

ELECTROPHYSIOLOGY OF CORONARY REPERFUSION:¹²⁰

A MECHANISM FOR REPERFUSION ARRHYTHMIAS

by

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A Thesis Submitted to the Faculty of the Graduate School
of Loyola University of Chicago in Partial Fulfillment
of the Requirements for the Degree of

Master of Science

October

1983

ACKNOWLEDGMENTS

My sincere gratitude is expressed to Dr. Walter C. Randall, the advisor and Chairman of my thesis committee, for his enthusiastic support, guidance and most of all for his influence on my training.

I wish to extend great appreciation to Dr. David E. Euler and Dr. Jerod M. Loeb for their advice, consultation and support.

May I also extend my thanks to the members of my thesis committee, Dr. Walter C. Randall, Dr. John F. Moran, Dr. H. Kurt Jacobs, and Dr. John B. Pace for their assistance in the preparation of this thesis.

Finally, I wish to acknowledge Dr. Rolf M. Gunnar for his support and inspiration, and my wife for her patient understanding and many sacrifices which have made this work possible.

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INTRODUCTION

In 1943 Harris and Rojas (1) first demonstrated a specific time course for ventricular arrhythmias during acute ischemia. Following coronary occlusion, they noted a progressive increase in the frequency of arrhythmic activity reaching maximal intensity within 6-10 minutes and then abating resulting in a relatively arrhythmic free quiescent period. Ventricular fibrillation, when present, was limited to the early arrhythmic period. These investigators further demonstrated that restoration of blood flow to acutely ischemic myocardium also gave rise to a rapid increase in arrhythmic activity which frequently terminated in reperfusion ventricular fibrillation. Since then numerous investigators have documented the frequent occurrence of malignant arrhythmias during coronary reperfusion (2-10).

Although there has been an extensive investigation of the mechanisms underlying the arrhythmias of acute myocardial ischemia (11-20), until recently there has been relatively little attempt to understand the mechanism for reperfusion arrhythmias. This may be related to the specialized conditions necessary to produce reperfusion arrhythmias - namely temporary myocardial ischemia. Since these conditions were usually produced in an experimental setting, the clinical significance of reperfusion arrhythmias was not recognized. However, recently the importance of reperfusion arrhythmias has begun to emerge. With the concept of coronary artery spasm firmly established (21,22), the functional components necessary to produce temporary myocardial ischemia and reperfusion are readily available in the clinical setting.

Furthermore, in a recent review of the arrhythmias which accompany coronary artery spasm, Kerin et al (23,24) noted that the arrhythmias frequently occurred at a time when the ischemia induced ST segment elevation was beginning or had completely normalized. Thus, these authors concluded that some of these arrhythmias may have resulted from a reperfusion mechanism. Reperfusion arrhythmias are also a frequent accompaniment of the use of thrombolytic therapy in patients suffering an acute myocardial infarction. In these patients, streptokinase frequently reestablishes coronary flow in occluded vessels presumably by clot lysis (25-27). The restoration of blood flow to the ischemic area is often heralded by reperfusion arrhythmias (25-27). Indeed, Goldberg and his co-workers have used the onset of reperfusion arrhythmias as a marker to signal restoration of antegrade flow during intracoronary thrombolytic therapy (27).

With the growing recognition of the frequency of reperfusion arrhythmias in the clinical setting, an understanding of the mechanisms responsible for these arrhythmias becomes important. Thus this investigation was undertaken to examine the mechanisms responsible for reperfusion arrhythmias. Because reperfusion is the reversal of an ischemic process, the electrophysiologic effects of acute ischemia must be included in any investigation of reperfusion electrophysiology. Therefore this thesis will begin with a literature review of the important contribution to our understanding of both ischemic as well as reperfusion arrhythmias. Finally, following completion and publication of the work contained in this thesis (10), investigations of

reperfusion electrophysiology have continued. Thus, in order to properly develop a comprehensive literature review of reperfusion electrophysiology, this thesis will occasionally make reference to the published results.

REVIEW OF RELATED LITERATURE

ISCHEMIC ARRHYTHMIAS

The derangements in cardiac rhythm which accompany acute coronary occlusion were well known to early experimenters of acute ischemia. In 1894 Porter (28) noted that coronary occlusion resulted in abnormal cardiac rhythms which frequently terminated in ventricular fibrillation. However, a thorough understanding of the rhythm disturbances resulting from acute ischemia did not come until the advent of the electrocardiogram. Using the electrocardiogram Thomas Lewis in 1909 first demonstrated the frequent occurrence of paroxysmal ventricular tachycardia and fibrillation with coronary occlusion in the experimental animal (29). Today, the ventricular arrhythmias which accompany myocardial ischemia in man are well recognized as a major cause of early mortality from acute myocardial infarction (30). This recognition forms the basis for the numerous investigations which have attempted to delineate the mechanisms responsible for these ischemic arrhythmias in the experimental setting.

In 1943 Harris and Rojas (1) made an observation which has greatly influenced later research. These investigators noted that ventricular arrhythmias after coronary occlusion occur in two phases separated by a quiescent period free of arrhythmic activity. The first, or early phase of arrhythmias, occupy the first few minutes after coronary occlusion and frequently culminates in ventricular fibrillation. The second, or delayed phase, begins several hours

after occlusion and continues for up to 72 hours. Ventricular fibrillation rarely occurs during this phase.

Late Phase Arrhythmias

Although Harris and Rojas (1) attributed both phases of arrhythmias to rapidly discharging automatic foci, subsequent investigations suggested the mechanisms differed for the two phases. Scherlag and his co-workers (14) compared the underlying idioventricular escape rate in vagally induced atrial arrested dogs during the early arrhythmic period (within 20 minutes of coronary occlusion) and during the later arrhythmic period (24 hours after coronary occlusion). These investigators noted that the underlying idioventricular escape rate during the early arrhythmic period was not different from preocclusive idioventricular rate - both averaging 39 beats per minute. However, in the 24 hour infarcted hearts, vagal arrest revealed a markedly enhanced ventricular automaticity which averaged 166 beats per minute. Heart rate also affected the two arrhythmic phases differently in this study. When atrial arrest was induced during the early arrhythmic period, there was a prompt cessation of premature ventricular ectopic activity. On the other hand, when heart rate was increased to 200 beats per minute by atrial pacing, the arrhythmias of the early phase were consistently exacerbated. This contrasts sharply to what was seen during the later arrhythmic period. Unlike the early arrhythmias,

the later 24 hour ventricular arrhythmias were easily suppressed by rapid atrial pacing and readily exposed by vagally induced atrial arrest. Thus, these investigators concluded that the arrhythmias of the later phase were due to enhanced automaticity while factors other than enhanced automaticity accounted for the early phase of arrhythmias.

The suggestion that enhanced automaticity is important in the genesis of late phase arrhythmias has been supported by others. Friedman et al (18) and Lazzara et al (19), recorded transmembrane action potentials from surviving dog Purkinje cells isolated from 24 hour infarcts. Both groups of investigators found that the Purkinje cells were excessively automatic. This observation is in accord with the finding of Horowitz et al (20) who recorded from close bipolar electrodes placed into the Purkinje network of 24 hour infarcted dogs hearts. These investigators showed that the ectopic beats of the delayed phase of arrhythmias were preceded by electrograms from Purkinje fibers suggesting a Purkinje cell origin for these arrhythmias.

Although it is clear that automaticity is enhanced during the late arrhythmic period and probably accounts for many of the spontaneous arrhythmias seen at this time, the possibility that other mechanisms might also be operative can not be excluded.

Early Phase Arrhythmias

The inability to demonstrate enhanced automaticity during the

early arrhythmic period suggests that alternative mechanisms might be operative at this time. The most plausible mechanism for early ischemic arrhythmias is that of reentry. The concept of reentry as a mechanism for ventricular arrhythmias was first investigated by Mines in 1913 (31). For reentry to occur, it is necessary for an area of tissue to show unidirectional block while still capable of conducting in the reverse direction. Additionally, the total transit time through the reentrant circuit must exceed the refractory period of the tissue proximal to the site of unidirectional block. In ventricular tissue with its relatively long refractory period, this necessitates that conduction be markedly slowed from the normal state. These conditions have been artificially produced in the tissue bath. Wit et al (32) subjected canine Purkinje fiber loops to high potassium concentrations. This markedly reduced resting membrane potential and caused action potentials with very slow upstrokes. Action potentials were recorded from different sites around the loop. In some experiments, a driven impulse entered the loop and activated the recording sites in a sequence which was compatible with unidirectional conduction around the loop. The site at which the impulse entered the loop was then reactivated a second time as the impulse returned. The second repetitive response could be abolished by cutting the loop, thus confirming the reentry hypothesis.

Although reentry is a proven mechanism in the tissue bath, it is much more difficult to prove in the intact heart. Indeed, the experimental evidence implicating reentry as a mechanism for arrhythmias in

the intact heart is indirect since the criteria needed to absolutely prove reentry cannot be satisfied. Despite this obstacle, the evidence favoring reentry as the mechanism for early ischemic arrhythmias has continued to mount. In 1943 Harris and Rojas (1) argued that if reentry were occurring during this phase of arrhythmias, slow conduction with continuous electrical activity should be recorded in the ischemic region from the time the impulse enters it until it reemerges to cause reexcitation of the remaining myocardium. Indeed, it was their inability to record these conditions which prompted them to discount reentry as the mechanism for the early occlusive arrhythmias. However, subsequently several different groups of investigators have studied the effects of acute ischemia on local electrophysiology with the use of bipolar electrodes (11-17, 33). Common to all of these studies was the finding that electrograms recorded from acutely ischemic myocardium exhibited a marked decrease in amplitude, an increase in duration and were activated later indicating slowed conduction. Scherlag and his co-workers (14) compared the electrograms of the subendocardial, subepicardial, and mid-myocardial layers. They recorded the greatest conduction slowing in the more superficial layers and inferred that reentry may result from slow conduction through this region. Other investigators have demonstrated a close relationship between conduction delay and ectopic beats. Boineau and Cox (12) recorded long fractionated electrograms from acutely ischemic myocardium which they interpreted as resulting from slow dyssynchronous activation of adjacent myocardial sites. They showed that ectopic beats appeared when the

duration of the electrogram extended beyond the T-wave of the EKG. Their recordings, and the similar findings of Waldo and Kaiser (13), answered the requirement of Harris and Rojas that continuous activation be observed before reentry could be considered as a mechanism for the generation of ectopic beats.

The electrophysiologic basis for the effects of acute ischemia on conduction velocity and electrogram amplitude as recorded from extracellular electrodes has been elucidated by investigations of the effects of acute ischemia on cellular electrophysiology. Downar et al (7) utilized a floating microelectrode technique to study the effects of acute ischemia on epicardial transmembrane action potentials in the isolated Langendorff perfused pig heart. They observed that ischemia produced a rapid loss of resting membrane potential as well as a progressive decrease in the amplitude and upstroke velocity (dV/dT of phase 0) of the action potential. This was associated with a rapid decrease in excitability as measured by an increase in the amount of current necessary to initiate a propagated response. In some cells the amplitude continued to diminish until the cell became totally unresponsive. This finding suggests that the marked decrease in electrogram amplitude recorded from bipolar electrodes during acute ischemia results from a severe depression of the underlying action potentials which generate the electrogram. Finally, since conduction velocity is primarily dependent upon excitability and upstroke velocity of the action potential (34), these findings provide an electrophysiologic basis at the cellular level for the effects of

ischemia on conduction velocity.

Perhaps the most convincing evidence for reentry in the intact heart comes from composite electrode recordings. The composite electrode was first conceived by Williams et al (16) and later popularized by El-Sherif and his co-workers (35) in the 3-7 day old canine infarct model. This electrode consisted of a large bipolar electrode with 8-12 pairs of 1-2 mm contact points covering a 2 x 3 cm area of epicardium. The electrode thereby sensed electrical activity over a wide area and recorded it as a single composite electrogram. When such an electrogram was recorded from the non-ischemic myocardium, a single spike was recorded indicating near simultaneous activation under the multiple contact points. However, when the electrode was placed over the ischemic zone, a long fractionated electrogram was recorded presumably reflecting slowed dyssynchronous activation under the multiple contact points. The degree of fractionation could be increased by premature stimulation or increasing the heart rate. When the length of the fractionated electrogram extended into or exceeded the T-wave, ventricular extrasystoles were produced. At this time the composite electrogram displayed continuous electrical activity which spanned the interval between the paced and spontaneous premature beat. The authors concluded that, "The demonstration of continuous electrical activity that regularly and predictably bridged the entire diastolic interval between initiating and reentrant beats as well as between consecutive reentrant beats constitutes the necessary missing link long sought to document reentry." As further support of their

contention that the composite electrograms were depicting reentrant pathways, they later showed that the antiarrhythmic agent lidocaine attenuated the fractionation on the composite electrogram as it prevented arrhythmias (36).

Although the composite electrode cannot quantitate conduction delay or precisely determine where the delay is occurring, its sensitivity for recording delayed conduction has made it a valuable asset in studying ischemic electrophysiology. Kaplinsky and his co-workers (37) used the concept of composite electrode recording to study the acutely ischemic myocardium. These investigators used a modified composite electrode consisting of multiple bipolar plunge electrodes connected in parallel to study the early occlusive arrhythmias in the dog heart. They regularly recorded delayed fractionated electrical activity which spanned the interval between paced and spontaneous premature beats. The compensatory pause which followed a premature beat was devoid of fractionated activity. The regular association of fractionated electrical activity with spontaneous premature beats prompted them to conclude that the early occlusive arrhythmias resulted from a reentrant mechanism.

The inability to demonstrate enhanced automaticity (14), the finding of delayed conduction (11-17,33), and the recording of continuous electrical activity between normal and premature beats (12, 13,37) support reentry as the most plausible mechanism responsible for early ischemic arrhythmias. However, since a reentry pathway has never been mapped in its entirety in the intact heart, this mechanism

remains an unproven theory and has not gone unchallenged. In a recent provocative investigation, Janse and his co-workers (38) have proposed an alternative explanation for early ischemic arrhythmias. These investigators recorded transmembrane action potential in ischemic and adjacent normal tissue from isolated Langendorff perfused porcine and canine hearts. They noted that because of conduction slowing in the ischemic zone, repolarization in the ischemic zone outlasts repolarization in the normal zone. This situation produces a potential difference between the two zones which in turn produces an injury current. The investigators theorized that this current may reach sufficient magnitude to reexcite the normal zone Purkinje fibers producing premature beats. This theory is actually a form of reentry in which some of the conduction through the reentrant circuit is by way of electrotonic interactions (the injury current) between the ischemic and normal zone. Many uncertainties still exist and further mapping studies, combined with microelectrode recordings from Purkinje cells, will have to be performed before this hypothesis will be proved or disproved.

BIOCHEMICAL CORRELATES OF ISCHEMIC ELECTROPHYSIOLOGY

Although the electrophysiologic changes accompanying acute ischemia are well known, the linkage between the electrophysiologic changes and the biochemical changes caused by ischemia are not well understood. Ischemia produces both a deprivation of oxygen and essential nutrients, as well as results in the accumulation of metabolic waste products of anaerobic metabolism and necrosis. An analysis of blood draining ischemic myocardium has demonstrated some of the metabolic abnormalities. This blood is high in potassium and hydrogen ion concentrations, and low in O_2 content (39-42). Downar et al (42) showed that porcine ventricular muscle fibers superfused with "ischemic blood" developed the same abnormal electrophysiologic properties that had been recorded from ischemic cells in the intact heart. In an attempt to identify the ischemic metabolites which produced these abnormalities, they went on to superfuse other muscle fibers with coronary venous blood from normal regions in which they equalized the concentrations of potassium, lactate, oxygen, and hydrogen ion to that of the blood from the ischemic region. The abnormal electrophysiologic properties could not be produced with this cocktail, leading these investigators to conclude that in addition to potassium, hydrogen ion and oxygen, other unidentified factors contribute to the electrophysiological abnormalities of the early phase of ischemia. More recently there has been interest that the lysophospholipids, lysophosphatyl choline (LPC) and lysophosphatyl ethanolamine (LPE) might be these unidentified factors (43,44). These catabolites of

membrane phospholipids have been shown to accumulate 20- to 35-fold in ischemic myocardium presumably as a consequence of activation of phospholipases and delayed washout in ischemic tissue (43). Corr et al (44) exposed canine Purkinje fibers to concentrations of LPC and LPE equivalent to those found in ischemic tissue in vivo. They found that these agents produced potent electrophysiologic effects which included concentration dependent decreases in resting membrane potential, maximal upstroke velocity (dV/dT) of phase 0, and action potential duration. This was associated with decreases in conduction velocity and decreased excitability of the fibers. In short, these agents produced most of the cellular electrophysiologic abnormalities that had previously been recorded from ischemic tissue in vivo or in vitro (7,42). Thus these authors concluded that "accumulation of lysophosphoglycerides in ischemic myocardium may be a major factor responsible for the electrophysiological changes seen in ischemic myocardium, and in turn may be a major precipitant of the early malignant ventricular dysrhythmias." Recently, Shaikh and Downar (45) challenged this "lysolipid hypothesis". These investigators pointed out that the methods used by Sobel et al (43) could result in hydrolysis of phospholipids thereby producing artifactual contamination with lysolipids. Using a modification of the extraction and purification method which circumvented this problem, these investigators noted less than a 1-fold increase in lysophospholipid levels (LPC and LPE) during ischemia in the porcine heart. Since these low concentrations of lysophospholipids were insufficient to induce electrophysiologic abnormalities,

these investigators doubted the significance of lysolipids as the sole biochemical-electrophysiologic link during ischemia. Since the functional significance of even slight elevations of lysophospholipids in the presence of other concomitant changes associated with ischemia has not been thoroughly investigated, the "lysolipid hypothesis" remains a viable theory. However, the precise role of lysophospholipids has not yet been determined.

REPERFUSION ARRHYTHMIAS

Historical Note

During their early studies on the contractile response of ischemic myocardium, Tennant and Wiggers (46) first noted that restoration of blood flow to ischemic myocardium resulted in severe ventricular arrhythmias, most notable, ventricular fibrillation. In their words, "During several experiments, ventricular fibrillation occurred either before or just after the release of the clamp." However, these investigators did not elaborate upon this observation and thus it was not until the classic work of Harris and Rojas in 1943 that reperfusion arrhythmias became better characterized (1). These investigators noted that, "The readmission of blood after several minutes of occlusion proved to be an efficient means of producing a rapid tachycardia, usually, but not always, leading to fibrillation." It was their observations which led to a greater recognition of reperfusion arrhythmias and set the stage for the numerous investigations that were to follow. These investigations included both studies which have led to a better characterization of these arrhythmias, as well as studies which have attempted to unravel the electrophysiologic mechanisms responsible for reperfusion arrhythmias.

Characterization of Reperfusion Arrhythmias

Several previous investigations have led to a better characteri-

zation of reperfusion arrhythmias. These studies have demonstrated the relative severity of reperfusion arrhythmias compared to occlusive arrhythmias, the effect of duration of ischemia on incidence and severity of reperfusion arrhythmias, the relationship between occlusive and reperfusion arrhythmias, and the effect of antiarrhythmic agents on these arrhythmias.

Following recognition of the phenomenon of reperfusion arrhythmias, the malignant potential of these arrhythmias rapidly became apparent. While investigating the effect of antiarrhythmic agents on ischemic and reperfusion arrhythmias in over 900 dogs, Stephenson and his co-workers (47) noted that ventricular fibrillation was more than two times as likely to occur during reperfusion than during the 30 minutes of coronary occlusion. The numerous studies which followed have generally demonstrated that ventricular fibrillation occurs at least as frequently, and usually more often, during reperfusion than during the period of coronary occlusion (48-52). Although ventricular fibrillation is the most notable rhythm disturbance during restoration of flow to ischemic myocardium, reperfusion arrhythmias are not limited to ventricular fibrillation. Indeed, reperfusion arrhythmias encompass a whole gamut of arrhythmias which range from occasional premature complexes and non-sustained ventricular tachycardia to ventricular fibrillation (10, 48-53).

Even though there is a high incidence of ventricular arrhythmias following reperfusion, the period of vulnerability to ventricular fibrillation appears to be short. When reperfusion ventricular fibrilla-

tion occurs, it almost always begins abruptly within the first few seconds of reperfusion (1,3,10, 46-49). Thus, if the animal survives this initial vulnerable period, ventricular fibrillation rarely occurs (48,49). This observation is in agreement with Corbalan et al (5) who used the ventricular fibrillation threshold as an index of vulnerability during reperfusion. These investigators demonstrated that the ventricular fibrillation threshold fell precipitously within seconds of reperfusion, but rapidly returned to control values within 2 minutes.

Although ventricular fibrillation is generally limited to the first few seconds of reperfusion, other ventricular arrhythmias are not. Kaplinski et al (48) studied reperfusion arrhythmias in dogs following 30 minutes of coronary occlusion. They noted a 65% incidence of ventricular fibrillation within 30 seconds of reperfusion. However, in dogs that survived these "instantaneous reperfusion arrhythmias" or in dogs resuscitated from ventricular fibrillation, a second surge of arrhythmias occurred beginning 2-7 minutes after reperfusion. These "delayed reperfusion arrhythmias" lasted several minutes and consisted of frequent isolated premature ventricular contractions as well as episodes of ventricular tachycardia. Ventricular fibrillation was rarely seen at this time. Thus these investigators concluded that reperfusion arrhythmias consisted of two distinct periods of ventricular arrhythmias: an "instantaneous" phase beginning within 30 seconds of reperfusion and characterized by a high incidence of ventricular fibrillation, as well as a "delayed" phase beginning minutes after

reperfusion and characterized by a very low incidence of ventricular fibrillation.

Because the mechanisms of the "instantaneous" and "delayed" reperfusion arrhythmias appear to differ (48), a distinction as to the type of reperfusion arrhythmia under discussion becomes important. Thus, in future references to reperfusion arrhythmias, when it becomes necessary to distinguish the type of reperfusion arrhythmia, this thesis will employ the definition of "instantaneous" and "delayed" reperfusion arrhythmias as defined by Kaplinski et al (48).

Both the incidence and severity of reperfusion arrhythmias vary with the antecedent duration of coronary occlusion. In a large study involving 98 dogs, Balke et al (49) systematically investigated the effect of duration of coronary occlusion on reperfusion arrhythmias. These investigators subjected dogs to coronary occlusions for periods ranging from 5 to 60 minutes and recorded the incidence of reperfusion ventricular tachycardia and ventricular fibrillation. They noted that ventricular tachycardia and ventricular fibrillation were rare following 5 minute occlusions. However, as the antecedent period of coronary artery ligation was lengthened from 5 to 30 minutes, 84% of animals developed reperfusion arrhythmias which included both ventricular fibrillation (67%) and ventricular tachycardia (17%). When animals were subjected to 60 minutes of ischemia prior to reperfusion a similar high incidence of reperfusion arrhythmias (78%) was seen. However, the majority of these arrhythmias were episodes of non-sustained ventricular tachycardia. Interestingly, ventricular fibrillation occurred

much less commonly (22%) when reperfusion followed a 60 minute period of coronary occlusion. Other investigators have confirmed the observation that reperfusion ventricular fibrillation occurs less frequently with longer durations of coronary occlusion. In dogs reperfused 2 hours after coronary artery occlusion, Karagueuzian et al (53) noted that protracted ventricular tachycardia occurred in all dogs. However, reperfusion ventricular fibrillation was not observed. Thus, although the incidence of reperfusion arrhythmias generally increases with duration of ischemia, ventricular fibrillation is most frequently observed following relatively brief (10 to 30 minutes) periods of occlusion.

Several investigators have demonstrated a relationship between coronary occlusive arrhythmias and subsequent reperfusion arrhythmias. In dogs subjected to 10 minutes of left anterior descending coronary artery occlusion, Murdock and his co-workers (10) noted that reperfusion arrhythmias were only observed in those animals demonstrating coronary occlusive arrhythmias. They also reported that the occurrence of occlusive arrhythmias did not guarantee subsequent reperfusion arrhythmias. In this respect, their results differed somewhat from those of Kaplinski et al (48) who investigated reperfusion arrhythmias after 30 minutes of coronary occlusion. These investigators noted that reperfusion arrhythmias occurred in every animal demonstrating arrhythmias during the period of coronary occlusion. More recently Balke et al (49) systematically analyzed the relationship between the coronary occlusive arrhythmias and reperfusion arrhythmias and cor-

related this with duration of coronary occlusion. In dogs reperfused after relatively brief periods of occlusion (5 - 10 minutes), only 60% of animals demonstrating occlusive arrhythmias developed reperfusion arrhythmias. Thus, the occurrence of occlusive arrhythmias did not guarantee the re-emergence of arrhythmias during reperfusion when the period of occlusion was brief. However, as the period of coronary occlusion was lengthened to 20, 30 or 60 minutes, reperfusion arrhythmias occurred in every animal demonstrating occlusive arrhythmias. In those dogs which failed to develop coronary occlusive arrhythmias, the vast majority (81%) also failed to develop reperfusion arrhythmias regardless of the duration of coronary occlusion. Furthermore, reperfusion ventricular fibrillation rarely occurred (3%) in the absence of coronary occlusive arrhythmias. Conversely, in animals resuscitated from ventricular fibrillation during the period of coronary occlusion, and subsequently reperfused, a re-emergence of ventricular fibrillation during reperfusion was uniformly observed. Thus, these investigations demonstrate that both the incidence and the severity of reperfusion arrhythmias are correlated with the arrhythmias during the antecedent period of coronary occlusion.

With the growing recognition of reperfusion arrhythmias in the clinical setting, the effects of antiarrhythmic therapy on the arrhythmias has become increasingly important. Consequently, the effects of antiarrhythmic agents on reperfusion arrhythmias has become the subject of an increasing number of investigations. These investigations have included the standard antiarrhythmic agents (lidocaine, procainamide,

and quinidine), certain newer experimental agents (amiodarone), various calcium antagonists (nifedipine, verapamil, diltiazem) as well as alpha and beta adrenergic antagonists. Although a number of experimental models have been employed in these studies, most investigations have utilized models employing relatively brief periods of ischemia (15 - 30 minutes) and have concentrated on the "instantaneous" malignant reperfusion arrhythmias. As early as 1960 Stephenson and his co-workers (47) studied the effects of a number of antiarrhythmic agents on reperfusion arrhythmias in a large group of dogs subjected to 30 minutes of left anterior descending coronary artery occlusion. These investigators used incidence of reperfusion ventricular fibrillation as the index of antiarrhythmic efficacy. In 330 control untreated dogs, a 71% incidence of reperfusion ventricular fibrillation was observed. This figure was compared to the incidence of reperfusion ventricular fibrillation in 324 dogs treated with standard antiarrhythmic agents. The drugs were begun 10 minutes after occlusion and continued through reperfusion. These investigators were unable to document any significant reduction in incidence of reperfusion ventricular fibrillation with procaine, procainamide, quinidine or lidocaine. Similar results were recently obtained by Naito et al (51) who used the same duration of ischemia in 154 dogs. They also found that lidocaine and procainamide were ineffective in decreasing the incidence of reperfusion ventricular fibrillation when compared to control untreated dogs. Additionally, they reported that the newer investigational antiarrhythmic agent, amiodarone, was also ineffective in reducing

reperfusion ventricular fibrillation.

The effect of the calcium antagonists on reperfusion arrhythmias has been the subject of several recent investigations. Sheehan and Epstein (50) investigated the effects of diltiazem and nifedipine on reperfusion ventricular fibrillation in dogs subjected to 30 minutes of coronary occlusion. Both drugs were ineffective in reducing the incidence of reperfusion ventricular fibrillation. Similar results were obtained by Ribeiro and his co-workers (54) who also reported that nifedipine was ineffective in reducing reperfusion ventricular fibrillation in dogs after 25 minutes of ischemia. However, the effects of verapamil on reperfusion arrhythmias is controversial. In dogs subjected to 30 minutes of coronary occlusion, Naito et al (51) reported there was no difference in incidence of reperfusion ventricular fibrillation between dogs treated with verapamil and control untreated dogs. These results differ from those reported by Ribeiro et al (54). Among 8 dogs pretreated with verapamil, no animal developed reperfusion ventricular tachycardia and only one developed ventricular fibrillation. Since reperfusion ventricular tachycardia or fibrillation occurred in 6 of 8 control untreated dogs (tachycardia in 3 and fibrillation in 3), they concluded that verapamil was effective in decreasing reperfusion arrhythmias. However, the small number of animals in each group makes interpretation of their results difficult, particularly in view of the much larger study by Naito et al (51) which failed to show an antiarrhythmic effect of verapamil.

The effect of beta adrenergic blocking agents on reperfusion

arrhythmias has been investigated in a number of models. Sommers and Jennings (56) investigated the effects of propranolol in dogs subjected to 20 to 25 minutes of circumflex coronary artery occlusion. They noted no difference in incidence of reperfusion ventricular fibrillation between treated and untreated dogs. Similar results were obtained in the feline model. Sheridan et al (57) subjected cats to 35 minutes of left anterior descending coronary artery occlusion. They noted that pretreatment with propranolol failed to significantly effect either the number of reperfusion premature ventricular beats or the incidence of reperfusion ventricular fibrillation.

Unlike beta adrenergic blockade, alpha blockade has been demonstrated to protect against reperfusion arrhythmias in the feline model. Sheridan et al (57) studied the effects of alpha blockade on reperfusion arrhythmias in cats after 35 minutes of ischemia. They noted that both prazosin and phentolamine abolished reperfusion ventricular fibrillation and markedly reduced the absolute number of reperfusion premature ventricular beats. They attributed this antiarrhythmic effect to an attenuation of alpha adrenergically mediated enhanced ventricular automaticity. Since alpha stimulation decreases Purkinje cell automaticity in the canine heart (58,59), and since the instantaneous reperfusion arrhythmias in dogs do not appear to be due to enhanced automaticity (8,10), the antiarrhythmic effects of alpha adrenergic blockade may not extend to this model. Nevertheless, the observation that alpha blocking agents exhibit antiarrhythmic properties in the feline model represents a convincing demonstration that

the outcome of the "instantaneous" malignant variety of reperfusion arrhythmias can be affected by specific therapy. The importance of this antiarrhythmic effect in elucidating the mechanisms responsible for reperfusion arrhythmias in the feline model will be discussed separately.

In contrast to the almost universal ineffectiveness of antiarrhythmic agents in the canine model of reperfusion arrhythmias, the Langendorff perfused rat heart is extremely sensitive to a variety of antiarrhythmic agents. Lubbe et al (60) studied the effects of lidocaine on reperfusion arrhythmias in the isolated rat heart rendered ischemic for 15 minutes by ligation of the left main coronary artery. In this model, 100% of control rats developed ventricular fibrillation during reperfusion. However, when lidocaine was added to the perfusate, a concentration related reduction in reperfusion ventricular fibrillation was observed with complete protection obtained at 75 micromoles/liter. Using the same model, Thandroyen and his co-workers (52) investigated the effects of adrenergic blocking agents on reperfusion arrhythmias. They noted that the beta antagonists, propranolol and metoprolol but not atenolol, prevented reperfusion ventricular fibrillation. Because propranolol and metoprolol exert membrane stabilizing effects, while atenolol does not, the authors concluded that the antiarrhythmic properties of these agents were due to a direct membrane effect rather than a beta antagonistic effect. These authors further demonstrated that the alpha antagonists, phentolamine (α_1 and α_2), prazosin (α_1) and yohimbine (α_2)

were also able to abolish reperfusion arrhythmias in this model. Because prior reserpinization, with subsequent depletion of myocardial catecholamines, was not nearly as effective as the alpha antagonists in preventing reperfusion ventricular fibrillation, the authors suggested that much of their antiarrhythmic action may also be due to a direct membrane effect. Although little is known about the membrane effects of prazosin and yohimbine, the membrane stabilizing effects of phentolamine have been well described. Rosen et al (61) noted that phentolamine decreases upstroke velocity (dV/dT of phase 0), prolongs action potential duration, and decreases automaticity in canine Purkinje fibers. Sheridan and Penny (62) noted similar findings in the isolated guinea pig heart and further demonstrated that the membrane effects of phentolamine were markedly accentuated during ischemia and reperfusion.

The ability of membrane active drugs to protect against reperfusion ventricular fibrillation in the rat heart, but not the dog heart, is probably related to differences in cardiac mass. In order for ventricular fibrillation to occur, areas of inexcitability due to previous depolarization must coexist with areas of excitability so that propagation of circus movement can occur (63). Thus a certain "critical mass" is required to initiate and sustain ventricular fibrillation (64,65). Since it is more difficult for smaller hearts to meet this requirement, it is not surprising that smaller hearts are more resistant to ventricular fibrillation (66). Indeed, spontaneous defibrillation is regularly observed in the rat heart (52), but very

uncommon in the canine or human heart. Since most antiarrhythmic agents prolong refractoriness, the mass of myocardium in the inexcitable phase is increased. In smaller hearts, with marginal ability to maintain ventricular fibrillation, this effect may prevent initiation or continuation of ventricular fibrillation. However, in larger hearts this prolongation in refractoriness may be greatly overshadowed by the increase in mass such that no antifibrillatory effect is observed. This fact underscores the importance of the particular model employed when generalizing to the clinical situation. In this regard the canine model more closely approximates the human heart and probably better portrays the clinical situation than does the rat model.

Flow Determinants of Reperfusion Arrhythmias

In 1955 Sewell and his co-workers (3) made an observation which has had a large impact upon subsequent investigation of temporary coronary artery occlusion. They noted that the tendency to induce reperfusion arrhythmias was intimately related to the rate of reperfusion. Thus in dogs rendered ischemic by coronary artery ligation, they observed that ventricular fibrillation was common when blood flow to the ischemic area was restored rapidly by completely releasing the coronary ligation. However, when blood flow was restored slowly, by intermittently releasing the coronary ligation, ventricular fibrillation could be prevented. This observation has led to the standard

practice of intermittently restoring flow to ischemic areas in laboratories involved in studies of temporary coronary artery occlusion (67). The importance of the rate of reperfusion on subsequent arrhythmias has been confirmed in a more recent investigation. Sheehan and Epstein (68) measured circumflex coronary artery flow with an electromagnetic flow meter during reperfusion after 30 minutes of ischemia in the dog. They noted that peak reperfusion flow was significantly higher in dogs which developed reperfusion ventricular fibrillation than in those dogs which did not fibrillate. They also demonstrated that when a flow limiting partial occlusion was created prior to reperfusion, a protective effect on subsequent ventricular fibrillation was observed.

Do reperfusion arrhythmias result from a sudden restoration of essential nutrients (O_2 , fatty acids, etc.) to ischemic areas or to the washout of ischemic metabolites? Available evidence implicates the latter theory for the "instantaneous" reperfusion arrhythmias in the dog. Petropoulos and Meijne (69) perfused the circumflex coronary artery with venous blood, low-molecular dextran, saline and Tyrode's solution after unspecified durations of circumflex occlusion. These investigators frequently observed ventricular fibrillation at the start of reperfusion with each of these preparations. They also noted that they could eliminate these reperfusion arrhythmias by beginning reperfusion at a low flow rate (4 ml/minute) and then gradually increasing the rate (25 ml/minute). The fact that reperfusion ventricular fibrillation occurred with a variety of preparations other than arterial blood suggests that the "instantaneous" reperfusion arrhyth-

mias in the canine model is associated with the rapid washout of ischemic metabolites.

Reperfusion Electrophysiology

Investigators of reperfusion electrophysiology have recently provided us with considerable insight into the mechanisms underlying reperfusion arrhythmias. Using the same technique employed to study ischemic arrhythmias, these studies have investigated the role of enhanced automaticity and reentry during coronary reperfusion. Available evidence now indicates that there is no single mechanism for reperfusion arrhythmias as both enhanced automaticity and reentry have been implicated in various studies of reperfusion arrhythmias.

Enhanced automaticity has been demonstrated in the feline model of reperfusion. Penkoske et al (9) studied reperfusion electrophysiology in cats subjected to 35 minutes of left anterior descending coronary artery occlusion. This model regularly produced reperfusion tachyarrhythmias which included a 25% incidence of ventricular fibrillation. These investigators recorded the idioventricular escape rate during ischemia and reperfusion by arresting supraventricular pacemakers with intense vagal stimulation. They found a greater than 300% increase in the idioventricular escape rate within 3 minutes of reperfusion. This corresponded with the arrhythmic period in this model. However, within 15 minutes of reperfusion the idioventricular escape

rate had returned to normal and no further ventricular arrhythmias were observed. As another index of automaticity, these investigators studied the effects of rapid atrial pacing (250 - 300 beat per minute) in an attempt to overdrive the reperfusion arrhythmias. They found that rapid atrial pacing regularly prevented reperfusion arrhythmias, presumably because of overdrive suppression of enhanced ventricular automaticity. Though it is clear that ventricular automaticity is enhanced during reperfusion in this model, this mechanism alone was insufficient to fully account for the arrhythmias seen. Since the idioventricular escape rate during reperfusion averaged 188 beats per minute, while the rate of reperfusion ventricular tachycardia was 250 - 300 beats per minute, other mechanisms must also have been operative. These investigators proposed that enhanced automaticity may have initiated the reperfusion arrhythmias while reentry may be responsible for maintaining the arrhythmias.

The enhanced automaticity during reperfusion in the feline model appears to be mediated through alpha adrenergic mechanisms. Sheridan et al (57) demonstrated that alpha blockade with phentolamine, but not beta blockade with propranolol, abolished the increase in idioventricular rate seen during reperfusion in cats after 35 minutes of coronary artery occlusion. This increase in idioventricular rate could also be prevented by depleting myocardial norepinephrine levels with 6-hydroxydopamine. To further examine adrenergic responsiveness during coronary reperfusion, these investigators infused the alpha agonist methoxamine directly into the left anterior coronary artery in animals depleted of

myocardial norepinephrine by prior treatment with 6-hydroxydopamine. Before coronary occlusion, the idioventricular rate of 47 beats per minute was not significantly altered by methoxamine. In contrast, early after coronary reperfusion methoxamine significantly increased the idioventricular rate to 125 beats per minute. Animals depleted of myocardial catecholamines, and subjected to reperfusion without methoxamine, did not exhibit an increase in idioventricular rate. Thus, the enhanced ventricular automaticity observed during reperfusion arrhythmias in the cat appears to be mediated by alpha adrenergic mechanisms. This may explain the potent antiarrhythmic properties of alpha antagonists in this model (57).

In contrast to the feline model of reperfusion arrhythmias, enhanced ventricular automaticity does not appear to be responsible for the "instantaneous" reperfusion arrhythmias seen in the canine model. In dogs with complete heart block, Levites et al (8) studied the idioventricular pacemaker rate and the effects of sudden termination of a 30 second period of rapid ventricular pacing on the time for ventricular escape to occur as indices of ventricular automaticity. Neither of these parameters showed evidence of enhanced automaticity during reperfusion after 15 minutes of left anterior descending coronary artery occlusion. Similar results were obtained by Murdock and his co-workers (10) who studied ventricular automaticity after 10 minutes of coronary artery occlusion in dogs with complete heart block. These investigators paced the right ventricle during the ischemic period and terminated the pace simultaneous with reperfusion.

This protocol resulted in a slow idioventricular rate during reperfusion which was not different from the control idioventricular rate. They also noted that reperfusion at this slow heart rate completely protected against reperfusion arrhythmias. As a further index of automaticity these investigators also studied the effect of heart rate on reperfusion arrhythmias. They observed that faster heart rates (220 beats per minute) potentiated reperfusion arrhythmias while slower rates exerted a protective effect. Since faster heart rates should suppress automatic foci (70), while slower rates should unmask them, these investigators concluded that mechanisms other than enhanced automaticity account for reperfusion arrhythmias in the dog after relatively brief periods of coronary occlusion.

In dogs which survived the "instantaneous" reperfusion arrhythmias, Kaplinski et al (48) found that some animals exhibited a second surge of arrhythmias several minutes later which they termed "delayed" reperfusion arrhythmias. Using the technique of vagal stimulation to arrest supraventricular pacemakers, these investigators studied the idioventricular rate at intervals of 2 - 3 minutes through 15 minutes of reperfusion after coronary occlusions of 30 minutes. They found a marked increase in ventricular automaticity with some animals exhibiting a 300% increase in the idioventricular rate. However, the period of enhanced automaticity was brief - lasting only 15 minutes. Because the period of enhanced automaticity paralleled the occurrence of the delayed reperfusion arrhythmias, these investigators concluded that a transient "increased ventricular automaticity rather than a reentrant

mechanism probably explains these delayed and less malignant reperfusion ventricular rhythms."

There is now considerable evidence implicating reentry as the most plausible mechanism for the "instantaneous" reperfusion arrhythmias observed in dogs. However, as with ischemic arrhythmias, the evidence for reentry is indirect and largely based upon conduction studies of reperfused myocardium. Since reentry is dependent upon locally slowed conduction, identification of this prerequisite becomes essential before reentry can be considered a mechanism for reperfusion arrhythmias. Consequently, the nature of conduction through reperfused myocardium has been an integral part of most investigations of reperfusion electrophysiology. Levine et al (6) measured conduction times during ischemia and reperfusion in dogs subjected to 15 minutes of coronary occlusion. They found that the slowed conduction noted during the ischemic period was rapidly reversed by reperfusion. The rapidity with which conduction slowing as a consequence of ischemia is reversed by reperfusion was studied by Murdock and his co-workers (10). These investigators used close bipolar electrodes placed into the subendocardial and subepicardial layers to assess conduction through 10 minutes of coronary occlusion and reperfusion. They found that within 10 seconds of reperfusion only 10.2% of the maximum delay recorded at 10 minutes of ischemia was still present in the subepicardium, while no delay was present in the subendocardium. Since reentry is dependent upon slowed conduction, and reperfusion rapidly reverses the ischemic induced conduction delay, these observations would initially appear to

negate a reentrant mechanism for reperfusion arrhythmias. Indeed, the similar finding of a rapid improvement in conduction after 35 minutes of coronary occlusion was taken as strong evidence against a reentrant mechanism in the feline model of reperfusion arrhythmias (9). However, although conduction improves with reperfusion, in those areas of the heart rendered unresponsive by ischemia, the conduction improvement will initially result in a reemergence of delayed electrograms as tissue responsiveness is restored. This was demonstrated by Murdock and his co-workers (10) who reported that they were frequently unable to record conduction throughout the ischemic period because of a progressive decrease in electrogram amplitude. In many cases the reduction in electrogram amplitude continued until no identifiable electrogram was present at 10 minutes of ischemia. They theorized that such electrograms were recorded from sites rendered severely depressed or totally unresponsive by the ischemic insult such that conduction through these areas ceased. With reperfusion, electrograms were once again recorded from these sites as tissue responsiveness was restored. However, during the recovery process, the newly emerged electrograms again demonstrated conduction delay which rapidly waned with progressive reperfusion. Thus, as ischemia was reversed with reperfusion, a sequence of events was created where actual measurable conduction delay was increased during reperfusion. These results were confirmed by Kaplinski et al (48) who recorded electrograms through 30 minutes of ischemia and reperfusion in the dog. They also found that reperfusion restored electrogram amplitude in severely depressed

regions, but in so doing, delayed conduction was recorded from regions in which no electrical activity was recorded before reperfusion. The demonstration of the reappearance of delayed conduction in areas previously depressed by ischemia provides the necessary prerequisite of slowed conduction in order to consider reentry a viable mechanism for reperfusion arrhythmias.

As with ischemic arrhythmias, perhaps the most convincing evidence for reentry as a mechanism for the instantaneous reperfusion arrhythmias in dogs comes from composite electrogram recordings. Murdock and his co-workers (10) employed this technique to characterize conduction during ischemia and reperfusion. These investigators noted that ischemia resulted in long polyphasic fractionated electrograms, presumably as a consequence of slowed dyssynchronous activation under the multiple contact points of the composite electrode. The degree of maximal fractionation corresponded to the early arrhythmic period with continuous electrical activity being recorded between the paced and spontaneous premature beats. Such observations have previously been interpreted as supporting a reentrant mechanism for the early occlusive arrhythmias (37). These investigators also noted that as ischemia progressed, the degree of fractionation of the composite electrogram diminished corresponding to the arrhythmic free, quiescent period of ischemia. However, during reperfusion a sudden increase in electrogram fractionation occurred resulting in a reappearance of long polyphasic electrograms at the time reperfusion arrhythmias occurred. The newly emerged fractionated electrical activity spanned the dias-

tolic interval resulting in continuous electrical activity between the paced and spontaneous premature beats. This reemergence of delayed electrical activity on composite electrograms was confirmed by Kaplinsky et al (48) and Naito et al (51) who studied reperfusion arrhythmias after 30 minutes of ischemia. These investigators also noted that reperfusion increased the duration of the composite electrogram. When taken together with observations of conduction from local bipolar electrograms, these investigators concluded that reperfusion arrhythmias resulted from a reemergence of slowed conduction through areas of myocardium severely depressed by the antecedent ischemic insult (10,48,51).

Thus, available evidence indicates that no single mechanism accounts for all reperfusion arrhythmias. Mechanisms appear to vary with species, duration of ischemia, and duration of reperfusion. With this in mind, the investigation which follows is limited to the study of the mechanisms responsible for the "instantaneous" reperfusion arrhythmias which occur in dogs after 10 minutes of left anterior descending coronary artery occlusion.

METHODS

Experimental Preparation

Experiments were performed on 37 mongrel dogs of either sex ranging in weight from 13-25 kg. The dogs were anesthetized with intravenous sodium pentobarbital, 30 mg/kg body weight, and mechanical ventilation was provided through a cuffed endotracheal tube via a Bird Mark 7 respirator. The femoral artery was isolated and cannulated to monitor arterial pressure. The heart was exposed through a left lateral thoracotomy and a pericardial cradle constructed. The left anterior descending coronary artery (LAD) was dissected free below the first diagonal branch and myocardial ischemia was produced with an atraumatic vascular occluder. Heart rate was maintained at 150-220 beats per minute via right atrial or right ventricular pacing with stimuli 2 msec in duration and 4-8 volts delivered from a Grass S5 stimulator.

Local ischemic zone conduction times were measured in 20 right atrial paced dogs. In 14 dogs the LAD was occluded for 3-5 minutes and epicardial mapping with a bipolar exploring electrode was instituted to identify areas of conduction delay. After release of the occlusion, 4 or 5 close bipolar electrodes were inserted into the subepicardium in the regions in which conduction delay was identified. An additional one or two electrodes were inserted into the subendocardium. In six other dogs, the electrodes were randomly inserted into the subepicardial and subendocardial regions without the prior use of

the mapping technique. In all experiments, a control electrode was inserted into the non-ischemic zone. Each electrode consisted of two stainless-steel, teflon-insulated wires (0.003 inches in diameter) threaded through a 25-gauge hypodermic needle. The needle was used to plunge the wires into the myocardium and was then removed leaving the wires in place.

In 12 additional right atrial paced dogs, a large bipolar composite electrode was sutured to the epicardium in the region supplied by the LAD. The construction of this electrode was as follows. Two-inch cloth surgical tape was folded upon itself so that the adhesive sides approximated. The resulting piece was cut to an approximate size of 2-1/2 x 3-1/2 cm. Through this piece, 2 silver wires (0.10 inches in diameter) were woven side by side in an "S" or "U" shaped pattern. The resulting electrode had two terminals and consisted of 12-15 contact points of 1-2 mm in length, covering an area of epicardium 2 x 3 cm. A similar electrode was sewn to a non-ischemic area.

All electrograms were amplified with Grass P511 preamplifiers with a low frequency cutoff of 30 Hz and displayed along with a lead II ECG on a Beckman 612 strip recorder, a Grass model 7 polygraph or a Siemens Elema model 803 direct writing mingograph at paper speeds of 25-200 mm/sec. Selected electrograms and a lead II EKG were recorded on a Tektronix 5111 storage oscilloscope at sweep speeds of 20 msec/cm for photographic purposes.

Ventricular automaticity was assessed in five dogs during reperfusion after complete atrioventricular (AV) block was produced by

injecting formalin into the AV node according to the method described by Loeb et al (71). The heart was exposed via a right thoracotomy using standard surgical techniques. A 25-gauge needle was inserted 1.5 cm lateral to the coronary sinus through the free wall of the right atrium. The needle was directed inferiorly toward the region of the AV node. The needle position was adjusted until a 0.2 ml injection of 2% lidocaine produced a transient period of 2^o or 3^o heart block. When the position was assured, 0.2 ml of 37% formalin was introduced into the region. This resulted in the immediate production of complete heart block. The chest was closed in the usual fashion and the animal allowed to recover. Lead II of the EKG was monitored daily to ensure the production of a stable idioventricular rhythm and absence of any other associated arrhythmias. Seven to 10 days after the initial surgery, the dogs were reanesthetized and prepared in the same manner as the other dogs, except that heart rate was maintained by right ventricular pacing.

Experimental Protocol

Local conduction times were measured through 10 minutes of ischemia and continuously during reperfusion. After LAD occlusion, progressive delay of the local electrogram within the ischemic zone was manifested as an increase in the time between onset of the QRS complex of the standard lead II EKG and the R wave of the local

electrogram. This time was measured in milliseconds at 10 minutes of ischemia from recordings at paper speeds of 200 mm/sec. The amount of ischemic delay in each local electrogram immediately before reperfusion (10 minutes of ischemia) was normalized and percent of maximal ischemic conduction delay at 5 and 10 seconds of reperfusion in each electrogram was determined for both the subendocardium and subepicardium. The mean \pm SEM of these normalized values was calculated. The mean and range of conduction delay in these regions was also determined. After conduction times were recorded during ischemia and reperfusion, the electrodes were repositioned and at least 30 minutes were allowed before additional conduction times were obtained.

Conduction delay on the composite electrogram appeared as a fractionation and increase in duration of the electrogram. A tracing of the composite electrogram at 100 mm/sec was obtained at each minute of ischemia and continuously during reperfusion. Representative tracings were obtained from the early arrhythmic period, the subsequent quiescent period and during reperfusion for each dog.

In dogs with complete AV block, ventricular automaticity was measured as the idioventricular escape rate following the temporary cessation of ventricular pacing. Control automaticity was assessed immediately before occlusion. Then, ischemia was produced and the dogs were paced at 150 beats per minute through the 10 minute period of ischemia. The occlusion was released simultaneously with cessation of pacing, providing an assessment of automaticity during reperfusion. The mean \pm SEM of the automatic rates was calculated. The "t" test

for paired data was used to compare the rates.

The five dogs with complete AV block were also used to study the effect of heart rate on reperfusion arrhythmias. In each dog, additional occlusions were instituted with heart rate held constant at 150 beats per minute during the ischemic period. After 10 minutes of ischemia, the heart rate was either maintained at 150 beats per minute during reperfusion or increased to 220 beats per minute 15 seconds before reperfusion. To rule out the possibility that repeated occlusions caused the observed effects of heart rate on reperfusion arrhythmias, the order in which we studied automaticity, 220 beats per minute and 150 beats per minute during reperfusion, was varied in each dog.

If ventricular fibrillation intervened during ischemia, the experiment was terminated. However, if ventricular fibrillation occurred only during reperfusion, defibrillation was accomplished with a 20 Joules DC pulse applied directly to the heart. At least 30 minutes were allowed before additional studies were undertaken.

RESULTS

Arrhythmias

Ventricular arrhythmias occurred in 33 of 37 animals during the 10 minute period of coronary artery occlusion. The frequency of arrhythmias generally reached a maximum within the first 6 - 8 minutes and then declined. Ventricular fibrillation, when present, occurred during the period of maximum ectopic activity. Thirty of 37 dogs survived the 10-minute period of ischemia. In each of these dogs, occlusive arrhythmias were generally absent or greatly diminished by 10 minutes of ischemia. A reemergence of ectopic activity was noted in 22 of 30 dogs after release of the occlusion. The severity of these reperfusion arrhythmias varied from two or three ectopic beats to ventricular fibrillation. Reperfusion arrhythmias were never observed unless ischemic arrhythmias developed. However, ischemic arrhythmias did not guarantee subsequent reperfusion arrhythmias. When arrhythmias developed during reperfusion, the onset was always noted within the first 10 seconds of release of the occlusion and usually within the first 5 seconds. The duration of the arrhythmic period during reperfusion was brief and generally lasted no more than 5 - 15 seconds unless ventricular fibrillation intervened.

After reperfusion, all animals were observed for at least 30 minutes. No additional reperfusion arrhythmias were noted in those animals which survived the early reperfusion arrhythmias.

Automaticity and Effect of Heart Rate

The five dogs with complete AV block showed no significant difference in ventricular automaticity between the preischemic and reperfused state. The rate of the idioventricular pacemaker immediately before occlusion was 47.6 ± 5.8 beats per minute and was unchanged (50.6 ± 6.0 beats per minute) during reperfusion ($p > 0.05$).

Although the severity of arrhythmias varied from dog to dog, heart rate had a consistent effect on the intensity of reperfusion arrhythmias. Figure 1 shows a typical experiment illustrating the effect of heart rate on reperfusion arrhythmias. When heart rate was maintained at 150 beats per minute during reperfusion, arrhythmias appeared in three of the five dogs tested. Ventricular fibrillation was not observed in these dogs at this rate. However, when the pacing rate was increased to 220 beats per min 15 seconds before reperfusion, arrhythmias appeared in all five dogs which culminated in ventricular fibrillation in three of these five. When pacing was terminated simultaneously with reperfusion, allowing for a slow idioventricular rhythm to appear, no arrhythmias appeared. The order in which the heart rate studies were performed could be altered without affecting the general outcome; i.e., more rapid heart rates always potentiated reperfusion arrhythmias, while slower heart rates had a protective effect.

FIGURE 1

THE EFFECT OF HEART RATE ON REPERFUSION ARRHYTHMIAS

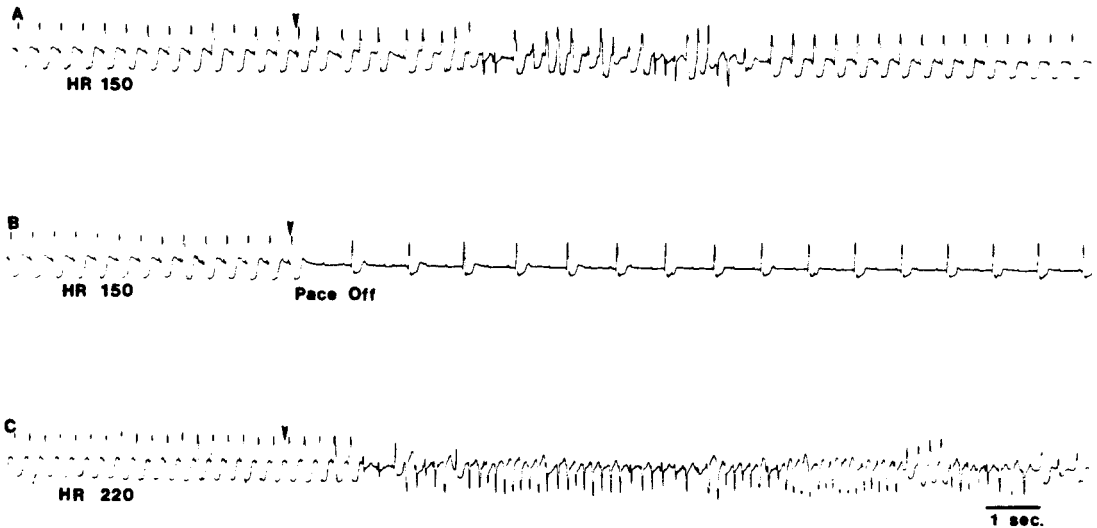


FIGURE 1. The effect of heart rate (HR) on reperfusion arrhythmias. Each panel is a lead II EKG recorded immediately before and during reperfusion. In each panel the occlusion was released at the arrow. In panel A, the pacing rate was maintained at 150 beats per minute during reperfusion and within seconds, a short run of ventricular tachycardia appeared. In panel B, the pace was terminated simultaneously with reperfusion, resulting in a slow idioventricular rhythm without reperfusion arrhythmias. In panel C, the pacing rate was increased from 150 to 220 beats per minute 15 seconds before reperfusion. Within 2 seconds of reperfusion a very rapid ventricular tachycardia appeared which lasted approximately 15 seconds before the paced rhythm resumed.

Local Conduction Studies

Close bipolar electrodes were used to measure local conduction times in 20 dogs. Measurements were excluded from 7 dogs due to the occurrence of ventricular fibrillation during either occlusion (5 dogs) or reperfusion (2 dogs). In the remaining 13 dogs, a total of 117 bipolar electrograms were recorded through 10 minutes of ischemia and 10 seconds of reperfusion. Ninety-three of these local electrograms were recorded from subepicardial sites and 24 were recorded from subendocardial sites. Ischemia produced conduction delay in 80 of the 93 electrograms recorded from the subepicardium and 10 of the 24 electrograms recorded from the subendocardium. For the electrograms showing conduction delay, the mean delay at 10 minutes of ischemia was 24.4 msec (range 5 - 55 msec) for the subepicardium and 6.3 msec (range 2 - 14 msec) for the subendocardium.

Reperfusion rapidly reversed the ischemia induced conduction delay. Within 5 seconds of reperfusion, the maximal ischemic delay had decreased to $40.3 \pm 2.6\%$ in the subepicardium and $16.6 \pm 10.2\%$ in the subendocardium. By 10 seconds of reperfusion, only $10.2 \pm 1.6\%$ of maximal delay was recorded in the subepicardium and no delay was recorded in the subendocardium.

Electrograms which demonstrated no delay during the ischemic period also showed no delay during reperfusion. Furthermore, on no occasion did reperfusion result in an increase in the ischemia induced conduction delay. In every case, the conduction delay resulting from ischemia rapidly returned to control with reperfusion. This improve-

ment began almost immediately and was progressive with each beat until control values were again achieved. It was even possible to demonstrate a small but definite improvement in conduction in each of the electrograms from the two animals which fibrillated within 3 seconds of reperfusion.

Conduction delay was observed in an additional 25 electrograms. However, progressive loss of electrogram amplitude precluded conduction time measurement at 10 minutes of ischemia. Figure 2 illustrates this phenomenon and furthermore demonstrates the reemergence of delayed electrical activity during reperfusion. Each panel consists of an oscilloscope trace of a lead II EKG and 3 local electrograms recorded from the subepicardium. Panel A was recorded immediately prior to occlusion. Panels B and C were recorded at 5 and 8 minutes of ischemia respectively. Note the progressive increase in conduction delay and decrease in electrogram amplitude. Panel D was recorded at 10 minutes of ischemia immediately prior to reperfusion. At this time the intrinsic deflection of each electrogram can no longer be recognized. However, by 5 seconds of reperfusion (E), local electrical activity has reappeared and each electrogram again demonstrates conduction delay when compared to control panel A. Thus as reperfusion reversed the electrophysiologic effects of ischemia, a situation was created whereby delayed conduction was initially recorded from electrograms showing no electrical activity at 10 minutes of ischemia. This period of conduction delay was brief. As shown in panel F, by 10 seconds of reperfusion each electrogram had returned to control as conduction rapidly improved.

FIGURE 2

LOCAL CONDUCTION STUDIES DURING ISCHEMIA AND REPERFUSION

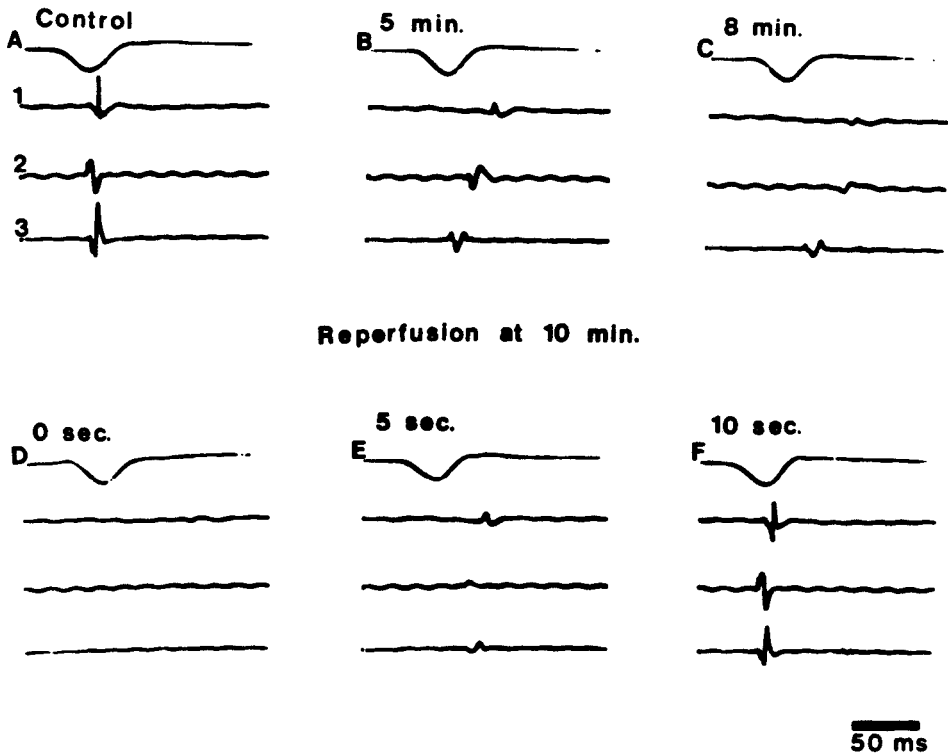


FIGURE 2. The establishment of delayed conduction in regions in which no electrical activity was identifiable at 10 minutes of ischemia. Each panel is an oscilloscope trace of a lead II EKG and three bipolar electrograms recorded from different regions of the subepicardium. Panel A was recorded immediately before occlusion. Panels B and C were recorded at 5 and 8 minutes of ischemia. Note the increase in conduction delay and progressive decrease in electrogram amplitude with continued ischemia so that by 10 minutes (panel D) no intrinsic deflections could be identified. However, by 5 seconds of reperfusion (panel E) the intrinsic deflections of the electrograms have reemerged and each again demonstrates conduction delay when compared with control panel A. With progressive reperfusion (panel F), conduction continues to improve and the electrograms return to control.

Composite Electrode Studies

Composite electrodes were utilized in 12 dogs to provide a qualitative assessment of conduction during ischemia and reperfusion. Ten of these 12 animals survived a 10 minute period of ischemia. Eight of the surviving animals demonstrated reperfusion arrhythmias.

Conduction slowing on the composite electrogram was manifest as an increase in duration of the electrogram resulting in delayed fractionated electrical activity. This phenomenon was only observed in electrograms recorded from the ischemic site. The degree of fractionation was always closely correlated with the presence of arrhythmic activity. Thus, after occlusion of the LAD, the degree of fractionation increased and became maximal during the early arrhythmic period and then declined along with the arrhythmias as ischemia progressed. Reperfusion led to a dramatic reemergence of delayed fractionated electrical activity and a simultaneous return of arrhythmias. This course of events is illustrated in figure 3. Each panel consists of a lead II EKG above and a composite electrogram within the ischemic zone below. Panel A was recorded immediately prior to occlusion. The composite electrogram at this time consisted of a discrete narrow complex indicating rapid and nearly simultaneous activation under the multiple contact points. Panel B was recorded at 6 minutes of ischemia during the arrhythmic period. Note that both atrial paced beats in this panel are followed by a short run of non sustained ventricular tachycardia. Examination of the corresponding composite electrograms demonstrates that each episode of tachycardia is preceded by extensive

FIGURE 3

CONDUCTION CHARACTERISTICS DURING ISCHEMIA AND REPERFUSION
USING A COMPOSITE ELECTRODE

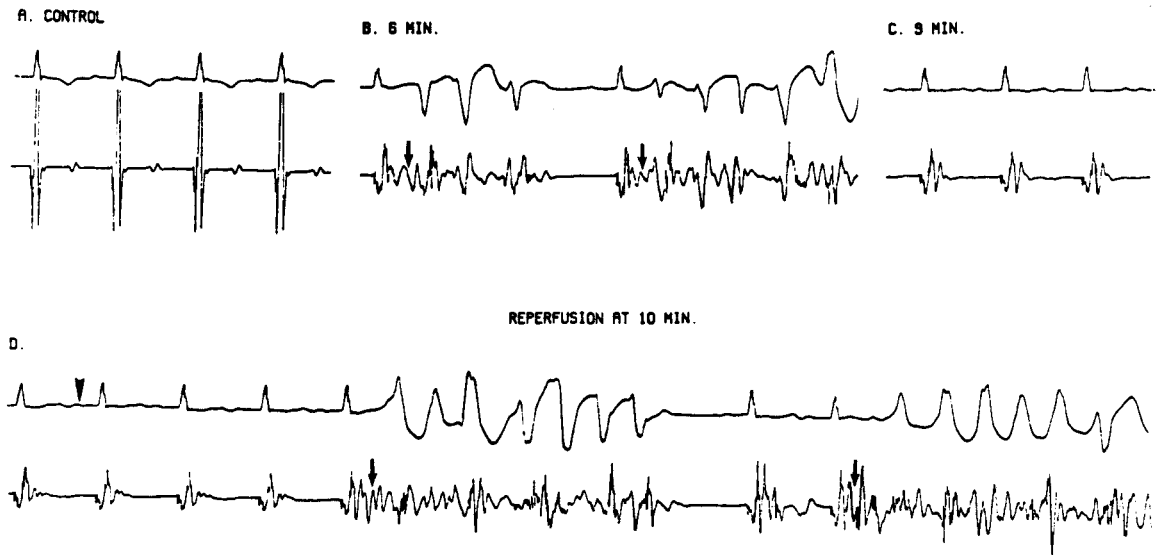


FIGURE 3. Conduction characteristics during ischemia and reperfusion using a composite electrode. Each panel is a lead II EKG (above) and a composite electrogram (below). Ischemia was characterized by an initial marked fractionation of the composite electrogram which maximized during the arrhythmic period (panel B). However, with progressive ischemia, arrhythmias abated and extensive electrogram fractionation was no longer observed (panel C). Reperfusion was characterized by a sudden increase in fractionation of the composite electrogram (panel D), which corresponded with a return of arrhythmias. See text for details.

fractionation of the composite electrogram (marked by small arrows) such that delayed electrical activity spans the entire interval between the paced and each initial spontaneous premature beat. Furthermore, this fractionation continues during the period of ventricular tachycardia while the compensatory pause, following the first episode of ventricular tachycardia, is devoid of this fractionated electrical activity. At 9 minutes of ischemia (C), the arrhythmias have abated and extensive fractionation of the composite electrogram is no longer observed. Panel D was recorded during reperfusion. The occlusion was released at the arrow in the upper trace. Note that within 2 seconds of reperfusion, a short run of ventricular tachycardia occurs. This is followed almost immediately by a second episode of reperfusion ventricular tachycardia which went on to culminate in ventricular fibrillation. Examination of the corresponding composite electrograms reveals that reperfusion has resulted in a dramatic increase in the degree of fractionation of the electrograms due to the reemergence of delayed electrical activity. This phenomenon is clearly shown in the two electrograms (marked with small arrows) preceding each bout of reperfusion ventricular tachycardia. Note that this reemergence of delayed fractionated electrical activity precedes the onset of the arrhythmia and during the period of tachycardia, continues to span the electrical diastolic interval.

In figure 3 the nature of the delayed fractionated electrical activity during reperfusion is not entirely clear. It is difficult to definitely determine whether the electrical activity represents delayed

depolarization activity and thus true delayed dyssynchronous conduction, or merely electrogram T-wave. However, additional experiments demonstrated that the reemergence of delayed electrical activity represented true depolarization activity. An example of such an experiment is illustrated in Figure 4. Each panel consists of a short trace of a lead II EKG above and a composite electrogram recorded from the ischemic zone below. Panel A was recorded immediately prior to occlusion and again a discrete narrow electrogram complex is evident. At 4 minutes of ischemia (B), the arrhythmic phase is present and the second paced beat is followed by 2 ectopic beats. The electrogram of the paced beat immediately prior to the ectopic beats (marked with small arrows) shows continuous fractionation which spanned the interval between the paced and ectopic beats. With progressive ischemia (C and D), the early arrhythmic period subsided and very little delayed fractionated electrical activity was observed.

Panel E represents a divided but continuous trace of the reperfusion period. The occlusion was released at the arrow in the upper trace and within 2 seconds, a short run of ventricular tachycardia occurred. Again, close examination of the electrogram preceding each set of ectopic beats reveals the presence of delayed electrical activity not present during the late ischemic period. This is seen most clearly in the 10th and 16th cycles where a small electrical spike (arrows) precedes the occurrence of ectopic activity. In the lower trace, ectopic activity is absent and the presence of newly emerged delayed electrical activity is even more apparent on the electrogram.

FIGURE 4

THE ORIGIN OF DELAYED ELECTRICAL ACTIVITY ON THE
COMPOSITE ELECTROGRAM DURING REPERFUSION

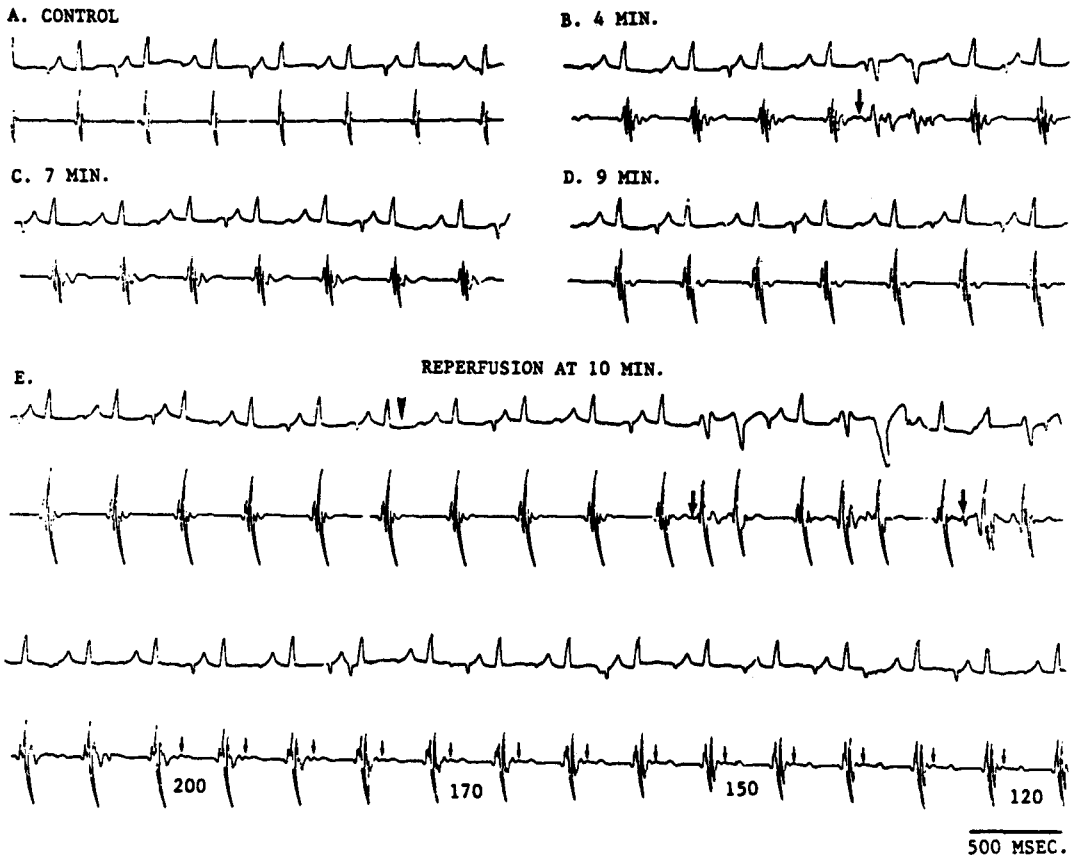


FIGURE 4. The reemergence of delayed, fractionated electrical activity during reperfusion. Each panel consists of a lead II EKG (above) and a composite electrogram (below). Note that the composite electrogram shows delayed, fractionated electrical activity during the arrhythmic period (panel B), disappearance of fractionation during the quiescent period (panel C and D) and a reemergence of delayed, fractionated electrical activity with reperfusion (panel E). Furthermore, as shown in the lower trace of panel E, the newly emerged delayed electrical activity moves toward the intrinsic deflection of the electrogram with progressive reperfusion, indicating this electrical activity results from depolarization of slow conducting tissue and not electrogram T wave. See text for details. Pacemaker artifact precedes each P-wave.

Furthermore, careful scrutiny of these electrical spikes (marked in each subsequent cycle by a small arrow) revealed a progressive movement toward the intrinsic deflection of the electrogram with reperfusion. This was demonstrated by a decrease in the coupling interval (shown under the electrogram) from 200 msec to 120 msec over 16 beats. The coupling interval was measured between the onset of the intrinsic deflection of the composite electrogram and the peak of the indicated electrical spike. The fact that the newly emerged electrical spikes move toward, and eventually converge with the intrinsic deflection of the electrogram with reperfusion, is consistent with the notion that these spikes represented a reemergence of depolarization activity arising from regions of slowly conducting tissue.

DISCUSSION

Originally considered an experimental curiosity, the clinical significance of reperfusion arrhythmias in man is now well established. Reperfusion arrhythmias are commonly observed in patients suffering an acute myocardial infarction in which thrombolytic agents have been used to restore blood flow to the ischemic area (25-27). However, perhaps more significant is the realization that reperfusion arrhythmias may occur spontaneously in the setting of coronary artery spasm. During their investigations of the arrhythmias which accompany coronary artery spasm, Kerin et al (23,24) noted that serious ventricular arrhythmias frequently occurred at a time when the ischemia induced ST segment elevation on the EKG was beginning or had completely resolved suggesting that the arrhythmias were occurring during reperfusion. Similar findings were reported by Maseri et al (72) who studied patients angiographically during episodes of coronary artery spasm. These investigators observed episodes of ventricular tachycardia and occasionally ventricular fibrillation when blood flow to an ischemic area was restored as a result of relaxation of coronary artery spasm. This concept was taken a step further by Elharrar and Zipes (73). Since most patients dying suddenly of ventricular fibrillation do not demonstrate occlusive coronary disease (74), these investigators suggested that reperfusion ventricular fibrillation resulting from relaxation of coronary artery spasm may be a mechanism for sudden death.

After the work of Harris and Rojas (1), numerous investigators

have confirmed malignant ventricular arrhythmias appearing within the first few minutes of occlusion and gradually diminishing with progressive ischemia (4,5,14). Scherlag et al (14) demonstrated that the early occlusive arrhythmias were exacerbated by rapid atrial pacing and were abolished during vagally induced atrial arrest, leading these investigators to discount enhanced automaticity as the mechanism responsible for the early occlusive arrhythmias. Recently, several studies have shown marked slowing and fractionation of conduction through acutely ischemic myocardium, establishing the prerequisites for reentry (11-14,37).

Although reentry is generally regarded as the most plausible explanation for the early occlusive arrhythmias, the mechanisms underlying the reemergence of arrhythmias with reperfusion are less clear. Experiments on the role of enhanced automaticity during reperfusion have yielded conflicting results. In dogs with complete AV block, Levites et al (8) studied the idioventricular pacemaker rate and the effects of sudden termination of a 30-second period of rapid ventricular pacing on the time for ventricular escape to occur as indices of ventricular automaticity. Neither of these parameters showed evidence of enhanced automaticity during reperfusion after 15 minutes of ischemia. However, in a more recent study, Penkoske et al (9) demonstrated an accelerated idioventricular rate in vagally arrested cats reperfused after 35 minutes of ischemia. Furthermore, they noted that rapid atrial pacing suppressed the arrhythmias of reperfusion and concluded that enhanced automaticity may play a role in the initiation of reper-

fusion arrhythmias. However, since the idioventricular rates (188 beats per minute) were not sufficient to account for the arrhythmias (250-300 beats per minute), they concluded that other mechanisms for the arrhythmias could also have been operative.

The present study found no evidence of enhanced automaticity during reperfusion. When pacing was terminated simultaneously with reperfusion, the result was a slow idioventricular escape rhythm which was not significantly different from the preocclusive rate. Furthermore, faster heart rates (220 beats per minute) potentiated the arrhythmias of reperfusion, while slower rates exerted a protective effect. Thus, this thesis found that the arrhythmias of reperfusion behaved similarly to the arrhythmias of early ischemia with respect to varying heart rate. Since faster pacing rates would be expected to suppress automatic foci (70), our results suggest that mechanisms other than enhanced automaticity account for the reperfusion arrhythmias observed in dogs after short periods of ischemia, in agreement with the work of Levites et al (8). The reason for the discrepancy between the present findings and those of Penkoske and her co-workers (9) is not clear but suggest that mechanisms of reperfusion arrhythmias may vary with species and/or duration of ischemia.

That duration of ischemia may influence mechanisms of reperfusion arrhythmias is suggested by comparing the present work to that of Kaplinski et al (48). Using a 30 minute period of coronary occlusion these investigators noted that dogs developed two distinct periods of reperfusion arrhythmias. Those arrhythmias beginning within seconds

of reperfusion were characterized by a high incidence of ventricular fibrillation and were termed "instantaneous reperfusion arrhythmias". However, in some dogs surviving the "instantaneous reperfusion arrhythmias", a second surge of arrhythmias occurred minutes later. These "delayed reperfusion arrhythmias" were characterized by a low incidence of ventricular fibrillation. The finding of an accelerated idioventricular rate during the period of delayed reperfusion arrhythmias led these investigators to conclude that the mechanism for the delayed phase of arrhythmias was enhanced automaticity (48).

Using a 10 minute period of coronary occlusion, this thesis did not demonstrate two periods of reperfusion arrhythmias. In the present study, all episodes of reperfusion arrhythmias began within 10 seconds of reperfusion and persisted only a few seconds unless ventricular fibrillation intervened. Thus these reperfusion arrhythmias appeared to be analogous to the "instantaneous reperfusion arrhythmias" reported by Kaplinsky et al (48). However, unlike the results reported by these co-workers, no additional reperfusion arrhythmias were observed after the termination of the initial phase of reperfusion arrhythmias. This finding suggests that it may take longer a duration of ischemia in order to produce the delayed period of enhanced automaticity reported by Kaplinsky and his co-workers (48).

Since reentry is dependent upon slow, nonuniform conduction, this thesis analyzed the nature of conduction during ischemia and reperfusion. The present study observed significant ischemic zone conduction delay in the subepicardium (mean 24.4 msec, range 5-55 msec) while only

minimal delay appeared in the subendocardium (mean 6.3 msec, range 2-14 msec). This is consistent with the work of Scherlag et al (14), who compared the electrograms of the subendocardial, subepicardial and intramural layers. They found the greatest delays in the subepicardial layers and inferred that reentry occurs in that region. This presumably results from the additive effects of slow conduction through deeper intramural layers as well as the subepicardial layers themselves.

The conduction delay that occurs as a consequence of ischemia is promptly abolished with reperfusion. In cats subjected to 35 minutes of ischemia, Penkoske et al (9) demonstrated that within 60 seconds of reperfusion, conduction time from the endocardial to the mid-myocardial regions of the ischemic zone returned to control while the residual delay in the epicardial region markedly improved. This thesis also demonstrated a prompt reversal of the ischemia-induced conduction delay. In every experiment, a rapid return toward normal conduction was observed on the local bipolar electrograms such that by 10 seconds of reperfusion only 10.2% of the ischemia-induced delay was observed in the subepicardium and no delay was observed in the subendocardium. Regardless of the region sampled or the amount of delay observed during ischemia, a further delay of conduction was never observed during reperfusion.

In addition to conduction delay, ischemia regularly produces a loss of electrogram amplitude (11-13,33). This phenomenon was also observed in the present study. Furthermore, as shown in figure 2, in

some regions this loss of electrogram amplitude continued such that by 10 minutes of ischemia no electrical activity was able to be recorded. However, within seconds of reperfusion a reemergence of electrograms was observed. Significantly, these newly emerged electrograms once again demonstrated conduction delay which waned with progressive reperfusion. Thus, although the electrophysiologic abnormalities of ischemia were rapidly reversed by reperfusion, the initial result of reperfusion was an actual increase in measurable conduction delay in those regions devoid of electrical activity as a result of the insult of ischemia.

The composite electrode, with its multiple contact points, has proved to be a valuable method for detecting areas of markedly delayed conduction by recording delayed, fractionated electrical activity (16,35,37). The recording of delayed, fractionated electrical activity from the epicardium in the present study always correlated well with the time course of arrhythmias. Thus, as shown in figures 3 and 4, the early arrhythmic period was marked by delayed, fractionated electrical activity that spanned the interval between the paced and ectopic beats, while the quiescent period demonstrated little fractionation. Reperfusion led to a dramatic reemergence of fractionated electrical activity, which was associated with a return of arrhythmias. Furthermore, as shown in figure 4, the newly emerged delayed fractionated electrical activity moved toward and eventually converged with the intrinsic deflection of the composite electrogram as conduction within the reperfused region improved. This finding demonstrates that the

reemergence of delayed fractionated electrical activity immediately after reperfusion results from a temporary reemergence of slowed dyssynchronous conduction. This delayed, fractionated electrical activity, which spanned the interval between paced and ectopic beats, is strongly suggestive of a reentrant mechanism (16,35,37).

In the present experiments, the frequency of ectopic activity reached a maximum within the first 6-8 minutes and then declined, leading to an ectopia-free quiescent period by 10 minutes of ischemia. Scherlag et al (14) attributed the onset of the quiescent period to a paradoxical improvement in conduction delay with progressive ischemia such that sufficient delay to sustain reentry was no longer present. In support of this, they reported electrograms that displayed less conduction delay at 30 minutes of ischemia than during the early arrhythmic period. However, since the arrhythmic period is generally over by 10 minutes (1), any mechanism that causes a decline in arrhythmias should manifest itself by this time. In the present study, an improvement in the ischemia-induced conduction delay on bipolar electrograms was never observed after the termination of the arrhythmic period. Instead, a progressive decrease in electrogram amplitude occurred, which in many cases continued until no electrical activity was recorded (fig. 1). In the intact porcine heart, Downar et al (7) demonstrated that ischemia led to a decrease in the upstroke velocity and amplitude of epicardial transmembrane action potentials, which often continued to total unresponsiveness of the fiber. Thus, in the present study, electrodes that recorded a complete loss of amplitude

during ischemia were probably positioned in areas in which a severe depression or unresponsiveness of fibers had occurred as a result of ischemia. The decrease in amplitude of the bipolar electrograms and the disappearance of delayed, fractionated electrical activity on the composite electrograms suggest that the quiescent period results not from an improvement in conduction, but rather from a further deterioration of tissue responsiveness with resultant block of reentrant pathways. It is this situation which appears to create the necessary environment for reperfusion arrhythmias. Since reperfusion promptly restores electrical activity in fibers rendered unresponsive by ischemia (7), it is likely that reperfusion also transiently reestablishes the conditions necessary for reentry. In the present study, reperfusion at 10 minutes of ischemia resulted in the reemergence of delayed, fractionated electrical activity in the composite electrograms (figs. 3 and 4) along with an increase in the amplitude of delayed electrical complexes in the close bipolar electrograms (fig. 2). Thus, it appears that reperfusion reestablishes slow conduction through severely depressed regions which allows reentrant pathways to form again resulting in the reemergence of ectopic activity.

Figure 5 is a simplified schematic representation which summarizes the mechanisms underlying the arrhythmias of ischemia and reperfusion as well as the quiescent period as suggested by the present study. In the figure, the cross-hatched areas represent normal myocardium, the black areas represent unresponsive tissue while the white areas represent regions of slow, nonuniform conduction. Tracings from top to

FIGURE 5

SCHEMATIC ILLUSTRATION OF MECHANISM OF ISCHEMIC AND REPERFUSION ARRHYTHMIA

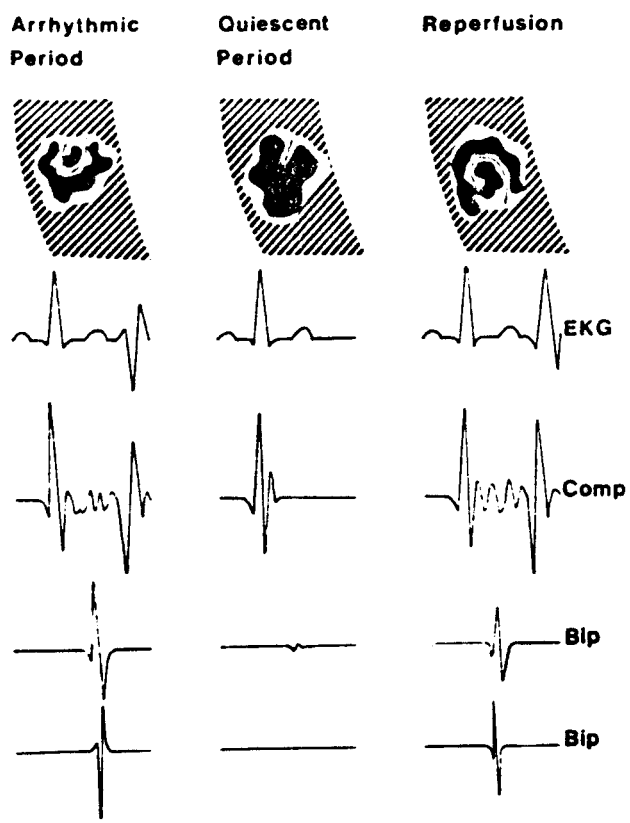


FIGURE 5. This schematic illustration depicts the mechanism purposed for the arrhythmias during ischemia and reperfusion as well as the absence of arrhythmias during the quiescent period. In this figure, the cross-hatched areas represent normal myocardium, the black areas represent unresponsive tissue while the arrows coursing through the white regions represent slowly conducting impulses through depressed tissue. Below each figure is a corresponding representation of an EKG, a composite electrogram (Comp) and 2 bipolar electrograms (Bip). See text for details.

bottom represent a standard EKG lead, a composite electrogram, and two bipolar electrograms recorded from the ischemic zone. During the arrhythmic period, slow conduction is shown by a fractionated composite electrogram as well as bipolar electrograms delayed beyond the QRS of the EKG. These conditions set up the prerequisites for reentry and an ectopic beat is shown on the EKG. As ischemia progresses, the myocardium becomes increasingly unresponsive and reentrant pathways become blocked, thus marking the onset of the quiescent period. At this time, the composite electrogram shows less fractionation while the bipolar electrograms display a progressive decrease or complete loss of amplitude. Reperfusion restores electrical activity to previously unresponsive tissue, but in doing so, transiently reestablishes areas of slow conduction allowing reentrant pathways to form again. This is manifest by a return of electrical activity on the bipolar electrogram and a reemergence of delayed fractionated electrical activity on the composite electrogram.

The reemergence of delayed electrical activity in regions rendered unresponsive by ischemia has been subsequently confirmed by others. Using a 30 minute period of ischemia Kaplinski et al (48) and Naito et al (51) employed both local bipolar as well as composite electrograms to assess conduction during ischemia and reperfusion. Both investigators demonstrated a reemergence of delayed electrograms within seconds of reperfusion leading them to similarly conclude that reentry was the underlying mechanism of these instantaneous reperfusion arrhythmias.

Clinical Implications

The arrhythmias which occur during reperfusion of ischemic myocardium in man vary considerably depending upon the setting in which they are found. Those reperfusion arrhythmias which occur following intracoronary thrombolysis in patients suffering acute myocardial infarction are generally benign. In a recent investigation of the arrhythmias which occur in this setting, Goldberg et al (27) noted that although these reperfusion arrhythmias occurred in the vast majority of patients, they rarely posed a serious problem and consequently did not warrant antiarrhythmic therapy. Since reperfusion with thrombolytic agents is generally delayed 2-5 hours after the onset of clinical symptoms of ischemia (25-27), the benign nature of these reperfusion arrhythmias could be related to the relatively long duration of antecedent ischemia. Investigations of the reperfusion arrhythmias in dogs which follow longer durations of ischemia (60-120 minutes) have consistently shown a low incidence of ventricular fibrillation (49,53,75).

Those reperfusion arrhythmias which occur following relaxation of a coronary artery in spasm have different characteristics. Maseri et al (72) reported that these arrhythmias consist of transient bouts of rapid ventricular tachycardia and occasionally ventricular fibrillation. Furthermore, they noted that these reperfusion arrhythmias were resistant to all standard antiarrhythmic agents. These characteristics are very similar to the reperfusion arrhythmias occurring in dogs after relatively brief periods (10-30 minutes) of coronary occlusion, sug-

gesting that the mechanisms may be similar (1-5,7,9,47-51,54-56). Since most episodes of coronary artery spasm last 5-15 minutes (21,24), the mechanisms indicated by the present study employing a 10 minute period of coronary occlusion may have particular relevance to the re-perfusion arrhythmias in the setting of coronary artery spasm.

SUMMARY

In order to gain insight into the mechanisms underlying reperfusion arrhythmias, this thesis studied ventricular automaticity and conduction characteristics in 37 dogs during 10 minutes of LAD occlusion and subsequent reperfusion. The frequency of ectopic activity reached a maximum within the first 6-8 minutes of LAD occlusion and then declined leading to an ectopic free quiescent period. The arrhythmias after occlusion were marked by prolonged ischemic zone conduction times as measured from local bipolar plunge electrodes while marked fractionation of electrical activity was recorded from specially constructed composite epicardial electrodes. The quiescent period was characterized by a loss of marked fractionation of electrical activity from composite recordings and a progressive decrease, or complete loss of electrogram amplitude from plunge electrodes. Reperfusion was characterized by a rapid improvement in both the ischemia-induced conduction delay and amplitude on the local bipolar electrogram. However, the composite electrode recorded a return of the marked fractionation of electrical activity associated with a return of arrhythmias.

Ventricular automaticity during reperfusion (50.6 ± 6.0 beats per minute) was assessed in 5 dogs with complete heart block and was not significantly different from control preocclusive automaticity (47.6 ± 5.8 beats per minute). In addition, reperfusion at a heart rate of 220 beats per minute was associated with an increase in frequency and severity of arrhythmias when compared to a heart rate of 150 beats per

minute.

It is concluded that the early ischemic arrhythmias result from conduction slowing through the ischemic zone establishing reentrant pathways while the quiescent period is a manifestation of further conduction suppression so that reentrant pathways become blocked. Reperfusion of this electrically unresponsive tissue results in a nonhomogenous improvement in conduction which transiently restores the condition necessary for reentry.

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APPROVAL SHEET

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The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science.

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