Survival of Subendocardial Purkinje Fibers after Extensive Myocardial Infarction in Dogs

IN VITRO AND IN VIVO CORRELATIONS

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ABSTRACT
Alterations in cardiac electrophysiology that accompany myocardial infarction were studied in dogs subjected to a two-stage ligation of the anterior descending coronary artery. A multipolar transmural needle electrode was used to record electrical activity from the in situ infarcted heart 24 hours after coronary occlusion. Bipolar electrogams recorded from subendocardial regions of infarcted myocardium demonstrated the persistence of early, rapid deflections suggesting Purkinje fiber activity, evidence of ventricular muscle activity in the infarct was absent in both subendocardial and intramural electrogams. The infarcted myocardium and the adjacent non-infarcted tissue were then excised and studied with intracellular microelectrodes in vitro. Transmembrane action potentials could be recorded from one or two cell layers of subendocardial Purkinje fibers at all sites within the infarcted region, but no ventricular muscle action potentials were found. Subendocardial Purkinje fibers which survived in the infarct had reduced maximum diastolic potentials, action potential amplitudes, and maximum depolarization velocities compared with normal subendocardial Purkinje fibers; also, action potential durations in these surviving fibers were extraordinarily prolonged. Spontaneous diastolic depolarization was evident in some surviving fibers. Since subendocardial Purkinje fibers that generate abnormal action potentials survive in an infarct, these fibers may participate in the genesis of ventricular arrhythmias that accompany infarction.

KEY WORDS coronary occlusion cardiac arrhythmias microelectrode bipolar electrogams transmembrane action potentials

Ventricular arrhythmias appearing after myocardial infarction may be due to an alteration in the electrophysiological properties of cardiac fibers in the area of the heart deprived of its normal blood supply. The elucidation of such alterations on a cellular level might enhance our understanding of these arrhythmias. Such an undertaking is technically difficult in the in situ heart. Therefore, we have undertaken studies designed to elucidate the cellular electrophysiological characteristics of isolated, superfused infarcted myocardium and to correlate these results with investigations performed on the in situ heart. This investigation is a new approach to the study of the electrophysiological events accompanying myocardial infarction.

Recent clinical studies (1-4) using mobile coronary care units and constant-monitoring techniques have indicated that the ventricular arrhythmias which accompany acute myocardial infarction commonly begin within 1 hour of the onset of symptoms and may persist for several days thereafter. In the dog subjected to experimental coronary artery occlusion by the technique described by Harris (5), ventricular arrhythmias occur in a similar pattern; there is sometimes an early, transient arrhythmic phase within the first hour following coronary artery ligation, and there is always a delayed arrhythmic phase that reaches its peak 16-24 hours later. The results of this study are confined to the electrophysiological properties of subendocardial cardiac fibers in the infarcted region during this late arrhythmic phase.
Methods

Electrophysiological studies were performed on both in situ infarcted myocardium and excised, superfused infarcted myocardium. In addition, isolated preparations from dogs without infarction were also studied.

Surgical Production of Myocardial Infarction.—Nine mongrel dogs, (10–14 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv), intubated with a cuffed endotracheal tube, and ventilated by a positive-pressure mechanical pump. A lead II electrocardiogram was continuously monitored and recorded on a switched-beam oscillographic recorder (Electronics for Medicine). Using sterile technique, the chest was opened through the fourth left intercostal space and the pericardium was reflected widely. The anterior descending branch of the left coronary artery was isolated from the accompanying vein 10–15 mm distal to its point of origin, and a two-stage ligation was performed according to the technique previously described by Harris (5). The chest was then closed in layers and an airtight seal was maintained.

All dogs subjected to this surgical procedure developed extensive infarction of the anterior left ventricular wall, left anterior papillary muscle, and anterior interventricular septum, as verified by subsequent histological study. Two of the dogs died within the first 12 hours after the coronary artery ligation. The remaining seven dogs developed ventricular arrhythmias consisting of single or multiple ventricular premature depolarizations or ventricular tachycardia by 20–24 hours after the surgical procedure. At this time, the dogs were reanesthetized with sodium pentobarbital (15 mg/kg, iv), and the chest was opened through the initial incision. Artificial ventilation was again maintained.

Electrophysiological Studies In Vivo.—In three dogs electrical activity of the infarcted myocardium was studied in situ. Initially, the epicardial surface of the anterior left ventricle was explored with a unipolar silver electrode, 1 mm in diameter, for electrophysiological localization of the infarcted region. In all studies, recordings from the epicardium overlying the anterior papillary muscle, the paraseptal free wall, and the interpapillary free wall demonstrated a QRS morphology without evidence of R waves. A drawing was then made of the epicardial surface of the heart, and six to ten sites within the infarcted region were explored with a transmural plunge electrode to record intramural and subendocardial activity. The location of these recording sites was indicated on the drawing in relation to anatomical landmarks, i.e., branches of the coronary arterial tree. The transmural electrode consisted of a 23-gauge needle containing 15 recording terminals located 1 mm apart along the length of the shaft. Each recording terminal was 0.1 mm in diameter. The leads from each terminal were connected to a switch box that enabled selection of any single recording terminal for unipolar recordings or any pair of contiguous terminals for bipolar recordings.

Both unipolar and bipolar recordings and a lead II electrocardiogram were monitored on a dual-beam oscilloscope (Tektronix 502) (input resistance = 1 meg-ohm, frequency response = d-c to 350 kc) and on a switched-beam oscillographic recorder (Electronics for Medicine). For bipolar electrograms the polarity was such that a downward (negative) deflection occurred when excitation spread from endocardium to epicardium. All data were recorded and stored on magnetic tape.

After termination of studies on the in situ heart, the locations of the intramural recording terminals were determined. The depth to which the transmural electrode could be inserted through the ventricular wall was limited by a sleeve around the shaft just above the most proximal recording terminal. After insertion of the electrode up to this sleeve, this proximal terminal was located in the epicardium. By determining the thickness of the ventricular wall at the recording sites, the intramural location of recording electrodes distal to the sleeve and the location of electrode terminals in the ventricular cavity were verified. All hearts were approximately the same size, and electrode terminals 12–15 were always located within the left ventricular cavity. The anatomical location of the transmural recording site was determined by observing the microscopic puncture marks on the endocardial surface through a dissection scope at a magnification of 20x during in vitro study of the endocardial surface. The location of these puncture marks was correlated with the epicardial map of the recording sites. Transmural recording sites were mainly confined to the anterior papillary muscle and the paraseptal free wall.

Electrophysiological Studies In Vitro.—After completion of these in situ studies, the hearts were rapidly removed and placed in cool, oxygenated Tyrode's solution with the following millimolar composition: NaCl 137, NaHCO _3_ 12, dextrose 5.5, NaH_2PO_4_ 1.8, MgCl_2_ 0.5, CaCl_2_ 2.8, and KCl 4.0. In addition, the hearts of the remaining four dogs with surgically induced myocardial infarctions that were not studied in situ were excised for in vitro study; six noninfarcted hearts from dogs which had not undergone prior surgery, were also excised for in vitro study. All hearts, infarcted and noninfarcted, were dissected in the oxygenated Tyrode's solution. A cut was made through the interpapillary free wall of the left ventricle, beginning at the atrioventricular groove and extending down to the apex of the heart. This cut was continued posteriorly up the middle of the interventricular septum between the origins of the anterior and posterior divisions of the left bundle branch and stopped at the aortic root. Another cut parallel and immediately distal to the anterior portion of the mitral annulus extending from the interpapillary free wall to the cut through the aortic root was then made. This procedure yielded a block of tissue that included the anterior papillary muscle, the left ventricular apex and portions of adjacent interpapillary free wall, the paraseptal free wall, and the interventricular septum. Also included was the anterior division of the left bundle branch which courses as a free-running false tendon from the septum to the tip of the papillary muscle (Fig. 1).

The epicardial one-third of the ventricular wall was then removed to facilitate the mounting of this tissue block in the superfusion chamber. During removal of
FIGURE 1
Isolated preparation of infarcted myocardium and bordering noninfarcted regions removed from the heart 24 hours after coronary occlusion. Photograph was taken immediately after completing the dissection of the freshly excised heart and before beginning in vitro superfusion; the endocardial surface is shown. VS = interventricular septum, PS = paraseptal free wall, IP = interpapillary free wall, PM = anterior papillary muscle, VA = left ventricular apex, AD = anterior division of left bundle branch, and FT = free-running false tendon. Note that the infarcted region consisting approximately of the apical two-thirds of the papillary muscle, paraseptal free wall, and ventricular septum appears pale and the noninfarcted tip of the papillary muscle and basal paraseptal free wall and ventricular septum are darker.

The isolated myocardium was stimulated through Teflon-coated bipolar silver-wire electrodes placed on the free-running false tendon at a point slightly distal to its emergence from the left bundle branch. Stimuli were rectangular pulses, 3-5 msec in duration and twice threshold voltage, and were generated by a pulse generator (Tektronix 160A). The stimuli were suitably isolated from ground. Initially, preparations isolated from infarcted hearts could not be stimulated at a regular rate due to the presence of rapid spontaneous activity. This activity occurred within several minutes after mounting in the tissue bath and persisted for 40-60 minutes before subsiding (6). After such rapid activity disappeared, the preparation was stimulated at a cycle length of 800 msec during electrophysiological measurements. In contrast, rapid spontaneous activity never occurred in noninfarcted preparations for more than several minutes after mounting in the tissue bath, allowing such preparations to be stimulated at a cycle length of 800 msec almost immediately after superfusion was begun.

Transmembrane action potentials were recorded through glass capillary microelectrodes filled with 3M KCl with tip resistances of 10-20 megohms. The microelectrodes had tip potentials of approximately 5 mv or less, which undoubtedly resulted in some error in recording absolute potential values. The microelectrodes were coupled with a silver-silver chloride wire to a high input impedance amplifier with capacitance neutralization (type NF1, Bioelectric Instruments, Inc.). The output of this amplifier was displayed on an oscilloscope (Tektronix 565) and photographed with an oscillographic camera (Grass C4). Extracellular electrograms were recorded through bipolar silver-wire electrodes and a suitable d-c amplifier and were simultaneously displayed on the oscilloscope. The maximal rate of depolarization ($V_{\text{max}}$) of all transmembrane action potentials was determined by electronic differentiation as previously described by Bigger et al. (7). The depth of the fluid over the preparation was maintained at a minimal level to minimize unwanted capacitance in the recording system. However, due to the topography of the preparation, fluid depth was greater over some areas than it was over others and ranged from 1-4 mm. Therefore, capacitance neutralization of the amplifier was monitored on each sweep of the oscilloscope by differentiation of a linear saw-toothed pulse 100 mv in amplitude with a known slope closely to the excised preparation, although occasionally infarcted myocardium on the anterior left ventricular free wall was not included in the preparation for convenience in mounting. In most of these preparations the basal septum and the portion of the papillary muscle above the insertion of the false tendon were not infarcted. We will refer to such noninfarcted regions as control areas to distinguish them from the noninfarcted tissue in preparations isolated from noninfarcted hearts, which we will refer to as normal. The border between infarcted and noninfarcted myocardium was distinct and visually recognizable (Fig. 1). Visual identification of the location of the infarct corresponded well with the results of subsequent histological studies.

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of rise along with the action potential upstroke. The saw-toothed pulse was injected into the tissue chamber through the 3M KCl-filled indifferent electrode. Capacitance neutralization of the amplifier was adjusted when necessary to provide a differentiated signal of this saw-toothed pulse which resembled, as nearly as possible, a square-wave pulse. By avoiding peaks on the rise of this square-wave pulse overcompensation was prevented. However, the possibility of some undercompensation was still present.

In all experiments, after an initial 60-minute equilibration period, transmembrane action potential characteristics of subendocardial fibers were documented by recording action potentials at 5-15-mm intervals over the entire endocardial surface of the preparation. In preliminary studies we verified that the transmembrane action potential characteristics were stable after this period of equilibration. Data were collected equally from all regions of the preparation. At each site, action potentials were recorded from the most superficial subendocardial fiber, i.e., the first transmembrane action potential recorded as the microelectrode was advanced downward through the endocardium by the micrometer drive of the micromanipulator, and then they were recorded from the underlying fibers. Action potentials could be recorded as deep as 15-20 fibers beneath the endocardial surface in noninfarcted myocardium without damaging the microelectrode. The number of subendocardial fibers from which records could be obtained at each site was determined by advancing the microelectrode through the subendocardium in steps of 1μm or less. After an action potential was recorded, the electrode was advanced downward until the potential returned to zero, and then it was advanced into the next fiber as indicated by the reappearance of a transmembrane action potential. A previous study (8) in other tissue (diaphragm muscle) has shown that the number of action potentials recorded in this fashion accorded reasonably well with the number of cell layers that can be detected by histological examination. Therefore, to simplify description of our results, the number of fibers from which we recorded action potentials during the downward advancement of the microelectrode at any endocardial site will be referred to as the number of cell layers, although we realize that the correlation between the number of action potentials at a given site and the number of anatomical cell layers is not exact. This procedure will aid in explicit differentiation of downward microelectrode movement from lateral microelectrode movement from one recording site on the endocardial surface to another. At each recording site, maximum diastolic potential, total action potential amplitude, Vmax, and time for 50% and 100% repolarization were measured for each fiber and plotted on a detailed drawing of the endocardial surface of the preparation. Thus, a profile of the characteristics of the subendocardial fibers was established. Mean values for each parameter in both infarcted regions and control regions of infarcted preparations were compared with mean values of these parameters in normal, noninfarcted preparations. For statistical analysis of these data, either Student's t-test or a modified t-test for populations with unequal variance as previously described by Cochran and Cox (9) was used.

Electrophysiological-Histological Correlations.—After electrophysiological investigation, the histology of each preparation was studied to verify the extent of infarction and to correlate the anatomical location of the infarct and the extent of tissue damage with the results of the electrophysiological study. At the conclusion of in vitro electrophysiological study, the entire isolated preparation was fixed in 10% neutral-buffered formaldehyde. After fixation the tissue was divided into blocks and embedded in paraffin by standard techniques. Each block contained a known region, i.e., anterior papillary muscle, basal anterior septum, etc. Step sections were cut at 6μ thickness perpendicular to the endocardial surface so that each section showed the full thickness of the preparation from the endocardium to the dissected epicardial surface of the ventricular wall. Selected sections of regions from which electrophysiological data had been collected were stained with hematoxylin-phloxine-safranin (HPS). In addition the hematoxylin-basic fuchsin-picric acid method was used to differentiate ischemic from nonischemic cardiac fibers. This method is described in detail by Lie et al. (10).

Results

ELECTRICAL ACTIVITY IN INFARCTED REGIONS IN SITU

The anterior left ventricular wall was visibly infarcted 20-24 hours after ligation of the left anterior descending coronary artery. It appeared pale in color and was delineated from the red, noninfarcted myocardium by a distinct border. The pale region corresponded to the area demonstrating a QS morphology in epicardial unipolar electrograms. This infarcted region and the bordering noninfarcted area were studied with the transmural electrode.

Unipolar recordings at all intramural sites in regions bordering the infarct demonstrated QRS configurations. In contrast, unipolar recordings at most sites of intramural electrode placement within the infarcted region did not demonstrate local electrical activity. Recordings were obtained from the left ventricular cavity and then sequentially from terminals along the shaft of the electrode which were located intramurally. Intramural unipolar complexes in the infarct had a QS form with smooth limbs (no notching). The initiation and the peak of such complexes were synchronous with corresponding parts of the cavity complex. Unipolar complexes recorded from the epicardial surface demonstrated small R waves indicative of some viable epicardial muscle fibers.

The transmural electrode was also used to obtain bipolar electrograms from both the infarcted and the bordering noninfarcted regions (Fig. 2). Again,
recordings were first obtained from electrode pairs in the left ventricular cavity and then from sequential pairs of electrodes in subendocardial and intramural regions. In noninfarcted areas, recordings obtained from the left ventricular cavity demonstrated a small negative deflection (100–200 μV) that was coincident with the QRS complex of the electrocardiogram (Fig. 2, section 1). Subendocardial and intramural bipolar recordings at all sites in noninfarcted regions were characterized by a large-amplitude (10–30 mv) rapid deflection indicating local activity (Fig. 2, section 1). At some subendocardial sites, this large-amplitude deflection was preceded by an earlier rapid deflection of low voltage signifying Purkinje fiber activity.

In the infarcted region bipolar recordings failed to demonstrate intramural electrical activity. At these sites bipolar recordings from the ventricular cavity again showed a low-voltage negative deflection coincident with the QRS complex (Fig. 2, sections 2 and 3). Bipolar recordings from subendocardial and intramural sites showed similar characteristics: broad, low-voltage (less than 1 mv) smooth complexes lasting the duration of the QRS complex of the surface electrocardiogram (ECG) (Fig. 2, sections 2 and 3). The rapid large-amplitude deflections seen in noninfarcted areas were not evident. However, in some subendocardial regions of the infarct the slow, low-voltage subendocardial deflection was preceded by a rapid deflection 200–600 μv in amplitude. During ventricular activation by impulses of sinus origin, the rapid deflections occurred 10–15 msec before the QRS complex of the surface ECG. During ectopic ventricular rhythms, this subendocardial deflection often occurred as early as 30–50 msec prior to the QRS complex. In some instances during ectopic

**FIGURE 2**

Bipolar recordings from infarcted and noninfarcted myocardium in the in situ heart 24 hours after coronary artery ligation. The extensive left ventricular infarct is depicted as the unshaded area adjacent to the anterior descending coronary artery. Noninfarcted regions are shaded. In each section on the right, the top trace is a lead II electrocardiogram (ECG). The second trace (C) shows the potential recorded within the left ventricular cavity with bipolar electrodes; the third and fourth traces are subendocardial (SE) and intramural (IM) bipolar electrograms recorded from the designated areas. Calibrations at the right apply only to the electrograms and not the ECG. The 5-mv calibration is for section 1 only. The 500-μv calibration is for sections 2 and 3: 1: Recordings from a noninfarcted region of the left ventricle. A low-amplitude wave was recorded from within the left ventricular cavity; this wave occurred simultaneously with the QRS complex of the surface ECG. An early, rapid deflection, 2 msec in duration, signifying Purkinje fiber activation is seen in the subendocardial electrogram and is followed by a deflection of greater amplitude and duration coincident with the QRS complex, denoting activation of ventricular muscle. A large-amplitude deflection, signifying ventricular muscle activity, is seen in the intramural electrogram. 2: Recordings from sites within the infarct for a ventricular premature depolarization: Recordings from sites within the infarct for a sinus beat. Amplification of electrograms in sections 2 and 3 is ten times that shown for noninfarcted area in section 1. Again, a slow wave lasting the duration of the QRS complex of the ECG was recorded within the left ventricular cavity. Similar slow deflections are seen in the subendocardial and intramural recordings. However, in the subendocardial recordings a rapid deflection (2 msec in duration) that signifies subendocardial Purkinje fiber activity is seen prior to the slow deflection. The late low-amplitude positive deflections seen in the intramural electrograms may indicate some residual local activity in these regions.
beats, the interval between the rapid deflection and the beginning of the QRS complex was less than that of sinus beats. These deflections were assumed to result from activity of subendocardial Purkinje fibers that survived the extensive infarction. Such rapid electrical deflections were not found at all subendocardial sites within the infarct. They were evident at 14 of the 32 subendocardial sites studied on the anterior papillary muscle and the paraseptal free wall in the three experiments.

**ELECTRICAL ACTIVITY OF SUBENDOCARDIAL REGIONS OF INFARCTED MYOCARDIUM IN VITRO**

*Survival of Subendocardial Purkinje Fibers.*—Electrical activity in subendocardial areas of the infarcted region was characterized in more detail by recording transmembrane action potentials from these areas during superfusion in vitro. The transmembrane potentials were compared with recordings obtained in the noninfarcted bordering (control) regions and with recordings obtained from preparations isolated from normal, noninfarcted hearts (normal).

At most recording sites in preparations from normal, noninfarcted hearts, as the microelectrode was advanced downward through the subendocardium, transmembrane action potentials identical to those previously described for Purkinje fibers (11) were encountered first. Two to four such action potentials were recorded sequentially as the electrode was advanced deeper through the subendocardium (Fig. 3). Only rarely was an action potential characteristic of ventricular muscle recorded from the most superficial fiber. Subjacent to these subendocardial Purkinje fibers, action potentials with characteristics of ventricular muscle fibers were recorded; at least fifteen such potentials were recorded as the electrode was advanced downward (Fig. 3). No action potentials characteristic of Purkinje fibers were ever recorded at these depths. Further downward advancement of the microelectrode usually resulted in destruction of its tip, thus precluding the impalement of deeper cells. Action potentials characteristic of Purkinje fibers were not found at the extreme tip of the anterior papillary muscle near the origins of the chordae tendineae; here, at all depths, only action potentials characteristic of ventricular muscle were recorded.

In infarcted preparations, the portion of the papillary muscle above the insertion of the false tendon was not involved in the infarct. Invariably, at sites from this region of the papillary muscle, action potentials were recorded from 2-4 subendocardial Purkinje fibers and 15-20 ventricular muscle cells during downward advancement of the electrode. Characteristics of the action potentials were

![Figure 3](image-url)

*Action potentials recorded at several subendocardial sites in isolated superfused preparations.* Each vertical column of action potentials indicates recordings obtained at a single site during downward advancement of the microelectrode through the subendocardium. Numbers at left indicate the sequence in which each action potential was recorded in each column (i.e., 1 indicates the first action potential recorded as the electrode was advanced downward through the endocardial surface, 2 indicates the second action potential recorded, etc.). Left: Recordings obtained at a representative site in a normal, noninfarcted preparation. The first three action potentials recorded were typical of Purkinje fibers (PF). Twelve consecutive action potentials typical of ventricular muscle (VM) were then recorded as the electrode was advanced downward through the subendocardium toward the epicardium. Right: Columns A, B, and C show action potentials recorded at three different representative subendocardial sites in the infarcted region of an infarcted preparation. At sites A and B only one and two action potentials of Purkinje fibers were recorded. No ventricular muscle action potentials were observed on further downward movement of the microelectrode toward the epicardium. At site C three Purkinje fiber action potentials and one potential which resembled a ventricular muscle action potential were recorded during downward advancement of the microelectrode. No other action potentials were recorded when the microelectrode was advanced deeper than the ventricular muscle fiber.
identical to those recorded from comparable regions in normal, noninfarcted preparations.

Compared with normal, noninfarcted preparations and with the control regions of infarcted preparations, at any one site within the infarcted zone the number of cells from which action potentials could be recorded was strikingly diminished. This diminution of electrophysiologically detectable cell layers occurred over an extremely short distance (less than 1 mm) that corresponded to the distinct, grossly apparent border between infarcted and control regions. At most sites within the infarct, action potentials could be recorded from only one or two cell layers of subendocardial Purkinje fibers; no other electrical activity or indication of a transmembrane potential was encountered with further downward advancement of the microelectrode. At these sites no ventricular muscle action potentials were found (Fig. 3). However, the number of cells from which action potentials could be recorded and the types of action potentials found varied at different sites in the infarct. At some sites we found the usual number of subendocardial Purkinje fiber potentials but no ventricular muscle potentials. Rarely, at a few sites, action potentials similar to those of ventricular muscle were recorded from one or two cells beneath the Purkinje fiber layers. At all sites within the infarcted zone, action potentials could be recorded from at least one subendocardial Purkinje fiber; electrical activity at a depth greater than five cell layers beneath the endocardial surface was never encountered (Fig. 3). The depth at any one site within the infarct from which action potentials were recorded remained constant throughout each experiment. No increase in the depth from which activity could be recorded occurred after superfusion with oxygenated Tyrode's solution for as long as 12 hours.

**Action Potential Characteristics of Subendocardial Purkinje Fibers.**—Transmembrane action potentials of subendocardial Purkinje fibers in the infarcted regions differed from those in normal, noninfarcted hearts. Table 1 presents mean values for maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ of the most superficial subendocardial Purkinje fibers (first cell layer) in both the infarcted and the control regions of the seven infarcted preparations and compares them with similar measurements on transmembrane potentials of superficial subendocardial Purkinje fibers in the six normal, noninfarcted preparations. In noninfarcted preparations there was no significant systematic variation in these parameters in different anatomical areas, and therefore mean values for the entire first cell layer of the subendocardial sample are presented. Maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ of surviving subendocardial Purkinje fibers in the infarcted region of infarcted preparations were significantly lower than these parameters in Purkinje fibers of normal preparations when the means of all recorded values were compared. Maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ of subendocardial Purkinje fibers in control regions bordering the infarcted areas were not significantly different from these parameters in preparations from normal, noninfarcted hearts (Table 1).

The reduction of maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ in subendocardial Purkinje fibers of infarcted myocardium was highly variable; these parameters were markedly reduced at some sites and in other regions they were less abnormal. Action potentials of some surviving Purkinje fibers had values for maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ that were within normal limits. However, a noticeable percent of Purkinje fiber action potentials that were sampled in the subendocardium of

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**TABLE 1**

Comparison of Electrophysiological Properties of Purkinje Fibers in Infarcted and Noninfarcted Preparations

|                          | Normal, noninfarcted hearts | Control regions of infarcted preparations | Infarcted regions |
|--------------------------|-----------------------------|------------------------------------------|------------------|
| Maximum diastolic potential (mV) | 87 ± 3.5                   | 86 ± 5.0                                 | 74 ± 9.0         |
| Action potential amplitude (mV) | 123 ± 0.0                  | 121 ± 8.0                               | 104 ± 14         |
| $V_{\text{max}}$ (V/sec)       | 494 ± 147                  | 486 ± 118                               | 246 ± 132        |

All values are means ± SD. N = number of impalements and NS = not significant. P values listed for control regions of infarcted preparations and infarcted regions of infarcted preparations are derived from comparison with normal, noninfarcted preparations.
infarcted regions had values for these parameters much lower than any other such values ever encountered in normal preparations (Figs. 4, 5).

Action potentials of subendocardial Purkinje fibers in some infarcted preparations were more depressed than those in others. Action potentials from the more severely depressed areas had maximum diastolic potentials less than −70 mV, action potential amplitudes less than 90 mV, and $V_{\text{max}}$ less than 100 v/sec. Little or no reversal of potential occurred during depolarization, and the time course of repolarization was slow and prolonged. Spontaneous diastolic depolarization was also noted in some of these severely depressed fibers. This depolarization was most apparent at long stimulus cycle lengths. Spontaneous diastolic depolarization was never observed in less depressed subendocardial Purkinje fibers within the infarcted region or in the control areas under the experimental conditions (Fig. 6).

In addition to the reduction in values for the electrophysiological parameters described above, transmembrane action potentials of subendocardial Purkinje fibers in the infarcted regions demonstrated a marked prolongation in the time course of repolarization. There were significant variations in action potential duration in different regions of both noninfarcted and infarcted preparations. However, the mean action potential duration of all Purkinje fibers sampled measured to both 50% and 100% repolarization was significantly longer for Purkinje fibers in the subendocardial regions of the infarcts. Values for the first cell layer of Purkinje fibers are compared in Table 2. Action potential durations of a large percent of surviving subendocardial Purkinje fibers in the infarct were much longer than any durations ever observed in fibers of noninfarcted preparations (Fig. 7). This increase in action potential duration was due to prolongation of both

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**Figure 4**

Frequency distribution of pooled values for maximum diastolic potential and action potential amplitude of superficial subendocardial Purkinje fibers (first cell layer) in six normal, noninfarcted preparations (solid columns) and in the infarcted regions of seven infarcted preparations (stippled columns). Ordinate is the percent of the total number of fibers impaled having values within the defined intervals indicated on the abscissa. Top: Note that the largest percent of sampled fibers in normal, noninfarcted preparations had maximum diastolic potentials of 80–89 mV. In contrast most of the sampled action potentials from infarcted preparations had maximum diastolic potentials below 80 mV. Bottom: Note that most of the action potentials recorded in normal, noninfarcted preparations had total amplitudes greater than 120 mV; most of the action potentials recorded in infarcted preparations had lower amplitudes.

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**Figure 5**

Frequency distribution of the maximum upstroke velocity ($V_{\text{max}}$) of subendocardial Purkinje fiber action potentials. Pooled results from the same experiments illustrated in Figure 4. Ordinate is the percent of the total number of fibers impaled having values of $V_{\text{max}}$ within the defined intervals indicated on the abscissa. Note that 70% of the action potentials of Purkinje fibers in infarcted regions (stippled columns) had $V_{\text{max}}$ of less than 300 v/sec; these low values were found in only 10% of fibers in noninfarcted preparations (solid columns).
Severe depression of transmembrane potentials of subendocardial Purkinje fibers within an infarct. Action potentials shown were recorded by moving the microelectrode laterally from the noninfarcted tip of the papillary muscle (control) across the border of the infarct represented by the broken line into the infarcted region. The top trace is the transmembrane action potential and is shown with a horizontal line denoting the zero reference potential. The bottom trace for the control data and the middle trace for the infarct data is the differentiated signal of a 100-mv saw-toothed pulse with a 200-v/sec slope of depolarization (square pulse) and the depolarization phase of the action potential. Note that maximum diastolic potential, action potential amplitude, and $V_{m}$ were diminished in the infarct compared with the control area. The middle section in the infarct data shows an action potential recorded from an area in which there was marked depression of these values. The bottom trace for the infarct data shows action potentials from the fiber in the middle section recorded at a slower sweep speed. Spontaneous diastolic depolarization is evident.

In addition, action potentials which resembled those of ventricular muscle, although seldom encountered, also had extremely long durations (400-500 msec). Since the action potentials of these cells were extremely prolonged, it was impossible to be certain that they were not Purkinje fibers (Fig. 8). However, the action potentials were recorded deep in the subendocardium; they were the fifth action potential encountered as the microelectrode was advanced downward. In noninfarcted preparations, Purkinje fiber action potentials were never found deeper than the fourth subendocardial cell.

### TABLE 2

|                      | N  | APD<sub>100</sub> (msec) | P             | APD<sub>50</sub> (msec) | P             |
|----------------------|----|--------------------------|---------------|--------------------------|---------------|
| Normal, noninfarcted | 309| 296 ± 23                 | 0.0001        | 186 ± 29                 | 0.0001        |
| Infarcted regions    | 271| 418 ± 35                 |               | 227 ± 29                 |               |

All values are means ± sd. APD<sub>100</sub> = time to 100% repolarization, APD<sub>50</sub> = time to 50% repolarization, and N = number of impalements.
ELECTROPHYSIOLOGICAL-HISTOLOGICAL CORRELATIONS

Histological studies of the anterior papillary muscle, interpapillary free wall, and anterior septum of infarcted preparations demonstrated homogeneous cellular changes that were characteristic of acute myocardial infarction as previously described by others (12, 13), extending from two-thirds to all the way through the thickness of the preparation. In HPS-stained sections, the sarcoplasm of the muscle fibers was homogeneous and glassy in appearance. Hyaline or coagulation necrosis of the fibers was plainly evident, resulting in a marked increase in eosinophilia of these fibers. There was also a distinct loss of cross-striations and pyknosis or a disappearance of nuclei within the fibers (Fig. 9). Areas of fragmented necrotic fibers were also seen. The interstitium was infiltrated by polymorphonuclear cells and lymphocytes, and
Comparison of action potential duration of subendocardial fibers recorded from similar regions of infarcted and non-infarcted preparations. In each section the top trace is the reference zero potential, the center trace is the transmembrane action potential, and the bottom trace is the differentiated signal of a 100-mv saw-toothed pulse with a 200-v/sec slope of depolarization and the depolarization phase of the action potential. Top Left: Action potential recorded from a subendocardial Purkinje fiber at the base of the anterior papillary muscle in a noninfarcted preparation. Top Middle: Action potential recorded from a subendocardial Purkinje fiber in the same region of an infarcted preparation. Note the typical increase in action potential duration and reduction in maximum diastolic potential, total action potential amplitude, and \( V_{MAX} \). Top Right: Action potential recorded from a subendocardial Purkinje fiber at the base of the anterior papillary muscle in a noninfarcted preparation. Top Middle: Action potential recorded from a subendocardial Purkinje fiber in the same region of an infarcted preparation. Note the typical increase in action potential duration and reduction in maximum diastolic potential, total action potential amplitude, and \( V_{MAX} \). Top Right: Action potential recorded from the infarct (solid line) with the action potential recording from the noninfarcted preparation (broken line) superimposed. Bottom Left: Action potential recorded from a ventricular muscle cell at the base of the anterior papillary muscle in a noninfarcted preparation. Bottom Middle: Action potential recorded from the fifth subendocardial fiber encountered during downward advancement of the microelectrode at the base of the anterior papillary muscle in an infarcted preparation, which may be a record from a ventricular muscle fiber. Bottom Right: The action potentials shown in the bottom left and middle are superimposed. Note the prolonged duration of the action potential recorded from the fiber in the infarct (solid trace) compared with that of the action potential recorded from the noninfarcted preparation (broken line).

Anitschkow cells were present. The infarcted area was clearly demarcated from adjacent normal muscle by the intensity of the phloxine-staining reaction and by the margination of the inflammatory infiltrate at the periphery.

In all preparations, the most superficial subendocardial fibers (one to four cells in depth from the endocardial surface) were intact and did not demonstrate any of the changes characteristic of infarction or necrosis. Myofilbrils, cross-striations, and nuclei were plainly evident in these fibers, which were separated from the underlying necrotic fibers by an expanded extracellular space. This separation may have been due to either edema or the cellular infiltrate (Fig. 9); it could also be an artifact of the sectioning procedure.

This difference between the most superficial subendocardial fibers and the deeper regions was emphasized further in sections stained with the hematoxylin-basic fuchsine-picroic acid stain (Fig. 10). Deep red fuchsine staining occurred in the subendocardium and throughout the ventricular wall, corresponding to companion sections demonstrating necrosis with HPS staining. However, the superficial subendocardial fibers which were not necrotic showed only slight affinity for the basic fuchsine dye and stained a light pink (Fig. 10).

Histological sections from regions where transmural electrode recordings in in situ studies showed only subendocardial electrical activity but no intramural activity demonstrated this pattern of necrotic myocardium subjacent to intact superficial subendocardial fibers. In infarcted preparations that had been studied in vitro, the same histological pattern was evident in step sections of regions in which action potentials could be recorded from only a few subendocardial cells. We could not correlate the exact number of transmembrane potentials recorded at each site with the number of intact fibers, since we did not localize exact microelectrode recording sites.

The border between infarcted and noninfarcted control regions was sharply delineated in histological sections (Fig. 11). The transition from normal to infarcted myocardium occurred over a distance of less than 10\( \mu \). This border corresponded exactly to the border which was observed grossly on the endocardial surface during in vitro study. The occurrence of sites where transmembrane action potentials could be recorded from 15-20 fibers during downward advancement of the microelectrode (control regions) corresponded to regions where histological sections demonstrated normal-appearing tissue throughout the entire thickness of the preparation.

**Discussion**

Ventricular arrhythmias are prevalent 20-24 hours after two-stage coronary artery ligation in the dog by the technique described by Harris (5). At this stage our histological studies demonstrated homoge-
Photomicrograph of the subendocardial region of infarcted myocardium stained with hematoxylin-phloxine-safranin. Histology of the tissue was examined after in situ and in vitro electrophysiological study. The endocardial surface is at the top of the section. Note that the first two cell layers are separated from the remaining myocardium by an expanded extracellular space. The cells in these first layers are normal in appearance. The myofibrils, cross-striations, and nuclei are plainly evident. Beneath the expanded extracellular space, the tissue has a necrotic appearance. The sarcoplasm of the muscle fibers is homogeneous and glassy in appearance, and there is a marked increase in eosinophilia of the fibers. Myofibrils are not seen, and the central nuclei are no longer evident.

Neuronal degenerative changes in at least two-thirds of the thickness of the infarcted ventricular wall. The QS morphology of epicardial and intramural unipolar recordings which we obtained in the infarcted area of the in situ heart verified the extensive nature of the infarct. Our bipolar recordings from the in situ heart did not demonstrate any local electrical activity within the infarcted wall. Previous studies have shown low-amplitude or continuous intramural electrical activity associated with the ventricular arrhythmias that occur within minutes after coronary occlusion (14-16). The slow, low-amplitude, long-duration deflections we found in bipolar recordings from subendocardial and intramural sites were similar to recordings we obtained within the ventricular cavity and therefore may have been due to the cavity potential. Similar broad smooth complexes of low voltage have been described by Durrer et al. (17) in bipolar recordings from the scarred zone that is completely devoid of muscle fibers 4–10 weeks after experimental myocardial infarction. Furthermore, Durrer et al. (17) have demonstrated that bipolar complexes with this morphology do not indicate local electrical activity, since identical complexes can be recorded within a sponge used to replace part of the left ventricular wall. This lack of intramural electrical activity within the infarcted
region suggests that different electrophysiological events are associated with arrhythmias occurring at this late stage of infarction compared with those underlying the arrhythmias observed immediately after occlusion. In the present study electrical activity was found only in bipolar recordings obtained from subendocardial areas of the infarct in the in situ heart. This activity appeared as a rapid deflection, occurring before inscription of the Q wave of the surface ECG. Characteristics of this deflection resemble those previously described for Purkinje fiber activity. During ventricular ectopic beats such regions often depolarized much earlier than the QRS deflection of the surface ECG. Durrer et al. (17) and Daniel et al. (18) have also demonstrated the persistence of subendocardial activity after coronary artery occlusion, but after less extensive myocardial infarction than in the present study.

Since the survival of subendocardial fibers in areas of extensive myocardial infarction may be a factor leading to ventricular arrhythmias 20-24 hours after coronary occlusion, we concluded that a more detailed electrophysiological investigation of the subendocardial region in the infarct was necessary to demonstrate what type of cardiac fibers had survived, i.e., ventricular muscle or Purkinje fibers, since previous investigations have suggested that Purkinje fibers are responsible for many cardiac arrhythmias (19, 20), and to determine whether the electrophysiological characteristics of those surviving fibers had been altered by the pathological process. For this purpose, intracellular microelectrodes for recording transmembrane electrical events in situ should provide invaluable data. Previous microelectrode studies of the in situ heart during coronary occlusion have been confined to analyses of the electrophysiological properties of epicardial ventricular muscle cells (21-23). However, the use of similar techniques to study subendocardial regions is not feasible at present.

We therefore investigated the cellular electrophysiology of this region by excising infarcts and superfusing them in a tissue chamber. We recognize that such a technique is limited in that it does not take into account possible influences of the autonomic nervous system, blood-borne factors, or the role of hypoxia, all of which may have profound effects on the in situ heart (24-29). However, it does define the basic electrophysiological properties of subendocardial fibers that survive in the subendocardium of the infarcted region.

Our microelectrode recordings demonstrated the presence of electrophysiologically viable fibers in the subendocardium of all infarcts. Results obtained by advancement of the electrode vertically through the subendocardium of the infarct indicated that action potential generation was limited for the most part to only one or two layers of subendocardial cells, although occasionally recordings could be obtained from as many as five layers of fibers beneath the endocardial surface. These results suggest that only a narrow rim of fibers several cells thick survived the extensive infarction, as confirmed by our histological observations. Previous pathological investigations in humans and in the rabbit have also demonstrated intact subendocardial fibers after transmural infarction. However, these microscopic studies did not indicate that surviving cells were part of the subendocardial Purkinje network (30-33). Our microelectrode recordings enabled these subendocardial fibers to be identified as fibers of the specialized conducting system by virtue of the characteristics of their transmembrane action potentials. Occasional action potentials that resembled those of ventricular muscle were found, but positive identification could not be made because of the prolonged repolarization phase, which resembled that of Purkinje fibers.

The subendocardial portions of the left ventricle are considered to be particularly prone to the effects of ischemia (30, 31, 34). Therefore, the observation that several subendocardial cell layers survive extensive infarction is somewhat surprising. One possible explanation of this finding is that the subendocardial regions of the left ventricle are adequately nourished by blood within the left ventricular cavity by retrograde perfusion through various ventricular sinusoidal channels (35), by retrograde perfusion through the left atrial venous system (36), or simply by diffusion of oxygen from ventricular cavity blood through the endocardium. With regard to this latter respect, the known ability of the peripheral specialized conducting system to withstand hypoxia (37) and the fact that the Qo2 of Purkinje fibers is less than that of ventricular muscle (38, 39) might further enhance the ability of subendocardial Purkinje fibers to survive. The resolution of this problem requires further investigation.

Although the subendocardial Purkinje fibers survived extensive infarction, their transmembrane action potentials were distinctly different from subendocardial Purkinje fibers in normal, noninfarcted preparations. None of these differences were
reversed by prolonged superfusion with well-oxygenated Tyrode's solution.

We have not determined the factors responsible for the altered transmembrane action potentials of these surviving subendocardial Purkinje fibers. The marked reductions of maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ which we observed in the infarct resemble the changes in these parameters that have been reported for Purkinje fibers subjected to conditions such as hypoxia, excessive stretch, or elevated external potassium concentration (11, 28, 29). However, these factors all cause an abbreviation of action potential duration and, in our studies, even the most depressed action potentials were greatly prolonged in duration. The mechanism underlying this prolongation of action potential duration is obscure. In normal hearts, action potential duration of ventricular muscle cells is considerably shorter than that of the subendocardial Purkinje fibers (11). If electrotonic interactions exist between these two types of cells, ventricular muscle cells would ordinarily have a tendency to hasten the repolarization of adjacent subendocardial Purkinje fibers (40). In an infarct in which no or few ventricular muscle cells survive, such an electrotonic interaction would no longer occur; prolongation of subendocardial Purkinje fiber repolarization might occur on this basis. On the other hand, such an explanation does not account for the reduction of maximum diastolic potential, action potential amplitude, and $V_{\text{max}}$ which we have observed.

The observed abnormalities of action potentials of surviving subendocardial Purkinje fibers might be due to changes in the cell membrane of these fibers resulting from prolonged exposure to a pathological environment in vivo. This situation might alter the ionic currents which flow during the generation of an action potential. Such a possibility requires further investigation.

Although after extensive myocardial infarction subendocardial Purkinje fibers remain structurally intact and generate action potentials characteristically different from those seen in noninfarcted hearts, we do not know the exact relationship, if any, of these findings to the mechanisms underlying the accompanying cardiac arrhythmias in the in situ heart.

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IN VITRO AND IN VIVO CORRELATIONS
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