Characterization and Localization of Ventricular Arrhythmias Resulting from Myocardial Ischemia and Infarction

By Benjamin J. Scherlag, Nabil El-Sherif, Ronald Hope, and Ralph Lazzara

ABSTRACT
Electrocardiograms and electrograms were recorded in 18 dogs anesthetized with sodium pentobarbital. Using endocardial and epicardial plunge wire electrodes in normal and ischemic or infarcted areas, activation of Purkinje and regular muscle tissue was studied within the first 20-30 minutes and 24 hours after anterior descending coronary artery ligation. The ventricular arrhythmias in the first 20 minutes were abolished during vagally induced atrial arrest, but ventricular automaticity was unchanged from that during the control period. These rate-related arrhythmias were uniformly associated with marked diminution and delay of epicardial activation in the ischemic zone. Slowing of the heart rate caused recovery of the timing, form, and duration of these epicardial potentials with the coincident disappearance of ventricular arrhythmias. The ventricular arrhythmias of the early phase spontaneously subsided with time 20-30 minutes after ligation; concurrently, epicardial activation in the ischemic zone improved. The ventricular arrhythmias noted 24 hours after coronary artery ligation were revealed by vagally induced atrial slowing and suppressed by rapid atrial pacing, indicating the existence of enhanced ventricular automaticity. There was a loss of endocardial muscle activation; Purkinje tissue was depressed but viable in the infarcted zone. The sequence of firing during many of the multifocal ventricular ectopic beats showed that the earliest activation arose from Purkinje tissue in the infarcted zone. However, other ectopic beats appeared to arise from infarcted epicardial muscle.

KEY WORDS
ventricular automaticity
ventricular electrograms
atrial pacing
anesthetized dogs
Purkinje fibers
reentry
vagal stimulation

Harris and Rojas in 1943 (1) described two distinct phases of ventricular arrhythmias after major coronary artery ligation in the dog. Sudden one-stage occlusion of the left anterior descending coronary artery close to its origin in the dog results in a high incidence of rapid paroxysmal ventricular tachycardia which usually degenerates into ventricular fibrillation within the first 20 minutes (1). If the dog survives the early arrhythmic episodes, a relatively quiescent period ensues followed by another prolonged interval of rapid ventricular ectopic activity. This later arrhythmic period starts 12-15 hours after ligation and lasts up to 72 hours after ligation. Harris and Rojas attributed both periods of arrhythmias to rapidly discharging automatic foci located at the borders of the ischemic or infarcted tissues and the normal zones, but in a previous study (2) we found evidence which indicates that the early arrhythmias do not result from enhanced automaticity. In the present study we utilized close bipolar recordings from Purkinje and regular muscle tissue in an attempt to gain insight into the electrophysiological mechanisms for the early and the later ventricular arrhythmias. In addition, a more precise localization of the site(s) of origin of these experimentally induced disordered rhythms was determined.

Methods
Eighteen adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). Under controlled ventilation, the thorax was opened at the fourth interscostal space, and the heart was exposed via a pericardiectomy. The left atrial appendage was reflected, and the left anterior descending coronary artery was exposed within 1 or 2 cm of its origin. Silk ligatures were then placed...
around the artery at the upper position in nine dogs and at the lower position in nine dogs.

Two silver wires (diameter 0.012 inches) were inserted into the distal portion of the right or left vago-sympathetic trunk (3). Vagus-sympathetic trunk stimulation (0.05 msec, 20 Hz, 1-10 v) allowed reduction of the heart rate and assessment of underlying ventricular automaticity. In addition, two fine stainless steel wires (diameter 0.003 inches) were inserted by a 25-gauge hypodermic needle into the left atrial appendage. Atrial pacing (2 msec, 180-200 pulses/min, 2-10 v) was accomplished by stimulation delivered from an S88 Grass stimulator and SIU isolation units.

To record from specialized ventricular conducting tissue and regular ventricular muscle, both an electrode catheter (4) and plunge wire electrodes (5) were employed. A bipolar electrode catheter was inserted into the right or left common carotid artery and positioned at the aortic root for recording His bundle activation (6). Furthermore, plunge wire recordings from the heart were made using two fine Teflon-coated stainless steel wires (diameter 0.003 inches). The wires were passed through 25-gauge needles 1½ inches in length and bent back at the bevel of the needle to form small hooks. After plunging the electrodes through the left ventricular wall into the left ventricular cavity, the needle could be removed, thus allowing the wire hooks to engage the endocardium. The cut ends of the wires served as close bipolar recording pairs (7). For epicardial recordings, similar plunge wires were placed just beneath the epicardium. Endocardial and epicardial electrodes were positioned in the anterior left ventricular wall (perfused by the anterior descending coronary artery) and in the lateral or posterior left ventricular wall (not perfused by the anterior descending coronary artery). In addition to the electrograms, recordings were made from standard electrocardiogram (ECG) leads. Electrical recordings were made at frequency limits between 0.1 and 2000 Hz and 40 and 200 Hz. Potentials were registered on an Electronics-for-Medicine oscillographic-photographic recorder at paper speeds of 25, 50, 100, and 200 mm/sec. A peripheral vein was cannulated for administering drugs, and a peripheral artery was cannulated for monitoring blood pressure by standard techniques.

PROCEDURE FOR STUDYING EARLY ARRHYTHMIAS

Before ligation of the anterior descending coronary artery, control records were made during (1) atrial pacing at 200/min and (2) vagally induced atrial arrest or complete atrioventricular (AV) nodal block to determine the idioventricular escape rate. After complete one-stage ligation of the left anterior descending coronary artery, the effects of atrial pacing were determined, and underlying ventricular automaticity was assessed at 2-5-minute intervals up to 30 minutes after occlusion. In six cases, the Harris two-stage ligation procedure was used to determine the basis of the differences in the reported responses to one- and two-stage ligation (8).

PROCEDURE FOR STUDYING LATE ARRHYTHMIAS

In 9 of the 18 dogs the thorax was opened under standard aseptic surgical procedures. The left anterior descending coronary artery was tied using either the one- or the two-stage ligation technique; the pericardium and the thorax were then closed. Appropriate antibiotic therapy was employed to prevent postoperative infection. The surviving dogs were anesthetized 24 hours later with pentobarbital, and the heart was exposed via a left thoracotomy. Recordings from an electrode catheter in the His bundle region and from plunge wire electrodes inserted into epicardial and endocardial sites within the infarcted and uninfarcted zones were obtained. In addition, recordings were made from two or more ECG leads. Vagus-sympathetic trunk stimulation and atrial pacing were performed as described in the preceding two sections; peripheral blood pressure was monitored throughout the experiment.

After recordings had been made during the various experimental procedures, the wires in the heart were cut off above the epicardial surface. The implanted sections were left in place. The heart was then excised and the left ventricle opened from base to apex to validate the exact position of the recording tips of the wire electrodes. Twenty-four hours after anterior descending coronary artery ligation, the infarcted zone was easily delineated; it was invariably located in the lower third of the left ventricle encompassing the anterior apical area and extending on to the third or one-half of the interventricular septum. The borders between the infarcted and the uninfarcted area were usually distinct, both on the epicardial and the endocardial surface. However, the infarction was more uniform on the endocardial surface than it was on the epicardial surface.

**Results**

**EARLY ARRHYTHMIAS**

In Table 1, the columns labeled Control summarize the heart rate during normal sinus rhythm and the idioventricular escape rate revealed by vagal stimulation (average 39 beats/min) before ligation. Within 20-30 minutes of acute ischemia in nine dogs (columns labeled Ischemia), the heart rate during normal sinus rhythm and vagally induced atrial arrest was unchanged. However, with atrial pacing at 200 beats/min ventricular arrhythmias were invariably produced during the first 20-30 minutes after anterior descending coronary artery ligation (2). Each of the nine cases showed either bigeminal or trigeminal rhythms and runs of ventricular tachycardia with an average rate of 275 beats/min (Table 1). Cessation of atrial pacing was followed by abolition or marked reduction of the ventricular arrhythmias (2).

Electrograms from the endocardium and the epicardium provided some insights into the site of origin of these early arrhythmias. In Figure 1, two standard ECG leads are shown. The His bundle recording and recordings from the close bipolar wires in the endocardium of the ischemic and normal zones and in the epicardium of both zones are also shown. The magnifications of the endocardial potentials in Figure 1A indicate rapid deflec-
TABLE 1

Underlying Ventricular Escape Rate in Control Hearts and within 20-30 Minutes after Coronary Artery Occlusion

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>Control (beats/min)</th>
<th>Ischemia (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Idioventricular rate</td>
<td>Idioventricular rate</td>
</tr>
<tr>
<td>1</td>
<td>152</td>
<td>158</td>
</tr>
<tr>
<td>2</td>
<td>148</td>
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<td>9</td>
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<td>107</td>
</tr>
<tr>
<td>AVG</td>
<td>140</td>
<td>139</td>
</tr>
<tr>
<td>± SD</td>
<td>29</td>
<td>27</td>
</tr>
</tbody>
</table>

NSR = heart rate during normal sinus rhythm, VT = ventricular tachycardia, B = bigeminal rhythm, and T = trigeminal rhythm.

* Ventricular arrhythmias were observed during atrial pacing at 200 beats/min.

A Control B 15 sec C 1.5 min D 2.0 min

PURKINJE and muscle activation before and immediately after coronary artery ligation. Traces from top to bottom are ECG leads aVR and aVF. His bundle electrogram (Hb), close bipolar electrograms from the endocardium in the control or normal zone (NZ endo) and ischemic zone (IZ endo), and close bipolar electrograms from the epicardium in the normal zone (NZ epi) and the ischemic zone (IZ epi). Both endocardial electrograms show Purkinje activation (arrows, see magnified insets) and larger and longer duration deflections representing endocardial muscle activation. Within 15 seconds after ligation, a marked diminution of the Purkinje activation in the ischemic zone was evident (B), but no changes in Purkinje or muscle activation in the normal areas were seen. The endocardial potential in the ischemic zone showed marked injury waves with loss of Purkinje activation 1.5 and 2 minutes after ligation (C and D). Also marked diminution of the epicardial muscle potential occurred in the ischemic zone with subsequent delay of the potential and broadening of its duration at 2 minutes (D).
tions prior to endocardial muscle activation which represent Purkinje tissue depolarization. Fifteen seconds after coronary artery ligation, the amplitude of the Purkinje deflection in the ischemic zone was markedly diminished but that in the normal zone remained unchanged throughout the experiment. No ventricular arrhythmias were seen at this time (B). In C, 1.5 minutes after coronary artery ligation, the endocardial muscle in the ischemic zone showed injury potentials. The epicardial activation in the ischemic zone was also undergoing a diminution in its amplitude with a slight delay in its timing. No arrhythmias were seen at this time. At 2 minutes, there was exacerbation of the endocardial injury potentials (D) with delay and a further decrease in the amplitude of the epicardial potential in the ischemic zone.

Figure 2 illustrates the onset of the ventricular arrhythmia that arose spontaneously 2.5 minutes after coronary artery ligation. This figure is a continuation of Figure 1. It shows that during sinus rhythm there was a progressive delay of the epicardial potential (arrows) in the ischemic zone as well as a marked broadening and diminution of the amplitude of this potential. In Figure 2A, the delay of the epicardial potential increased progressively so that it was being activated during the S-T segment. It should be emphasized that this ischemic area most probably represented a small fraction of the ventricular muscle, since its late activation was not associated with a change in the QRS complex of the surface ECG. With progressive delay of this potential, activation occurred at the end of the T wave of the surface ECG (second beat, B). There was then an abrupt change from normal sinus rhythm to ventricular tachycardia which went on to ventricular fibrillation. Note the fractionation of epicardial activation in the ischemic zone and the 2:1 and 3:1 relationship between epicardial normal zone and ischemic zone activation during this arrhythmia.

Figure 3 illustrates the effects of vagal stimulation causing slowing of the sinus rate during the time when epicardial potentials in the ischemic...
Effect of vagal slowing of the heart on the dissociated activation of epicardial sites in the ischemic zone. Traces from top to bottom are standard ECG leads I, aVR and aVF and two close bipolar electrogroms in the epicardium of the ischemic zone (IZ epi). The slow, markedly delayed activation of epicardial sites in the ischemic zone during normal sinus rhythm (NSR) is shown in A. During normal sinus rhythm, a multifocal ventricular tachycardia (starred beats, VENT. TACH) occurred. On vagal slowing of the heart rate (arrow, VS) sinus rhythm was restored. In B, note the relative recovery of timing and configuration of the epicardial potentials in the ischemic zone and their closer association to each other and the ventricular activation as seen on the standard ECG leads. In C, the sinus rhythm stabilized 30 minutes after acute coronary artery ligation. Note the further recovery of the configuration, upstroke, and timing of the epicardial potentials in the ischemic zone.

These findings suggest a close temporal relationship between deterioration of local epicardial potentials and the early ventricular arrhythmias. To further define this relationship, in 20 additional dogs the delay of epicardial activation in the ischemic zone was examined from the time of occlusion until the onset of ventricular arrhythmias and ventricular fibrillation. Figure 4 is a graphic presentation of these data; on the abscissa, T represents the relative time of onset of ventricular fibrillation (Q-T interval). The potentials from the ischemic epicardium showed marked diminution and delay. In the first two sinus beats in Figure 3, diminution and delay of the epicardial potentials in the ischemic zone were evident and closely associated with the onset of ventricular tachycardia (starred beats). Vagal stimulation initiated during ventricular tachycardia caused slowing of the sinus rate with some recovery of amplitude and timing of the epicardial deflections (B). In C, 20-30 minutes after acute left anterior descending coronary artery ligation—after the cessation of the arrhythmic episodes—the epicardial potentials have further recovered amplitude and temporal relationship to other ventricular activation.

Relationship between delay in epicardial activation in recorded electrogroms (ordinate) and the time of onset (T, abscissa) of ventricular tachycardia normalized in each of 20 dogs. The average time of onset of ventricular tachycardia was 4 minutes in absolute terms. The potentials from the ischemic epicardium (circles) showed variable but significantly greater average delay than did the potentials from the nonischemic epicardium (crosses). This finding was particularly evident just prior to the onset of ventricular tachycardia when some recorded potentials showed delayed activation well beyond the end of the average Q-T interval (254 msec, range 190 to 320 msec).
tachycardia in each dog after coronary artery occlusion at time zero. The average time for onset of ventricular tachycardia in absolute terms was 4 minutes for all dogs. On the ordinate, the range of delay of epicardial activation measured from the onset of the QRS complex is shown for the ischemic zone (circles) and the normal zone (crosses). It should be noted that all of the recorded potentials from the epicardium of the ischemic zone showed variable degrees of delay. Ventricular fibrillation occurred within 2-10 minutes of occlusion. The average delay followed an exponential curve with delay becoming marked prior to the onset of ventricular fibrillation. In four instances the recorded potentials showed delayed activation which occurred after the end of the T wave of the standard ECG. The occurrence of maximum delay invariably preceded the onset of ventricular tachycardia and ventricular fibrillation. The sequence of events leading to ventricular fibrillation in these instances paralleled those shown in Figures 1 and 2.

**LATE ARRHYTHMIAS**

In contrast to the arrhythmias found in the early stages of myocardial ischemia, the ventricular arrhythmias which appeared 24 hours after coronary artery ligation showed different functional characteristics. In Table 2 the underlying ventricular automaticity, manifested during vagally induced atrial arrest in nine control dogs, is compared with the underlying and overt ventricular automaticity seen during similar periods of vagal stimulation in nine dogs 24 hours after coronary artery ligation.

Note that the escape idioventricular rate in the control dogs was 39 beats/min compared with a normal sinus rate of 140 beats/min. In the 24-hour infarcted heart, not only was normal sinus rhythm significantly higher (170 beats/min) than that in the control state but also vagal stimulation revealed an enhanced ventricular automaticity which averaged 166 beats/min.

Unlike the early arrhythmias, the later 24-hour ventricular arrhythmias were easily suppressed by overdrive at various pacing rates (Fig. 5) but readily exposed by vagal stimulation which caused slowing of the sinus rate (Fig. 6).

Figure 6 demonstrates that vagal suppression of the sinus rhythm revealed enhanced automaticity in the 24-hour infarcted heart. In this example, during normal sinus rhythm at a rate of 129 beats/min, vagosympathetic stimulation inhibited the sinus rhythm and revealed an underlying ventricular ectopic rhythm, initially irregular, which rapidly regularized at a rate of 77 beats/min. Abruptly, another regular ectopic focus superseded the initial idioventricular rhythm with the new focus beating at a rate of 86 beats/min.

To determine the site of origin of the enhanced ventricular ectopia, bipolar recordings from the endocardium and the epicardium of the infarcted and the normal zone were examined. Figure 7 shows a comparison of the amplitude of Purkinje tissue activation in the infarcted and the normal endocardium 24 hours after coronary artery occlusion. The Purkinje fibers appeared to be viable in the infarcted zone but depressed. Muscle potentials in the infarcted zone showed only slow waves.
of low amplitude compared with those in the normal zone.

In Figure 8, recordings from the normal and infarcted zones of the endocardium and the epicardium in the 24-hour infarcted dog heart are shown. The two top traces are standard ECG leads aVR and II. Several normal beats and ectopic beats of various configurations were recorded by the bipolar electrodes at three endocardial sites within the infarcted zone; an endocardial recording in the normal zone and the epicardial electrogram from the infarcted zone are also shown. In all the normal beats, the normal zone endocardial potential, which had the largest amplitude, preceded the other recorded potentials. In the ectopic beats, a potential in one of the endocardial sites in the infarcted zone (starred beats) always preceded the normal zone endocardial potential. In the latter cases, the potential in the infarcted zone occurred at the beginning of or prior to the onset of the surface QRS complex.

Not all ectopic beats could be ascribed to an endocardial origin. Figure 9 shows ectopic beats which appeared in several cardiac cycles 24 hours after coronary ligation. In A the ectopic beat had a short “coupling” time, 205 msec, with the earliest activity in all leads arising from the epicardium of the infarcted zone. In B and C, the same beats occurred later in relationship to the sinus beats (260–280 msec) and produced various degrees of fusion with the next sinus beat. In both these latter beats, the earliest recorded activation arose in the epicardium of the infarcted zone (starred beats).

Discussion

EARLY ARRHYTHMIAS

The prevailing concepts relating to the genesis of cardiac arrhythmias are enhanced automaticity of normal or ectopic pacemakers, marked slowing of conduction in specific areas of the heart leading to reentry and reexcitation, or a combination of these two processes (9). Harris and Rojas (1) suggested that the early arrhythmias occurring after anterior descending coronary artery occlusion in the dog were the result of rapidly discharging automatic foci (enhanced automaticity). In the present study and in previous work (2), the use of vagally induced atrial arrest allowed assessment of underlying automaticity; the idioventricular escape rate averaged 39 beats/min both before and up to 20 minutes after coronary artery occlusion (Table 1). On the other hand, ventricular arrhythmias arising minutes after occlusion showed an average rate of 275 beats/min. These data do not appear to be consistent with enhanced automaticity unless such activity is transient and capable of being provoked by rapid atrial pacing. Several previous studies have presented suggestive evidence implicating a reentrant mechanism in the
CORONARY OCCLUSION ARRHYTHMIAS

Early ventricular arrhythmias that occur after coronary artery occlusion (10-15). Although some degree of dispersion of recovery of excitability in ischemic tissues has clearly been shown by Han and Moe (16), the sine qua non for reentry, that is, marked disparities in conduction time or activation of ischemic tissues, has been difficult to demonstrate in the intact heart. Indeed, our previous study indicated that the conduction times between the onset of ventricular activation (His bundle potential) and the endocardial recordings in normal and ischemic zones were unchanged from control after acute coronary artery occlusion (2). In that study, recordings were made specifically from the endocardium in the ischemic zone based on the expectation that reentry would be more likely within the His-Purkinje tissue or at Purkinje-muscle junctions (9).

Several findings from this and previous (2) studies suggest that reentrant activation within ischemic myocardial muscle may be responsible for the early cardiac arrhythmias resulting from acute coronary artery ligation. The marked delay in activation of localized subepicardial sites clearly conforms to the degree of delay necessary for reentry to occur (17-19). In the present study, the association of the progressive delay of activation in the epicardium and the onset of ventricular tachycardia leading to ventricular fibrillation was observed in 20 dogs; the greatest delay (up to 320 msec) occurred beyond the T wave with the concomitant onset of ventricular fibrillation. Although not all of the activation recorded in the ischemic zone showed marked delay, in four cases the onset of the lethal arrhythmia provided a sequence of events like that depicted in Figures 1 and 2. Delay of activation as great as 200 msec has been noted by others (20, 21) in ischemic and infarcted myocardial tissue. However, the present data consistently demonstrated a progressive delay of ventricular activation at local epicardial sites within minutes of coronary artery occlusion leading to ventricular arrhythmias. Slowing of the heart rate caused a reversal of this delay in activation at the sites from which recordings were made as well as abolition of the ventricular arrhythmia (Fig. 3). These early ventricular arrhythmias subsided spontaneously after 15-20 minutes (Fig. 3). At this time, activation of previously delayed subepicardial sites returned toward control status (Fig. 3C). It is interesting to note that the two-stage ligation of Harris (8), which results in few if any early episodes of
ventricular arrhythmias, caused no delay in activation at subepicardial sites.

It should be pointed out that, although the degree of delay (slow conduction) found in the present study was compatible with reentry, the systematic delineation of the reentrant circuit and the determination of the sites of unidirectional block were not defined as they were in previous studies with bovine and canine Purkinje fibers (22). Thus, definite evidence for a reentrant mechanism is lacking. Recently, Cranefield (19) described certain in vitro conditions which could allow a quiescent cell to become abruptly automatic because of the introduction of a single depolarizing impulse. Thus, the possibility exists that ischemia establishes conditions in specific areas of the heart which allow development of automatic activity when these areas are excited by supraventricular impulses.

LATE ARRHYTHMIAS

Harris (8) and others (23, 24) have described the electrocardiographic findings 24 hours subsequent to left anterior descending coronary artery ligation. We found, as these investigators have reported, the frequent occurrence of ventricular ectopic beats interspersed with sinus rhythm. Some dogs showed periods of unifocal and multifocal ventricular tachycardia with only a few sinus beats. Less commonly seen was an intact sinus rhythm with only occasional ventricular premature or fusion beats. Vagal inhibition of supraventricular activity for intervals one to several minutes in duration invariably revealed rapid unifocal and multifocal ventricular ectopic beats (Figs. 5 and 6). The persistence of these ectopic rhythms, when they were observed for long intervals of vagal inhibition of sinus rhythm, was consistent with automatically discharging foci. However, transient slowing or irregularity of any given ventricular ectopic focus was frequently observed (Fig. 6). This response has also been found in recordings from single cells in the infarcted endocardium in vitro (25). Resumption of sinus rhythm after vagal stimulation or atrial pacing at rates higher than the sinus rate (up to 270 beats/min) invariably suppressed the ventricular ectopic beats (Fig. 5). Therefore, in contrast to the ventricular arrhythmias occurring within 20 minutes after ligation, these late arrhythmias were revealed by vagal stimulation and overdriven by atrial pacing. The former arrhythmias were suppressed by vagal slowing of the heart rate and enhanced by increasing the heart rate with atrial pacing.

To determine the site of origin of these multifocal automatic ventricular arrhythmias, epicardial and endocardial recordings were utilized. Of interest was the finding that the endocardial muscle in the infarcted zone, in almost all areas from which recordings were made, showed only a small wave in contrast to the large-amplitude deflection of shorter duration found in normal zones. Durrer et al. (26) recorded similar deflections in myocardium that was chronically infarcted. They suggested that these slow waves resulted from activity in adjacent viable myocardium. Attempts to record transmembrane action potentials from infarcted endocardial muscle have confirmed the lack of electrical activity, but other endocardial muscle cells at the same depth in normal zones show normal transmembrane action potentials (25, 27). A comparison of

FIGURE 7

Comparison of bipolar endocardial recordings from infarcted (IZ endo) and normal (NZ endo) areas of the left ventricle 24 hours after coronary artery occlusion. Traces from top to bottom are ECG leads I, aVR, and aVF and bipolar electrograms from the endocardium of the infarcted and normal zones. Purkinje (P) and ordinary myocardial (M) potentials are distinguishable on the electrograms recorded from the normal zone. On the electrograms recorded from the infarcted zone, Purkinje spikes are superimposed on a small slow wave which extends throughout most of the QRS complex. Vertical bars represent a calibration of 1 mc for each bipolar recording. Note the marked diminution of Purkinje potentials and particularly muscle potentials in the infarcted zone compared with their amplitude in the normal zone.

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Purkinje potentials in endocardial zones of infarcted areas showed depressed but detectable electrical activity (Fig. 7). Here again, transmembrane action potentials in vitro recorded from infarcted and normal zones have revealed reductions in membrane potentials and increases in the duration of the action potentials of Purkinje cells in the infarcted zone compared with those in the normal zone (25, 27). Furthermore, true pacemaker activity as well as enhanced phase 4 depolarization of Purkinje cells in the infarcted endocardium have been reported by us (25) and by others (27) in the 24-hour infarcted endocardium in vitro.

The occurrence of ectopic beats which apparently do not have a Purkinje or an endocardial origin (Fig. 9) raises several interesting questions. Under ordinary circumstances only the specialized tissue of the ventricles—the Purkinje fibers—is presumed to have the ability to exhibit intrinsic rhythmicity or automaticity (28). Recent studies of working myocardium taken from atria and ventricles of patients during surgery has indicated that the pathologic working myocardium appears to be a source of rapid ectopic rhythms which are characterized by phase 4 depolarization and pacemaker-like cells (29). Solberg et al. (30), using left

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

**FIGURE 8**

Localization of the site of origin of ventricular ectopic beats in the 24-hour infarcted dog heart. Traces from top to bottom are ECG leads aVR and II and bipolar electrograms from endocardial (endo) sites in the infarcted (IZ) and normal (NZ) zones as well as from an epicardial site in the infarcted zone (IZ epi) during normal sinus beats (N). Note the earliest activation of Purkinje potentials recorded in the normal zone. Also note the marked difference in the duration and the configuration of the endocardial muscle potentials recorded in the infarcted and normal zones. The epicardial activity in the infarcted zone consisted of a diminutive potential. In several ectopic beats, early activation of Purkinje potentials in the infarcted zone was observed (starred beats), whereas endocardial activation in the normal zone occurred somewhat later as did activation of the normal zone epicardium.
ventricular myocardial slices from infarcted dog hearts, have found slow phase 4 depolarization and pacemaker activity presumably arising from cells of regular cardiac muscle, i.e., non-Purkinje cells. The ectopic beats shown in Figure 9 indicated that the Purkinje activation occurred well after the onset of ventricular activation as seen on the surface ECG. These beats could be due to reentry with variable coupling (18). Another possibility is that these beats arose in Purkinje cells from the left ventricle in the normal or border zones with marked conduction delay due to infarction at the particular endocardial sites from which recordings were made (Purkinje potentials in the ischemic zone). This possibility is not likely because of the close correspondence between activation of normal and infarcted endocardial zones in other ectopic beats as well as during normal ventricular activation (Fig. 7A and B). The possibility that some beats arise in Purkinje tissue in the right ventricle or at another distant site must also be considered. Evidence for this possibility cannot be cited at present.

FACTORS RESPONSIBLE FOR EARLY AND LATE VENTRICULAR ARRYTHMIAS

Harris (31) has suggested that potassium can act as an excitatory agent for the early as well as the late ventricular arrhythmias which result from coronary artery ligation. Other reports (32, 33) have provided evidence substantiating this view. Of particular relevance to the early arrhythmias is the recent report of Ettinger et al. (34), whose study involved perfusing the apical portion of the left ventricle with isotonic KCl through the anterior descending coronary artery. Within minutes of the onset of this perfusion, marked delay and deterioration of epicardial activation were 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-endocardial relationships consistent with a reentry phenomenon.

It is doubtful that the late ventricular arrhythmias could be the result of the persistent effect of potassium released from infarcted cells. It is well known that phase 4 depolarization is strikingly depressed by high concentrations of extracellular potassium (28). It also appears unlikely that hypoxia plays an important role as an arrhythmogenic factor in the 24-hour infarcted dog heart. Previous studies have shown that hypoxia reduces rather than enhances the automatic firing rate of infarcted tissue (35, 36).

These results and data from a previous work (2) provide a different point of departure from generally accepted views of the site of origin of ventricular arrhythmias resulting from ischemia and infarction. Previous investigators (1, 8) believed that the critical sites of arrhythmia formation were at the border of the ischemic or infarcted tissue and the normal myocardium. It seems likely to us that regular ventricular muscle and Purkinje tissue...
within the infarcted and ischemic zones represent important sites of ventricular arrhythmia initiation and perpetuation.

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