Two Periods of Early Ventricular Arrhythmia in the Canine Acute Myocardial Infarction Model


SUMMARY The time course of ventricular arrhythmias in the early period (0–30 minutes) after ligation of the left anterior descending coronary artery was studied in 41 open-chest mongrel dogs anesthetized with pentobarbital sodium (Nembutal). ECGs and seven single and composite electrograms from various regions in and around the ischemic zone were recorded throughout the experiments. Two periods of ventricular arrhythmias were clearly seen. The first occurred 2–10 minutes after coronary ligation, peaking at 5–6 minutes, and was designated as immediate ventricular arrhythmias (IVAs). There was a distinct correlation between incidence, severity, onset and termination of IVA and the degree of local delay and fragmentation of the normal sinus activation spread in the ischemic subepicardial zone. The second wave of ventricular arrhythmias occurred 12–30 minutes after ligation independently of the previous increased delay and fragmentation of activation in the ischemic subepicardium. Delayed ventricular arrhythmias (DVAs) were as severe as IVAs — there were nine instances of ventricular fibrillation during DVA and seven during IVA. While the mechanism of IVA is most probably related to reentry accompanied by delay and fragmentation of ischemic subepicardial activation, the mechanism of DVA remains unclear. Our evidence suggests that DVAs are also reentrant, with the reentry pathways located in deep myocardial structures or involving microscopic pathways at the Purkinje muscle junction.

THE CANINE HEART has served for many years as a useful model in the study of the electrophysiologic consequences of acute and chronic myocardial ischemia and infarction.1–16 These studies are concerned with a critical reevaluation of the immediate post-ligation ventricular arrhythmias (Harris phase I). During previous studies9–10 we have noticed that Harris phase I ventricular arrhythmias after ligation were not always dependent on continuous subepicardial activation or diastolic bridging. Furthermore, the time course of development of ventricular arrhythmia appeared to differ from current generally accepted concepts. We have, therefore, analyzed the exact time course of ventricular arrhythmias after coronary artery ligation and attempted to correlate these events with the local disturbance of activation in the ischemic zone.

Materials and Methods

The study was performed on 41 mongrel dogs weighing 18–30 kg. The dogs were anesthetized by the intravenous administration of pentobarbital sodium 30 mg/kg. Room air ventilation was maintained with a Harvard large-animal respirator by means of a cuffed endotracheal tube. The chest was opened and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was dissected and freed from its bed 1–2 cm from its origin. Plunge bipolar, Teflon-coated electrodes were positioned at various endocardial and subepicardial points in the ischemic zone. Seven electrograms were recorded from seven (single) bipolar electrodes (26 dogs) or from groups of composites of bipolar electrodes (15 dogs). The data from the composite and sets of bipolar electrograms were combined, as there was no significant difference in the measurements of fragmentation and delay between the two methods of recording. The composite electrodes consisted of five bipolar electrodes positioned in the subepicardium in a 1-cm area in the center of the ischemic zone. Recordings of lead 2 of the ECG (0.5–200 Hz) and of seven electrograms (50–1000 Hz) were obtained on a Hewlett-Packard (model 4578) eight-channel photographic recorder. The low-frequency limit was set at 50 Hz in order to prevent distortion of the baseline by large and abnormal T waves that appear after the production of ischemia.11,16 In 20 experiments, a continuous, slow-speed recording of the ECG was obtained on a 5115 Tektronix storage oscilloscope, which enabled us to record a continuous ECG throughout the experiment, except for 15–20 seconds lost while changing the Polaroid film. Frequent and prolonged recordings on the Hewlett-Packard recorder were obtained at paper speeds of 100 and 200 mm/sec in all dogs throughout the experiments.

After recording the control data, the left anterior descending coronary artery was ligated in one stage.14 The experiment was continued for at least 30 minutes, until all surviving dogs had no further arrhythmias.

Quantitation of Ventricular Arrhythmias

Dogs were considered arrhythmia-free if they had less than two ventricular premature depolarizations per minute. Three successive ventricular depolarizations constituted an episode of ventricular tachycardia.

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FIGURE 1. Lead 2 of the ECG and two electrograms from the central ischemic zone in a dog, in the control state and 4 minutes after ligation of the left anterior descending coronary artery. The gain setting of the composite electrograms in millivolts is indicated to the right of the control and post-ligation tracings. IZ = ischemic zone; endo = endocardial surface; epi = epicardial surface. The amplitude of the local electrogram was markedly reduced by a factor of 5–20 4 minutes after ligation. Note also that the normal subepicardial activation of 40 msec is markedly increased by ischemia. Delays of 155 and 165 msec from the inception of IZ endo to the last sharp activity in the IZ epi are indicated.

EPICARDIAL DELAYS AND INCIDENCE OF VENTRICULAR ARRHYTHMIAS AFTER CORONARY LIGATION IN 41 DOGS

The graph shows the incidence of ventricular arrhythmias after coronary ligation in 41 dogs, with different types of ventricular arrhythmias (NO VA, VPD, VT, VF) plotted against time after coronary ligation. The x-axis represents minutes after coronary ligation, while the y-axis represents the number of dogs.

MSEC OF EPICARDIAL DELAY
0 25 50 75 100 125 150

MINUTES AFTER CORONARY LIGATION
0 5 10 15 20 25 30

NO VA
VPD
VT
VF

NUMBER OF DOGS
0 10 20 30 40 50
ARRHYTHMIAS IN ACUTE EXPERIMENTAL MI/Kaplinsky et al. 399

Figure 3. The correlation between the incidence of immediate ventricular arrhythmias (IVA) and the maximal degree of subepicardial delay that was detected during normal sinus complexes in all dogs. VA = ventricular arrhythmias; VPD = ventricular premature depolarizations; VT = ventricular tachycardia; VF = ventricular fibrillation. The p values shown above the VPD, VT and VF bars indicate the significance level of the increase in subepicardial delay from no VA, to VPD to VT and to VF. There was a significant increase in the subepicardial delay in the dogs with VPDs vs those with no VA.

Because ventricular arrhythmias appeared in two distinct waves during the first 30 minutes after ligation (Harris phase I), we designated the first group of arrhythmias, appearing during the first 10 minutes, as immediate ventricular arrhythmias (IVAs) and the second surge, appearing between 12–30 minutes, as delayed ventricular arrhythmias (DVAs). We quantitated the degree of delay and fragmentation in the ischemic subepicardial zone after coronary artery ligation by measuring the maximal time delay between the activation of the ischemic endocardial zone and the last distinct and sharp activity in the corresponding subepicardial surface during normal sinus complexes (fig. 1). The maximal time delay was measured every minute from 2–8 minutes, every 2 minutes from 8–12 minutes, every 3 minutes from 12–18 minutes, and every 4 minutes thereafter.

To observe the delayed and fragmented activity, we increased the gain of the local electrogram of the ischemic subepicardium from five to 20 times. With the amplifier frequency response setting at 50–1000 Hz, the local normal ventricular depolarization caused a spike in the order of magnitude of 10.0 mV. As ischemia developed, the local activity could decrease in magnitude by a factor of 10–20 (fig. 1).

Results

Within 1–2 minutes after ligation of the left anterior descending coronary artery, the local electrograms in the area of the ischemic zone became reduced in amplitude (fig. 1). Significant delay and fragmentation of the normally conducted beats were observed in the center of the subepicardial surface of the ischemic zone (fig. 1). As the activation delay in the ischemic zone progressed, the frequency and severity of the ventricular arrhythmias increased. Figure 2 describes the time relation between the mean maximal activation delay of normally conducted complexes of sinus origin in the ischemic subepicardial zone of all the dogs and the incidence and severity of ventricular arrhythmias. Conduction delay developed immediately after ligation and reached its peak within 5 minutes. In the ensuing 5–10 minutes, the degree of delay and fragmentation gradually diminished. There was no difference in the degree of fragmentation as measured by single or composite electrograms. Concurrently, there was a significant reduction in the incidence of arrhythmias. The arrhythmias, which appeared early and disappeared as the degree of delay and fragmentation became less pronounced, were designated as IVAs. Thus, only a few dogs displayed ectopic activity during the eleventh and twelfth minutes after coronary ligation (fig.

Figure 2. Summary of sequential changes in the mean and standard error of local subepicardial activation of the ischemic zone (indicated by the black dots), and the incidence and severity of ventricular arrhythmias (indicated by the lower vertical bars) in all dogs. The clear zone above the bars represents the number of dogs not showing arrhythmias at that particular time. The biphasic appearance of the ventricular arrhythmias (VA) during the first 30 minutes after ligation is clearly seen. The appearance and disappearance of the first wave of ectopic activity (the immediate ventricular arrhythmias, IVAs) is closely associated with the rapid increase and subsequent decrease in local ischemic subepicardial delay of the normal sinus complexes. The second surge, or the delayed ventricular arrhythmias (DVAs), is clearly independent of further changes in local activation in the ischemic subepicardium. The peak of subepicardial delay coincides with the peak of ectopic activity. The stepwise decline in the total number of dogs represents the loss of dogs due to ventricular fibrillation (VF). VPD = ventricular premature depolarization; VT = ventricular tachycardia.
2). As the experiment continued, the conduction delay became less pronounced, and reached a plateau at approximately 15 minutes. This reduction in conduction delay was also associated with a reduction in the voltage of the local electrograms (fig. 1). However, a second surge of DVA appeared without any prior change in the activation pattern in the ischemic subepicardial zone during normal sinus complexes. The second period of ectopic activity (DVA) reached its climax during the seventeenth and eighteenth minutes after ligation, and declined gradually thereafter (fig. 2).

The severity of the rhythm disorders during the IVA phase denoted a close relation to the degree of activation delay during normal sinus complexes (fig. 3). This period of activation-delay-dependent arrhythmia usually lasted 8–10 minutes, but occasionally continued for several more minutes before disappearing. One dog had sustained ischemic subepicardial delay and fragmentation for 13.5 minutes, after which ventricular fibrillation developed.

Comparisons of actual tracings of acute IVA and DVA are shown in figures 4 and 5. Delay and fragmentation of the normal impulse occurred in Wannkebach fashion (from 115–150 msec in beats 1–3, fig. 4A, epi) and finally led to a ventricular premature complex (complex 4) 5 minutes after coronary ligation. In contrast, diastolic activity and fragmentation did not progressively increase before the premature ventricular complex in the ischemic subepicardium after 20 minutes (fig. 4B). Figure 5 compared two episodes of ventricular tachycardia in the same dog shown in figure 4 at 6 and 20 minutes after coronary ligation. In figure 5A, epi, complexes 2–5 (delay and fragmentation of 150–250 msec), continuous fragmented ischemic subepicardial activity bridges the diastolic interval between the ventricular tachycardia complexes. In contrast, we saw no diastolic bridging activity after the first normal complex at 20 minutes or during the episode of ventricular tachycardia (subepicardial activation spread of only 95–125 msec in fig. 5B, complexes 2–5). As with the activation sequence during IVA, ischemic endocardial activation preceded that in all other regions during DVA.

The DVAs associated with acute ischemia were as severe as the IVAs. There were seven instances of ventricular fibrillation associated with delay and fragmentation in the ischemic subepicardium during IVA among the 41 dogs in the study, compared with nine instances among 33 dogs that survived the initial 10–12 minutes. Figure 6 is a comparison of the maximal degree of delay and fragmentation of the sinus impulse in the ischemic subepicardial zone in dogs
that had ventricular fibrillation in either of the two periods of ectopic activity (IVA and DVA) with that of dogs that had no arrhythmias at the corresponding times. It is clear from this graph that the ventricular fibrillation of the IVA is associated with severe subepicardial delay of the normally conducted beats, whereas the ventricular fibrillation of the DVA is not associated with this subepicardial delay.

Of the 17 dogs that had IVA and survived, 14 also had DVA (72%) after a quiescent interval of 3–10 minutes. Seven of these dogs with DVA succumbed to ventricular fibrillation. In contrast, only seven of the 16 dogs (44%) that were arrhythmia-free for the initial 12 minutes had DVA, with only two instances of ventricular fibrillation. The other nine dogs were, therefore, free of arrhythmias during the entire acute post-ligation period.

Discussion

Experimental studies, both in the intact animal and in superfused tissue, have always been important tools to identify possible mechanisms of cardiac arrhythmias. Two periods of ventricular arrhythmias have been shown in the experimental animal with coronary occlusion: an early period, lasting 10–30 minutes, with a high incidence of ventricular fibrillation (Harris phase I), and a later and longer period appearing after 6–8 hours, persisting for 2–3 days, which seems to be less ominous. Several studies have strongly suggested that the late and prolonged ventricular arrhythmias were the result of an increase in the automaticity of surviving Purkinje fibers in the infarcted area. Other recent studies reported that early ventricular arrhythmias occurring immediately (0–10 minutes) after coronary ligation were the result of reentry.

The classic reports of early ventricular arrhythmias after coronary ligation (Harris phase I) described its occurrence 2–30 minutes after ligation, with peak activity during the first 10 minutes. After the extensive studies by Boineau and Cox, Scherlag et al., Waldo and Kaiser, and El-Sherif et al., this acute early phase was clearly attributed to reentry because of the demonstrated diastolic bridging activity in the
ischemic subepicardial zone. Review of the data from these research groups9–13 and the early publications of Harris and Rojas9 suggests that all of the reentrant subepicardial activity occurred during the first 10 minutes after ligation.

Our study shows that the so-called early postligation period ventricular arrhythmias are not due to a single mechanism. It became evident to us that there was a clear temporal separation into two phases (IVA and DVA), both occurring within the first 30 minutes after ligation. However, the temporal relation between these two phases differed in individual animals. Furthermore, a significant number of dogs had only one of the two phases of arrhythmias. Both phases were ominous, as ventricular fibrillation developed in either group (seven during the IVA period and nine during the DVA period), accounting for an overall 41% incidence of ventricular fibrillation; our findings were similar to the data available in the literature21 for one-stage ligation of the left anterior descending coronary artery in the dog.

Even though both acute phases of ventricular arrhythmias occur early after ligation and bear a close temporal relation to each other, a single mechanism cannot account for these two periods of ventricular arrhythmias. The IVAs were always associated with marked delay and fragmentation of the normal sinus complexes in the ischemic subepicardium, leading to delayed activity bridging the diastolic intervals (figs. 2–5). They appeared as the delay increased, and disappeared as the ischemic subepicardial delay decreased. In contrast, the DVAs occurred without antecedent fragmented subepicardial activity (figs. 2, 4 and 5). Furthermore, in all dogs, the delay and fragmentation of the local ischemic subepicardial activity continued to diminish before the appearance of DVA (figs. 2, 4, and 5). The classic local ischemic subepicardial conduction blocks18 (2:1, Wenckebach type, etc.) occurring just before the appearance of the IVAs were never observed before the appearance of the DVAs (figs. 4 and 5). Although it can be argued that the failure to detect increased delay and fragmented activity before the ectopic complexes of DVA resulted from insufficient electrode placement, the consistent observation of this sequence of events in all 21 episodes of DVA using multiple bipolar and composite electrodes suggests that the mechanism of the ventricular premature systoles of DVA differed from that of IVA. The increase in subepicardial ischemic zone delay and fragmentation of the ectopic complex of DVA appeared to be related to the acute change in cycle length (fig. 4B, activation spread of 140 msec in epi electrogram of complex 4), and should be clearly differentiated from the primary delay and fragmentation of the normally conducted sinus beats, which occurred in the IVA phase and were independent of preceding cycle length18–14 (fig. 4A, activation spread increase from 115–150 in complexes 1–3).

**Figure 6.** Peak delay of ischemic subepicardial activation during normal sinus complexes in dogs that developed ventricular fibrillation (VF) and in the dogs without ventricular fibrillation (VA) during the two phases of early arrhythmias after coronary ligation: immediate ventricular arrhythmias (IVAs) and delayed ventricular arrhythmias (DVAs). The dogs that subsequently developed VF during the IVAs had a significantly greater degree of subepicardial delay in the ischemic zone during the first 10 minutes after coronary artery ligation (p<0.001). At the time of DVA the degree of subepicardial delay in the dogs that developed VF was similar to that in the dogs that failed to develop VAs. Measurements represent composite and bipolar electrograms. NS = not significant.
The exact measurement of the extent to which depolarization in the ischemic subepicardial zone is delayed and fragmented is sometimes difficult. Consequently, we have increased the low-frequency cut-off to 50 Hz and used only the distinct and sharp deflections for the measurement of activation pattern (figs. 1, 4 and 5).

There is little doubt that the IVA phase is the result of reentry, as shown in many previous studies, which, in retrospect, appears to be the IVA described in our study. We could not show diastolic bridging activity as the mechanism for the DVA, and thus we could not actually prove reentry as the primary mechanism. On the other hand, this resurgence of the DVA is not likely to be due to increased automaticity, because it was shown that acute ischemia depresses automaticity in Purkinje fibers. Furthermore, studies in the whole animal have shown that enhanced automaticity after coronary artery ligation is delayed beyond the period corresponding to the DVA phase in our study.

Our concepts of the canine model for myocardial ischemia-induced ventricular arrhythmias must be readjusted according to the new findings in this study. The following may be a more precise delineation of the chain of events. One of the immediate effects of acute coronary ligation is severe electrophysiologic disturbance in subepicardial layers of the ischemic zone. This leads to IVA within 2-4 minutes, associated with reentry. The latter is directly associated with bridging activity during diastole (figs. 2-5). However, within 10-12 minutes this erratic activity at the subepicardial ischemic layer diminishes, and the IVAs disappear (fig. 2). As ischemia is prolonged, a second surge of ventricular arrhythmias appears (DVAs), but these mechanisms appear independent of local activity in the ischemic subepicardial layers (figs. 2, 4-6). However, these DVAs are as dangerous as the IVAs, as nine of the 33 dogs that survived the IVA developed ventricular fibrillation. The two phases of acute ventricular arrhythmias are only partially interdependent. Although most dogs with IVAs develop DVAs after a period of quiescence (14 of 17), the DVAs may very well be the first manifestation of rhythm disorders after coronary ligation. In the surviving dogs, all ventricular arrhythmias disappear within 30 minutes, and normal sinus rhythm prevails. What we regarded until now as a homogeneous Harris phase I of ventricular arrhythmias after ligation actually comprises two distinct periods of potential ventricular arrhythmias, possibly differing in their mechanisms and site of initiation (or both).

Electrophysiologic and pharmacologic studies in the search for possible mechanisms and management of acute ischemic arrhythmias should consider these two phases of ventricular rhythm disturbances. Furthermore, studies on reperfusion ventricular arrhythmias must be correlated with the exact phase of arrhythmia development in which reperfusion occurs.

References
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