite these limitations, all the episodes of tachycardia progressing to fibrillation presented the similar trend of increasing delay.

The analysis of all episodes of tachycardia studied is presented in figure 6. Curve A represents the average delay of those beats that led to fibrillation and B those that spontaneously terminated prior to fibrillation. It can be seen that in both total ventricular activation time initially increases. In A this trend continues whereas in B this ultimately falls to a level below which the arrhythmia was initiated and sinus rhythm was regained. This finding indicates that conduction delay is an essential prerequisite for the initiation and maintenance of re-entry arrhythmias.

Certainly it would appear that the changes in conduction time during the period of study were closely related to the outcome of the two types of arrhythmia.

![Figure 4](http://circ.ahajournals.org/)

*Figure 4* Ventricular tachycardia initiated by IZ extrasystole. Conduction delay between endocardium and epicardium at IZ recording sites is shown above arrows. After an initial increase, delay decreases and the arrhythmia terminates.

_Circulation, Volume 30, December 1974_
The use of a composite electrode, by effectively increasing the number of bipolar contact sites within the ischemic area, enhanced the possibility of detecting the most delayed potentials. Although these were not specifically sought, analysis of composite electrode recordings up to and during arrhythmia yielded more information from which the temporal sequence of activation delay could be deduced. Bipolar recordings were much less consistent in demonstrating these patterns.

It became apparent during the early part of this study, when occlusion up to the stage of arrhythmia was observed without premature ventricular stimulation, that the extrasystoles that initiated tachycardia and finally fibrillation had no specific relationship to the so-called vulnerable period. Extrasystoles were capable of producing arrhythmias irrespective of their diastolic coupling time and in many examples diastolic timing far removed from that part of the T wave which is classically considered to be vulnerable were seen. The relationship between the R-R, Q-T, and coupling intervals of ectopic beats initiating ventricular tachycardia is presented in table 1. In five dogs, ventricular extrasystoles induced in both normal and ischemic zones at variable coupling intervals were analyzed with respect to their arrhythmogenic properties. In those animals surviving repeated occlusions in which results permitted comparative analysis, it was found that arrhythmias could be initiated by extrasystoles from both zones irrespective of their diastolic timing; indeed, ectopic ventricular activity arising late enough to produce fusion with the supraventricular pacemakers also produced arrhythmia (fig. 3). The time from occlusion to onset of ventricular arrhythmias was consistently shorter when induced by early diastolic ectopic beats (mean 3 min, 38 sec, ± 51 sec) than by late diastolic ectopic beats (average 4 min, 25 sec, ± 63 sec). However, this difference was of borderline significance (P = 0.075).

Discussion

Wiggers' in 1940 demonstrated the phenomenon of ventricular vulnerability by inducing fibrillation in the normal dog heart with a high intensity stimulus...
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Table 1
Relationship Between R-R, Q-T, and Coupling Intervals of Spontaneous and Pacing-Induced Ventricular Ectopic Beats Initiating Ventricular Tachycardia

<table>
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*Episodes of ventricular tachycardia terminating in ventricular fibrillation.

Abbreviations: CI = coupling interval; VT = ventricular tachycardia; VF = ventricular fibrillation.

delivered at or near the peak of the T wave. It has since been shown that myocardial ischemia significantly increases the degree of dispersion of recovery during this phase of the cardiac cycle. The findings of the present study that during the early stages of myocardial ischemia ventricular ectopic beats falling early or late in diastole can induce tachycardia and fibrillation appear to be at variance with previous experimental and clinical evidence. It should be noted that observations similar to ours have been made in the clinical setting. Recently a systematic clinical study by DeSoyza et al.9 showed that the R-on-T phenomenon did not predict the occurrence of ventricular tachycardia in the first 24 hours of acute myocardial infarction. Several of our findings indicate that a mechanism similar to that represented by the R-on-T phenomenon may be responsible for ventricular arrhythmias initiated outside this phase of the cardiac cycle also.

Marked delay of local activation should be accompanied by marked delay of recovery of excitability. It was a common finding that as fragmentation and delay occurred after coronary occlusion there was a progressive increase in the voltage required to excite local areas in the ischemic zone, even at the end of diastole. Also, total failure of excitation at high levels of stimulation was common. The ability to stimulate adjacent sites in the ischemic zones, even with marked prematurity, clearly indicates a dispersion of recovery of excitability at least equal to the degree of delay of activation. Thus, the relative refractory period of closely adjacent tissues was markedly dispersed, a finding which agrees with the hypothesis proposed by Wiggers12 and restated by Han et al.13 that "vulnerability during the relative refractory period is due to nonuniform excitability of the tissues then premature responses should be characterized by a lower fibrillation threshold and a longer duration of the vulnerable period."

It would appear that electrophysiological alterations caused by ischemia markedly increase the duration of the vulnerable phase of the ventricle. One might postulate that after coronary occlusion, heterogeneous areas of delay of local activation initially cause ventricular premature beats to occur and these ventricular premature beats cause further dispersion of excitation initiating successive re-entrant beats or ventricular tachycardia. The ability to sustain ventricular tachycardia, and the ultimate outcome of the arrhythmia, may be due in part to the number of re-entry circuits involved and the degree of delay or block in each circuit. In a circuit showing sufficient slowing of conduction for re-entry to occur but without block, ventricular tachycardia could sustain itself. If another adjacent circuit became available for excitation from the initial circuit, further fragmentation of the potential could occur leading to ventricular fibrillation. If, however, delay and slowing of conduction to the point of block occurred in a given circuit prior to the connection of this circuit to another, ventricular tachycardia could spontaneously terminate.

An alternative explanation of these data might be found in the recent reports of the effects of acute ischemia on His-Purkinje conduction and refractoriness. El-Sherif et al.14 and Lazzara et al.15 have shown that ischemia not only induces marked depression of conduction in the His-Purkinje system but also alters its basic responsiveness. Specifically, stimuli falling well after full repolarization of ischemic cells either failed to produce a propagated action potential or produced poor action potentials with a long preceding foot or prepotential. Thus, ischemia con-
verted the "voltage"-dependent responsiveness of normal tissue into a "time"-dependent responsiveness or refractoriness. If a similar type of change occurs in human myocardium as a result of ischemia, stimuli falling relatively late in diastole may fail to produce a propagated response or produce a poor depolarization which is conducted with marked delay. Thus the late extrasystole in the ischemic myocardium may produce malignant arrhythmias due to the alteration of basic responsiveness of the tissue and not secondary to the conduction disturbance. This may also account for the earlier onset of ventricular tachycardia with induced ectopic beats than during atrial pacing alone.

The Electrophysiological Basis of the Malignant Ventricular Ectopic Beat

This study indicates that in the setting of acute ischemia in the dog the malignancy of a ventricular premature beat is not related primarily to the particular portion of the cardiac cycle in which it falls, but rather depends on the underlying alterations of activation in ischemic epicardium. During the first one or two minutes of ischemia, the sinus beats and induced ventricular premature beats usually showed no fragmentation or delay of recorded activity in the ischemic zone. However, at an average of four minutes, when local ventricular activation in the ischemic zone began to manifest delay and fractionation, the ventricular premature beat caused greater fragmentation and delay leading to ventricular tachycardia and ventricular fibrillation. Delayed activation, up to 200 msec in ischemic and infarcted myocardium, has been previously noted by other investigators.16, 17, 18 The induced ventricular premature beat consistently produced ventricular tachycardia before this arrhythmia occurred spontaneously, and ventricular premature stimuli delivered in the ischemic zone caused a significantly earlier appearance of ventricular tachycardia and ventricular fibrillation than those delivered in the normal zone.

Previous studies have shown that premature beats normally show dispersion of ventricular activation and depression of recovery of excitability and that when a "premature response is invoked in an irregularly excitable field (ischemic zone) its propagation . . . must also be irregular."19 Thus, both prematurity and ischemia are responsible for activation delay of the premature ventricular beat, and in this respect the situation differs from that of the regularly timed conducted supraventricular beat. It is not unexpected therefore that this additional mechanism would result in greater fragmentation and delay with earlier appearance of an arrhythmia.

Another possible indication of the irregular or variable wavefront of the ventricular premature beat, even when it occurs late in the cycle, is reflected in the changing QRS morphology of ventricular premature beats just prior to the onset of ventricular arrhythmias. This finding was always associated with increasing delay and fractionation of local epicardial activation in the ischemic zone and is consistent with the existence of variable conduction pathways from the site of excitation to the rest of the ventricle. Harris,19 in reviewing his previous work, concluded that the early arrhythmias are probably due to potassium liberated from ischemic cells. In a recent report by Ettinger et al.20 relatively local perfusion of the apical portion of the left ventricle was performed with isotonic KCl through the anterior descending coronary artery. Within minutes of the onset of this perfusion marked delay and deterioration of epicardial activity was found concomitant with the occurrence of ventricular ectopic activity leading to ventricular tachycardia and fibrillation. These ventricular arrhythmias were characterized by coupled beating and epicardial and endocardial relationships consistent with the re-entry phenomenon. It is interesting to note that Anderson et al.21 working with human ventricular myocardium exposed to a high potassium concentration, postulated that conduction delay and block in the myocardium could give rise to QRS configurational changes.

Present Concepts Concerning Genesis and Nature of Ventricular Arrhythmias and Myocardial Ischemia

Since the introduction of the concept of vulnerability by Wiggers1 and the recognition of the R-on-T phenomenon by Smirk and Palmer2 in the clinical setting, the concept of the fibrillation threshold has occupied an important place in the literature. This concept has been extended by the work of Han et al.,11, 15 who proposed that the temporal dispersion of recovery of excitability was the predisposing condition favoring the onset of fragmentation of activation and re-entry. However, we believe the concepts of fibrillation threshold and recovery of excitability have theoretical and practical shortcomings which seriously restrict their usefulness in the understanding of the origin and nature of ventricular arrhythmias.

First the concept of fibrillation threshold assumes the occurrence of a ventricular premature beat at an appropriately timed interval, i.e., R-on-T phenomenon, without offering any explanation for the occurrence of this potentially malignant extrasystole. Secondly, the level of the fibrillation threshold may not always be a reliable indicator of the susceptibility or stability of a given heart to a lethal arrhythmia. For example, Kent et al.28 have reported that the infusion of nitroglycerin and phenylephrine during myocardial ischemia increased the ventricular fibrillation

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threshold to control, nonischemic levels. A similar study,29 reported that 50% of the dogs receiving these drugs developed spontaneous ventricular fibrillation after coronary artery ligation, whereas 92% of the ischemic untreated group died with this arrhythmia. Although there was a significant reduction in the incidence of arrhythmia in the treated group, it could be inferred that the 50% who developed fibrillation would have had a normal ventricular fibrillation threshold. This apparent inconsistency may reflect the different mechanisms responsible for ventricular fibrillation. Thus determination of ventricular fibrillation threshold necessitates delivery of a high intensity impulse during the “vulnerable” phase when enhanced automaticity may be responsible for the initiation of the arrhythmia.10 However ventricular fibrillation induced by spontaneous ectopic beats occurring either early or late in diastole may be due to a re-entry mechanism.6, 8

The determination of recovery of excitability presents similar problems. Although it has been shown that ventricular premature beats occurring during myocardial ischemia cause dispersion of recovery of ventricular excitability, the degree of such dispersion did not exceed 40 msec in the experiments described by Han et al.11 This degree of nonuniform recovery of excitability would not be sufficient to establish re-entry since the “impulse destined to reenter the ventricle must survive for some 300 msec if it is to outlast the ventricular refractory period.”24 From a practical standpoint the method for determination of recovery of excitability requires several test procedures to determine “the earliest successful S2 shock artifact”11 at multiple points in the ventricle. In the dynamic setting of myocardial ischemia in which the ischemic zone shows marked heterogeneity, such determinations become a formidable task even for a computer.

The delay and fragmentation of potentials recorded from the ischemic area cause prolongation of the total ventricular activation time. This increases further as ischemia and delay progress. The relationship between this delay of ventricular activation and the onset of ventricular arrhythmias has previously been reported in the dog during the early phases of acute myocardial ischemia.6, 8 A similar mechanism, though not due to ischemia, has been shown to be responsible for the initiation of atrial fibrillation during retrograde conduction from the ventricle.26 Dispersion of atrial activation due to A-V nodal desynchronization of retrograde conduction resulted in an increased total atrial activation time. The arrhythmogenic potential of ventricular ectopic beats during experimental acute myocardial infarction appears to be largely determined by this electrophysiological mechanism rather than by the coupling interval of these beats.

At any given degree of delay, early ectopic beats exhibit more dispersion than those falling later in diastole and therefore under these circumstances are more liable to evoke an arrhythmia. However, late diastolic ectopic beats will become dangerous by inducing fibrillation when the underlying dispersion of ventricular activation is great. At the present time it is not possible to determine in any individual situation the degree of heterogeneity of activity which has developed after ischemia other than by multiple direct electrode recordings. In view of this, and the potential increase in dispersion which may occur as a result of further subclinical ischemia during infarction, it would seem prudent to ascribe potential malignant properties to all ventricular ectopic beats, irrespective of their diastolic timing, during the early stage of acute myocardial infarction.

Acknowledgment

We gratefully acknowledge Mr. Jorge Rodriguez, Dr. Joseph Herbstman, Messrs. Israel Dingle and David Young, Jr., for their technical assistance, Mrs. Teresa Vallone for statistical analysis, and Mrs. Marie Ellis for her secretarial assistance.

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Circulation. 1974;50:1163-1172
doi: 10.1161/01.CIR.50.6.1163

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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