Automatic and Triggered Impulse Initiation in Canine Subepicardial Ventricular Muscle Cells From Border Zones of 24-Hour Transmural Infarcts

New Mechanisms for Malignant Cardiac Arrhythmias?

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With standard microelectrode techniques, electrical activity of cells in the epicardial border zones of infarcts in the canine heart were studied. Either automaticity or triggered activity (or both) occurred in each of the 12 preparations studied from 24-hour infarcts. One 24-hour preparation had continuous activity indistinguishable from low-potential (abnormal) automaticity. This automaticity was not effected by flecainide 1–5 mg/l. Two other 24-hour subepicardial muscle preparations also were automatic. However, nine preparations from the subepicardium were not automatic during superfusion with standard Tyrode’s solution. Delayed afterdepolarizations (DADs) and triggered activity could be induced in all of these preparations by treatment with catecholamines. The amplitude of these DADs was directly related to the stimulus rate of the train of impulses used to elicit them, and their coupling interval was inversely related to this rate of stimulation. Triggered activity occurred from maximal diastolic potentials of −58 to −88 mV in the 24-hour infarct zone preparations. In seven preparations from 72–96-hour infarct zones, the epicardial muscle cells did not show triggered activity after treatment with catecholamines. In one preparation from a 72-hour infarct, however, 3–5-mV DADs occurred. No DADs or triggered impulses occurred in subepicardial muscle from normal, noninfarcted hearts. Thus, triggered impulses and low-potential automaticity could contribute to arrhythmias occurring in the canine heart 24 hours after coronary ligation. (*Circulation* 1988;78:1020–1030)

Multiform ventricular tachycardias occur 24 hours after ligation of the left anterior descending coronary artery in the canine heart. These tachycardias are frequently used to model the arrhythmias that occur in humans hospitalized after myocardial infarction. Most investigators have concluded that the ectopic beats primarily originate in subendocardial Purkinje fibers that survive on the endocardial surface of the infarct. However, some ectopic activity may also begin in working myocardium on the lateral or epicardial borders of the infarct. It is known that a thin rim of surviving ventricular muscle cells on the epicardial border of the 24-hour infarct can support reentrant activation. Although microelectrode studies of subepicardial ventricular muscle tissue preparations studied 20–24 hours after coronary ligation have indicated that the cells are partially depolarized and have abnormal transmembrane action potentials, they have not suggested that these tissues can produce arrhythmias by spontaneous impulse initiation.

Therefore, the present study was designed to determine whether spontaneous impulse initiation can occur in ventricular muscle cells on the borders of infarcts studied 1 day after coronary occlusion. Small preparations were isolated from the epicardial border zone of normal and of both 1-day-old and 3–4-day-old infarcts of the canine heart. Stimulus regimes to elicit delayed afterdepolarizations (DADs) and triggered activity were used. Because it is known that catecholamines can enhance triggered and automatic foci, the effects of norepinephrine or isoproterenol on these preparations were examined.

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Materials and Methods

Healthy, heartworm-negative, 15–20-kg adult mongrel dogs were anesthetized with sodium pentobarbital (30–40 mg/kg i.v.). Under aseptic conditions, a left thoracotomy was performed through the fourth intercostal space, and the proximal left anterior descending coronary artery was ligated by a two-stage technique. Then, the thoracotomy was closed in layers, and the animal was taken to the recovery room. Antibiotics (oxacillin 1 g and gentamycin 20 mg) were administered intramuscularly every 24 hours to prevent wound infections. After 1–4 days of recuperation, the animals were reanesthetized with pentobarbital andocardiotomies were performed rapidly. Each excised heart was placed into a beaker of room-temperature, oxygenated Tyrode’s solution and washed of residual blood. Then, the experimental preparations were carefully dissected from the epicardial surface of the heart overlying the central zone of the infarct and from comparable endocardial sites adjacent to the central necrotic zone. The tissue preparations (n = 12) varied between 5 × 5 mm in surface area to 10 × 15 mm in area and were usually about 1 mm thick. In addition, hearts were excised from normal dogs by the same techniques and tissues obtained for studies on noninfarcted preparations (n = 6).

The preparations were carefully placed on the 2 × 2-cm Plexiglas platform of a Purkinje fiber tissue bath and held gently in position with a grid of 5-0 surgical silk carried by an outer frame of Teflon. Physical trauma to the epicardial or endocardial surface, which faced upward in the bath, was minimized. The tissues were superfused at a rate of 12–15 ml/min with warmed Tyrode’s solution containing (mM) NaCl 131, NaHCO3 18, NaH2PO4 1.8, MgCl2 0.5, CaCl2 2.7, KCl 4, and dextrose 5.5. The reservoir of superfusate was equilibrated with 95% O2-5% CO2 to maintain pH in the tissue bath between 7.2 and 7.4. In addition, disodium ethylenediaminetetraacetate was added to the reservoir of Tyrode’s solution in a concentration of 50 μM in any experiments in which norepinephrine or isoproterenol was used to minimize oxidation of the catecholamines. The temperature of the solution in the bath was 38–39°C during these experiments; this range is slightly below normal core temperature in dogs. The tissue bath temperature did not vary by more than 0.1°C during any single experiment.

The techniques used for recording transmembrane action potentials with standard microelectrodes, and for stimulating the preparations, have been described in detail. Data were recorded on a four-channel polygraph (Model 2400, Gould, Cleveland, Ohio), and the transmembrane potentials were continuously monitored on an oscilloscope (Model 5113, Tektronix). After stable impalements were obtained, any spontaneous activity was monitored.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Tracings of induction of delayed afterdepolarizations in a preparation of subepicardial muscle obtained 3 days after coronary ligation by isoproterenol 1 μM. Upper trace: Effects of 20 beats at a cycle length of 600 msec; 3-mV afterdepolarization follows last driven beat. Lower trace: 5-mV afterdepolarization after train at a cycle length of 250 msec. No afterdepolarizations occurred before treatment with catecholamines. Note zero reference potentials to the left of each trace, 60 mV calibration bar to right, and 1-second time marks below. (For further discussion, see text.)
for 15–30 minutes to verify that it was consistent. In nine preparations, isoproterenol 0.1–1 μM was added to the superfusate, and the effects were observed. In two preparations, norepinephrine bitartrate 0.1–1 μM was tested in the same way. When these catecholamines were being used, the room was darkened to reduce the photolytic oxidation of the drug.

Data are presented as mean ± SEM. DAD amplitudes were measured on the records from the Gould recorder as the difference (mV) between the end of phase three and the apex of the DADs. Coupling intervals were measured between the last driven upstroke and the apex of the DAD.

**Results**

Automaticity or triggered activity did not occur before, during, or after treatment with isoproterenol or less than 1 μM in left ventricular epicardial preparations from either the anterior wall of normal, noninfarcted canine hearts (n = 6) or the infarcted surfaces of canine hearts studied 3–4 days after ligation of the left anterior descending coronary artery (n = 4). However, there were electrophysiological differences between the two types of preparation. Diastolic membrane potential was −87 ± 3 mV in normal subepicardial muscle cells and averaged −81 ± 2 mV in the muscle cells from the 3–4-day-old infarct zones (p<0.05). Moreover, in one preparation taken from the center of a 72-hour-old infarct, isoproterenol 1 μM did induce small (2–5 mV) DADs (Figure 1). These DADs did not produce triggered impulses and occurred only transiently. That is, tachyphylaxis occurred after about 15 minutes of superfusion with isoproterenol-Tyrode’s solution. After that, even though the β-agonist continued to be superfused, DADs did not occur. This tachyphylaxis did not appear to be voltage-dependent. Resting membrane potential was between −84 and −82 early on, both before treatment with isoproterenol and shortly after treatment, when DADs could be induced. After the DADs had disappeared, resting potential was about −82 mV.

In contrast to the results obtained in the control tissues and 3–4-day postligation tissues, spontaneous impulse initiation occurred either before or after treatment with catecholamines in every subepicardial ventricular muscle preparation excised from the 24-hour infarct zones. In three of the preparations, automaticity or triggering occurred during the control period while the tissue was being superfused with standard Tyrode’s solution. In general, such automatic or triggered activity occurred only in the preparations with the lower diastolic potentials. Specifically, maximum diastolic potentials averaged −64 ± 6 mV in the three spontaneously active preparations. In the remaining nine subepicardial preparations from 24-hour infarcts, no spontaneous impulse initiation occurred during the control period. These “quiescent” preparations could be driven at cycle lengths as short as 300 msec during the control period without eliciting DADs or triggered activity. Diastolic (resting) potentials averaged −78 ± 1 mV in the nine quiescent preparations during the control period.

**FIGURE 2. Tracings of induction of delayed afterdepolarizations (DADs) and triggered activity in 24-hour infarct zone subepicardial muscle by isoproterenol. Panel A: Control data; 30-beat, 300-msec train does not induce DADs. Panels B and C: Effects of isoproterenol 1 μM after stimulus trains at 300 and 400 msec, respectively. (For further discussion, see text.) Horizontal bar above trace C shows period of stimulation. Format as in Figure 1. Voltage and time calibration bar at lower right (60 mV and 4 seconds, respectively).**
As with the 72-hour infarct zone preparations, tachyphylaxis was encountered during studies of the effects of isoproterenol in the 24-hour preparations. Tachyphylaxis occurred in three of the four preparations in which the relations of DAD amplitude to stimulus regime parameters were studied and overall in four of the nine preparations that were quiescent during the control period. In these four studies, the amplitude of the DADs would generally be greatest 5–10 minutes after beginning treatment with isoproterenol. Then, after 15–30 minutes of treatment, the response would be reduced or disappear entirely. Resting membrane potential (E_m) in these preparations did not change significantly after treatment with the catecholamine was begun or later as tachyphylaxis developed. In most experiments, E_m had decreased 1–3 mV when DADs could no longer be elicited, but in a few preparations, it increased 1–5 mV. Thus, the tachyphylaxis was not associated with an “accelerated recovery” of diastolic potential induced by the catecholamines.

As mentioned above, three preparations of ventricular muscle from over 24-hour infarct zones were spontaneously active even before treatment with catecholamines was begun.

In one preparation (Figure 4), irregular bursts of action potentials occurred during the control period. After treatment with norepinephrine 0.3 μM, the bursts became longer and more regular and were terminated with 6–9 mV DADs. About 6 minutes after superfusion with the catecholamine was begun, the preparation was continuously activated at a cycle length of about 500 msec. After a final 27-second pause, this rate of impulse initiation was stable for about 30 minutes. After that time, the continuous triggered activity was interrupted by a 35-second stimulus train at a cycle length of 300 msec. Shorter trains did not stop the triggering, but a 15-second train did lead to transient slowing (Figure 4).

In an epicardial preparation from another 24-hour infarct zone, the muscle cells were firing at cycle lengths of about 560 msec immediately after it was isolated. The MDPs varied between −57 and −62 mV in the “pacemaker” action potentials. Occasionally, the sustained triggered activity in this preparation arrested spontaneously. These periods of arrest were begun with DADs. Most cells in the preparation had resting transmembrane potentials between −75 and −80 mV during the quiescent periods. If a single stimulated impulse was delivered during these periods of arrest (Figure 5, upper left), the driven action potential would induce a sustained triggered rhythm from MDPs of −60 to −70 mV at a cycle length of about 550 msec. The run of triggered activity depicted in Figure 5 lasted about 4 minutes (Figure 5, upper right). Many similar 3–8-minute bursts of rapid impulse initiation occurred during the control period. After treatment with isoproterenol 0.1 μM, triggered activity occurred at slightly shorter cycle lengths, or about

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**Figure 3.** Plots of amplitude (upper panel) and coupling interval (lower panel) of delayed afterdepolarizations induced by isoproterenol. Horizontal axis shows cycle length of stimulation in m sec; vertical axes show amplitude in millivolts and coupling intervals in m sec. Circles show results of 30-beat trains; triangles show effects of 10-beat trains. (For further discussion, see text.)

After the quiescent infarct zone preparations were treated with isoproterenol or norepinephrine, DADs or triggered activity occurred within 2–5 minutes. Usually, relatively high catecholamine concentrations of 1 μM were necessary to elicit DADs. The induction of DADs was not associated with consistent changes of diastolic potential. In two experiments, lower concentrations of catecholamines (0.3–0.5 μM) were able to produce significant effects. In five of the nine quiescent preparations, the “threshold” concentration of catecholamine produced triggered rhythms that were sustained for 1–15 minutes (Figure 2). In the remaining four preparations, treatment with catecholamines did not induce triggering. Here, stimulus trains of 10–30 beats were followed by DADs. In these four experiments, the effects of the cycle length of stimulation could be studied on the amplitude and coupling interval of the DADs. The mean resting potential of the muscle cells (n=8) studied was −82 ± 2 mV during these determinations. In three of these experiments, isoproterenol 1 μM was required to elicit DADs, and in one experiment, a concentration of 0.5 μM was used successfully.

The amplitude of the DADs was inversely related to the basic cycle length of the stimulus train (Figure 3). That is, the faster the rate of stimulation, the larger the DAD became. The coupling interval (CI) of the DADs was directly related to the basic cycle length of stimulation (Figure 3).
500 msec (Figure 5, lower traces). However, stable impalements could not be maintained after exposure to the catecholamine. On several occasions, MDP gradually declined during a triggered burst until the activity stopped and membrane potential stabilized at −15 to −5 mV. After about 15 minutes of treatment with isoproterenol, rapid triggered activity could no longer be elicited.

In one additional pair of studies, two preparations from a 24-hour infarcted heart were placed in a dual bath and superfused simultaneously. One preparation was from the endocardial surface of the infarct, and a second preparation was from the epicardial surface. The Purkinje fibers on the endocardial surface were firing slowly (Figure 6, lower traces), while the epicardial muscle cells were found to be firing in a sustained rhythm at about a 580-msec cycle length when they were first impaled (Figure 6, upper traces). The epicardial cells continued to fire at this cycle length for 2 hours. The rhythm could not be interrupted by overdrive stimulation or single premature stimuli. Treatment with flecainide 1 mg/l and then 5 mg/l for 30 minutes each did not decrease the rate of the epicardial pacemaker but stopped the activity in the endocardial preparation.

**Discussion**

After occlusion of the left anterior descending coronary artery in dogs, ventricular arrhythmias occur in two phases. The first phase occurs within 30 minutes of occlusion. Most of this arrhythmic activity is caused by reentry in the ischemic zone.19–21 The reentrant rhythms are probably initiated by “focal” mechanisms in the subendocardial ischemic zone.19–21 The exact nature of these focal mechanisms is still unknown.22

After the phase one arrhythmias subside, a quiescent period of sinus tachycardia occurs.23,24 Then, 4–6 hours after coronary occlusion, the delayed phase of ventricular ectopic activity begins in the canine heart.23–25 If these hearts are isolated and perfused in vitro, the rate of ventricular ectopic activity is faster after 6 hours than it is at 24 hours.23 However, after 6–8 hours, the subendocardial Purkinje fibers bordering the infarct have normal action potentials. Rapid pacemaker activity can be recorded from cells with maximum diastolic potentials (MDPs)
Figure 5. Tracings of triggered activity in muscle preparation from epicardial surface of 1-day-old myocardial infarction. Upper left panel: Initiation of triggered activity, in the absence of catecholamine, by a single stimulus. Upper right panel: Termination of this triggered activity. Lower left panel: Initiation of triggered activity after treatment with isoproterenol. Lower right panel: Termination of this activity. Note 1-second time marks above each panel. Voltage calibration at lower right, 60 mV. Horizontal bar at lower right represents 2 seconds in upper left trace, 200 msec and 20 seconds at upper right trace, 2 seconds in lower left trace, and 10 seconds at lower right trace. Note zero reference potentials to left of each row of traces.

of about −70 mV that are located about seven cell layers beneath the endocardium. That far beneath the endocardial surface, the fibers are probably working ventricular myocardial cells.

Between 30 minutes and 15–18 hours after ligation, the necrotic region within the ischemic zone gradually expands until it reaches the subendocardial Purkinje fibers. Multifocal ventricular arrhythmias continue from about 18 hours until 36–48 hours after ligation. Most evidence suggests that the primary foci of these arrhythmias is in the Purkinje fibers adjacent to the necrotic region. However, data from the in situ dog heart published by Scherlag et al indicates that other foci can be located on the epicardial border of 24-hour infarcts. The present data support that conclusion. Some years ago

Figure 6. Tracings of continuous rhythmic activity in a preparation of subepicardial muscle (upper two traces) and a preparation of subendocardial Purkinje fibers (lower two traces). Records at fast (50 mm/sec) and slow (2 mm/sec) paper speeds shown at left and right, respectively. Zero reference potentials at left; 60-mV calibration bar at right center. One-second time marks between first and second trace. (For further discussion, see text.)
we studied the activation sequences of multifocal ectopic activity in isolated blood-perfused canine hearts with 24-hour infarcts. Using relatively simple techniques, we confirmed that most of the impulses originated on the endocardial surface of the infarct zone. A preliminary report of this study was presented. At that time, data was presented on one heart in which only one QRS configuration that occurred very frequently was mapped. The site of earliest activation of this beat was on the epicardial surface of the infarct near its lateral border (Figure 7). The endocardial activation sequence on the left ventricular surface was similar to the sequence that occurred during supraventricular beats (Figure 8) and was quite different than those that occurred during ventricular beats in other preparations (Figures 9 and 10). Thus, the present study confirms our earlier results that independent of increased sympathetic tone or specific humoral factors, epicardial impulses can provoke significant ventricular ectopic activity in the 24-hour infarcted heart. These epicardial impulses can be either automatic or triggered.

It is well established that ventricular muscle can become automatic if it is depolarized by DC currents to the diastolic voltage range of -50 to -60 mV. In the present study, slow automaticity occurred in the 24-hour infarct zone ventricular muscle fibers. This automaticity occurred in both standard and catecholamine-containing Tyrode's solution from MDPs of -60 to -70 mV and led to bursts of triggered action potentials (Figure 4). In addition, rapid impulse initiation from MDPs of -58 to -60 mV was recorded (Figure 6). If this rapid activity were encountered in a subendocardial Purkinje fiber at 24 hours after ligation, it would probably be classified as "abnormal" or "low-potential automaticity." This classification would be based on extensive studies of responses to overdrive stimulation, temperature, and drugs.

However, in the majority of the epicardial ventricular muscle preparations from 24-hour infarct zones, no automaticity occurred. Furthermore, sustained triggered activity from MDPs of about -60 mV did occur (Figure 5). Therefore, whether the rapid impulse initiation depicted in Figure 6 reflects low-potential automaticity or "continuous triggered activity" is uncertain. We can only conclude that this continuous rhythmic activity, whether it is triggered or automatic, may be a cause of significant arrhythmias. It would be of interest to study this activity further; this may be difficult, however, because it appears to occur only occasionally in the experimental model.

**FIGURE 7.** Activation sequence map of ventricular beat in isolated blood-perfused canine heart 24 hours after coronary ligation. Sketch at upper left shows activation of Purkinje fibers on left ventricular endocardial surface; anterior papillary muscle shown at left of sketch, septal surface at right. At lower left, left ventricular subendocardial muscle activation sequence is shown in similar sketch. Epicardial activation sequence (anterior view) of heart shown by sketch at upper right. Border of anteroseptal infarct indicated by dashed line in each sketch. Trace of atrioventricular electrogram configuration of these beats shown center right; zero reference time indicated by arrow, 100-msec calibration bar below. Activation time "zone" codes are shown by arrow below electrogram. Note site of earliest activation occurred on epicardial surface of infarct; activation spread concentrically from there. Earliest endocardial activation about 10 msec after epicardial breakthrough. (For further discussion, see text.)
It is well established that DADs can occur in isolated papillary muscles.\textsuperscript{28,33–36} It is also well established that DAD amplitude can be increased by \( \beta \)-adrenergic agonists and that if the DAD amplitude becomes large enough, triggered activity will result.\textsuperscript{12,37–39} Because catecholamine levels in the plasma are elevated after myocardial infarction,\textsuperscript{40,41} it is quite likely that the phenomena reported here could contribute to arrhythmias in the 24-hour infarcted heart. In view of the lack of effect of flecainide (1 and 5 mg/l) on the rate of some of this activity (Figure 6), it is possible that these mechanisms could be responsible for drug-resistant tachycardias.

The ionic mechanisms responsible for triggering or automaticity in these infarct zone subepicardial cells probably are not simple. Transient inward current (\( I_{\text{Na}} \)) occurs in ventricular muscle;\textsuperscript{42} this current can produce triggered activity. Recently, "repetitive action potential discharge" in enzymatically isolated guinea pig ventricular myocytes treated with isoproterenol 0.1 \( \mu \text{M} \) has been reported.\textsuperscript{43} This triggered activity was attributed to a cyclic adenosine monophosphate (cAMP)-dependent inward sodium current, which could be increased by \( \beta \)-receptor stimulation or forskolin.\textsuperscript{43} Egan et al\textsuperscript{43} used a variety of blockers and superfuse compositions to study this catecholamine-induced sodium current (\( I_{\text{Na}}, \)). The results suggested that \( I_{\text{Na}}, \) "is generated by mechanisms distinct from the well-documented effects of catecholamines on \( I_{\text{f}}, I_{\text{Ca}}, I_{\text{K}} \) and the \( \text{Na}^+/\text{K}^+ \) pump," as well as \( I_{\text{i}}, \).\textsuperscript{43}

Thus, it is possible that enhanced \( I_{\text{Na}}, I_{\text{Na}}, I_{\text{Ca}}, \) and \( I_{\text{K}} \) could contribute to impulse initiation in catecholamine-treated 24-hour infarct zone myocardial tissues. Recent studies by Escande et al\textsuperscript{44} suggest that more than one current contributes to diastolic depolarization in low-potential automaticity. They found that this automaticity is "modulated by sarcoplasmic reticulum--dependent processes" and suggested that "mechanisms similar to those generating DADs would also contribute to abnormal pacemaker depolarization." "Evoked oscillations" of \( [\text{Ca}^{2+}]_i \) could lead to DADs, whereas nonoscillatory (abnormal) prolongation of the \( [\text{Ca}^{2+}]_i \) transient would lead to low-potential automaticity.\textsuperscript{44} Thus, slight changes in current intensities may induce impulse initiation or shift its characteristics from triggered activity to low-potential automaticity.

It is well known that catecholamine-dependent responses can develop tachyphylaxis.\textsuperscript{43,45} This is usually explained by receptor desensitization. This desensitization probably does not result from depletion of intracellular adenosine triphosphate or cAMP,\textsuperscript{42} but it may result from phosphorylation of an internal site on the receptor that is exposed during activation.\textsuperscript{45} This mechanism can explain much of tachyphylaxis that occurred in our studies. However, it is also possible that "calcium over-
"load" was involved here. In at least one case (Figure 5), the preparations seemed to go into “contracture” and depolarize before the loss of responsiveness to isoproterenol. This may reflect local “isoproterenol toxicity.”

In earlier studies, we found that in most preparations of Purkinje fibers from 24-hour infarct zones, abnormal or low-potential automaticity occurs from MDPs of about −55 mV. Triggered activity also can occur in these 24-hour infarct zone preparations, but this tends to occur after the Purkinje fibers begin to recover in vitro and achieve MDPs of about −75 mV.17,46 The present experiments suggest that the type of impulse initiation that can occur in 24-hour infarct zone subepicardial muscle also is determined by $E_m$. Automaticity only occurred in these preparations when the muscle cells had low MDPs (−64 ± 6 mV). In contrast to our results with 24-hour Purkinje fibers,17,46,47 recovery during the first 3 hours of superfusion was not prominent in our 24-hour epicardial border zone preparations. This is in agreement with the results of another recent study on 24-hour epicardial border zone cells. This study reported that during 7 hours of superfusion, only small and very gradual hyperpolarization, averaging 2 mV/hr, occurred from control values of −70 ± 11 mV.48 In most of the present epicardial border zone preparations, resting potentials were from −75 to −85 mV. In these preparations, no DADs or triggered activity occurred during the control period. Triggered activity and/or DADs only occurred in these cells after treatment with β-adrenergic agonists. The appearance and disappearance of these triggered phenomena were not associated with changes in diastolic potential.

In summary, previous results2-7,23 suggest that the endocardial surface of the infarct is the primary site of origin of the multifocal ventricular arrhythmias that occur in the canine heart 24 hours after coronary ligation. However, some ectopic activity in the 24-hour infarcted heart may originate in ventricular muscle cells bordering the infarct zone. In our hands, significant mortality occurs between 8 and 18 hours after ligation in the "Harris 2-stage" infarction model. During most of this time period, the Purkinje fibers are quite normal and do not generate ectopic impulses.26 From 20 hours on, when the ectopic activity is caused mainly by Purkinje fiber activity, few arrhythmic deaths occur. This suggests that the arrhythmias caused by ventricular muscle activity at 8–18 hours are more malignant than those caused at 20–36 hours by Purkinje fiber automaticity. Therefore, it may be important to begin to study these early delayed-phase arrhythmias in some detail because they have received relatively little attention. Also, the effects of antiarrhythmic drugs on automaticity and triggered activity in infarct zone ventricular muscle may be more relevant than are drug effects on infarct zone Purkinje fibers. However, because the
lateral and epicardial border zones of 8–18-hour infarcts may be many cell layers below the surface of the ventricle, the “arrhythmogenic” cells in preparations from these infarcts may not be easily accessible to microelectrode techniques. After 24 hours, when the necrotic zone has expanded and is closer to the epicardium, study of the cellular electrophysiology of the arrhythmogenic muscle tissue in vitro may be more feasible. Thus, preparations such as those studied here may provide a convenient model of the malignant arrhythmic activity that occurs in the earlier infarcts.

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