Protracted Ventricular Tachycardia Induced by Premature Stimulation of the Canine Heart after Coronary Artery Occlusion and Reperfusion

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SUMMARY The effects of premature ventricular stimuli were studied in two groups of dogs with infarcts, one group subjected to permanent occlusion of the left anterior descending coronary artery and the other to temporary occlusion for 2 hours. In dogs with permanent occlusion, spontaneous ventricular arrhythmias occurred after 3-6 hours. In 13 dogs with temporary occlusion, ventricular arrhythmias occurred immediately after reperfusion and then persisted. In five dogs with temporary occlusion, ventricular arrhythmias did not occur spontaneously until 13-15 hours after occlusion. On days 2-8 after surgery, after sinus rhythm had returned, the ventricles of each awake dog were stimulated. After permanent occlusion, premature stimuli occurring on the T wave usually induced from one to 10 repetitive responses on days 2-4. Protracted ventricular tachycardia (lasting >10 seconds) was induced in only two of 10 dogs. The response to premature stimuli was similar after temporary occlusion when ventricular arrhythmias did not occur spontaneously until 13-15 hours after occlusion. Protracted tachycardia was not induced. In the dogs with temporary occlusion, which initially had continuous arrhythmias, premature stimuli occurring on the T wave on days 3-5 after surgery induced both repetitive responses and protracted ventricular tachycardia. Stimuli applied to the ventricles during tachycardia terminated it. Histological studies on all infarcts showed that, after permanent occlusion, necrosis was uniform; after temporary occlusion, viable myocardium survived in the necrotic region. These salvaged myocardial fibers may provide reentrant pathways, causing long-lasting tachycardia. Circ Res 44: 833-846, 1979

NOT all myocardial cells in an ischemic region die immediately and simultaneously after a coronary artery occlusion; rather, cell death continues for at least several hours and possibly more (Reimer et al., 1977). This prolonged survival of myocardium prior to death has led to the suggestion that interventions might be designed which, if performed soon enough after an occlusion, could prevent the eventual death of ischemic cells (Braunwald et al., 1974; Maroko and Braunwald, 1973). This would reduce the size of the infarct and improve the function of the infarcted heart. Both pharmacological and surgical interventions (coronary revascularization) have been used with varying degrees of success in limiting infarct size (Braunwald et al., 1974; Maroko and Braunwald, 1973). In some of these studies, myocardial contractility of the ischemic region has been assessed after the intervention and found to be improved (Puri, 1975; Theroux et al., 1976). However, little attention has been paid to the electrical properties of the salvaged ischemic tissue. Although cell death is prevented, the salvaged ischemic myocardial cells may not be electrically normal and therefore might contribute to electrical instability of the heart.

In the present study we evaluated some of the electrophysiological properties of the canine heart with an area of ischemic and salvaged myocardium. The intervention we used to salvage myocardium that had been made acutely ischemic by a 2-hour period of coronary occlusion was coronary artery reperfusion (Maroko et al., 1972). We found that, in reperfused hearts, long-lasting periods of ventricular tachycardia could be induced by single ventricular premature stimuli for several days after reperfusion, whereas in hearts with permanent occlusion it usually could not. The results suggest that hearts with salvaged ischemic myocardium are abnormal electrophysiologically for at least several days. They also indicate that myocardial infarcts resulting from temporary coronary artery occlusion (which may be caused by coronary artery spasm) may have different electrophysiological properties than infarcts caused by permanent occlusion.
Methods

Surgical Procedures

We studied some electrophysiological properties of the heart in two groups of dogs with myocardial infarcts. Mongrel dogs of either sex weighing 12-17 kg were anesthetized with sodium pentobarbital (30-35 mg/kg, iv), intubated with a cuffed endotracheal tube, and ventilated by a positive pressure Harvard pump. A lead II electrocardiogram (ECG) was monitored continuously on a Grass polygraph (model 7). A left thoracotomy was performed through the 4th intercostal space under sterile conditions. The pericardium was reflected widely, and the left anterior descending coronary artery (LAD) was dissected free from adjoining connective tissues and veins 10-15 mm distal to its point of origin. A double suture (2.0 surgical silk) was passed around the isolated artery just proximal to the main diagonal branch. In 12 dogs the isolated LAD was occluded permanently by the two-stage ligation technique previously described by Harris (1950). This group is referred to as the permanently occluded group. In 23 dogs the LAD was occluded temporarily and then reperfused. In these dogs the occlusion was accomplished in two stages, as described by Harris (1950), but was done by abutting a short piece of polyethylene tubing firmly against the artery rather than by tying the suture. At the end of a 2-hour complete occlusion period the polyethylene tubing and the surgical silk were removed. Gentle massage at the occluded site with a cotton ball facilitated the reopening of the artery and reflow. This group with temporary artery occlusion will be referred to as the reperfused group.

An intravenous bolus injection of lidocaine (5 mg/kg) was administered prophylactically 3 minutes prior to reperfusion in an attempt to decrease the high incidence of ventricular fibrillation that often occurs soon after reperfusion. In a separate study using radioactive microspheres we verified that blood flow to the ischemic myocardium is reestablished when the occluder is released after 2 hours. However, coronary flow during reperfusion is only about 50% of normal (Karaguezian, 1978). These results confirm previous studies reported by Parker et al. (1975) and Willerson et al. (1975). Reperfusion after a 2-hour period of occlusion salvages ischemic myocardium, yet the time of occlusion is long enough also to cause significant infarction (Maroko et al., 1972; Smith et al., 1974; Costantini et al., 1975; Bolooki, 1975).

In all the dogs in the two groups, two pentipolar plaque electrodes (13 by 11 mm) with interelectrode distances of 3 mm were sutured to the epicardial surface of the heart prior to the coronary occlusion, one electrode on the left atrial appendage and the other on the anterior surface of the right ventricle near the outflow tract. The electrodes were used to record bipolar electrograms and to stimulate the heart. The chest then was closed in layers and an airtight seal maintained. During the closure of the chest, two circular silver electrodes with a diameter of 2.5 mm were sutured subcutaneously, one on the dorsal and the other on the ventral aspect of the thorax, to record an ECG from the awake dog. Since the leads from these silver electrodes were connected to the DC input of a vertical amplifier, the recording obtained was a bipolar electrogram from across the chest wall in which atrial and ventricular activation could be identified, thereby enabling the rhythm of the heart to be determined. The leads from all the electrodes were exteriorized together through the skin and connected to a plug sutured in place at the nape of the neck. The dogs then were allowed to recover from surgery.

With the use of needle electrodes, a lead II ECG was recorded continuously from eight dogs in the permanently occluded group for 12-16 hours after coronary occlusion on a Grass polygraph (model 7) at a paper speed of 10 mm/sec. The number of premature ventricular depolarizations and the time of their appearance were analyzed directly from the paper record. In 14 dogs in the reperfused group, continuous electrocardiographic monitoring for 24 hours after surgery was achieved by telemetering the bipolar signal from the subcutaneous electrodes to a Holter tape recorder (Avionics electrocardiocorder, model 400). Subsequent analysis of the 24-hour Holter electrogram was made on a composite electrocardioscanner (Avionics model 650).

Stimulating and Recording Techniques

Two dogs in the permanently occluded group and five dogs in the reperfused group died during the first 24 hours after surgery. All the surviving dogs in both groups developed spontaneous ventricular arrhythmias during the first 24 hours following surgery; these arrhythmias subsided by the 2nd or 3rd day. Beginning on day 2 (48 hours postoperatively) and on each of 7 subsequent days, the dogs were studied in the conscious state while they were standing in a sling. The bipolar subcutaneous leads, one pair of atrial leads, and one pair of ventricular leads were led into the input of the amplifiers of a DR8 Electronics for Medicine Multichannel Oscilloscopic Photographic recorder and to the vertical amplifiers of a dual-beam oscilloscope (Textronix RM 565) to record and monitor the ECG from across the chest wall and the local electrograms. One pair of ventricular electrodes also was connected to a programmable digital stimulator (designed by Dr. Lawrence Eisenberg, The Rockefeller University).

The ventricles of the awake dog were driven at cycle lengths of 400, 350, and 300 msec with isolated rectangular pulses 2 msec in duration and approxi-
Electrophysiological-Histological Correlation

The in situ electrophysiological studies on individual dogs were repeated on days 2–9 (see Results). Following the conclusion of the studies, the dogs were killed and the infarcts processed for histological investigation. In both the permanently occluded and the reperfused groups, the infarct encompassed regions of (1) the anterior papillary muscle, (2) the paraseptal free wall, (3) the interpapillary wall and anterior left ventricular wall, and (4) the interventricular septum. This entire area was dissected free and fixed in 10% neutral buffered formaldehyde. After fixation, the infarcted tissue was divided into four blocks, each extending from the base to the apex of the heart. Each block contained one of the four regions of the anterior left ventricle. The blocks contained the entire infarcted region and were embedded in paraffin by standard techniques. Step sections were cut at 6-μm thickness perpendicular to the endocardial surface so that each section included the full thickness of the infarct from the endocardium to the epicardium. The sections were stained with hematoxylin and eosin or hematoxylin-phloxine-safranin. From four to six stained histological sections from each of the four different blocks were projected from a photographic enlarger at a magnification of 10X onto graph paper. Necrotic areas were outlined on the graph paper from the enlarged projection. The necrotic areas of the enlarged histological sections were identified by their deep acid-staining characteristics, and necrosis was confirmed by subsequent microscopic evaluation. The pattern of myocardial necrosis thereby was determined. The extent of the myocardial necrosis in the left anteroseptal ventricular wall also was quantified. To do this, the areas of necrosis traced on the graph paper were measured and necrosis was calculated as the percent of the total cross-sectional area of each section, as described by Reimer et al. (1977).

Results

Spontaneously Occurring Ventricular Arrhythmias in Hearts with Permanent and Temporary Coronary Artery Occlusion

Permanently Occluded Group

Normal sinus rhythm with occasional ventricular premature contractions persisted for 3–6.5 hours after two-stage ligation of the LAD. The frequency of ventricular premature contractions then increased progressively during the next 10 hours. Frequent periods of ventricular tachycardia were present 24 hours after occlusion. Periods of tachycardia usually began with a ventricular escape which occurred well after the T wave of the preceding beat. The characteristics of this arrhythmia have been described previously in detail (Harris, 1950; Scherlag et al., 1974). Four dogs still had short periods of ventricular tachycardia 2 days after coronary occlusion. The remaining six dogs had sinus rhythm at this time. All dogs were in normal sinus rhythm 3 days after coronary artery occlusion.

Reperfused Group

All dogs developed multiform ventricular premature contractions and short periods of ventricular tachycardia within minutes after release of the coronary artery occlusion. In 13 of the 18 dogs, the frequency of ventricular premature contractions increased with time and, after 8 hours of reperfusion, persistent ventricular tachycardia (98% of the beats being of ventricular origin) was present. Continuous ventricular tachycardia was present for an additional 10–15 hours, and then the frequency of ventricular beats began to decline. By the 2nd day, eight of the dogs were in sinus rhythm and five still had episodes of ventricular tachycardia. By the 3rd day of reperfusion, all dogs were in normal sinus rhythm. In the remaining five dogs, the initial ventricular tachycardia that occurred soon after reper-
fusion subsided within 3 hours, and normal sinus rhythm with occasional ventricular premature contractions ensued for the next 10-12 hours. The frequency of ventricular premature contractions then steadily increased during the next 9 hours until they comprised 40 ± 8% of the rhythm at 24 hours. After 2 days of reperfusion, all the dogs in this subgroup were in normal sinus rhythm. Ventricular tachycardia, which occurred in all dogs in the reperfused group at 24 hours, also began with a ventricular escape that occurred well after the T wave of the preceding beat, and this arrhythmia appeared identical to the tachycardia in the permanently occluded group.

Effects of Ventricular Premature Stimulation on Cardiac Rhythm

Permanently Occluded Group

Five dogs were studied on each of days 2-9 after occlusion, two were studied on each day until day 7, two on each day until day 5, and one dog was studied on day 2 only.

In six of the 10 dogs studied 2 days after coronary artery occlusion (the six dogs in normal sinus rhythm), early premature ventricular stimuli induced single or multiple (from two to 10 beats) nondriven ventricular depolarizations which followed the stimulated ventricular depolarization at short coupling intervals (Fig. 1). The R-R interval of the repetitive depolarizations ranged from 140 to 240 msec (mean of 187 ± 17 msec), and the repetitive activity lasted for 2.5 seconds at most (mean of 1.6 ± 0.1 seconds; from one to 10 impulses), with the exception of two instances of induced repetitive activity in two dogs which are described below. Thereafter, normal sinus rhythm ensued after a pause of 300-800 msec. These six dogs also had induced repetitive activity with identical characteristics on days 3 and 4. By day 5 repetitive activity could not be induced in any of the dogs. Nondriven ventricular depolarizations could not be induced by a single premature ventricular stimulus in the remaining four dogs.

The premature impulses that induced nondriven ventricular depolarizations invariably fell on the T wave of the preceding regularly driven impulse (Fig. 1). In two of the six dogs, repetitive responses were induced over the entire duration of the T wave in which the premature stimulus excited the ventricle (up to the ventricular refractory period). In general, there was an increase in the number of induced, repetitive responses as the premature stimulus occurred at shorter coupling intervals. In the remaining dogs (four of six), closely coupled premature stimuli at intervals 10-40 msec longer than the refractory period of the ventricle did not induce extra depolarizations, although premature stimuli at longer coupling intervals did.

The longest and shortest coupling intervals of stimulated premature impulses that caused nondri-
ven activity (outer and inner boundaries of the zone of repetitive activity) are shown in Figure 2. On days 2 and 3 the total duration of this zone was not significantly different ($P > 0.1$), and the duration was not significantly altered by changing the basic cycle length. However, both the outer and inner boundaries occurred at shorter premature coupling intervals as the basic cycle length was decreased. By day 4 the total duration of the zone of repetitive activity at all basic cycle lengths was significantly decreased from previous days. Decreasing the basic cycle length did not cause the outer and inner boundaries to shift to short coupling intervals. Reduction of the basic cycle length from 350 to 300 msec shortened significantly ($P < 0.01$) the duration of the zone (Fig. 2).

Although in most dogs with permanent occlusion the induced tachycardia lasted only for periods up to 2.5 seconds, in two dogs two instances of induced tachycardia were protracted. In one of these two dogs, on day 2, a premature stimulus falling on the ascending limb of the T wave initiated protracted tachycardia lasting for more than 25 minutes. During the tachycardia, QRS morphology was uniform and the cycle length was constant at 155 msec. The tachycardia was terminated by overdriving the ventricle at a cycle length of 114 msec for 5 seconds. This tachycardia could not be reinitiated on subsequent trials on the same day nor on any of the 7 following days on which this dog was studied. In the second dog, protracted ventricular tachycardia was initiated by a premature stimulus falling on the apex of the T wave. The cycle length of the tachycardia was 140 msec initially, and the QRS morphology was uniform. After 50 seconds the cycle length abruptly decreased from 140 to 120 msec, and fibrillation occurred 5 seconds later. The dog could not be defibrillated. In none of the remaining eight dogs could a protracted tachycardia be induced during the entire 9-day study period, nor did any other dogs fibrillate.

Reperfused Group

We have divided these dogs into two subgroups, one group consisting of the 13 dogs that developed continuous premature ventricular contractions and tachycardia immediately after reperfusion, and the other group consisting of the five dogs that spontaneously developed ventricular tachycardia 12-15 hours after release of the occlusion (see Results on spontaneously occurring arrhythmias).

**Figure 2** Zone of repetitive activity in dogs with permanent LAD occlusion. The coupling intervals of stimulated premature impulses that induced repetitive activity are on the ordinate. The vertical bars indicate the range of coupling intervals of premature impulses that induced repetitive responses at each of three basic drive cycle lengths; 400 msec (stippled bar), 350 msec (striped bar), and 300 msec (solid bar). Repetitive response zones are shown for days 2, 3, and 4 after occlusion. The thick horizontal line below each bar is the effective refractory period of the ventricular muscle under the stimulating electrode at each of the basic cycle lengths.
FIGURE 3 Initiation of protracted ventricular tachycardia in a representative dog on the 3rd day of reperfusion. The ECG is shown in each panel. In panels A–D, the ventricles are being driven at a cycle length of 350 msec, and a single stimulated premature impulse (arrow) is induced in the ventricle. In panel A, the coupling interval of the induced premature impulse is 205 msec. This is followed by a nondriven impulse. Sinus rhythm resumes after a pause of 390 msec. In panel B, the coupling interval of the stimulated premature impulse is 195 msec; this is followed by five nondriven impulses. The QRS morphology and the cycle length of the nondriven impulses are variable. After a pause of 720 msec, sinus rhythm reoccurs. In panel C, the cycle length of the stimulated premature impulse is 190 msec; this is followed by a long period of tachycardia. The cycle lengths of the initial eight beats varied between 175–260 msec. Thereafter, the QRS during tachycardia was uniform and had a stable cycle length (275 msec). The tachycardia lasted for 10 minutes. The lower trace in panel C shows the electrocardiogram 8 minutes after the initiation of the tachycardia. In panel D, a single stimulated premature impulse, induced at a coupling interval of 170 msec is followed by two nondriven impulses. Sinus rhythm occurs after a pause of 760 msec.

The outer boundary of the zone of repetitive responses (longest coupling interval that induced repetitive responses) occurred on the descending limb of the T wave. The inner boundary usually did not extend to the ventricular refractory period, i.e., premature stimuli with coupling intervals shorter than those inducing repetitive responses still elicited a single ventricular response in eight of the 11 dogs. The outer boundary of the induced tachycardia zone (the longest coupled premature impulse that induced protracted tachycardia lasting greater than 10 seconds) and the inner boundary of this tachycardia zone (shortest coupled premature impulse that induced protracted tachycardia) were confined within the repetitive response zone, as shown in Figure 4.

The duration of both the zone of repetitive responses and the induced tachycardia zone was a function of the basic drive cycle length. Both zones shortened significantly ($P < 0.05$) when the basic cycle length was decreased. The outer and inner boundaries of the tachycardia zone also shortened significantly ($P < 0.05$) as basic cycle length decreased, as did the outer boundary of the repetitive response zone. However, the inner boundary of the repetitive response zone did not change significantly as cycle length was decreased from 400 to 350 msec but did decrease significantly ($P < 0.05$) at a basic cycle length of 300 msec.

In all dogs (eight of eight), premature stimuli also induced repetitive ventricular depolarizations and protracted tachycardia on the following (4th) day of reperfusion (Fig. 5). The cycle length of tachycardia remained the same in four dogs and de-
increased in four dogs. The duration of induced tachycardia was not significantly different from day 3 (13.8 ± 3 minutes; P > 0.1). The duration of both the zone of repetitive responses and the induced tachycardia zone on day 4 was significantly shorter at all the basic cycle lengths than on day 3 (P < 0.01), and the outer boundaries shifted significantly (P < 0.05) to shorter values (Fig. 4). The coupling intervals of the inner boundaries of the tachycardia zone also shifted to shorter values, but the coupling intervals of the inner boundaries of the repetitive response zone did not change significantly (P > 0.05). Tachycardia of long duration (15-23 minutes) could be induced in two of six dogs studied on the 5th day, but only when the ventricle was driven at basic cycle lengths of 400 and 350 msec and not at a basic cycle length of 300 msec. These two dogs also had inducible protracted tachycardia on days 3 and 4. Nondriven ventricular depolarizations or tachycardia could not be induced in any of the dogs (five of five) studied on any of the following days (6–9).

The effects of ventricular premature stimulation on cardiac rhythm during normal sinus rhythm also was studied in two dogs. Premature impulses applied to the ventricle during sinus rhythm on days 3 and 4 after reperfusion initiated nondriven repetitive ventricular depolarizations and protracted tachycardia in both dogs, the characteristics of which were the same as for the tachycardia induced while driving the ventricles.

Long periods of ventricular tachycardia could not be induced on any of the study days (days 2–9) in the five dogs in which the onset of spontaneous ventricular tachycardia was delayed for 13–15 hours following reperfusion. Nonstimulated ventricular depolarizations could not be induced on day 2 in any dogs, but on days 3 and 4 from one to eight nonstimulated repetitive ventricular depolarizations followed properly timed premature stimuli on the T wave in three of these five dogs. The short periods of tachycardia lasted 1-2 seconds (mean 1.7 ± 0.3 seconds). This is significantly shorter than the tachycardia of long duration that could be induced in the group of reperfused dogs described above (P < 0.001). It is not significantly different from the duration of repetitive responses induced in the permanently occluded group. Nonstimulated ventricular depolarizations were not induced by premature stimuli in dogs in this subgroup studied on days 5–9.

**Termination of Sustained Ventricular Tachycardia.** Protracted ventricular tachycardia induced by premature stimuli either terminated spontaneously or could be terminated by electrical stimuli applied to the ventricle. When the tachycardia terminated spontaneously the following patterns occurred: (1) abrupt termination with no prior change in cycle length or QRS morphology (33 episodes in eight dogs; Figure 6A), (2) lengthening by 15–45 msec of the last one or two cycles and then termination (31 episodes in three dogs; Figure 6B), and (3) abrupt termination after a spontaneous premature depolarization of the ventricle (nine episodes in two dogs; Figure 6C). In each dog more than one pattern of spontaneous termination of the induced tachycardia was observed.

Premature stimuli were applied to the ventricle
FIGURE 6 Patterns of spontaneous termination of induced ventricular tachycardia in dogs with reperfused infarcts. Records are taken from three different periods of tachycardia in three dogs. In each panel the upper trace is the ECG, and the lower trace is an atrial electrogram. Panel A illustrates abrupt termination of the tachycardia with no prior detectable change in the cycle length of the tachycardia and QRS morphology. Panel B shows spontaneous termination of the tachycardia after lengthening of the last two cycles from 190 to 225 msec. In panel C, a tachycardia with a cycle length of 210 msec terminates abruptly after spontaneous premature depolarization of the ventricle. The premature depolarization of the ventricle that terminated tachycardia may have been caused by a sinus impulse which conducted to the ventricle or may have been a premature impulse of ventricular origin.

during 17 periods of induced tachycardia in five dogs. A single induced early premature ventricular depolarization terminated 14 of these periods of tachycardia abruptly in three dogs (Fig. 7). The premature impulses that did not terminate the tachycardia (those occurring at longer coupling intervals) always were followed by a ventricular depolarization with a fully compensatory cycle length.

Four episodes of tachycardia in two dogs could not be terminated by a single premature depolarization, no matter when it occurred in the cycle. In these instances, two closely coupled (198 ± 4 msec), premature impulses applied early in the cardiac cycle successfully terminated the tachycardia (Fig. 7).

Anatomy of Infarcts Caused by Permanent and Temporary Coronary Artery Occlusion

Infarcts in Dogs with Permanent Coronary Artery Occlusion

In all of the dogs in this group the infarcts were large and uniform in appearance. The infarcts involved the anterior septum, paraseptal wall, anterior papillary muscle, and part of the interpapillary and anterior free wall of the left ventricle, and extended from the midportion of the anterior papillary muscle and ventricular septum to the apex of the heart. The infarcts were transmural in two dogs, extending from endocardium to epicardium. In six dogs they involved only the inner two-thirds of the ventricular wall. The lateral, superior, and inferior margins of the infarct were defined sharply by a distinct, almost linear, margin between necrotic and viable myocardium. On the epicardial margins of these infarcts that were not transmural the separation between necrotic and viable myocardium was less sharply defined. This epicardial margin was
irregular, and occasionally small areas of ischemic myocardium were separated from the main infarct and surrounded by viable tissue. On the endocardial surface from two to four layers of intact myocardial cells, previously identified as subendocardial Purkinje fibers (Friedman et al., 1975), were found (Fig. 8).

The ischemic and necrotic myocardium was homogeneous in appearance. All muscle cells within the borders of the infarct were either necrotic, with

**Figure 8** Photomicrographs of infarcted regions in hearts 3 days (panel A) and 5 days (panel B) after permanent occlusion of the LAD in the dog. In panel A, the infarct extends to the endocardial surface (top of the section). The sarcoplasm of the necrotic muscle fibers is homogeneous and has a glassy appearance. Hyaline or coagulation necrosis of the fibers is evidenced by eosinophilia. There is also distinct loss of cross-striations and nuclei within the fibers as clearly seen at higher magnification in panel C. There is a sharp border zone between infarcted and noninfarcted tissue (filled arrows in panel A). Note that the first one to two cell layers on the endocardial surface in panel A (unfilled arrow) are separated from the remaining myocardium. Deep within the infarct (panel B) the muscle cells are uniformly necrotic. Granulation tissue is interspersed with necrotic areas. The absence of cross-striations and nuclei in the necrotic fibers seen in panels A and B is evident in panel C. The sections were stained with hematoxylin-phloxine-safranin. (Panels A and B are magnified 38×, panel C 375×.)
loss of nuclei and cross-striations (days 2-4), or replaced by proliferating fibroblasts (days 5-9). The mean cross-sectional infarct size was 38.8 ± 2.5% (mean ± SEM) of the anterior ventricular wall and septum.

Infarcts in Dogs with Temporary Coronary Artery Occlusion

The reperfused infarcts were divided into two groups based on the pattern of the early spontaneous arrhythmias described in the Results and on the presence or absence of the induced protracted ventricular tachycardia. The infarcts in the dogs in which long periods of ventricular tachycardia could be induced were large and extended over the same regions of the left ventricle as the infarcts produced by permanent occlusion. Many of the infarcts were hemorrhagic. The mean cross-sectional infarct size was 31.2 ± 6.5% of the left anterior ventricular wall and the septum. This was not significantly different from the permanently occluded infarcts (P > 0.1).

The structure of these reperfused infarcts was different from the structure of infarcts caused by permanent occlusion. The lateral margins as well as the epicardial margin were extremely irregular. Areas of viable myocardium at these margins were surrounded by ischemic and necrotic myocardium, and infarcted areas were surrounded by viable myocardium. It was impossible to define accurately the exact borders of the infarct, although areas of ischemic and necrotic myocardium extended from the endocardium to the epicardium in one-third of all specimens. On the endocardial surface, from two to four layers of subendocardial Purkinje fibers always were clearly separated from the underlying ventricular wall by a clear space, presumably composed of edematous ground substance of the subendocardium. Beneath the endocardial Purkinje cells was an irregular zone of viable myocardium measuring from five to 15 cell layers in depth (Fig. 9). Unlike infarcts caused by permanent coronary artery occlusion, in which tissue necrosis was homogeneous throughout the infarct, in infarcts caused by temporary occlusion regions of viable myocardium were found throughout the infarct. These regions of viable myocardium either appeared completely surrounded by ischemic and necrotic myocardium or were continuous with viable myocardium bordering the infarct. In the early infarcts (2-4 days), normal-appearing cells with distinct nuclei and cross-striations (viable cells) were adjacent to cells that were without nuclei or cross-striations and with deeply staining cytoplasm (ischemic and drying cells). Inflammatory cells were prominent. In the older infarcts (5-9 days), necrotic muscle cells, fibroblasts, and capillary proliferation were prominent. The viable myocardium within the infarcted region was distinguished by intact nuclei and distinct cross-striations.

The reperfused infarcts in dogs in which protracted ventricular tachycardia could not be induced were small and confined to the endocardial one-third of the ventricular wall. They were in the same region of the ventricle as the larger infarcts. Histologically, the areas of infarction in the small reperfused infarcts were identical to the infarcted myocardium in the large reperfused infarcts. The mean cross-sectional infarct size in this subgroup was 10.6 ± 2.2% of the left anterior ventricular wall and septum. This was significantly smaller than the infarcts in both the permanently occluded group (P < 0.001) and the reperfused subgroup in which protracted ventricular tachycardia was induced (P < 0.01).

Discussion

Arrhythmias after Reperfusion

Early revascularization after a coronary artery occlusion might be beneficial to some patients (Ross, 1974). Such revascularization may cause a reduction in infarct size and an improvement in contractility of at least some of the ischemic myocardium after reperfusion (Braunwald et al., 1974; Maroko and Braunwald, 1973; Puri, 1975; Theroux et al., 1976; Maroko et al., 1972; Smith et al., 1974; Costantini et al., 1975; Boloohk, 1975). In addition to a return of contractility, it is important that the salvaged ischemic myocardium not be electrically abnormal, because abnormalities in electrical activity can result in cardiac arrhythmias. Abnormalities in electrical activity that cause arrhythmias have been shown to occur soon after a period of coronary occlusion followed by reperfusion (Tennant and Wiggers, 1935; Battle et al., 1974; Levites et al., 1975; Bigger et al., 1977). In our study these reperfusion arrhythmias in the dogs that developed extensive infarction were continuous and merged with the delayed arrhythmic phase that is present 1 day after coronary occlusion (Mathur et al., 1975). In dogs that developed smaller infarcts, the reperfusion arrhythmias subsided within several hours. The possible mechanisms for these early reperfusion arrhythmias have been discussed elsewhere (Tennant and Wiggers, 1935; Battle et al., 1974; Levites et al., 1975; Bigger et al., 1975). Our data also show that abnormal electrophysiology of some reperfused hearts persists for at least 3-5 days after coronary occlusion. Premature stimulation of the ventricles of reperfused hearts with extensive infarcts consistently evoked long periods of ventricular tachycardia on days 3-5 after reperfusion was begun. Such long periods of tachycardia usually could not be induced after permanent coronary occlusion, although premature stimuli did induce tachycardia lasting up to 10 impulses. El-Sherif et al. (1977a, 1977b) have previously shown that repetitive ventricular activity can be induced in open-chest anesthetized dogs by either rapid ventricular stimulation or by premature stimuli 3-7 days after permanent LAD occlusion. They did not specify the exact duration of the tachycardia once induced.
Their acute studies did not permit them to define the number of days during which repetitive activity could be induced in each animal. Also, Wolff et al. (1968) have induced ventricular tachycardia after the spontaneous phase of arrhythmias subsided in dogs with permanent coronary artery occlusions by applying “low energy” shocks across the heart (transthoracically). This situation is quite unlike the tachycardia initiated by a premature impulse arising in a circumscribed region of the heart.

In our studies we investigated only the effects of single ventricular premature stimuli applied to a noninfarcted region of the heart. We do not know whether the differences in response to stimulation between hearts with permanent occlusion and some hearts with temporary occlusion would occur if
other procedures were used in an attempt to induce tachycardia, such as rapid driving of the ventricle or inducing the premature stimulus within the infarcted area. Kaplinsky et al. (1972) have shown previously that stimulation of the ventricles of anesthetized dogs 5 days after permanent LAD occlusion, at rates of 300–500 beats/min can induce sustained ventricular tachycardia.

**Effects of Reperfusion on Infarct Size and Morphology**

We assume that the arrhythmias that we induced with premature stimuli arise from myocardium within or immediately adjacent to the infarct, although further studies using direct recordings from the heart are necessary to prove this. However, if our assumption is correct, the ability to induce with a premature stimulus long periods of tachycardia in reperfused hearts that developed extensive infarction may have resulted from the effects of the reperfusion on the infarct structure or the electrophysiology of the ischemic myocardial cells that were salvaged by reperfusion. (We use the term "salvage" to mean that cells survived after reperfusion that would have died if the coronary artery had remained occluded.) The percent of the left anteroseptal ventricular wall that was infarcted in these hearts was not significantly less than the extent of the infarcts caused by permanent occlusion. Nevertheless, the presence of large regions of intact myocardium throughout the infarcted area, which we did not find after permanent occlusion, suggests that reperfusion did occur and did alter infarct morphology by salvaging myocardial cells. This heterogeneous infarct structure after reperfusion also has been described by others (Maroko et al., 1972; Smith et al., 1974; Constantini et al., 1975). Our observation that, despite the presence of these areas of salvaged myocardial cells, the percent of infarcted left ventricular wall of these reperfused hearts was the same as that after permanent occlusion may mean that the borders of the infarct were extended and encompassed more of the left ventricle. The frequent presence of higher heart rates during the initial 12–15 hours in the reperfused group because of the continuous ventricular arrhythmias and the hemorrhage that sometimes occurred after reperfusion could have contributed to this extension of the infarct borders (Braunwald et al., 1974; Bresnahan et al., 1974). For these reasons, although reperfusion may salvage ischemic myocardium, there always are a significant number of hearts in each study group which sustain large infarcts (Costantini et al., 1975; Boloooki, 1975; Bresnahan et al., 1974).

In some dogs, only very small infarcts resulted after reperfusion, and protracted periods of tachycardia could not be induced. In these dogs, reperfusion may have salvaged more myocardium, but since we could not predict how big the infarcts in these hearts would be if the coronary artery had remained occluded, we cannot be sure how much myocardium was at risk after the complete occlusion (Shell et al., 1971).

**Possible Mechanisms for Induced Ventricular Arrhythmias after Temporary Coronary Artery Occlusion**

The induction of protracted ventricular tachycardia with a regular rate and uniform QRS morphology by a short-duration premature stimulus occurring on the T wave is not attributable to the normal vulnerable properties of the ventricle. Premature stimulation of the ventricles during the T wave in the normal heart can induce rapid repetitive activity (Wiggers and Wegría, 1940; Wiggers et al., 1940; Moe et al., 1941). However, the repetitive activity usually lasts for only 5–15 seconds, and the cycle lengths are not constant. At the end of this brief period, repetitive activity either ceases or degenerates into fibrillation. Single stimuli applied to normal myocardium, which are used to demonstrate ventricular vulnerability, often must be stronger and of longer duration than those used in this study (Zipes, 1975). We produced fibrillation in only one dog in our entire series, and this fibrillation occurred only after a sustained period of tachycardia with a stable cycle length. The induction of protracted tachycardia also is not due only to the coronary occlusion, since it usually did not occur in dogs with permanent occlusion. It appears that the reperfusion was required to provide the necessary conditions.

Tachycardia induced and terminated by electrical stimulation may be caused either by reentry or by afterdepolarizations (Wit et al., 1976). Our data do not indicate which of these mechanisms is operative after reperfusion. If the induced tachycardia in the reperfused hearts is caused by reentry, the surviving muscle fibers in the ischemic region may provide convenient, long, reentrant pathways not present in the more homogeneous infarcts caused by permanent occlusion. Also, the longer perimeter of reperfused infarcts resulting from extension of the borders may facilitate reentry if the reentrant loop is around the infarct border. Determination of the pattern of ventricular activation during tachycardia, therefore, might assist us in ascertaining whether the arrhythmia is caused by reentry. As yet we do not know this activation pattern. If the tachycardia was caused by reentry, the consistent morphology of the QRS complex suggests that the reentrant pathway had the same location for each impulse. The studies by El-Sherif et al., (1977a, 1977b) have provided highly suggestive data that ventricular tachycardia induced by electrical stimulation after permanent LAD occlusion is caused by reentry in the epicardial muscle overlying the infarct.

Ventricular tachycardia, induced by electrical stimulation in reperfused hearts, follows a well-defined time course. Tachycardia cannot be induced...
until 3 days after coronary artery occlusion, is present between days 3 and 5, and cannot be induced thereafter. At present the reasons for the delayed onset of susceptibility to tachycardia or for its disappearance are not known. There may be time-dependent changes in infarct structure that can provide a clue. It may require several days of ischemia for the electrophysiological properties of cells in the ischemic region to be altered sufficiently to provide the proper conditions for inducible tachycardia. At this time there may be intact myocardial cells in the infarct with altered structure indicative of ischemia. After days 3-5 tachycardia may not be induced because, as the infarct ages, collateralization may restore adequate perfusion, restoring both the electrophysiological properties and structure of surviving cells to normal. On the other hand, myocardial fibers with abnormal action potentials that cause tachycardia eventually may become quiescent as a result of a progressive decline in flow to these sites (Cobb et al., 1976). If this occurs, ischemic myocardial cells may eventually undergo necrosis.

Possible Clinical Correlations of Induced Ventricular Tachycardia

In addition to suggesting that surgical revascularization might under certain conditions cause cardiac arrhythmias, our data also may have relevance to events that are associated with spontaneously occurring infarction. Myocardial infarction in humans can be caused by temporary coronary occlusion followed by spontaneous reperfusion (Roberts and Buja, 1972). Infarction caused by temporary occlusion might lead to arrhythmias of the type we have described for the canine heart. Clinical studies have shown that premature stimulation of the ventricle of some patients with a history of cardiac ischemia and infarction can induce ventricular tachycardia, with characteristics that are similar to the tachycardia we induced in reperfused hearts (Wellens et al., 1974, 1976; Denes et al., 1976; Josephson et al., 1978). At the present, no data are available to describe the anatomy of infarcts in patients in whom tachycardia can be induced by electrical stimulation. It may be that the presence of numerous viable cells scattered within the necrotic tissue can at times predispose the ventricle to serious arrhythmias in humans, or that tachycardias occur when the borders of the infarct extend over a greater area of the ventricles.

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