Disparate Electrophysiological Alterations Accompanying Dysrhythmia due to Coronary Occlusion and Reperfusion in the Cat

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SUMMARY The electrophysiologic changes associated with dysrhythmias induced by coronary occlusion and by subsequent reperfusion were characterized with six complimentary approaches in chloralose-anesthetized cats (n = 57) with proximal occlusion of the left anterior descending (LAD) coronary artery. Occlusion led to reproducible ventricular dysrhythmia which abated in 35 minutes. The electrophysiologic effects of reperfusion initiated at this time could be studied. Simultaneous bipolar electrograms (epi-, myo- and endocardial) from ischemic and normal zones were analyzed by computer. Before the onset of the dysrhythmia induced by occlusion, conduction was markedly slowed, with dV/dt decreasing to 34% ± 6% of control and conduction time (endo- to epicardial activation) prolonged to 328 ± 77% of control. However, these values returned toward normal with reperfusion, even though it also consistently induced dysrhythmia. The idioventricular escape rate (determined by intense vagal stimulation) was 62 ± 6 beats/min during the dysrhythmia induced by occlusion (equal to control), but increased during the reperfusion dysrhythmia to 188 ± 12 beats/min. The occlusion dysrhythmia was exacerbated, but the reperfusion dysrhythmia was suppressed by rapid atrial pacing. The refractory period progressively shortened after occlusion and remained decreased during early reperfusion. Thus, increased conduction time through myocardial and epicardial regions, asynchronous depolarization and shortening of the refractory period accompanied dysrhythmia induced by occlusion.

In contrast, the dysrhythmia induced by reperfusion was characterized by normal conduction time, through myocardial regions with continued significant epicardial delay, overdrive suppression, synchronous depolarization and a high idioventricular rate.

THE MECHANISMS RESPONSIBLE for ventricular dysrhythmia leading to sudden death in patients with coronary artery disease are obscure. Sudden, marked impairment of coronary flow may be responsible, but many patients dying suddenly on pathological examination do not have complete coronary occlusions. Spasm of a normal or partially obstructed coronary artery may contribute. Both experimental coronary occlusion and reperfusion are associated with malignant ventricular dysrhythmias in animals, including ventricular fibrillation. Dysrhythmias seen with coronary artery disease may be due to the effects of both coronary occlusion and partial or complete reperfusion, since collateral flow to ischemic zones increases as soon as 1 hour after experimental coronary ligation and since relief of spasm may occur spontaneously.

Furthermore, platelet aggregation and lysis may occur in vivo with phasic alteration of flow and subsequent dysrhythmia.

Distinct etiologic differences may exist between disturbances of rhythm associated with coronary occlusion and those associated with reperfusion. For example, Axelrod et al. observed that the dysrhythmia induced by occlusion was characterized by extra-systoles which gradually increased in frequency and culminated in ventricular fibrillation within minutes, while the dysrhythmia induced by reperfusion was characterized by ventricular fibrillation within 1 minute. Coronary reperfusion within 1 hour of the onset of occlusion in most animal species leads to: 1) reduction of ST segment alterations, 2) decreased infarct size determined histologically or enzymatically, and 3) improvement in the mechanical performance of ischemic ventricular muscle. Although coronary occlusion alone leads to prolongation of bipolar electrograms, decreased magnitude of the electromotive force, delay of conduction from the endocardial to the epicardial layers of the ischemic zone and shortening of refractory periods, it is uncertain whether these alterations are partially or completely reversed before the onset of dysrrhythmia induced by reperfusion. Although prolongation of the electrogram and decrease in local refractory periods are reversed by reperfusion, the temporal relation to the onset of malignant dysrhythmia has not yet been resolved. Likewise, coronary occlusion consistently decreases the ventricular fibrillation threshold (VFT), while results with reperfusion are conflicting. The purpose of the present study was to determine whether distinct electrophysiologica differences implicating different fundamental mechanisms underlie dysrhythmias induced by coronary occlusion compared to reperfusion with the use of an animal preparation exhibiting consistent ventric-
ular dysrhythmia early after coronary occlusion and reperfusion. Emphasis was placed on comparing the electrophysiological alterations at the onset of each type of dysrhythmia, rather than concentrating on changes which evolve during the course of occlusion and subsequent reperfusion.

Methods

Adult cats (n = 57) were anesthetized with ketamine HCl (12.5 mg/kg) and α-chloralose (75 mg/kg), selected to minimize depression of cardiac reflexes by anesthesia. The α-chloralose (Establishments Kuhlman, Paris, France) was dissolved by heating in distilled water, and the solution was cooled to body temperature before use. After endotracheal intubation, the animals were ventilated mechanically with a mixture of oxygen and room air to maintain normal arterial pH, Pco2 and Po2. Blood gases were monitored every 5 minutes in selected animals. Muscular relaxation was maintained by intravenous injection of decamethonium bromide (0.25 mg/kg) at 30-minute intervals. Left thoracotomy was performed by excision of ribs 2–4, and body temperature maintained at 37.5°C via a thermostatic esophageal probe controlling an infrared lamp. The pericardium was opened and sutured to the chest wall to form a cradle, and the left anterior descending (LAD) coronary artery was isolated at its bifurcation from the main left trunk, proximal to all branch points, under microscopic visualization. Care was taken to avoid the pericoronal nerve coursing parallel to the artery. A 3-0 cotton suture was placed under the vessel, and polyethylene tubing was threaded around the suture. The tubing was advanced to the artery and clamped to produce complete occlusion. Reperfusion was instituted by releasing the clamp and sliding the tubing retrograde on the suture. Catheters were inserted in the femoral artery and vein for recording systemic arterial pressure and administering drugs. A Gould-Brush Model 260 recorder was used to monitor multiple lead surface ECGs and systemic arterial pressure. A specially designed plexiglass chamber placed over the thorax was used to maintain the epicardial surface of the heart within the physiological temperature range by continuous circulation of humidified (100%) and warmed (40°C) room air through the chamber throughout the entire experimental procedure.

Bipolar electrograms from epi-, myo-, and endocardial areas of ischemic and normal zones of the left ventricle were obtained as previously described. Briefly, simultaneous and calibrated electrogram recordings from each level of the heart wall, in both ischemic and nonischemic regions were obtained and amplified with low frequency cutoff (3 db) at 1 Hz and high frequency cutoff (3 db) at 1 kHz, stored on FM magnetic tape, and displayed on an eight-channel monitor oscilloscope. The location of each electrode was verified at the termination of each experiment. Variance in electrode placement from experiment to experiment was minimized by placing the ischemic zone-electrodes 3 mm lateral to the LAD coronary artery just distal to the first medial branch and placing the normal zone-electrode on the lateral left ventricular wall adjacent to the first major branch of the left circumflex coronary artery.

Automated analysis of the bipolar wavforms was performed in real time with a PDP-12 computer system and interactive controlling software written in LINC/PDP-8 assembly language as previously described using a joystick on the computer console whereby the operator sets a threshold for acquisition of each pulse. The threshold is always at the 20 mV(msec) mark. The following parameters are measured for each bipolar electrogram: 1) maximum (MAX = 100%) and minimum (MIN = 0%) — the highest absolute voltage detected after threshold and the lowest detected within the 20 msec preceding threshold; 2) MAX — MIN, the difference (mV) between MAX and MIN; 3) rise time (RT) — the interval (msec) during which voltage increases from 25% to 75% of MAX — MIN; 4) pulse width (PW) at 50% amplitude (msec); and 5) the rate of rise of voltage (mV/msec) from 25% to 75% of MAX — MIN. Acquisition of data occurs during each systole and analysis during diastole. Thus, as soon as each electrogram has been analyzed, acquisition is reinitiated automatically. This system of analysis gives no information as to the relative conduction time between two electrode points, since only individual deflections are analyzed. Furthermore, capture of the electrogram in the analysis window always occurs at the 20 msec mark and is independent of any delay of activation to that electrode. The system used calculates the mean ± SD for each derived parameter and displays all parameters graphically as a function of time using a Houston Instruments DPI-5H incremental plotter. Thus, the graphics display allows visualization of each parameter for each pulse during the control period and the intervals after coronary occlusion and after reperfusion.

Conduction time through the ventricular wall in both ischemic and normal zones, as well as conduction delay induced by ischemia, were determined from displays of each of the six bipolar electrograms plus the surface electrocardiogram on a Honeywell Fiberoptics recorder (frequency response 8 kHz) at a chart speed of 1000 mm/sec; analog signals were stored on FM tape. Time of activation at each electrode site was defined as the major deflection of the electrogram, and 1 msec timing marks were used throughout the analysis; no selective amplifier delay was present in the electronic circuits. The initial upstroke of the electrogram during the ischemic interval may represent electrical activity at more distant sites with the ischemic area electrical activity being the more delayed spikes. However, fractionation of the electrogram into several spikes rarely, if ever, occurs within 3 minutes of coronary occlusion; thus, analysis of activation time at the onset of the dysrhythmia was determined from bipolar electrograms with a single deflection. The point of activation was always taken as the middle or steep portion of the initial deflection, since this coincides with unipolar activation in the
same region.\textsuperscript{32} If this activation time represented electrical activity at more distant sites rather than activation at the ischemic electrode, the conduction delay would be greater than that calculated. Furthermore, since the initial deflection during the control period before coronary occlusion was at the endocardial region of the ischemic zone with subsequent activation of myocardial and epicardial regions, this technique would overlook possible delays in transmission through endocardial regions of the ischemic zone. This possibility was investigated in five experiments in which electrograms from six endocardial plunge electrodes were simultaneously recorded throughout the control, occlusion and reperfusion procedures, with subsequent determination of the relative endocardial conduction time.

To determine the intrinsic idioventricular rate during 1) control periods, 2) the entire interval of dysrhythmia induced by occlusion and 3) the entire interval of dysrhythmia induced by reperfusion, intense right cervical vagus nerve stimulation was employed to induce complete atrioventricular block during spontaneous rhythm. Although vagal stimulation per se has been shown to decrease automaticity modestly in latent pacemakers\textsuperscript{34, 35} this effect should be evident before occlusion, as well as after occlusion and reperfusion. A bipolar platinum electrode connected to a Grass stimulator with a photon coupled isolator (W-P Instruments) was placed distally on the cervical vagal nerve trunk after decentralization to eliminate afferent nerve activation. Cervical vagal nerve stimulation in the cat, as opposed to other species, produces a pure parasympathetic response, since there are no sympathetic fibers coursing with the feline vagal trunk.\textsuperscript{36} Parameters of stimulation were: 2 msec impulse duration, 5 V and variable frequency ranging between 10–25 Hz adjusted to produce complete atrioventricular dissociation with a constant ventricular escape rate.

In selected experiments, atrial pacing (n = 8) was used (Medtronic, Model 5320) to assess the influence of changes in atrial rate on the two types of ventricular dysrhythmias and to determine whether the two dysrhythmias were affected by this procedure. The pacemaker leads were sutured to the right atrial appendage adjacent to the sinoatrial node. A current of 1 milliamp was used for capture. The rate used for overdrive suppression was 50–100 beats/min in excess of the intrinsic sinus rate.

In an additional series of experiments (n = 9), gold disc electrodes were sutured to the epicardial surface of the ischemic and normal zones for intermittent determination of the effective refractory period in each zone. The electrodes were fabricated as follows: four small gold discs with attached stainless steel wires were imbedded in a silicone mat. Each disc was separated from the adjacent one by 1 mm. Two bipolar contact points were used to record the local bipolar electrogram used as the triggering input to a pulse generator with adjustable delay (W. P. Instruments Anapulse Stimulator, Model 301-T). The remaining two bipolar contacts were used for local stimulation of the same zone. The current intensity was set at two times diastolic threshold and the delay was decreased in 4 msec increments until no propagated premature response was initiated. This interval was taken as the effective refractory period of either the ischemic or normal zone. The diastolic threshold was reassessed at 5-minute intervals throughout the coronary occlusion and reperfusion procedures, since this value progressively changes.\textsuperscript{37} With the use of this technique, simultaneous, local effective refractory periods could be determined in either the ischemic or normal zones throughout the interval of coronary occlusion and subsequent reperfusion. For this set of experiments only, a more distal LAD occlusion was performed, resulting in a smaller ischemic zone and few spontaneous premature beats. Results obtained with distal occlusions are comparable, since in three animals with proximal LAD occlusion, with ideal circumstances, the time course of change in refractory periods was identical to that seen with distal occlusion. During all refractory period determinations constant right atrial pacing was used.

Results

Characteristics of the Dysrhythmias Induced by Occlusion and Reperfusion

Specific characteristics of coronary occlusion induced in the feline model used in these studies include:\textsuperscript{28, 30} 1) ventricular dysrhythmia with a consistent onset time, duration and associated overall mortality due to ventricular fibrillation; 2) consistent frequency of premature ventricular complexes (PVCs) during the 35 minutes after occlusion; 3) coronary artery anatomy and distribution similar to that in man; and 4) consistent alterations in heart rate, systemic arterial pressure, cardiac output and total peripheral resistance. In the present study, coronary reperfusion was performed 35 minutes after coronary occlusion, at a time when the dysrhythmia due to coronary occlusion itself had always abated. A comparison of the characteristics between the dysrhythmias induced by coronary occlusion and those resulting from coronary reperfusion is shown in table 1. Dysrhythmia induced by reperfusion was characterized by a very rapid onset time and relatively short duration. Mortality rates due to ventricular fibrillation were similar in the two settings. Although the total number of PVCs was greater after occlusion, the rate of PVCs (mean number of PVCs/min) was higher after coronary reperfusion. Although this does not establish an etiologic difference between these two dysrhythmias, the consistency of the dysrhythmias in each setting allows assessment of possible underlying electrophysiological alterations.

In addition to the differences in the parameters listed above, the occlusion dysrhythmia consistently exhibited initial isolated premature ventricular complexes, then couplets and salvos with few runs of rapid ventricular tachycardia, while the dysrhythmias occurring during reperfusion uniformly showed a rapid unifocal pattern with many runs of rapid ventricular tachycardia.
The hemodynamic perturbations resulting from coronary occlusion with subsequent reperfusion are shown in Table 2. All values were obtained during periods of normal sinus rhythm. As reported previously with this preparation, coronary occlusion induced an immediate fall in diastolic and systolic and mean systemic arterial pressure. Most important, heart rate and systemic arterial pressure were similar before the onset of either the dysrhythmia induced by coronary occlusion or reperfusion (Table 2), obviating the need for correcting for hemodynamic variables.

**Influence of Coronary Occlusion and Reperfusion on Bipolar Electrogram Recordings**

Results of previous experiments have demonstrated that in this preparation, bipolar waveforms obtained simultaneously from the epicardial, myocardial, and endocardial areas of the left ventricular wall remain stable, with no significant alterations in pulse width, rise time, dV/dt or amplitude for up to 7 hours. After termination of the arrhythmic phase due to coronary occlusion, these parameters remain unchanged for up to 1 hour. Thus, any alterations in waveform parameters induced by reperfusion 35 minutes after occlusion should be a reflection of the effects of reperfusion per se. Fractionation of the electrogram into several components rarely occurred during the analysis up to the onset of the dysrhythmia induced by occlusion. Furthermore, fractionation of the electrogram was never seen after reperfusion, indicating that computer analysis of the initial depolarization was sufficient to characterize and compare the changes preceding the development of the two dysrhythmic intervals. Results of a representative experiment illustrating the alterations in electrograms from both the ischemic and normal zones before and during coronary occlusion and subsequent reperfusion are shown in Figure 1. It should be noted that capture of the electrogram in the analysis window always occurs at the 20 msec mark and is independent of any delay of activation to that electrode. During the control period before coronary occlusion, the electrograms vary slightly in duration between the normal and ischemic zone, a phenomenon completely dependent on the direction of the advancing wavefront through the electrode zone. This variation is avoided by comparing all results in electrograms to control values in electrograms recorded from the same electrode. Coronary occlusion resulted in an increase in pulse width and rise time with a corresponding fall in dV/dt of the local electrogram recorded from the ischemic zone, reaching a nadir just before the ventricular dysrhythmia. In contrast, after reperfusion and just before the onset of ventricular dysrhythmia (30 seconds post-reperfusion), pulse parameters began to return toward control values (increased dV/dt and decreased pulse width), suggesting that different electrophysiological alterations may underlie the two malignant ventricular dysrhythmias. No significant alterations in the waveforms recorded from the normal zone were seen after either coronary occlusion or reperfusion (Fig. 1).

Data from 18 experiments are illustrated in figures...
FIGURE 1. Computer-generated digital reconstruction of typical electrograms obtained from ischemic (left panels) and normal zones (right panels) of the left ventricle, before and after coronary occlusion and after coronary reperfusion. The waveforms shown are digital reconstructions obtained with a high speed plotter with each pulse shown as 500 data points (50 msec at 10 kHz sampling rate).

2 and 3 with data for pulse width, and rate of rise of voltage (dV/dt) expressed as a percentage of the initial control value (100%). After coronary occlusion and immediately before the onset of the dysrhythmia induced by occlusion (period 2), pulse width increased significantly and dV/dt fell in all three levels of the ischemic zone (figs. 2 and 3). Partial regression of the alterations in pulse width and dV/dt were seen in epicardial levels of the ischemic zone before the termination of ventricular dysrhythmia induced by coronary occlusion. The changes in rise time were similar but in opposite direction to the changes in dV/dt. Rise time calculated by computer was used to calculate dV/dt. Although the peak rate of rise of voltage (dV/dt) had already returned toward control in epicardial areas at the time of spontaneous termination of the dysrhythmia, it remained abnormal in myocardial and endocardial areas (fig. 3).

In contrast to the marked alterations in pulse parameters just before the dysrhythmia induced by coronary occlusion, reperfusion did not significantly alter pulse width, rise time, dV/dt or amplitude of
Figure 2. Summated pulse width data from the electrograms of 18 animals from the ischemic zones during five time periods: 1 — control period; 2 — before the onset of the occlusion dysrhythmia; 3 — normal sinus rhythm after the dysrhythmia has abated; 4 — before the onset of the reperfusion dysrhythmia; and 5 — normal sinus rhythm after the cessation of reperfusion dysrhythmia. Data from the epicardial level (---●---), myocardial level (- -○- -) and endocardial level (***▲***;) of the ischemic zone are presented. Values shown are percentage changes from average values in the control period (100%) and are expressed as mean ± SEM. The asterisk designates a significant difference from the control period at the P < 0.05 significance level.

Figure 3. The combined dV/dt (rate of rise of voltage with respect to time) data from 18 animals subjected to coronary occlusion and reperfusion. The figure illustrates the changes in dV/dt in three levels of the ischemic zone — epicardium (---●---), mid-myocardium (- -○- -) and endocardium (***▲***;) during five time periods: 1 — control; 2 — before the onset of the occlusion dysrhythmia; 3 — normal sinus rhythm after the dysrhythmia has abated; 4 — before the onset of the reperfusion dysrhythmia; and 5 — after the cessation of the reperfusion dysrhythmia. Values shown are percentage changes from average values in the control period and are expressed as mean ± SEM. The asterisk designates a significant difference from the control value at the P < 0.05 significance level.
pulses recorded from epi-, myo- or endocardial regions of the ischemic zone, compared to values just before reperfusion (period 3). Both pulse width and dV/dt returned toward control levels in epicardial regions within 30 seconds after reperfusion and before the onset of the dysrhythmia induced by reperfusion. Therefore, it appears that epicardial regions demonstrated improvement in localized conduction (increased dV/dt), while myocardial and endocardial regions exhibited continued localized depression in conduction (decreased dV/dt) soon after coronary occlusion (fig. 3, period 4). At the time of termination of the dysrhythmia induced by reperfusion (period 5), all pulse parameters in all three regions had returned to values seen before coronary occlusion. This suggests that immediately after reperfusion of the coronary arterial bed, continued improvement in dV/dt occurred in epicardial regions of the ischemic zone, with later improvement in the myocardial and endocardial regions.

The bipolar electrogram technique used derives information only from a local area of the heart wall where the electrode is engaged. To determine whether the apparent, localized slowed conduction manifested by decreased dV/dt during occlusion, and persistent slowed myo- and endocardial conduction during reperfusion were localized or diffuse throughout the entire zone of ischemic tissue, recordings from the same electrodes were used to determine the sequence of impulse activation through the entire heart wall.

Conduction Time

Relative conduction time was measured by determining the sequence of electrogram activation through the three levels of the heart wall in both the ischemic and normal zones. Due to electrode placement (the ischemic zone electrode was near the anterior septum and the normal zone electrode was on the lateral wall of the heart), the wave of normal depolarization was first seen in the endocardial area of the ischemic zone, with subsequent activation of myocardial, followed by epicardial, areas. Impulse activation in the normal zone lagged behind that in the ischemic zone because of the lateral position of the electrodes, but the pattern of endocardial to epicardial activation was the same.

Conduction time through the ischemic zone differed markedly during the two types of ventricular dysrhythmia (fig. 4). The earliest activation in the control period was at the endocardial electrode of the ischemic zone, which was therefore chosen as the reference point for each experiment. The pattern of conduction was determined by mapping the interval to the initial fast deflection of the electrogram in each level from the initial deflection in the endocardial layer of the ischemic zone. Results were expressed as percentages of the interval under control conditions (i.e., before ischemia).

Before the onset of the dysrhythmia induced by occlusion, conduction time was markedly increased throughout the ventricular wall of the ischemic zone.

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Conduction time (delay of activation from endo- to epicardial and endo- to mid-myocardial levels) in ischemic zones during five time intervals. Values are expressed as percentages of control values (mean ± SEM). The asterisk designates a significant difference from the control value.
After the dysrhythmia had subsided, conduction time from endocardial through myocardial levels of the ischemic zone returned to normal. In contrast, conduction time to the epicardial area of the ischemic zone remained prolonged.

Immediately before the dysrhythmia induced by reperfusion, no conduction delay was seen from endocardial to myocardial regions. Residual conduction delay to the epicardium induced by the antecedent occlusion continued to resolve (fig. 4, panel 4). Conduction time through the ischemic zone had become normal at the time when normal sinus rhythm was restored after reperfusion. Thus, the dysrhythmia induced by coronary occlusion was characterized by marked conduction delay in the ischemic region, while dysrhythmia resulting from reperfusion occurred without significant conduction delay except in epicardial regions. Even the epicardial conduction delay continued to regress. It is possible that delays in conduction time in endocardial regions during both occlusion and reperfusion would not have been detected because the endocardial region was used as a reference point. However, in five experiments in which three endocardial electrodes were used in the ischemic region, no conduction delay was seen during either coronary occlusion or subsequent reperfusion. There is an apparent paradox between the depressed dV/dt obtained from local electrograms recorded from myocardial and endocardial areas immediately after reperfusion (fig. 3, period 4) and the normal overall conduction time through myocardial regions immediately after reperfusion (fig. 4). This difference suggests that although conduction time was normalized through mid-myocardial areas early after reperfusion, localized areas of depressed conduction velocity were still apparent, which indicates the heterogeneity of recovery after reperfusion. This phenomenon has also been reported by others.28

**Idioventricular Escape Rates After Coronary Occlusion and Reperfusion**

The idioventricular escape rate was normal throughout the entire interval after coronary occlusion (fig. 5). In contrast, reperfusion consistently induced a marked increase in the idioventricular escape rate, suggesting that mechanisms such as enhanced ventricular automaticity might be operative. Vagal stimulation attenuated the dysrhythmia after coronary occlusion, and sometimes restored sinus rhythm. During reperfusion, vagal stimulation consistently exacerbated ventricular dysrhythmia, and increased the incidence of ventricular fibrillation (25–75%). In the one animal that survived reperfusion with vagal stimulation, the idioventricular rate returned to control values.

**Alterations In Local Effective Refractory Periods During Coronary Occlusion and Reperfusion**

In six animals, coronary occlusion for 35 minutes was followed by reperfusion and in three, occlusion was maintained for 65 minutes without subsequent reperfusion. The effective refractory period during the control interval varied from 124 msec–186 msec. Results expressed as percentages of control value are shown in figure 6. In the ischemic zone, a progressive and significant decrease occurred which was not altered immediately by coronary reperfusion. Thus, at the time of onset of the reperfusion dysrhythmia, a continued significant decrease in effective refractory period in the ischemic zone was still present. Subsequently, after the reperfusion dysrhythmia had
abated, the refractory period returned to normal. The spontaneous return of refractory period to control levels during continuous occlusion occurred when the dysrhythmia induced by occlusion had abated, suggesting that shortened refractory period may have been involved in maintenance of the dysrhythmia. Although the mechanisms responsible for the spontaneous recovery in refractory period are unknown, possible mechanisms include an increase in collateral flow with washout of noxious metabolites, including potassium and lactate. Decreases in refractoriness in the normal zone, possibly attributable to systemic sympathoadrenal activity, were seen only during the 30-40 minute interval after coronary occlusion. Thus, early coronary reperfusion appears to have no significant effect on refractory period, compared to continuous coronary occlusion, at time when the dysrhythmia due to reperfusion evolves.

Response of the Dysrhythmias Induced by Coronary Occlusion and Reperfusion to Rapid Atrial Pacing

In 10 animals, rapid right atrial pacing (250-300 beats/min) was performed in an attempt to overdrive the two dysrhythmias. Results from a representative experiment are shown in figure 7. After coronary occlusion, rapid atrial pacing consistently exacerbated the ventricular dysrhythmia and no overdrive suppression was apparent (panels A and B). However, the dysrhythmia induced by reperfusion was prevented regularly by rapid atrial pacing, presumably because of overdrive suppression of enhanced ventricular automaticity (fig. 7). Before atrial pacing during reperfusion, the coupling intervals of premature beats were shorter than the pacing cycle length, indicating that atrial pacing may have suppressed ventricular pacemakers, with a resultant rate lower than the previous normal to ectopic cycle length. However, this does not rule out slowed conduction as a contributing mechanism, since rapid atrial pacing can also abolish dysrhythmia dependent on slowed conduction by producing conduction block. Clearly, the two dysrhythmias, regardless of etiology, respond in opposite fashions to rapid atrial pacing. Since the idioventricular rate was enhanced to a mean value of 188 beats/min immediately after coronary reperfusion (fig. 5), and the rate of the ventricular tachycardia during reperfusion was higher (250-300 beats/min, fig. 7, panels C and D), possibly an enhanced ventricular pacemaker played a role in the initiation of the tachycardia and localized conduction depression (fig. 3, period 4) maintained the ventricular tachycardia. Thus, it is possible that both slowed conduction and enhanced ventricular pacemaker activity are important progenitors early after coronary reperfusion.

Discussion

The purpose of the present study was to delineate the electrophysiological factors underlying dys-
CORONARY OCCLUSION

A

CORONARY REPERFUSION

C

D

FIGURE 7. The influence of right atrial pacing on the two types of dysrhythmias. The upper two panels (A and B) depict a continuous ECG (lead II) tracing during the dysrhythmia induced by coronary occlusion and the lower two panels (C and D) depict a continuous tracing during the dysrhythmia induced by coronary reperfusion. Arrows indicate the initiation and cessation of pacing. During coronary occlusion (A and B) pacing failed to alleviate the dysrhythmia, while during reperfusion (C) atrial pacing suppressed the dysrhythmia.

rhythms resulting from coronary occlusion and reperfusion, since both may be important in sudden death in man. The major characteristics of the two types of dysrhythmia are summarized in table 3. Based upon results obtained with several different electrophysiological techniques, the two dysrhythmias appear to be associated with different electrophysiological alterations.

The dysrhythmia induced by occlusion exhibits a slower repetitive pattern of ectopic beats, gradually increasing in frequency until ventricular fibrillation ensues. In contrast, the dysrhythmia induced by reperfusion exhibits an abrupt onset time, rapid rate with typically unifocal complexes, and rapid progression to ventricular fibrillation, findings compatible with those of Axelrod et al. 8

The results with computer analysis of bipolar extracellular recordings must be qualified, since they reflect the summated electrical changes of many cells within the localized region surrounding the electrode. Nevertheless, Singer and colleagues 86 reported that changes in the bipolar electrogram obtained from endocardial ventricular tissue closely correlated with the action potential from attached Purkinje tissue under varied conditions. Thus, this technique allows acquisition of information in the intact animal in which continuous intracellular recordings throughout various levels of the heart wall would not be possible. Both slowed conduction, reflected by a rapid decrease in dV/dt, and asynchrony of depolarization manifested by an increase in pulse width confined to the ischemic zone electrograms, became maximal just before the onset of the occlusion dysrhythmia and partially regressed just before the termination of the occlusion...
TABLE 3. Characteristics of Occlusion vs Reperfusion Dysrhythmia

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<tr>
<th>Occlusion-Dysrhythmia</th>
<th>Reperfusion-Dysrhythmia</th>
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<tr>
<td>1. Slower onset, longer duration characterized by couplets and salvos with few runs of VT*</td>
<td>1. Rapid onset, shorter duration, characterized by rapid unifocal pattern with many runs of VT*</td>
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<tr>
<td>2. Slowed conduction, delayed conduction from endocardium to myocardium and epicardium in ischemic zone</td>
<td>2. Improvement in conduction, accelerated conduction from endocardium to myocardium in ischemic zone</td>
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<tr>
<td>3. Slow idioventricular rate</td>
<td>3. Rapid idioventricular rate</td>
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<tr>
<td>4. Dysrhythmia terminated by intense vagal stimulation</td>
<td>4. Dysrhythmia exacerbated by intense vagal stimulation</td>
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<tr>
<td>5. Rapid atrial pacing leads to exacerbation of the dysrhythmia</td>
<td>5. Rapid atrial pacing suppresses the dysrhythmia</td>
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<td>6. Refractory period shortened</td>
<td>6. Refractory period shortened</td>
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*VT = ventricular tachycardia.

dysrhythmia.\(^{39, 40}\) Corresponding changes have been seen in recordings of epicardial transmembrane action potentials in intact porcine hearts.\(^{28}\) In contrast, with the dysrhythmia induced by reperfusion, different changes were seen in regional electrograms, with progressive return toward control of dV/dt, rise time, pulse width and amplitude throughout the reperfusion period at a time when the dysrhythmia was evident. Thus, although localized slowed conduction and asynchrony of depolarization in the individual levels of the heart appear to underlie dysrhythmia induced by occlusion, the dysrhythmia induced by reperfusion may result from different derangements.

After coronary occlusion, a significant delay of conduction activation from the endocardial to myocardial and epicardial layers was seen, similar to observations by others using the surface ECG as the reference point.\(^{39}\) However, within 1 minute of reperfusion, conduction time from the endocardial to the mid-myocardial region of the ischemic zone showed no delay and delay to the epicardial region continued to regress. This finding is not unexpected, since in isolated perfused hearts, even total unresponsiveness with loss of the transmembrane action potential with ischemia can be reversed rapidly by reperfusion.\(^{28}\) Since significant conduction delay to epicardial regions was still apparent early after reperfusion, slowed conduction could contribute to dysrhythmia under these conditions. The apparent paradox between the continued depression in dV/dt of the local electrograms in midmyocardial and endocardial regions after reperfusion (fig. 3, period 4) and the total improvement in overall conduction time through the same region assessed by analysis of activation time through the heart wall (fig. 4), suggests that slowed conduction within localized regions of the heart wall may be important in maintaining the dysrhythmia early after coronary reperfusion. Furthermore, the fact that the idioventricular rate was increased soon after coronary reperfusion to 188 beats/min but the overall rate of the ventricular tachycardia was routinely 250–300 beats/min (fig. 7) suggests that enhanced ventricular pacemaker activity may have initiated the tachycardia, but the dysrhythmia was maintained by localized and slowed conduction within ischemic regions. This explanation is also supported by the atrial pacing studies, where rapid overdriven suppression (fig. 7) alleviated the dysrhythmia due to reperfusion. Thus, phenomena such as microreentry\(^{41}\) may be operative early after coronary reperfusion. Slowed conduction does not appear to be a primary precipitant of the dysrhythmia induced by reperfusion, but may be important in the maintenance of the rapid ventricular dysrhythmia.

In the present study, dysrhythmia induced by coronary occlusion could not be suppressed by rapid atrial pacing. On the contrary, it was generally exacerbated by this maneuver. The dramatic increase in conduction time in ischemic tissue evidenced by a marked decrease in dV/dt of the local electrogram, and a delay in endocardial-to-epicardial activation time occurring soon after coronary occlusion, suggests that the dysrhythmia was dependent on slowed conduction velocity through ischemic tissue. When marked heterogeneity of depolarization is seen as well, with widening of the local electrogram, an increased number of impulses entering the ischemic areas within a given interval would increase the likelihood for decrement\(^{42, 43}\) and be expected to exacerbate dysrhythmia dependent on slowed conduction velocity. In contrast, the dysrhythmia induced by coronary reperfusion was consistently overdriven by rapid atrial pacing. The observation that the pacing rate was lower than the intrinsic R-R' interval of spontaneous ectopies indicates that pacing may have suppressed latent ventricular pacemakers.\(^{42}\) Rapid pacing could have abolished a dysrhythmia dependent on slowed conduction after reperfusion by producing conduction block, but the dysrhythmia induced by occlusion is exacerbated by this procedure, as shown in this study as well as by others.\(^{39, 40}\) The discrepancy between the continued depression in dV/dt of the local electrograms in endocardial and myocardial regions early after reperfusion (fig. 3, period 4), and apparent recovery of overall conduction time through the same zone (fig. 4) suggests that localized conduction depression may be operative, which is not apparent by analysis of overall conduction time. Another plausible explanation may be the known dissociation between dV/dt of intracellular action potentials and overall conduction, assessed in isolated Purkinje fibers during hyperkalemia.\(^{44}\)

The intrinsic idioventricular rate differed markedly with respect to the two types of rhythm disturbances. It remained normal during the entire interval after occlusion alone, suggesting that ventricular automaticity was not enhanced.\(^{39, 40}\) However,
dysrhythmia induced by reperfusion was associated with marked acceleration of idioventricular rate. In the one animal that survived the combination of coronary reperfusion and vagal stimulation, the intrinsic idioventricular rate returned to control levels after the dysrhythmia abated. Although others26, 27 have reported that both complete and partial coronary occlusion results in inconsistent ventricular dysrhythmias without enhancement of the idioventricular rate, the technique used to measure the rate entailed destruction of the His bundle with formaldehyde, which might have damaged some idioventricular pacemakers as well. In addition, the ventricular rate was measured 3–5 minutes after reperfusion following complete occlusion,26 and 15 minutes after reperfusion following partial occlusion,27 at a time when the enhanced rate may have abated. In the present study, the idioventricular rate rose within 1 minute after reperfusion, and the increase was associated with the onset of the dysrhythmia. However, it is possible that vagal stimulation obliterated exit block present during the interval early after reperfusion and allowed a rapid reentrant circuit to propagate unopposed by supraventricular impulses. Vagal stimulation per se, independent of changes in heart rate, partially alleviates the dysrhythmia seen after coronary occlusion.44-47 However, vagal stimulation led to ventricular fibrillation in all animals studied after reperfusion except one, suggesting that parasympathetic stimulation may affect the two types of dysrhythmias quite differently.

The changes in refractory periods in the ischemic zones were qualitatively similar after coronary occlusion and reperfusion. Their progressive shortening after occlusion and persistent reduction during early reperfusion suggests that the same change may contribute to both types of dysrhythmias. As others have noted,26, 27, 64, 65 refractory periods do return to control levels after coronary reperfusion, but not during the interval of maximum dysrhythmia.

Although definitive evidence establishing reentrant mechanisms as the cause of ventricular dysrhythmia requires complete mapping of the reentrant circuit, and unequivocal demonstration of enhanced automaticity requires localization of the ectopic focus, the data obtained in the present study strongly suggest that dysrhythmias due to coronary occlusion differ fundamentally from those due to reperfusion. Dysrhythmias induced by occlusion are characterized by slowed conduction, asynchronous depolarization, slow idioventricular rate, and exacerbation with atrial pacing rather than override suppression. Conversely, dysrhythmias induced by reperfusion occur with improvement in the conduction delay, synchronous depolarization, and a rapid idioventricular rate, and is consistently suppressible by atrial pacing. However, since localized conduction block may be operative during early reperfusion, this may also account for the malignant dysrhythmias in this setting.

Although adrenergic influences may be a factor in the dysrhythmias induced by coronary occlusion judg-

from assessments of regional myocardial cyclic AMP,31 adrenergic influences may be of less importance in the dysrhythmia induced by coronary reperfusion.60 Sympathectomy fails to alter the incidence of ventricular fibrillation after reperfusion31 and neither α- nor β-receptor blockade alters the decrease in ventricular fibrillation threshold with coronary reperfusion.62

Enhanced efferent parasympathetic tone may be protective during the dysrhythmia induced by coronary occlusion,44-47 but may exacerbate dysrhythmia due to reperfusion, as shown in the present study. These apparent marked differences in response to autonomic neural stimulation and their therapeutic implications appear to reflect different underlying electrophysiological alterations associated with the two types of dysrhythmia.

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References

Disparate electrophysiological alterations accompanying dysrhythmia due to coronary occlusion and reperfusion in the cat.
P A Penkoske, B E Sobel and P B Corr

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