Instantaneous and Delayed Ventricular Arrhythmias After Reperfusion of Acutely Ischemic Myocardium: Evidence for Multiple Mechanisms

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SUMMARY  To characterize the electrophysiologic properties of the ventricular arrhythmias occurring during reperfusion after acute coronary artery ligation, a study was undertaken to correlate the time course of appearance of such arrhythmias with specific electrophysiologic mechanisms. Thirty-seven dogs survived 30-minute ligations of the left descending coronary artery, and all had either instantaneous (onset at 0–1 minute) or delayed (onset at 2–7 minutes) ventricular arrhythmias on reperfusion. Local electrograms recorded from ischemic myocardium were markedly abnormal after 30 minutes of coronary artery ligation, but rapidly returned to approximately normal within 1–2 minutes after reperfusion. Instantaneous reperfusion ventricular arrhythmias occurred in the midst of the recovery process when fragmented activity was recorded on electrograms from the ischemic area. This activity increased in amplitude, was of long duration (i.e., spanning diastole) and was associated with the occurrence of ventricular fibrillation in 24 of 37 dogs. By 3 minutes after reperfusion, all electrical activity was again synchronous and inscribed completely within the QRS complex. However, in eight of 19 dogs that survived the initial reperfusion period, including six resuscitated from ventricular fibrillation, there was a second surge of ventricular arrhythmias that was independent of diastolic or asynchronous electrical activity. In contrast to the instantaneous reperfusion ventricular arrhythmias, the delayed arrhythmias (2–7 minutes after reperfusion) were associated with electrophysiologic properties characteristic of enhanced automaticity and only infrequently degenerated to ventricular fibrillation. Although the incidence of ventricular arrhythmias during the antecedent period of coronary artery ligation and the occurrence of instantaneous reperfusion arrhythmias were closely correlated, the delayed ventricular arrhythmias of reperfusion and those occurring during the antecedent coronary artery ligation period were not correlated. Distinct electrophysiologic mechanisms are apparently associated with a specific time course of appearance and with the severity of ventricular arrhythmias that occur when blood flow is suddenly restored to acutely ischemic myocardium.

THE SUDDEN ONSET of ventricular tachycardia and fibrillation upon the release of a coronary artery occlusion in the experimental animal was observed as early as the 19th century. A wealth of experimental data has subsequently confirmed this phenomenon. While new information identifying the mechanisms of the arrhythmias induced by coronary ligation has been described, the precise mechanism of the rhythm disorders observed upon reperfusion remains unclear. Differences between the ventricular arrhythmias of ligation and those of reperfusion suggest that multiple mechanisms may account for the rhythm disorders attendant upon ligation and reperfusion. Reperfusion arrhythmias are usually sudden in onset and deteriorate to ventricular fibrillation within 5–30 seconds. Arrhythmias due to coronary ligation, however, are gradual in onset and develop over a period of several minutes. Several therapeutic maneuvers that are generally successful in preventing ligation arrhythmias are ineffective in the presence of reperfusion arrhythmias, which appear to be more malignant because the incidence of ventricular fibrillation after reperfusion exceeds that after ligation. Myocardial vulnerability to ventricular fibrillation and to repetitive ventricular responses has been found to be transiently increased after both ligation and reperfusion. Although the increase and subsequent decrease in vulnerability after ligation are gradual and occur over many minutes, the changes after reperfusion are more immediate and short-lived. The present study was designed to characterize the electrophysiologic properties of ventricular arrhythmias occurring immediately after reperfusion of acutely ischemic myocardium and to correlate the time course of their appearance with specific electrophysiologic mechanisms. A 30-minute coronary artery ligation model was chosen to include dogs with both “immediate” and “delayed” ventricular arrhythmias of the acute ligation period.

Materials and Methods

This study was performed on 37 of 53 mongrel dogs (weight 18–30 kg) that survived 30 minutes of coronary artery ligation. Dogs were anesthetized with pentobarbital (30 mg/kg). Hearts were exposed via the fourth left intercostal space and suspended in a pericardial cradle. Ventilation was maintained by a Harvard room air respirator by means of a cuffed en-
dotracheal tube. A loose ligature was positioned around the left anterior descending coronary artery 1.5–2.0 cm from its origin distal to the anterior septal branch, but proximal to all diagonal branches. Teflon-coated, silver, bipolar, plunge-electrode wires (0.1 mm in diameter) were positioned at 10–15 sites in the endocardial and subepicardial regions of the expected ischemic and normal zones. Intramyocardial bipolar electrodes with an interelectrode distance of 5 mm or less were positioned in the ischemic zone at measured depths below the epicardial surface. The location of the recording electrodes was confirmed at postmortem examination. All electrograms were recorded on a Hewlett-Packard eight-channel photographic recorder (Model 4578), with a frequency response of 50–1000 Hz. This band width was chosen to facilitate clear delineation of the activation spikes.15,16 Lead 2 of the ECG was recorded at 0.5–200 Hz. Because the amplitude of electrograms in the ischemic zone markedly diminished after ligation, extremely high gains (0.1–25 mV/1.5 cm) were used to record electrical activity in the ischemic zone during reperfusion. A scalar ECG lead and seven bipolar plunge electrograms were recorded throughout the experiment.

The left anterior descending coronary artery was ligated in one stage over a chronic wire 1 mm in diameter. Thirty minutes after coronary artery ligation, the ligature was cut over the chronic wire and blood flow was immediately restored. The observations continued until all arrhythmias disappeared in the dogs that survived and for a minimum of 60 minutes after reperfusion. Resuscitation was attempted in 10 of the 24 dogs that developed ventricular fibrillation immediately after reperfusion to determine if dogs susceptible to ventricular fibrillation immediately after reperfusion were also susceptible to delayed reperfusion ventricular arrhythmias. Only the six dogs in which normal sinus rhythm was restored immediately after one or two successive DC shocks of 20–40 watt-sec were monitored further. Further resuscitation was not attempted in the other dogs that developed ventricular fibrillation. Dogs were numbered 1–37 to facilitate the analysis of data and not in chronological sequence.

Definition of Instantaneous and Delayed Arrhythmias

There were two distinct periods of ventricular arrhythmias after reperfusion; those appearing less than 1 minute after reperfusion were designated instantaneous and those that were first appeared 2–7 minutes after reperfusion were designated delayed reperfusion ventricular arrhythmias. The following ventricular arrhythmias were tabulated: ventricular ectopic beats (≥ 2/min), ventricular tachycardia (≥ triplets) and ventricular fibrillation.

Results

Thirty-seven dogs were reperfused after 30 minutes of left anterior descending coronary artery ligation. Their course is detailed in figure 1.

Incidence and Time Course of Ventricular Arrhythmias After Reperfusion

Figure 2 details the time course of appearance and incidence of reperfusion ventricular arrhythmias in the 37 dogs. Ventricular fibrillation developed in 24 dogs within 1 minute after reperfusion (mean, 17 seconds) (figs. 1 and 2). Eighteen of these dogs could not be resuscitated and were eliminated from further studies (dogs 20–37). Six dogs that were immediately resuscitated from ventricular fibrillation by a DC shock of 20–40 watt-sec promptly resumed normal sinus rhythm and were then observed further (dogs 3, 4, 9, 14, 17 and 18) for the occurrence of arrhythmias. Four other dogs (dogs 1, 6, 15 and 19) had short episodes of ventricular tachycardia within 1 minute after reperfusion (mean 28 seconds) that lasted for less than 1 minute and did not degenerate to ventricular fibrillation. Nine dogs had no arrhythmias during the first minute after reperfusion.

Determination of Ventricular Automaticity

The presence of ventricular automaticity was determined by dissecting the cervical portion of the right vagus nerve and positioning stainless steel electrodes adjacent to the nerve.19 Trains of 1-msec stimuli at 30 Hz were given for 10–20 seconds. The intensity of the stimuli was adjusted to achieve sinus arrest. The rate of the idioventricular escape rhythm was then determined. We performed the procedure 3–4 minutes before reperfusion and at 2–3-minute intervals after reperfusion in the dogs that survived the instantaneous arrhythmias of reperfusion. Using our methods, we could not perform vagal stimulation immediately after reperfusion without interfering with effective and complete reperfusion. Nor was it possible to exclude possible effects of concomitant sympathetic stimulation resulting from our methods of vagal stimulation.20

![Figure 1. Fate of the 37 dogs after reperfusion. The reperfusion time is indicated on the left. Six of the 24 dogs that developed instantaneous ventricular fibrillation (VF) were promptly resuscitated and their subsequent course was monitored. VT = ventricular tachycardia; NSR = normal sinus rhythm.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.63.2.334)
Thus, 19 dogs (six with ventricular fibrillation and resuscitated, four with ventricular tachycardia and nine with no ventricular arrhythmias) survived the first minute after reperfusion. A second surge of ventricular ectopic activity, delayed ventricular arrhythmias, appeared in eight of the 19 survivors (dogs 1, 2, 5–7, 9, 18 and 19) at an interval of 2–7 minutes after the restoration of blood flow (mean appearance time, 4 minutes) and subsided within 15 minutes after reperfusion in each case. Notably, there was only one instance of ventricular fibrillation among the eight dogs in which late ventricular arrhythmias developed (fig. 2, dog 18). This was in contrast to the high incidence of ventricular fibrillation associated with the ventricular arrhythmias occurring instantaneously with reperfusion (one of eight vs 24 of 28, p < 0.005).

Correlation Between the Instantaneous Arrhythmias and Changes in Local Electrical Activity in the Reperfused Area

Continuous recordings of the ECG and local electrograms revealed two major findings during the first 2 minutes of reperfusion: (1) a rapid and consistent increase in the amplitude of one or more of the local electrograms and (2) appearance of electrical activity late in the cardiac cycle, spilling over into diastole (fig. 3). For example, just before reperfusion and, as illustrated in figure 3, at the exact moment of reperfusion (i.e., 1 second), the amplitude of local activity appeared markedly depressed in the epicardial ischemic zone. Note, especially the recordings made from sites labeled IZepi and IZepi₂ and the very high gains of these two tracings. Typically, the duration of this low-amplitude fragmented activity recorded in ischemic areas appeared prolonged, but could not be measured with certainty. Six seconds after reperfusion, the amplitude in all IZepi electrograms had in-
creased markedly. The increase in amplitude of this activity made it possible to identify delayed diastolic activity ($IZ_\text{epi}$, arrows) with greater certainty. The increase in amplitude of this late diastolic activity was followed by a premature ventricular complex. This dysrhythmia deteriorated seconds later into ventricular fibrillation (not shown). These rapid changes in local electrograms were often heterogeneous and asynchronous. Presumably, these changes in local electrical activity reflected concomitant changes in blood flow to these reperfused areas. The extent or uniformity of the return of blood flow to ischemic tissue, however, could not be directly evaluated by the methods of the present study, so we could not correlate the occurrence of either ligation or reperfusion ventricular arrhythmias with the extent of ischemic injury.

Only one dog had delayed diastolic activity of increasing amplitude during reperfusion and without the associated instantaneous reperfusion ventricular arrhythmias. By 3 minutes into the reperfusion period, electrical activity in all previously ischemic muscle layers was again synchronous and inscribed completely within the QRS complex in all dogs (fig. 4).

Observation of the 19 dogs that survived the initial reperfusion period revealed an unexpected, delayed surge of ventricular arrhythmias and ventricular tachycardia in eight of these dogs (fig. 2, dogs 1, 2, 5–7, 9, 18 and 19). The mean rate of the delayed ventricular tachycardia was 190 beats/min (range 160–250 beats/min). With one exception, these ventricular tachycardias were self-limited, with gradual onset and cessation and were associated with many fusion complexes (fig. 4). We observed many long periods of isorhythmic atrioventricular dissociation due to ventricular tachycardia in which dominance of the sinus and ectopic rhythms interchanged frequently. Local electrical activity recorded in the previously ischemic region was synchronous and did not extend beyond the QRS complex during the period of delayed reperfusion arrhythmias. In all instances, the earliest electrical activity recorded during the delayed ventricular arrhythmias was from the endocardial surface of the left ventricle and preceded epicardial activation (fig. 4).

**Changes in Ventricular Automaticity**

Vagal stimulation was performed in six dogs before reperfusion and was repeated at intervals of 2–3 minutes in five dogs that survived the instantaneous reperfusion arrhythmias. Figure 5 displays the ECGs recorded at various times in dog 6, which did not have ventricular fibrillation immediately after reperfusion.

![Figure 4](http://circ.ahajournals.org/content/63/2/336)  
**Figure 4.** Lead 2 of the ECG and seven composite electrograms from various regions, 3 minutes after reperfusion. Each electrogram represents a composite of five to six bipolar electrodes, all located at the same designated area. $IZ =$ ischemic zone of left ventricle, central portion; $BZ =$ border zone in the ischemic area but within 0.5 cm from the normal zone, all in the left ventricle; $NZ =$ normal zone surrounding the ischemic zone in the left ventricle; endo = endocardial surface; epi = epicardial surface; $RV =$ endocardial surface of right ventricle adjacent to the junction of the septum and the anterior wall. Local activity in the $IZ$ and $BZ$ was synchronous and occurred within the QRS complex without delay or fragmentation. Complex 1 was of normal sinus origin. Complex 2 was a fusion complex, as indicated by the slight change in the configuration of the QRS complex and all the electrograms from the left ventricle. The electrogram recorded from the right ventricle ($RV$) remained unchanged, suggesting that this site was activated by the normal sinus impulse. After complex 2, a stable ventricular tachycardia dominated the cardiac rhythm until interference by the sinus mechanism in complex 8 allowed resumption of normal sinus rhythm. Note the lack of fragmentation in the local activities, especially in $IZ_\text{epi}$. During the ectopic rhythm, the earliest recorded activity was from the endocardial surface of the left ventricle (arrow) and preceded epicardial activation.
Just before reperfusion, the frequency of the escape idioventricular rhythm revealed by vagal stimulation was 77 beats/min. The rate reached 180 beats/min within 5 minutes of reperfusion. At 6 minutes, the idioventricular rate accelerated to 222 beats/min, overtaking the normal sinus mechanism and becoming the dominant ventricular mechanism. Increased ventricular automaticity in three other dogs was also evident with vagal stimulation (fig. 6). Automaticity, as evaluated by the rate of the idioventricular rhythm during vagal suppression of the sinus mechanism, was maximal when the delayed reperfusion ventricular arrhythmias were most prevalent (3–12 minutes). By 15 minutes after reperfusion, when the delayed arrhythmias had spontaneously subsided, abnormal automaticity had also lessened (fig. 6). At the time of the maximal increase in ventricular automaticity, no delay was observed in the electrograms located in the ischemic area (figs. 4 and 7). Thus, the duration of the local electrograms was consistently decreased at the time of the delayed reperfusion arrhythmias (fig. 7). The demonstration of accelerated idioventricular rates during this period after reperfusion does not, of course, provide proof for a specific arrhythmia mechanism.

Further analysis of the data showed a good correlation between the occurrence of ligation and instantaneous reperfusion ventricular arrhythmias. In fact, every dog that had a ventricular arrhythmia during the
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30-minute coronary ligation and survived to reperfusion also had instantaneous reperfusion ventricular arrhythmias. In contrast, the delayed reperfusion ventricular arrhythmias occurred independently of the rhythm disorders seen during ligation and those occurring instantaneously after reperfusion.

Discussion

The high incidence of severe ventricular arrhythmias after coronary artery ligation has been shown to be associated with marked disturbances of local myocardial activity in the ischemic zone.6,10,18 Two principal changes have been observed in the electrical activation of the ischemic zone after coronary ligation: (1) marked reduction in the amplitude of the activation spikes in all of the myocardial layers and (2) severe delay and fragmentation of activation spreading into diastole.6,10,18 The time course of events during which these alterations develop corresponds closely to the appearance and disappearance of ventricular arrhythmias.6,10,18 Other investigators have observed that the maximal disturbances in local electrical activity coincide with the marked increase in vulnerability to ventricular arrhythmias that occurs 3–5 minutes after coronary ligation.6,6,17

In contrast, after reperfusion, there appears to be an instantaneous onset of ventricular arrhythmias6–8 (fig. 2). This difference in the time course of the ligation and reperfusion arrhythmias has prompted some investigators to postulate that the mechanisms responsible for the rhythm disorders at ligation might be different from those observed at the moment of reperfusion.6–8,14,15

An important observation in the present study was the rapid recovery of local electrical activity in the reperfused zone. Thus, local activity in the reperfused area became synchronous, without delay and without fragmentation, within 3 minutes after reperfusion (fig. 3). The immediate reperfusion arrhythmias occurred in association with the very early stages of this recovery period (fig. 3). During the initial seconds after reperfusion, there was a rapid but heterogeneous increase in the amplitude of local delayed and fragmented electrical activity that was associated with the onset of malignant ventricular arrhythmias. It could be postulated that the sudden appearance of these reperfusion arrhythmias, coincident with the apparent recovery of electrical activity in the ischemic zone, was a result of the inhomogeneity in this recovery process. Such inhomogeneity could provide the appropriate milieu for reentrant arrhythmias.

The susceptibility to instantaneous ventricular fibrillation paralleled the immediate changes in local electrical activity (amplitude, duration) after reperfusion. By 60 seconds after reperfusion, when electrical activity had been fully restored, the risk for ventricular fibrillation had subsided markedly. The failure to record delayed activity using a limited number of bipolar electrodes does not exclude the presence of such activity in zones in which electrodes were not implanted. However, the abundance of such activity in the dogs with instantaneous reperfusion ventricular arrhythmias and the lack of this activity in all eight dogs with delayed reperfusion ventricular arrhythmias, using more than 60 infarction sites, is noteworthy.

Some clues to the electrophysiologic mechanisms of these delayed reperfusion arrhythmias can be inferred from the vagal stimulation studies. For example, the gradual increase in the idioventricular rate from 77 beats/min just before reperfusion (time “0”) to 180 beats/min 5 minutes after reperfusion, with further acceleration to 222 beats/min, is seen in a representative dog in figure 5 (also see fig. 6). This mildly accelerated idioventricular rate (before reperfusion) of 77 beats/min could be attributed to changes in sympathetic tone or possibly to our method of vagal stimulation, which may have resulted in concomitant sympathetic stimulation.20 The occurrence of these delayed reperfusion ventricular arrhythmias closely paralleled the marked changes in automaticity present 3–12 minutes after reperfusion. Thus, increased ventricular automaticity rather than a reentrant mechanism probably explains these delayed and less malignant reperfusion ventricular rhythms. Several other features suggest a transient increase in ventricular automaticity as the basis for the delayed reperfusion ventricular arrhythmias. These arrhythmias occurred when local electrical activity was already syn-
chronous, with no delay or fragmentation (figs. 4 and 7). In addition, the onset and cessation of these arrhythmias resembled the behavior of accelerated idioventricular rhythms with many fusion complexes. These experiments, however, do not provide direct proof of either increased or abnormal automaticity as the mechanism for delayed reperfusion arrhythmias. Moreover, it was not possible to exclude completely an automatic mechanism contributing to the instantaneous reperfusion ventricular arrhythmias, as vagal stimulation studies were not done during the first minute of reperfusion. Although no sudden changes in heart rate occurred just before the onset of these arrhythmias, this does not exclude the presence of less marked increases in ventricular automaticity that may have been masked by the sinus tachycardia. Murdock and co-workers reported that automaticity was normal during reperfusion, but in their experiments, dogs were studied after only 10 minutes of ischemia, and the left anterior descending coronary artery was occluded more distally, after the first diagonal branch. In addition, their methods included formalin injection into the atrioventricular nodal area, which may have also affected sympathetic fibers coursing to the ventricle or other potential pacemaker tissue.

The real incidence of the delayed increase in automaticity might actually have been even higher than that observed using the methods of the present study. This is suggested by studies in a cat reperfusion model. Evidence for this was also obtained in our experiments in which the right cervical vagus nerve was stimulated. In four of the five dogs that survived the initial postreperfusion period and underwent vagal stimulation, we noted distinct evidence for increased automaticity (figs. 6 and 7). From the data presented in this study, it was not possible to reach a conclusion concerning the mechanisms by which reperfused myocardial cells, and presumably Purkinje fibers as well, might have developed a transient increase in automatic pacemaker activity. The marked increase in idioventricular rate to the range of 220 beats/min in one dog may have been related to additional superimposed pathologic mechanisms as suggested by Vassalle and co-workers. Presumably, changes occurring in the 30-minute period of ischemia before reperfusion in the present study were sufficient to result in an increase in the idioventricular rate.

Thus, the present studies suggest that multiple mechanisms are responsible for instantaneous and delayed reperfusion ventricular arrhythmias. First, there is extremely rapid washout of the metabolites, potassium and other accumulated substances that contribute to the severe membrane depression observed during coronary artery ligation. This washout should facilitate the rapid recovery of electrophysiologic properties of affected myocardial cell membranes and presumably plays a role in the occurrence of the instantaneous reperfusion arrhythmias. In the rapid transition from severe depression of electrical activity to almost normal activity, there was a transient period of partial recovery highlighted by increased amplitude of the local delayed and fragmented myocardial electrical activity conducive to a reentrant mechanism. Second, a rapid but nonuniform recovery of severely depressed tissue may result in greater inhomogeneity of the local electrophysiologic properties, contributing further to this arrhythmogenic milieu. And, in fact, if blood flow is restored slowly, the incidence of reperfusion arrhythmias is less than with rapid reperfusion. Third, it is also possible that acute occlusion of a coronary artery followed by acute reperfusion may subject myocardium to additional hyperemic and subsequently hemorrhagic injury. Fourth, enhanced \( \alpha \)-adrenergic responsiveness during myocardial ischemia could be responsible for both immediate and delayed reperfusion ventricular arrhythmias induced by catecholamines released during ligation and reperfusion. Other mechanisms contributing to the delayed reperfusion ventricular arrhythmias are less clear. The methods of the present study do not allow us to speculate further than to suggest the possible role of delayed or partial recovery of either myocardial or specialized Purkinje fibers as the etiology for these arrhythmias. In addition, because of limitations in methodology, we could not correlate either the severity or time course of reperfusion ventricular arrhythmias with the extent of ischemic myocardium.

In conclusion, two distinct periods of ventricular arrhythmias occur in the minutes after reperfusion in dogs previously subjected to 30 minutes of proximal left anterior descending coronary artery ligation. Arrhythmias that occur instantaneously with reperfusion show rapid changes in local electrical activity conducive to a reentrant mechanism, frequently terminate in ventricular fibrillation and are very closely associated with the occurrence of ventricular arrhythmias during the antecedent period of coronary artery ligation. In contrast, reperfusion ventricular arrhythmias that occur just minutes later have electrophysiologic properties more characteristic of increased automaticity, infrequently degenerate to ventricular fibrillation and occur independently of the ventricular arrhythmias of the antecedent period of coronary artery ligation.

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