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DRUG INDUCED CHANGES IN THE CONDUCTIVITY AND EXCITABILITY OF THE NORMAL AND INFARCTED DOG VENTRICLE

by

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DRUG-INDUCED CHANGES IN THE CONDUCTIVITY AND EXCITABILITY OF THE NORMAL AND INFARCTED DOG VENTRICLE

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ABSTRACT

The conduction characteristics of artificially applied stimulus were studied in the dog heart. The heart rate was controlled by destroying the AV-node and pacing the heart from a stimulating electrode in the left ventricle. Extrasystoles of varying coupling intervals were superimposed on the basic drive interval after every twentieth beat. Alternatively hearts were driven at increasing rates. Conduction times were measured from proximal stimulating electrodes, located within 1 cm of the recording electrode, or from distal stimulating electrodes that were more than 3 cm from the recording site. Endocardial, epicardial, and in some instances intramural recordings were made from the mid-anterior portion of the left ventricle. Estimates of endocardial Purkinje conduction as well as transmural conduction were obtained during distal stimulation. An alternate measure of myocardial conduction was obtained during proximal stimulation.

In the normal heart endocardial conduction times did not change with changing heart rates but increased during extrasystoles of short coupling interval as the refractory period of the Purkinje system was entered. Transmural conduction time (TMCT) similarly did not change at changing heart rates. However during extrasystoles from a distal electrode TMCT decreased at short coupling intervals suggestive of supernormal myocardial conduction. This was found

to be due to a reversal in activation sequence of the inner layers of the heart wall during early extrasystoles. TMCT never increased because as the impulse was gated through the Purkinje system the refractory period of the myocardium was never entered. Proximal stimulation allowed assessment of myocardial conduction characteristics. TMCT determined during proximal stimulation never showed a supernormal period but increased at short coupling intervals, as the relative refractory period of the myocardium was entered.

Lidocaine at low doses (1.25 and 2.5 mg/kg) caused speeding of conduction of short-coupled extrasystoles in the Purkinje system. At 2.5 mg/kg and higher doses (5.0 and 10.0 mg/kg)lidocaine caused slowing of midrange and short-coupled extrasystoles in the Purkinje system. Lidocaine caused depression of myocardial conduction at doses of 2.5 mg/kg and higher removing the apparent supernormal phase of TMCT. Lidocaine caused an increase in the relative refractory period but did not produce a detectable change in the functional or effective refractory periods.

Disopyramide, unlike lidocaine, caused a dose-dependent increase in the effective and functional refractory periods but did not increase the length of the relative refractory period. However the drug did not change the manner in which the heart conducted within its refractory period causing a parallel shift to the right of the conduction curves. At 3.0 mg/kg disopyramide had a quinidine-like action causing slowing of conduction of all extrasystoles independent of

the coupling interval. Also unlike lidocaine, disopyramide did not remove the apparent supernormal phase of transmural conduction.

Composite electrodes were used to record electrical activation of a large area of the epicardium before and after occlusion of the left anterior descending (LAD) coronary artery. Within minutes after occlusion of the LAD, the normal epicardial composite electrogram, characterized by a rapid biphasic deflections was changed to a series of low amplitude deflections of long duration. Continuous electrical activity was seen in the ischemic zone bridging the diastolic interval between normal and arrhythmic heart beats and between successive arrhythmic beats but not between normal beats.

Acute ischemia was also associated with an increase in TMCT which occurred within the first ten minutes of LAD occlusion and remained elevated for a further 80 minute period. Increases in TMCT induced by ischemia varied widely between animals ranging from 0 to 200%. This increase in TMCT was evident at all extrasystolic coupling intervals but did not obscure the apparent supernormal myocardial conduction seen under control conditions. TMCT in the ischemic zone was dependent upon heart rate; increasing rates caused an increase in TMCT. Ischemia caused slowing of endocardial (Purkinje) conduction of short-coupled extrasystoles but did not change with changing heart rates.

Lidocaine caused dose-dependent slowing of conduction in the ischemic myocardium which was greatest at the shortest coupling intervals and the highest heart rates. This slowing of conduction was greater in ischemic tissue than that found in normal tissue but no good correlation was found between the increase in TMCT due to ischemia alone and the depressant action of the drug. Lidocaine caused slowing of endocardial conduction of early extrasystoles in the ischemic zone at the higher dosages, an effect similar to that seen in normal hearts. Lidocaine also caused slowing of endocardial conduction at high heart rates in the ischemic zone.

Preliminary results indicate disopyramide, like lidocaine has a much greater effect in ischemic than normal tissue. Disopyramide appears to slow both endocardial and transmural conduction in the infarcted zone.

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All the accessory sciences seem to be intelligently united to enrich medicine with their new discoveries; yet the light which they have imparted has reflected merely a glimmering ray on a path where many of those who are hastening have already been bewildered.

Slow experience and correct observation must establish or destroy those brilliant theories and ingenious systems, the seducing fruit of a vivid and fertile imagination; and they must appear before these two rigid judges, observation and experience, in order to know whether, like so many others, after having shone a moment, they will, in their turn, be buried in oblivion, in order to be rediscovered in whole or in part, after an indefinite passage of time.

From, Lectures of Corvisart, C.E. Horeau, ed. Essai sur les Maladies et les Lesions organignes Du Coeur et des gros Vaisseaux. Paris, L'Imprimerie de Migneret, 1806, p. 20.

SECTION I

INTRODUCTION

"In describing the results of experiments of a physiological nature it is the natural custom to discuss the observations of previous workers in the same field." These words were written by Sir Thomas Lewis in the early part of the century and are as appropriate today as when they were written. The results in this thesis deal primarily with conduction in and activation of the canine ventricle and a brief review of the literature existing on this subject will be presented chronologically in the introduction.

Epicardial activation of the ventricle: influence of the underlying Purkinje system.

Although earlier work on the subject exists, the real foundations of cardiac electrophysiology as we know it today were layed by the work of Sir Thomas Lewis. In 1915 he reported on the ventricular activation of the toad ventricle (59). Using a string galvanometer he was able to measure activation times with an accuracy of better than $\pm$ 1 ms. He concluded that in the toad heart, like that of the mammal the excitation process spreads from within outwards. He found the epicardial surface near the center of the ventricle to be the first area to be activated, followed by the base and apex of the heart, within the ensuing 20 ms. He reported that the apex was usually activated before the base but in some animals, the reverse was found to be true. Harris (41) several years later, reported the left basal and

left central areas of the turtle heart were first to display epicardial activation which spread towards the apex. Total ventricular activation time varied according to the season, ranging from 70 ms in the winter to approximately 25 ms during the summer.

A more comprehensive study on the ventricular activation process was carried out by Lewis and Rothschild (61) on the larger heart of the dog. In this study they used mainly unipolar electrodes (one electrode on the heart and an indifferent electrode on the chest wall) to measure activation times. They believed it was not possible to distinguish between currents emanating from an intrinsic source (excited muscle beneath the contacts) or an extrinsic source (excited muscle at a distance from the contacts) using the bipolar electrodes employed by other workers who preceded them. Activation time was measured as the time between the R wave in the surface electrocardiogram and the appearance of the intrinsic deflection in the electrogram. As in the toads heart, Lewis and Rothschild found the central area of the ventricle to be the first to show signs of activation, followed by the apical and basal areas. They made several observations that led them to conclude that the activation process in the ventricles is different from that of the atrium where the impulse is conducted in a radial fashion away from the S-A node. Firstly, they found areas on the right ventricle that were activated simultaneously with a site on the left ventricle. Secondly, they found

large areas within each ventricle that were activated simultaneously. Thirdly, total activation of the ventricular surface required only 20 to 30 ms, only half the time required for electrical activation of the atria, a much smaller segment of the heart. They concluded because the ventricles were activated so rapidly they must be activated via "specialized channels" which they correctly assumed to be the endocardial Purkinje system. They were not satisfied with merely advancing this hypothesis but went on to prove it conclusively in the following manner. They recorded activation times from both ventricles before and after transecting the right bundle branch. They found after the transection the activation sequence in the left ventricle remained unchanged. In contrast, conduction times to all recording sites in the right ventricle were increased 3-4 fold. Also they showed that the conduction time between two epicardial electrodes in line with a third electrode (stimulating electrode) was unchanged by cutting the superficial muscle layers between them. Finally, by recording simultaneously from the endocardial and epicardial surface at the same location in the heart, it was noted the endocardial electrode always received the wave of excitation first. This observation was made during sinus rhythm and when the heart was stimulated electrically at a site located at a distance from the contacts which was several times greater than the thickness of the heart wall. Thus they had established the mechanism by which the heart becomes

activated electrically both during a normal heart beat and one produced by epicardial stimulation of the ventricles. From these results they concluded that "the time at which the excitation wave appears at any point on the surface of the ventricle is controlled by two chief factors; firstly, by the length of the Purkinje tract from its starting point to the network immediately beneath the point in question; and secondly, by the thickness of the ventricular wall."

Harris (41) also studied the spread of excitation in the ventricles, confirming the earlier results of Lewis and extending the study to the heart of the cat and monkey. Unlike Lewis, Harris used a bipolar electrode which he called a contiguous electrode, indicating the contacts of the electrode were very close together but not in contact. In the dog heart he found the onset of contiguous spikes to coincide with the upstroke of the unipolar electrogram. From his observations Harris found the location of earliest activation to be in the trabeculated region of the right ventricle. The total duration of electrical systole, as he measured it, ranged from 18 to 22 ms which was slightly less than that measured by Lewis (61) or Wiggers (110) which ranged up to 30 ms. He suggested that this may be due to the difference in the size of animals used, since he also demonstrated the heart of the cat (a smaller animal) to be activated in a sequentially equivalent manner to that of the dog but in approximately half the time. Harris was also able to show almost simultaneous activation in the right

ventricle of the rhesus monkey which made it unique from the rest of the animals he had studied. Finally Harris showed, as had Lewis 25 years earlier, that for records "made with internal and external leads opposite each other and separated only by the thickness of the myocardium, that the deflection of the internal lead always preceded the external deflection." In the right ventricle of the dog, this difference ranged from 1 to 12 ms whereas in the turtle ventricle it ranged from 15 to 40 ms.

By the early 1950's the concept of ventricular activation via the endocardial Purkinje network had become widely accepted. However Pruitt et al. (78) challenged this hypothesis in a publication in which they claimed that rapid endocardial conduction was not due to conduction within the specialized cells of the Purkinje system but due rather to the organization of the muscle cells of the endocardium. In their words "the subendocardial bands of myocardium form a network through which excitation can move rapidly along the long axis of the fibers." Their assumption was based on the following observations. Firstly, ventricular cavity potentials recorded in both the left and right ventricles occurred simulatenously with activation at the epicardial surfaces. Secondly, they observed a loss in endocardial potentials and not epicardial potentials when poisons such as potassium chloride, cocaine, silver nitrate, or phenol were introduced into the ventricular cavity. They concluded that the excitation process occurred via the myocardium, in

a direction perpendicular to the surface of the epicardium and that the myocardium was not activated in an endocardial to epicardial direction as had been earlier proposed. To support this theory they were able to show conduction in a strip of ventricular wall, isolated except for an attachment to the heart at one end was much more rapid in the direction of the long axis of the muscle cells. Also no differences were found between endocardial or epicardial conduction times in these segments.

Activation of the ventricular wall

By the early 1950's advances in technology were such that it became possible to make multi-channel recordings, whereas earlier methods had restricted workers to a maximum of three channels. It was at this time that the three dimensional analysis of the ventricular activation process was begun and detailed studies of intramural activation simultaneously appeared from a number of laboratories. Scher et al. (87) were one of the first to examine the sequence of activation in the wall of the mammalian ventricle, using multipolar needle electrodes (which allowed simultaneous recordings to be made from all levels of the heart wall). They reported excitation of the ventricular wall to occur in an orderly fashion from the endocardium to the epicardium without any discontinuties even though different muscle bundles were crossed by the wavefront.

Conduction velocity in the myocardium was estimated to vary from 150 - 500 mm/sec. The septum unlike the free wall, often showed bizarre patterns of activation with frequent reversals of direction of spread with little time difference from within outwards. In a subsequent publication Scher et al. (88) recorded intramurally at several locations of the ventricle and constructed isochronous planes of activation. From these planes they were able to calculate the angle at which the excitation wave entered the myocardium. Earlier calculations of myocardial conduction were based on the assumption that intramural activation from the endocardium to epicardium was perpendicular to either surface which gave an apparent speed of conduction of up to 600 mm/s. Their corrected value for muscle conduction was given as 300 mm/s and endocardial conduction had a calculated average value of 1800 mm/s. In the same publication Scher et al. report occassional bidirectional activation of the endocardial layers especially in the region of the papillary muscles. This they passed off as being artifact due to injury as these observations were not common enough to support the view of Purkinje penetration into the heart wall.

Concurrent with the reports of Scher were those of Durrer et al. from the Netherlands. In a series of four reports (26, 27, 29, 30) these workers exhaustively studied all aspects of ventricular activation in the dog heart. They reported synchronous activation of the inner 2/5 of the heart wall which they suggested was due to the rapidly

conducting Purkinje system which penetrated to that depth. The outer 3/5 of the wall, in their estimation, were activated sequentially in an endo-epicardial direction at the rate of 500 mm/s. Also they showed records to suggest that the transition zone between these 2 layers of myocardium could exhibit an epi-endocardial direction of activation which was termed a "reversal phenomenon". In the fourth paper in the series Durrer et al. (29) showed that this reversal phenomenon, as well as the synchronous activation of the inner layers of the heart wall, disappeared when the heart was stimulated from endocardum near their recording electrodes. This led them to conclude that the Purkinje fibers "within" the myocardium were not being activated by their stimulation procedure. By measuring conduction times between recording sites along the length of the multi-contact needle during endocardial stimulation myocardial conduction velocity was estimated to be 350 - 600 mm/s.

Scher et al. (89) recorded from seven multicontact needle electrodes simultaneously in order to visualize ventricular activation during premature ventricular systoles. Endocardial conduction of extrasystoles varied from a low value of 300 mm/s at the base of the septum to a high of 1400 mm/s in the apical areas of the ventricle. Transmural velocity through the thickness of the wall was determined when the extrasystole was delivered from either the endocardial or epicardial tip of one of the recording

electrodes. It was found to be 300 mm/s whether in an endo-epicardial or epi-endocardial direction. Also they reported the spread of extrasystoles in the myocardium was not influenced by the fiber direction of the muscle proposed by Pruitt et al. (78). Conduction velocities of premature systoles were found to be similar to those during normal beats. However, myocardial conduction as low as 100 mm/s was often found within 1 - 2 mm of the stimulating electrodes during the extrasystoles. No evidence of synchronous activation was found in the endocardial layers of the myocardium and they suggested that intramural Purkinje penetration was unlikely. However, in a follow up publication Scher and Young (90) admit to observing this phenomenon earlier reported by Durrer (29, 30). They suggested that it results from penetration of Purkinje fibers under papillary muscles and trabeculations, and from uneveness of the endocardial surface, rather than from intramural penetration of Purkinje fibers. Durrer and van der Tweel (28) in another publication also reported on the intramural conduction of extrasystoles. They reasoned that if the endocardium is activated by the Purkinje system, electrical stimulation of the Purkinje should give rise to complexes with the same time relations as during normal beats including the reversal phenomenon previously reported. However endocardial recordings which exhibited Purkinje activity during normal beats consistently failed to do so during extrasystoles. Therefore it was postulated

that the ventricles are excited in a different manner during extrasystoles, especially in the areas proximal to the stimulating electrodes. In one experiment they were successful in selectively stimulating a Purkinje fiber with a very low current of .1 ma and maintained the reversal phenomenon apparent during normal beats. Increasing the current to 15 ma resulted in only muscle conduction intramurally and loss of the reversal phenomenon. They advanced the following hypothesis: "If the Purkinje system penetrates into the left ventricle wall it might be supposed that, with increasing distance from the endocardium, the meshes of this system become wider towards the epicardial surface. An activation wave originating from a Purkinje fiber can travel in all directions, that is, also in an epicardial-endocardial direction, from the point of transition into a ventricular muscle fiber, until it collides with tissue activated by activation waves originating from adjacent Purkinje fibers. If the meshes are wide enough, a reversed complex can be found between two of our terminals."

Pipberger et al. (77) also examined the intramural activation in the dog. They reported that deep layers of the heart wall showed no regular sequence of activation but were activated almost simultaneously, whereas the outer layers were activated in a sequential manner from the inside out. (However, they recorded activity at depths up to 20 mm from the epicardum and there is some question as to whether their electrode was recording myocardial activity or cavity

activity at this depth.) Their estimate for the rate of intramural activation was 755 ± 268 mm/s in the outer layers of the wall. Significant increases in conduction velocity were found at the apex after passing a 3 mm limit of depth and at the base, at 5 mm depth. This they attributed to Purkinje penetration into the myocardium up to this depth. Although epi-endocardial direction of propogation was observed at the endocardium, no concurrent reversal in polarity was observed in electrograms recorded from that area as Durrer et al. (30) had reported.

Sodi-Pallares et al. (95), not convinced by the work of others, also examined the electrical process in the left ventricular wall of the dog, attempting to settle the question as to the depth of Purkinje penetration. They reported up to 50% of their endocardial recordings showed Purkinje activity preceding muscle potentials. These were lost at a distance of 1 - 2 mm (in rare instances 3 - 4 mm) from the endocardium. Their conception of ventricular activation is as follows: " Taking into account the totality of Purkinje fibers, the ventricular activation process can be conceived as a number of closed spheres, which independently cause a sequence of simultaneous activated points toward the endocardium and toward the epicardium. Thus, some points in the middle or outer thirds of the free left ventricular wall may be activated before other points close to the endocardium, with the result that the activation process for those points would follow a reverse, i.e., epi-endocardial direction."

Activation of the interventricular septum.

The activation process in the septum begins near its center close to the termination of the bundle branches just above the anterior papillary muscle on the right side, and an area near the midline on the left side according to Amer et al. (3). Scher et al. (91) studied the intramural activation of the septum using multicontact needle electrodes, and demonstrated that the septum is activated from both the left and right sides towards its center. However the predominant direction of activation was from the left to right. The activation spreads along the apical-basal axis towards the apex and the base with the latter being activated last. They concluded that the septum, like the ventricular myocardium is a functional syncytium, and no boundary separates the two halves, the same point of view held by Sodi-Pallares and co-workers (96). Durrer et al. (29) became involved in a study of the septum and reported similar findings to those of Scher described above. Durrer reported no barrier to conduction to exist in the septum and that conduction occured equally well in both directions, i.e. from left to right and vice versa, at a velocity of 500 - 600 mm/s. They found no evidence for Purkinje penetration into the septum.

Electrical activation of the goat and human heart.

Having exhaustively studied the dog heart, researchers in the field turned their attention to studying the activation sequence in the hearts of other species., Again, Durrer and van der Tweel (28) were at the forefront of this research. Their results indicated that in the goat heart unlike that of the dog, activation of the successive layers of the ventricular wall occurs almost synchronously. However, as in the dog they found a reversal phenomenon to exist in which the electrograms recorded intramurally were not all of the same polarity suggesting propogation in an epi-endocardial direction in certain layers. Purkinje spikes were seen in many layers of the muscle and not confined to the endocardial layers as was the case in the canine heart. On the basis of these results they concluded the Purkinje system in the goat extended to the epicardial surface, in agreement with the anatomical studies of Ter Borg (102) and Lewis and Rothschild (62). Hamlin and Scher (38) found results consistent with those of Durrer and van der Tweel for the goat heart. They reported all areas except the extreme base and a small apical epicardial region of the left ventricle were excited in a single burst of depolarization occupying less than 10 ms. They were not able to determine intramural conduction velocity accurately (their estimates ranged from 100 mm/s to infinity) because they could not predict the direction of the wave of

excitation in the goat heart. They attributed the near synchronous activation of the free ventricular wall to deep Purkinje penetration.

The first detailed description of the excitatory process in the human heart was offered by Barker et al. (6). Using a unipolar exploring electrode epicardial activation times were calculated relative to the onset of the QRS deflection in a lead II electrocardiogram. They found the order of excitation differed in some respects from that described in the dog by Lewis and Rothchild (61). The earliest points of activation were determined to be along the A-V groove at the base of the right ventricle. They considered the differences in results between man and dog to be due to anatomical differences between species in the conducting tracts in the right ventricle. There exists in the literature other reports on the activation of the human heart but it was not until the work of Roos et al. (81) that detailed mapping of epicardial and intramural excitation of the human heart was performed. Unipolar and bipolar records were taken with activation times calculated relative to the left ventricular cavity potential which was used as a time reference. They found epicardial excitation to occur first in the antero-paraseptal region of the right ventricle, about 20 ms after the beginning of ventricular depolarization. The base of the right ventricle was activated after 60 ms and the pulmonary conus followed 10 ms later. In the left ventricle excitation spread from the

septal area (40 ms) to the lateral border (60 - 70 ms) and finally to the posteral-basal region (70 - 80 ms) - results similar to those reported for the dog heart. These results differed from those of Barker et al. but this was attributed to the different time reference used in the two studies. Barker et al. had used the beginning of lead II, which Roos et al. explained could lag behind the true start of ventricular activation by 20 - 25 ms, and unlike the cavity potential which they used could be influenced by respiration. Intramural recordings by Roos et al. demonstrated in the left ventricular wall, excitation spreads in a predominantly endo-epicardial direction similar to the dog heart. However no "reversal phenomenon" or spread of activation in a epi-endocardial direction was observed in the human heart as had been reported in the canine heart by Durrer et al. (30). It was concluded that intramural Purkinje penetration was not present as regularly as in the dog. Intramural conduction velocity was estimated to be 300 mm/s. A more extensive study of the human heart was carried out by Durrer et al. (25) who used isolated human hearts. The epicardial excitation pattern in the isolated human heart corresponded well to that of the in situ heart documented by Roos et al. However there were some discrepancies observed in intramural conduction velocities between the two different preparations. Intramyocardial conduction velocity was calculated from the conduction times required for the electrical wavefront to

propagate between contacts of a multicontact needle electrode (inserted into the free wall of the ventricle) when the heart was stimulated from one end of the needle electrode. Propagation of the driven beat along the needle electrode occurred smoothly in a uniform manner with a mean conduction velocity of 464 mm/s $\pm$ 27 mm/s in both epi-endocardial and endo-epicardial directions. Equivalent values were found for propagation through the interventricular septum. In order to validate their results observed in the isolated human heart, control experiments were carried out in dog hearts where the intramural activation sequence was studied *in situ* and after isolation from the body. They found equivalent patterns of intramural and total ventricular activation after isolation but that the activation process was completed in a time frame which was 20% less than the *in situ* heart. Intramural conduction velocity was 300 mm/s *in situ* heart whereas, in the isolated heart, the rate of conduction had increased to 450 mm/s. The increases took place within the initial 30 minutes after isolation. This led them to speculate that measurements made in the isolated heart may not accurately describe the *in situ* situation. However, this idea was rejected because the times calculated for total ventricular activation in the isolated heart corresponded well with the duration times of the QRS complex in the EKG's recorded from the whole animal. No adequate explanation for the increase in conduction velocity upon isolation was offered.

Alterations in epicardial and intramural activation during acute myocardial infarction.

Harris (42, 44) was one of the first to examine the time course of electrophysiological changes accompanying acute occlusion of a coronary artery. He was able to demonstrate electrograms of reduced amplitude and increased duration recorded from the ischemic area of the heart within the first few minutes following occlusion of the left anterior descending coronary artery (LAD). In some instances there was a complete disappearance of all electrical activity within the ischemic zone or electrical activity that was independent of the electrical events recorded from the normal areas of the heart. Harris also noted that fibrillation if it were to occur, would occur within the initial ten minutes of occlusion. Fibrillation was always preceded by a run of ventricular tachycardia which was thought to originate from an automatic focus located in the border zone between normal and ischemic tissue, an area which displayed abnormally large amplitude electrograms during this period.

More recent literature, (1970-80), suggests that arrhythmias associated with acute ischemic episodes are the result of reentrant impulses emerging from ischemic myocardial muscle to reexcite the heart. Boineau and Cox (9) were one of the first to put forth this idea, demonstrating areas of local fibrillation or delayed

electrical activation in the ischemic area. Occlusion brought on a decrease in amplitude, a marked increase in duration, and fragmentation of bipolar electrograms which was greatest in the center of the ischemic area and diminished towards the border zone between ischemic and nonischemic areas. Asynchronous electrical activity persisted in the ischemic zone for periods longer than 200 ms and was correlated with the occurrence of ventricular arrhythmias. Additional work by Cox, Daniel, and Boineau (19) described the changes evoked by ischemia on intramural electrical activity. Conduction times along a multicontact needle electrode from the endocardium towards the epicardium were determined during sinus rhythm. Under normal conditions this "transmural conduction time" had a value of 15 ms which progressively increased to 25 ms during a six hour occlusion. Also, Purkinje potentials recorded at the endocardium were resistant to ischemia of up to 18 hours duration whereas there was a progressive loss of amplitude or electromotive force (E.M.F.) of the corresponding subendocardial muscle potentials. The normal gradient of bipolar potentials which existed transmurally under control conditions was lost during ischemia with intramural sites showing a time-dependent decrease in E.M.F. Kaplinsky et al. (54) have recorded intramyocardial activation in the infarcted zone of the dog heart during the initial thirty minutes following ligation of the left anterior descending

coronary artery. Marked delay, fragmentation and reduction in amplitude of electrograms occurred in the subepicardial and intramyocardial muscle layers during the first ten minutes of ligation and were coincidental with the appearance of ventricular arrhythmias. Electrograms recorded from subendocardial muscle layers remained synchronous during this period. A second period of ventricular arrhythmias 10 - 30 minutes after ligation was not accompanied by delayed or fragmented electrical activity at any of the intramyocardial sites and it was proposed that these two periods of arrhythmias had different etiologies.

Waldo and Kaiser (108) also studied the electrophysiological changes associated with acute myocardial infarction. They too recorded continuous electrical activity within the infarcted zone which, when it persisted beyond the T wave of the preceding beat, resulted in ventricular extrasystoles or even ventricular tachycardia and fibrillation. Scherlag et al. (92) found a delay in epicardial activation in the infarcted zone of the heart during the first few minutes of coronary occlusion. Progressive delay in activation of the epicardium preceded the development of ventricular arrhythmias and/or fibrillation. Williams et al. (112) showed that the delayed activation within the ischemic zone was accentuated during spontaneous or induced ventricular premature contractions. Also noted was an increase in the conduction delay between

the endocardium and the epicardium during ischemia which was increased further during premature beats. Kaplinsky et al. (53, 55) reported similar findings of delayed activation and fractionation of potentials within the ischemic zone bridging the diastolic period and preceding ventricular arrhythmias. They reported that ischemic damage to the left ventricle could result in premature beats arising from either the left or right ventricle as the border zone of the infarct often extended into the right ventricle. Schick et al. (93) demonstrated an increase in conduction time of up to 20 ms to electrodes located within the ischemic zone with no change in conduction time to electrodes located to non-infarcted areas of the heart. Maximum increases in conduction time following a one stage ligation of the LAD occurred within 30 minutes of arterial occlusion and a correlation was made between increases in conduction time and the occurrence of arrhythmias of ventricular origin. Ogawa et al. (74) have demonstrated that a peak increase in epicardial activation time in infarcted dog hearts occurred within the first 10 minutes of LAD occlusion. This was correlated well with the appearance of ventricular arrhythmias.

Recently, Janse et al. (51) have recorded DC-extracellular electrograms simultaneously from 60 epicardial and intramural sites in isolated perfused canine and porcine hearts. Isopotential maps of the ventricular

surface were constructed for the normal heart and also at varying intervals up to 15 minutes after ligation of the LAD. It was concluded that arrhythmias during the initial minutes of ischemia were caused by two factors: (1), ectopic foci located at the border between normal and ischemic tissue and (2), macro- and micro-reentry in ischemic myocardium.

Excitability and refractory characteristics of ventricular tissues.

Mendez et al. (63) have made a study of the influence of cycle length upon the refractory period of auricles, ventricles and A-V node in the dog. In studying the refractory period of the ventricle, the ventricles were driven electrically at five different cycle lengths and the functional refractory period (FRP) determined at each rate. Also, by using 3 stimulators in series they calculated the FRP for extrasystoles of coupling intervals equivalent to (and shorter than) the basic drive intervals. It was found that, when recording electrodes were located within a few mm of the stimulating electrode the "FRP values were a curvilinear function of the immediately preceding cycle length, with values for all but very early premature beats falling close to the curve describing the basic cycle". When a second set of recording electrodes were employed at a distance of several cm from the stimulating electrodes it

was found that the FRP determined at the more distant set was longer by 5 - 15 ms at all frequencies. This was attributed to slowed conduction of extrasystoles in the tissue lying between the two pairs of recording electrodes (up to a distance of 10 - 20 mm from the stimulating electrode). Although the FRP determined at the near and far electrodes decreased in a parallel fashion with increasing heart rates, the FRP determined for the earliest achievable extrasystole (at each one of the drive rates) was considerably larger at the distant site. This was thought to be due to a differential effect of cycle length upon the refractory period of muscle and the conduction system. It was postulated that there was a cumulative effect of frequency on the refractory period of the Purkinje system with the result that it took the Purkinje system several beats for a new refractory period to be achieved as the cycle length was changed, whereas in the muscle this was achieved within the time span of one beat. This was evident by the fact that refractory periods of premature beats were longer than those of basic cycles having the same preceding cycle length over a conduction pathway which involved Purkinje tissue, whereas this was not found to be the case in a conduction pathway involving only muscle tissue.

Janse et al. (52) have also studied the changes induced in the refractory period of the dog ventricle following sudden changes in heart rate. It was found that during a rapid increse or decrease in heart rate, the heart required

a time period of up to 500 beats before a new steady-state value of the duration of the effective refractory period (ERP) was established. This phenomenon was reported for myocardial tissue and could not be attributed to a cumulative effect on the conduction system as postulated in the paper of Mendez et al. (63) discussed above. They also reported that changes in the FRP (the shortest interval between two propagated responses) recorded within a 2 mm distance of the stimulating electrode parallelled the changes observed in the ERP. Also, the slowing of conduction during refractoriness was confined to this 2 mm distance surrounding the stimulating electrode such that propagation of the wave front intramurally at distances greater than 2 mm occurred at normal diastolic velocity. This last result is in agreement with earlier results of van Dam et al. (105) who studied the origin and propagation of extrasystoles within the myocardium of the dog heart. The myocardium was stimulated from the endocardial tip of a multicontact needle electrode and conduction times of normal and premature beats were determined along the length of the electrode up to a maximum distance of 3 mm from the stimulus site. Unipolar and bipolar recordings both indicated that the delay in appearance of extrasystoles following stimulation during the refractory period was due to an increase in latency and not due to slowed conduction. All extrasystoles were conducted at the same rate, once propagation began. Han and Moe (40) determined the recovery

of excitability (the ERP) of the dog myocardium at 12 recording sites located concentrically around a central stimulating electrode within a radius of 4 mm. It was demonstrated that "the degree of temporal dispersion of recovery of excitability in the ventricular muscle was minimal after a basic beat, but it was increased significantly following an early premature beat". It was suggested that a train of premature beats would lead to an increasing degree of nonuniformity of recovery and fibrillation.

Rosenblueth (82) made a study of the FRP of cardiac tissues. He found as had Mendez et al. (63), that the FRP determined at two locations in the ventricle, was greatest at the set of recording electrodes located furthest from the stimulating electrode. No attempt was made to determine if differences existed between the FRP of the Purkinje system and the myocardium. A series of theoretical curves were constructed to try and explain the influence of conduction distance on the measurement of the FRP.

van Dam et al. (106) conducted a very elegant experiment on impulse propagation and recovery of excitability of the conduction system of the dog heart. Unlike earlier studies of others in which Purkinje conduction was inferred from recordings made at the epicardial surface, van Dam et al. made recordings directly from the Purkinje system in the in situ heart while the animal was maintained on cardio-pulmonary bypass.

Electrodes were placed in the heart over the His bundle, right bundle branch, Purkinje-papillary muscle junctions in both ventricles, papillary muscles in both ventricles, and also the left ventricular surface. Stimulation and/or recordings were made from each location in order to determine the refractory characteristics of the specialized conducting system. They found that at a constant heart rate the absolute and relative refractory periods were longer for the Purkinje system than for ventricular muscle of the same heart. The effect of refractoriness on conduction was examined by stimulating the bundle of His and measuring the conduction time of extrasystoles to the recording electrodes, in the locations mentioned above. Purkinje conduction during non-premature beats was estimated at 2400 mm/s, however "advancing the stimulus into the refractory period produced an increase in the latency of response at the site of stimulus. The impulse was further delayed when it entered partially refractory fibers, and the overall conduction velocity often decreased as much as 50 per cent." The slowing of extrasystoles was mostly confined to the bundle branches and the Purkinje-muscle junctions. When the stimulus site was in the right atrium, most of the slowing of conduction occurred in the A-V node, but additional slowing was evident in the Purkinje system. Finally when the stimulus site was moved to the epicardial surface of the left ventricle, it was found that extrasystoles were delayed

by refractoriness, only at their site of origin, and spread throughout the ventricle via the Purkinje system without further slowing.

Myerburg et al. (69) have mapped action potential duration and local refractory periods throughout the specialized conduction system of the dog heart. It was found that local refractory periods, determined near the distal end of the conducting system, 2 to 3 mm proximal to the termination of Purkinje fibers in muscle, were greater than refractory periods of Purkinje fibers proximal or distal to that area. A good correlation was shown to exist between local refractory periods along the Purkinje system and local action potential durations. This area, by nature of its long functional refractory period served a protective function, blocking the propagation to the myocardium of extrasystoles with very short coupling intervals. Thus, the area of maximum action potential duration behaved as the limiting segment or "gate" for conduction of premature impulses. In a subsequent publication Myerburg et al. (68) studied the functional characteristics of this so called "gate" in the Purkinje system. It was reported that, in preparations with Purkinje conduction velocities considered to be normal (2400 mm/s), little or no slowing of conduction of premature beats was observed within the Purkinje system. However, block of the premature beats occurred in the area of the gate. In preparations in which conduction of normal beats was depressed, it was found that "premature impulses

initiated proximal to the gates with coupling intervals shorter than the refractory period at the gates were conducted across the gates at least in part because of slowed conduction which allowed tissue in advance of the propagating wave front "enough time to repolarize". The influence of increasing frequency on the functional properties of the gate cells was also studied. It was found that the differences in action potential durations between the bundle branches and the distal Purkinje system (gating area) were decreased or lost altogether at increasing frequencies of stimuation so that conduction block could occur in the bundle branches. However, in a majority of the preparations block of conduction at high drive rates still occurred in the area of the gate. Thus, this gating mechanism of the distal Purkinje system appeared to be responsible for the block and/or delay in the propagation of extrasystoles and normal beats during rapid rates of stimulation. Lazzara et al. (58) evaluated the "gate" hypothesis in the in vivo situation. They measured conduction times from a stimulation point on the bundle of His to proximal and distal areas of the bundle branches, and to the papillary muscles. Their findings indicate the important sites of block of premature stimuli to be in the proximal main bundle branches whereas the gate hypothesis predicted premature impulses to be blocked within a few mm of the Purkinje muscle junction. Neither Myerburg et al. nor Lazzara et al. ever reported impulse propagation through

the Purkinje system, with conduction block occurring in the myocardium. This result might be anticipated for extrasystoles applied during a rapid rate of stimulation if the results of Moore et al. (65) are considered. They demonstrated that the action potential duration and functional refractory period of false tendons were considerably greater than those recorded in the papillary muscle of the same canine heart at low driving frequencies. However, as the driving frequency was increased this discrepancy between tissue types was lost so that at the highest driving frequency the action potential duration and refractory periods were nearly identical in Purkinje and muscle cells. It was also noted that the functional refractory period of epicardial muscle cells was less than that of papillary muscles. This difference was similarly lost at high driving frequencies.

The refractory characteristics of cardiac muscle in the left ventricular wall was examined by van Dam and Durrer (104). Refractory periods were determined for all levels of the heart wall from the endocardial to the epicardial surface using a multicontact needle electrode for stimulation and recording. It was found that the duration of the FRP was nearly equivalent in the middle and outer part of the ventricular wall, whereas the FRP of the innermost layer was approximately 15 ms longer than the middle and subepicardial layers. It was concluded that an extrasystole arising after the end of the FRP would be conducted in a homogeneous way and would meet no refractory

tissue on its way, when spreading from the endocardium in a direction perpendicular to the epicardial surface. Similar but more extensive experiments of the same nature were carried out by Burgess et al. (13) twelve years later. The FRP was determined for a large number of sites in the left ventricular free wall and the interventricular septum. Their results corresponded well with van Dam and Durrer's findings of longer endocardial than epicardial refractory periods. However, they did not confirm the findings of van Dam and Durrer that the shortest FRP's were located in the middle layer of the heart wall. Also, Burgess et al. were able to show the FRP of the apex of the ventricle was longer than the FRP of the base, and a difference in FRP values between the left and right side of the septum. "That is, areas of the ventricle normally activated early had long refractory periods and those areas activated late had short refractory periods". In studying refractory periods, workers have been attempting, indirectly to characterize the recovery process in the heart. In a more recent publication, Burgess (12), recorded monophasic action potentials from the surface of the heart using suction electrodes and was able to ascertain a more direct measure of repolarization by plotting times the action potentials were 50% and 90% returned to the base line. Isochrone maps of the repolarization sequence were constructed and compared to maps of activation sequence. It was found the repolarization sequence corresponded well to the activation

sequence on the anterior but not on the posterior surface of the heart. It was suggested a better indication of the repolarization process could be obtained by measuring transmembrane action potentials *in vivo*.

Supernormal conduction.

In discussing refractory and excitability characteristics of the ventricles, it is important that the phenomenon of supernormal conduction be mentioned. The word supernormal is defined as meaning - "exceeding or going beyond the normal". Supernormal conduction then is a term used to describe abnormally rapid conduction or conduction that occurs when block is expected. Spear and Moore (99) have recently published a brief review of the literature on the subject of supernormal conduction and excitability. In their words "supernormal conduction can be caused by a variety of mechanisms including the presence of a period of supernormal excitability. The term supernormal excitability refers to a reduced current requirement to excite a tissue at a specific period of its activity cycle". Examples of supernormal excitability are much more prevalent in the literature than examples of supernormal conduction.

A supernormal phase in the recovery of excitability was first shown in nerve fibers by Adrian and Lucas (2) and later by Adrian (1) in ventricular muscle which was perfused by acidified Ringer solution. Lewis and Master (60)

observed a supernormal phase of recovery in the conducting system of the human heart in two clinical cases of complete heart block. Both patients studied showed complete A-V dissociation except when the P wave of the electrocardiogram occurred in a limited phase of the cardiac cycle (during ventricular activation or early in diastole). During this phase atrial beats were propagated to the ventricle in the normal sequence. In one case this phenomenon was associated with slight supernormal conduction (an abbreviated P-R interval) and the other with a decreased conduction velocity (lengthened P-R interval). The suggestion was made that "conductivity" and "excitability" may be separate and distinct qualities in the heart. Hoff and Nahum (46) identified a supernormal period of excitability in the feline heart subsequent to the relative refractory period, lasting 40 to 100 ms. This period invariably fell either on the T wave or the U wave of the electrocardiogram. Supernormality was not observed in all hearts and varied widely in degree when it was present. Supernormal excitability was found in the hearts of animals under barbiturate anesthesia, while in decerebrate animals it was seldom seen. Childers et al. (15) showed supernormal excitability to be a characteristic of the specialized atrial tissue in Bachmann's bundle in dogs. As well, Peuch et al. (76) have demonstrated supernormal conduction to occur in the atrium of the dog heart. Ferrier and Dresel (33) reported supernormal ventricular conduction in isolated

blood perfused dog hearts. The average maximum decrease measured in ventricular conduction time in 7 of 9 hearts exhibiting supernormal conduction was 5 ms. Arbel et al. (4) stimulated the His bundle and ventricles in anesthetized dogs and found during a period 50 to 90 ms following the relative refractory period, during which ventricular conduction times were decreased by 1 - 11%. In a concurrent in vitro study it was noted that conduction velocity in canine false tendons was a function of resting membrane potential, so that supernormal conduction occurred during phase 3 repolarization and phase 4 depolarization. Hoffman and Cranefield (47) reported a supernormal period in cardiac muscle associated with the terminal part of phase 3 of the transmembrane action potential. Full recovery time of the cell following depolarization ordinarily coincided with the end of the supernormal period and with full repolarization. Spear and Moore (97) found that 17 $\pm$ 4.6%less current was required to evoke an action potential during the supernormal period than during diastole in right and left canine false tendons. The supernormal period lasted on an average of 88.2 $\pm$ 23.6 ms in fibers driven at basic cycle length of 800 ms. They found the duration of the supernormal period was independent of action potential duration but is a voltage dependent phenomenon in agreement with Arbel et al. (4). They showed that, at increasing drive frequencies, the duration of action potentials recorded in Purkinje cells of the dog heart decreased but not the

corresponding supernormal period, so that the ratio of the supernormal period to the total refractory period was increased (98). Spear and Moore (99) were also able to demonstrate supernormal conduction to exist coincidently with supernormal excitability and suggested the latter to be the cause of the former since raising the K^+ level in their tissue removed both types of supernormality. This correlation of excitability and conduction velocity was confirmed by Peon et al. (75) in canine Purkinje fibers. They demonstrated that the measurement of upstroke velocity is of little or no value in the prediction of conduction velocity. Rather, variations in conduction velocity appeared to be a function of excitability and not upstroke velocity or take off potential of the cell. Spear and Moore presented evidence to suggest that the supernormal conduction recorded during premature beats may be due to a shift of the site of origin of the action potential and therefore could not be called supernormal, in the true sense of the word. This same phenomenon was also documented as early as 1963 by van Dam et al. (107). Hondeghem and Jensen (48) recorded extracellularly from the Purkinje-myocardial junction of the dog heart and discovered the Purkinje myocardial conduction delay to decrease in premature beats - an apparent supernormal conduction. It was concluded that the Purkinje and myocardial cells from which they recorded did not belong to the same single conduction unit and that they had not recorded true Purkinje-muscle conduction

times. However, it seems more likely that the site of origin of the action potential may have shifted in a manner similar to that documented by van Dam and by Spear and Moore, giving an erroneous measure of conduction time.

Although much work has been done in the past examining conduction characteristics of isolated sections of the heart, whether it be conduction within the specialized conduction system, or within a confined section of the myocardium, very few reports exist in the literature comparing conduction within the Purkinje conduction and muscle conduction simultaneously in the whole heart. It was the purpose of this project to develop an in vivo dog model which would provide a means of accessing Purkinje conduction and myocardial conduction in the hearts simultaneously. Of particular interest were the conduction characteristics of the myocardium or heart muscle, as recent reports in the literature suggest that arrhythmias associated with acute myocardial infarction may be due to re-entry within the ischemic muscle. Therefore, the objectives of this study were:

1. to examine the changes in conduction time in the Purkinje system and myocardium of the canine ventricle associated with increasing heart rates and premature beats under normal conditions and also during the initial hours of myocardial infarction.
2. to try and determine if the two antiarrhythmic drugs, lidocaine and disopyramide, affected Purkinje and/or muscle

conduction differently.

3. to determine whether the effects of lidocaine and disopyramide on conduction were different in ischemic than normal tissue.

4. to determine whether the supernormal conduction shown to occur in the His-Purkinje system of the heart also exists in ventricular muscle.

SECTION II

METHODS

A. SURGICAL TECHNIQUES

1. Preparation of the animal.

Experiments were performed in mongrel dogs ranging in mass from 10-24 kg. The animals were anesthetised with sodium pentobarbital (30 mg/kg), the trachea intubated and the animals respired with room air (20 ml/kg, 16 times per minute) using a Palmer Ideal respirator. The chest was opened by a mid-sternal incision and the heart suspended in a pericardial cradle. Blood presure was monitored via a catheter in the femoral or carotid artery and maintenance doses of anesthetic and/or drugs were given through a catheter placed in the femoral vein. Body temperature was monitored by a rectal thermometer and maintained at 37-38°C by a thermostatically controlled heating pad. A lead II electrocardiogram was taken throughout each experiment and displayed along with the blood pressure on a Grass polygraph recorder.

2. Occlusion of the left coronary artery.

In animals in which a myocardial infarction was desired the left anterior descending coronary artery was dissected free of the myocardium approximately 1 cm from its origin and distal to the first diagonal branch. A silk suture was placed around the artery and through a short piece of

polyethylene tubing. The artery was then snared up against the end of the tubing and the loose ends of the suture were held securely against the other end of the tubing with a pair of hemostats (see Fig. 1). The coronary artery was always occluded with a one stage ligation. If the hearts fibrillated within the first 15 minutes of occlusion they were defibrillated with a DC pulse of 10-20 watts/seconds.

3. Destruction of the AV-node.

In animals in which conduction times were determined for extrasystoles it was necessary to drive the heart at a very slow rate after destruction of the AV-node. This was accomplished by inserting a specially constructed needle (see Fig. 2) into the right atrium and moving it about the AV-groove in the area of the tricuspid valve until the heart missed a beat or two (i.e. a temporary AV dissociation was achieved). This was taken as the area of the AV-node and .1 - .2 cc of 40% formaldehyde was injected into the node. This usually resulted in an AV block as determined by the electrocardiogram and the heart was then driven through stimulating electrodes which had previously been sewn onto the ventricle. If an AV block was not achieved the needle was moved and another .1 - .2 cc injected. This procedure was repeated until a block was achieved or a total of .6 cc formaldehyde was injected. If a block was not achieved

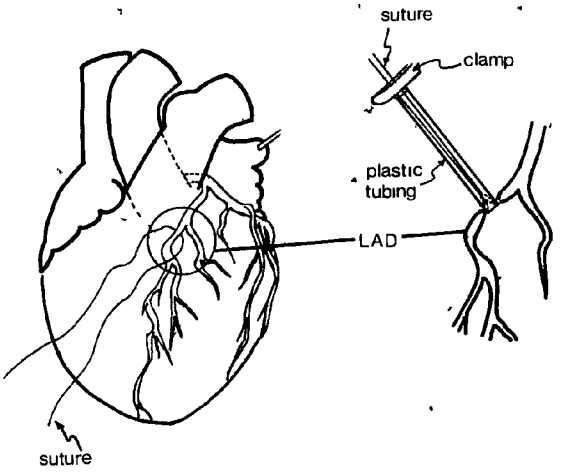

Fig. 1. Method of occluding the left anterior coronary artery. A silk suture is placed around the artery and fed through a piece of polyethylene tubing. The artery is then snared up against the tubing completing the ligation.

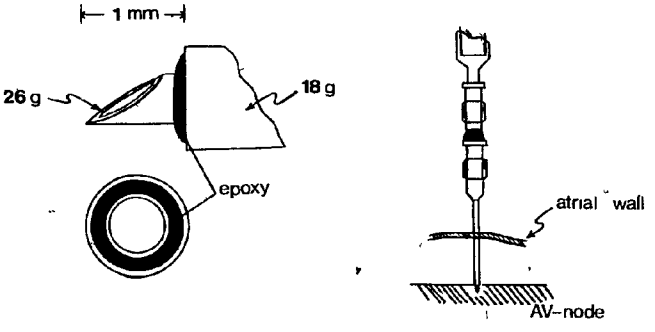

Fig. 2. Specially constructed needle used to inject formaldehyde into the A-V node.

after .6 cc of formaldehyde the heart was allowed to recover for 10 minutes and the procedure repeated.

The formaldehyde was injected into the AV-node from a 1 cc Hamilton syringe containing a modified needle tip. The needle was constructed by inserting a 1 1/2 inch 26 gauge needle into a 1 inch 18 gauge needle until the tip of the former protruded by 1 mm. (Fig. 2). The two needles were then fastened together with epoxy and placed on a syringe. This restricted the penetration into the tissue of the smaller gauge needle to a depth of 1 mm and prevented the needle from being pushed through the septum into the left ventricle. The formaldehyde was then injected into the tissue through the inner needle as indicated in the figure.

B. STIMULATION PROTOCOL

Electrical stimulation of the hearts was carried out through steel electrodes positioned in up to four locations in the heart.

Distal stim.	A.	epicardium at the base of the left ventricle
	B.	endocardium at the base of the left ventricle
Proximal stim.	C.	endocardium in the mid-anterior area of of the left ventricle

D. epicardium in the mid-anterior area of the left ventricle

When the heart was stimulated at sites A or B the distance to the recording electrode was always greater than 3 cm, this was called distal stimulation whereas with stimulation at sites C or D the distance to the recording electrode varied between 1 - 10 mm and this was called proximal stimulation. The protocol most often used was to sew a 1 cm x 1 cm acrylic plaque containing 2 platinum leads 1 mm apart to the ventricle. This provided a means for epicardial stimulation. A multicontact needle electrode* was inserted into the myocardium perpendicular to the epicardial surface through a hole in the plaque. This electrode allowed selective stimulation of the endocardium of the ventricle. Hearts were driven at a voltage of 2 - 4 times threshold with Frederick Haer Inc. Pulsar 61 stimulators (threshold was usually 1 - 2 volts).

Three types of experiments were carried out. 1) In experiments in which the conduction of extrasystoles was of interest, the heart was stimulated at a slow basic drive interval of 800 - 600 ms and extrasystoles introduced after every 20th beat from a second stimulator connected in series with the basic drive stimulator, so that all stimuli drove the heart through the same pair of electrodes (see Fig. 3). Extrasystoles varied in coupling intervals from 400 ms to

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*Electrode constructed by J. Kassell (Duke University).

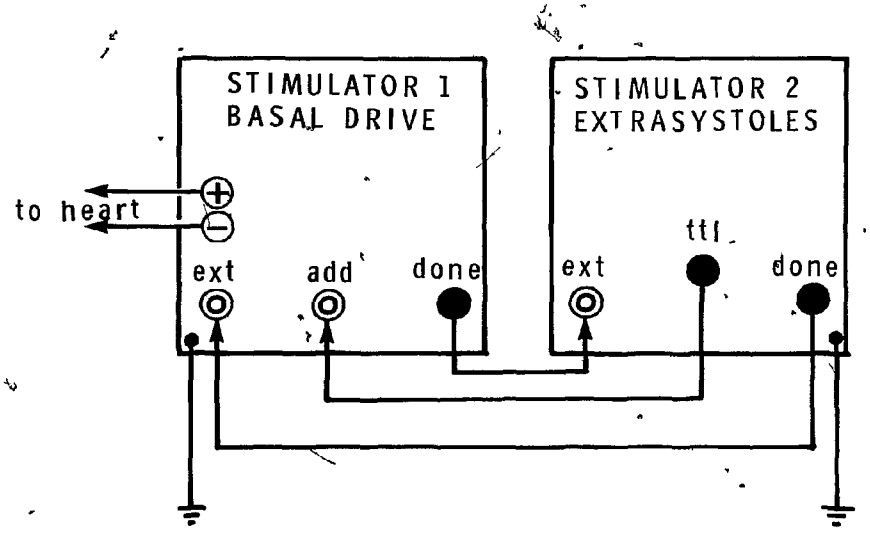


Fig. 3. Stimulators connected in series used to stimulate the heart. The basal drive was delivered by stimulator 1 and extrasystoles introduced after every 20th beat by stimulator 2.

the ERP. 2) In a second group of animals in which conduction times were studied as a function of heart rate, the hearts were driven at basic drive intervals of 800, 400, 350, 300 and 250 ms or heart rates of 75, 150, 170, 200, and 240 bpm respectively, using a single stimulator. 3) In a third group of animals electrical activation of a large area of the left ventricle was studied using a composite electrode sewn to the epicardial surface. Activation was studied during normal sinus rhythm.

C. RECORDING

1. Electrodes:

a) Composite electrodes.

In twelve experiments, recordings were made from a large area of the epicardial surface using composite electrodes. These electrodes were constructed by weaving the ends of two 12" pieces of teflon coated .005" platinium wire through a 1 x 2 cm piece of packing tape as illustrated in Fig. 4. One side of the tape was covered by a second piece of tape and the teflon covering of the remaining exposed sections of wire were then scraped away. The composite electrodes were fastened to the epicardium with silk sutures placed at the four corners of the electrode. Two composite electrodes were sewn to the heart, one to the mid-anterior portion of the left ventricle, the other to the mid-

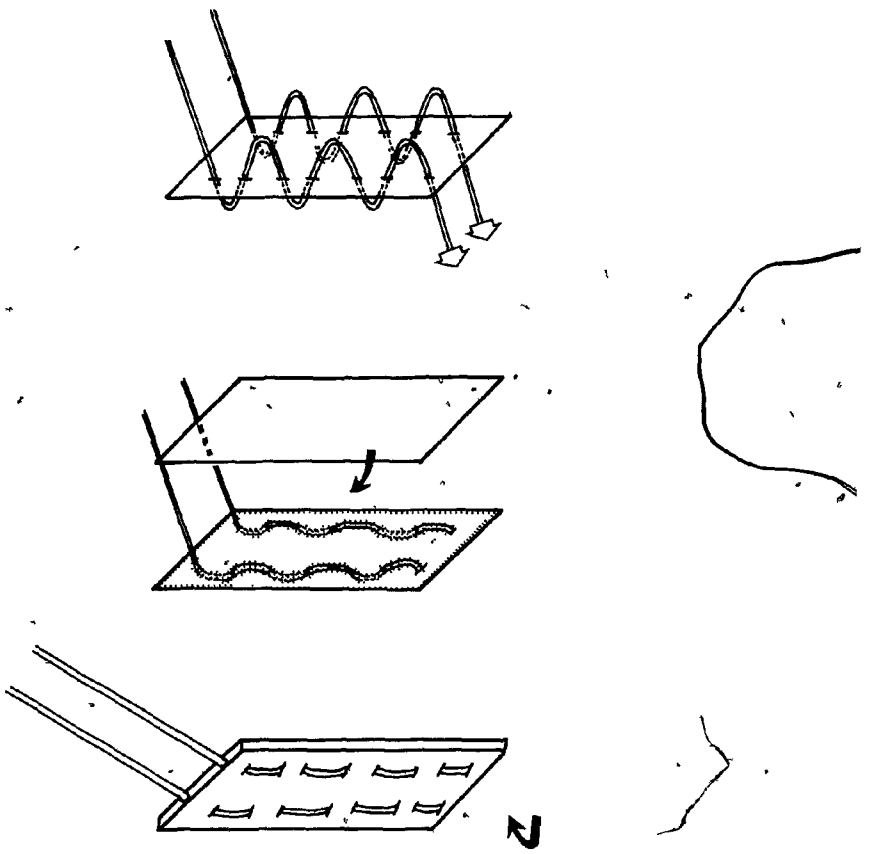


Fig. 4. Procedure for construction of composite electrodes. Two pieces of .005" teflon coated wire are woven through a 1 x 2 cm piece of tape and then covered by a second piece of tape. The remaining exposed faces of wire are then scraped with a knife to remove the insulation and the electrode sewn to the heart with the exposed wire against the epicardium.

posterior surface of the left ventricle. The former was used to record myocardial activity in an area made ischemic by occlusion of the LAD, while the latter recorded potentials from an area of the heart that was not made ischemic by LAD occlusion and served as a control recording.

b) Local bipolar electrograms.

In 32 other experiments electrograms were recorded from more localized areas of the left ventricle. Bipolar electrograms were recorded at the epicardial surface by one of two techniques, either through stainless electrodes sewn to the epicardium 1 mm apart or through an acrylic plaque. The 1 x 2 cm acrylic plaque contained 2 platinum wires 1 mm apart insulated except at the tip. The plaque was sewn to the heart so that the exposed wire tips were pressed against the epicardium. This plaque was also used for stimulation as described in section D. Endocardial bipolar recordings were made through two .003" teflon coated stainless steel wires. These electrodes were made by scraping the teflon coating off a 1/4" section at each end of a 5" piece of wire. A small hook was then shaped in one end of the wire and the wire placed into a 1", 23 gauge needle so that the hook just protruded out of the bevelled end of the needle. The needle was pushed into the heart to a depth of 1 cm and then withdrawn leaving the electrode wire embedded in the endocardium. Two wires were inserted into the endocardium in this manner so that the interelectrode distance was 1 -2 mm allowing close bipolar recordings to be made.

Alternately, endocardial potentials were recorded from the tip of a multi-contact needle electrode. This electrode was constructed from a 21 gauge needle and contained 12 recording sites 1 mm apart. This needle was passed through a hole in an acrylic plaque electrode sewn to the epicardium and pushed into the heart to a depth of 12 mm as indicated in Fig. 5. Bipolar signals were obtained from the needle electrode by recording from needle sites 1 mm apart. The needle electrode was also used to record intramural activation of the left ventricular wall. This was accomplished by making 5 bipolar recording along the length of the needle from the endocardium to the epicardium, usually at 2 mm intervals. At the termination of each experiment the hearts were cut open to ensure the needle site determined to be endocardial from electrical characteristics was in fact located in the endocardium.

Recording of bipolar electrograms were always made from the mid-anterior portion of the left ventricle in the area supplied by the LAD.

2. Recording System

a) Composite electrodes: Composite electrograms were recorded from the anterior and posterior surface of the left ventricle. The signals were amplified in the EKG amplifers of an E for M, DR-8 recorder and records made on photographic paper at speeds of 100 - 200 mm/s.

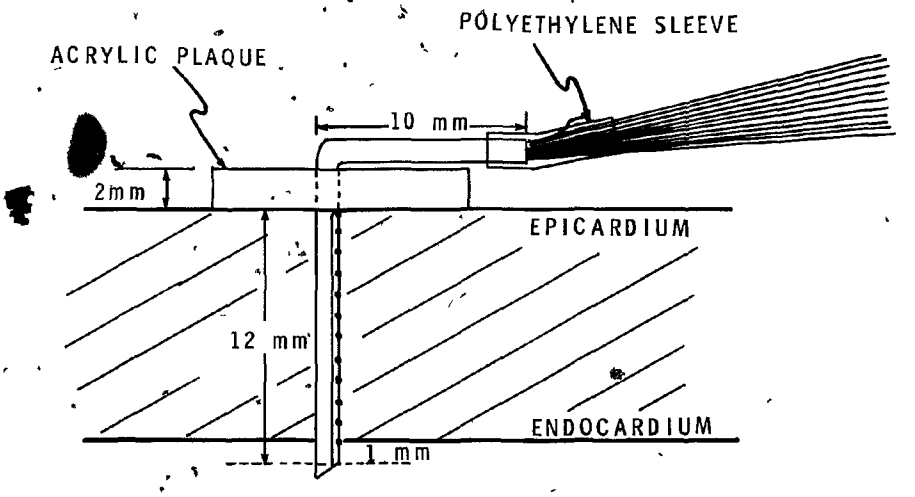


Fig. 5. Multicontact needle electrode used to record intramurally from the heart wall. The electrode was tied to an acrylic plaque which in turn was sewn to the epicardium. Bipolar recordings were made between adjacent contacts at 2 mm intervals along the length of the needle from the endocardium to the epicardial.

Few quantitative measurements were made on these tracings; rather the qualitative changes in signal amplitude and duration associated with acute myocardial infarction were studied. Records were taken at one minute intervals within the first 10 minutes of occlusion then at 15 minute intervals over the next few hours. In a few experiments, endocardial recordings were made from plunge electrodes inserted through the composite electrode to the endocardial surface.

b) Transmural bipolar recordings.

In 32 experiments two recordings were made from the heart; an epicardial and endocardial potential. These bipolar electrograms were amplified by WP Instruments DAM-6A differential amplifiers with frequencies below 30 Hz filtered out. The electrograms were displayed on a Tektronix 565 oscilloscope and simultaneously recorded on a Tandberg series 115 FM tape recorder. Also recorded were two signals generated by the stimulators 1) the stimulus artifact, and 2) the "done" pulse which corresponded to the stimulus artifact of the last beat of the basic drive cycle (see Fig. 6). All recordings were made at a tape speed of 3 3/4 ips giving an effective frequency bandpass of 30 - 1250 Hz. Analogue signals were later retrieved from tape and fed into the A/D converter of a PDP/11 computer, sampled at a rate of 6000 Hz (see appendix for program) and plotted using a Houston Instrument plotter, giving a resolution equivalent

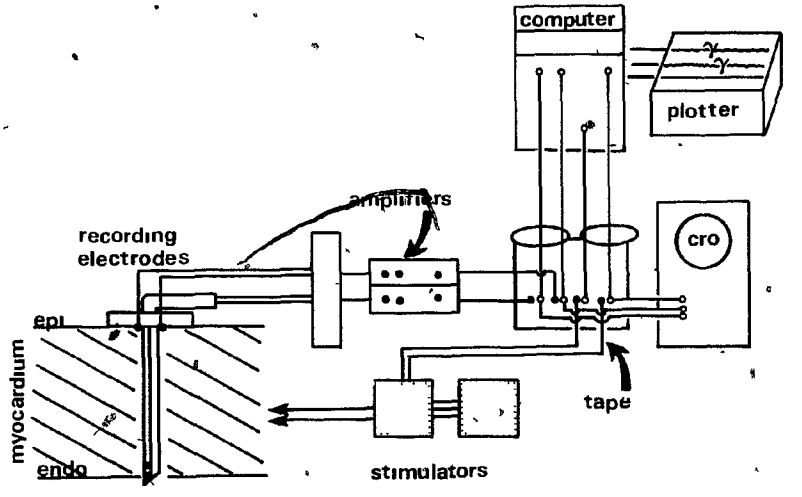


Fig. 6. Setup used for stimulating and recording from the heart in experiments in which only two electrograms were recorded; an endocardial electrogram and an epicardial electrogram from a transmurally opposed location.

to a recorder speed of 1000 mm/s and allowing measurement towithin 0.5 ms. Alternatively, the taped signals were played back at 1/4 tape speed in a Gould recorder run at 125 mm/s giving an equivalency of 500 mm/s and allowing measurement to within 1 ms.

c) Multiple intramural recordings.

In 8 experiments conduction times to 5 levels within the myocardium were determined using the multicontact needle electrodes described above. The electrically active endocardium was determined to be the endocardial most bipolar recording site on the needle electrode to display a muscle (and/or Purkinje) potential and not a cavity potential as described by Roos et al. (81). The 5 intramural electrograms were amplified by an E for M recorder at filter frequencies between 40 - 2000 Hz. Signals were displayed on a Tektronix 565 oscilloscope and simultaneously recorded on a Hewlett Packard 3955 seven channel FM tape recorder at tape speed of 7 1/2 ips along with the stimulus artifact. A hard copy of the electrograms could be obtained as they were being recorded to ensure proper gain on all channels, with a Gould model 660 recorder connected to the output of the tape recorder. This recording setup is represented schematically in Fig. 7. Analogue signals were later retrieved from tape at 1 5/8 ips (1/4 recording speed) and played into the Gould recorder run at a speed of 200 mm/s. This gave an equivalent paper speed of 800 mm/s and allowed a measurement

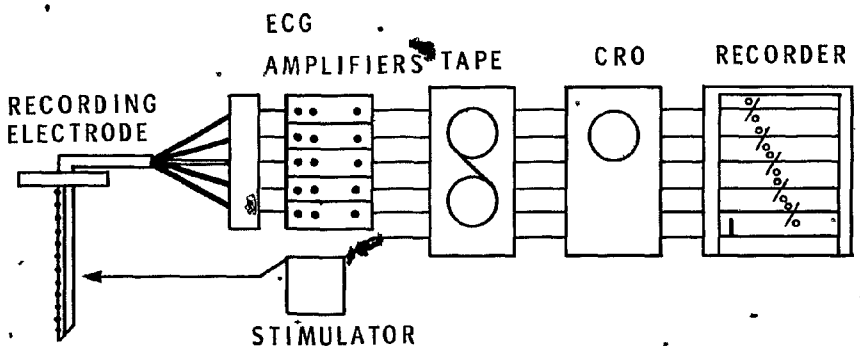


Fig. 7. Setup used for recording 5 electrograms simultaneously from the heart.

accuracy of better than ± 1 ms.

D. ANALYSIS OF RECORDS

1. Composite electrograms. No quantitative measurements were made on these tracings, however qualitative changes in signal amplitude and duration associated with acute myocardial infarction were studied.

2. Local bipolar electrograms. Conduction times to endocardial, intramural, and epicardial electrodes were measured from the stimulus artifact to the first major deflection of the bipolar electrograms, or alternately, to the zero cross-over point of the electrogram. The following measurements were made:

SS = basic cycle interval; interval between stimuli during the basal drive.

SM = conduction time from the stimulating electrode to recording electrode during the basal drive.

SS'= coupling interval of extrasystoles.

S'M' = conduction time of extrasystoles from the stimulating electrode to the recording electrode. $S'M'_{en}$ and $S'M'_{ep}$ represent conduction times to the endocardial and epicardial electrodes respectively.

TMCT = transmural conduction time calculated as the difference in the activation times of the epicardium and endocardium. For stimulation of the heart at a site greater than 3 cm from the recording electrodes TMCT = $(S'M'_{ep} - S'M'_{en})$.
However when the heart was stimulated at the endocardium at a site transmurally opposed to the recording electrode TMCT = $S'M'_{ep}$.

MCT = minimum conduction time between stimulating and recording electrodes.

ΔCT = increase in conduction time above the minimum conduction time during the relative refractory period.

CT_{max} = maximum achievable conduction time between a stimulating and recording electrode: the conduction time at the effective refractory period.

MM' = time between muscle activation on the last beat of the basal drive and muscle activation associated with the extrasystole.

ERP = effective refractory period; minimum interval between applied stimuli which resulted in ventricular activation.

RRP = relative refractory period; the period between the ERP and the coupling interval at which the conduction time of extrasystoles first exceeded the MCT by more than 2 ms.

FRP = functional refractory period; minimum extrasystole interval obtainable at a recording site during stimulation at another site within the heart.

E. DRUGS

1. Lidocaine

Cumulative doses of lidocaine (1.25, 2.50, 5.0 and 10.0 mg/kg) were given in bolus injections 15 min apart. Electrical recordings were made 5 min after each injection. In animals in which myocardial infarction was artifically induced, lidocaine injections were begun 40 min after the occlusion of the coronary artery.

2. Disopyramide

Disopyramide was given in slow injections over a 5 min period to give cumulative doses of 1.0 and 3.0 mg/kg. The two injections were given 30 min apart and recording made 10 min after the beginning of each injection of the drug. In one animal in which infarction was induced by LAD occlusion, disopyramide injections were begun 40 min after the start of occlusion.

SECTION III

RESULTS

A. THE NORMAL HEART

1. Ventricular Conduction of extrasystoles (6 dogs).

a) Endocardial Conduction of extrasystoles.

1) Control conditions: Fig. 8 shows results from a single experiment and is a plot of conduction times (CT) from an epicardial stimulating electrode (site A, Fig. 9) to a distal endocardial electrode (site C, Fig. 9) and a transmurally opposed epicardial electrode (site D, Fig. 9) as a function of the coupling interval of the applied extrasystole. Conduction times to both electrodes remained constant and at a minimum at coupling intervals greater than 260 ms. These conduction times were termed endocardial and epicardial minimum conduction times (MCT_{en} and MCT_{ep}). Conduction times to both electrodes increased sharply at coupling intervals below 260 ms, which marks the beginning of the relative refractory period (RRP) in this experiment. The increase in conduction time within the RRP is presented as ΔCT in Fig. 8. The difference in conduction times to epicardial and endocardial electrodes was taken as the transmural conduction time, TMCT. Not indicated in Fig. 8 but shown in the upper panel of Fig. 41, and seen in approximately 50% of the animals was a period of supernormal conduction preceding the relative refractory period in which conduction times to both electrodes decreased by as much as

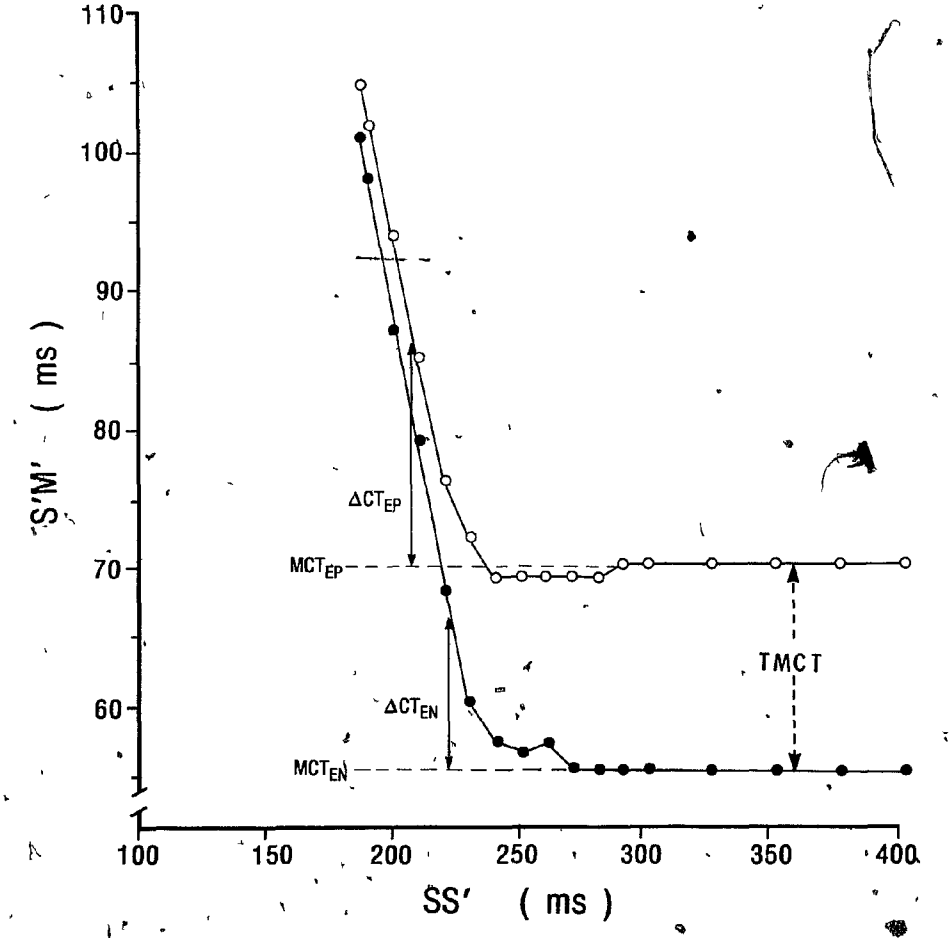


Fig. 8. Relationship between conduction time and coupling interval of premature responses. SS' is the coupling interval between the last regular stimulus and the test stimulus. Dots represent conduction time to an endocardial recording electrode and circles to a transmurally opposed epicardial recording electrode. The heart was stimulated at an epicardial site approximately 3.5 cm from the recording electrodes.

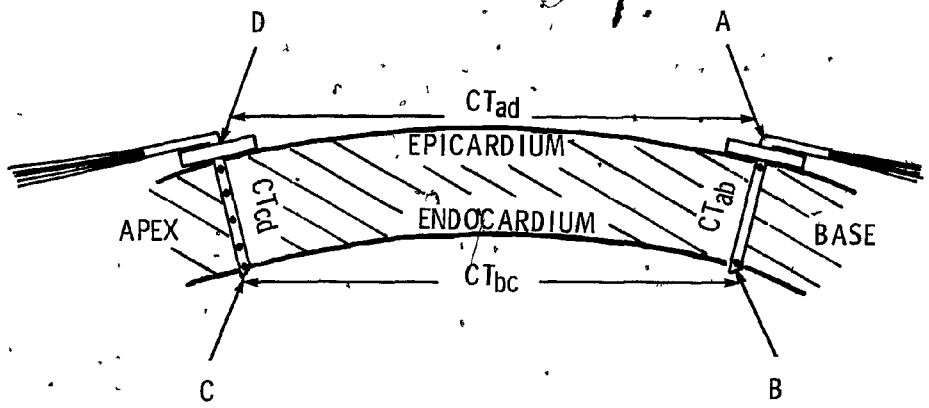


Fig. 9. A cutaway view of the left ventricular free wall showing the sites of both stimulation and recording. Recordings were always made from the mid-anterior portion of the left ventricle from sites C and D (in some experiments 3 additional recordings were made intramurally between sites C and D) while the heart was driven from any one of the four locations A, B, C, or D.

10% below the minimum conduction time. This represents supernormal conduction in the Purkinje system and has been reported by others (4, 33).

11) Effect of lidocaine on endocardial conduction of extrasystoles: lidocaine caused slowing of conduction of midrange extraystoles (MREs, intervals 250 - 400 ms) at 2.5, 5.0 and 10.0 mg/kg in all animals tested; 1.25 mg/kg was ineffective in most animals. Fig. 10 shows the effect of lidocaine on ventricular conduction for the same animal as that represented in Fig. 8. The slowing of MRE's was slightly more pronounced at the epicardial (Fig. 10B) than the endocardial (Fig. 10A) electrode, suggesting lidocaine slows conduction in both Purkinje and myocardial tissues.

Figure 10 also indicates that early extrasystoles reached the recording sites more rapidly after small doses of lidocaine than in the control. Thus the post drug curves of conduction time as a function of coupling intervals crossed the control. This phenomenon is seen more clearly in Fig. 11A and 11B for endocardial and epicardial conduction respectively, for lidocaine 1.25 mg/kg. The changes were somewhat smaller and more variable at the epicardial electrode, suggesting lidocaine did not speed conduction in the myocardium i.e. that the epicardial electrode merely reflected the speeding which had already occurred. Statistical evaluation of the results was difficult because the relationship between coupling

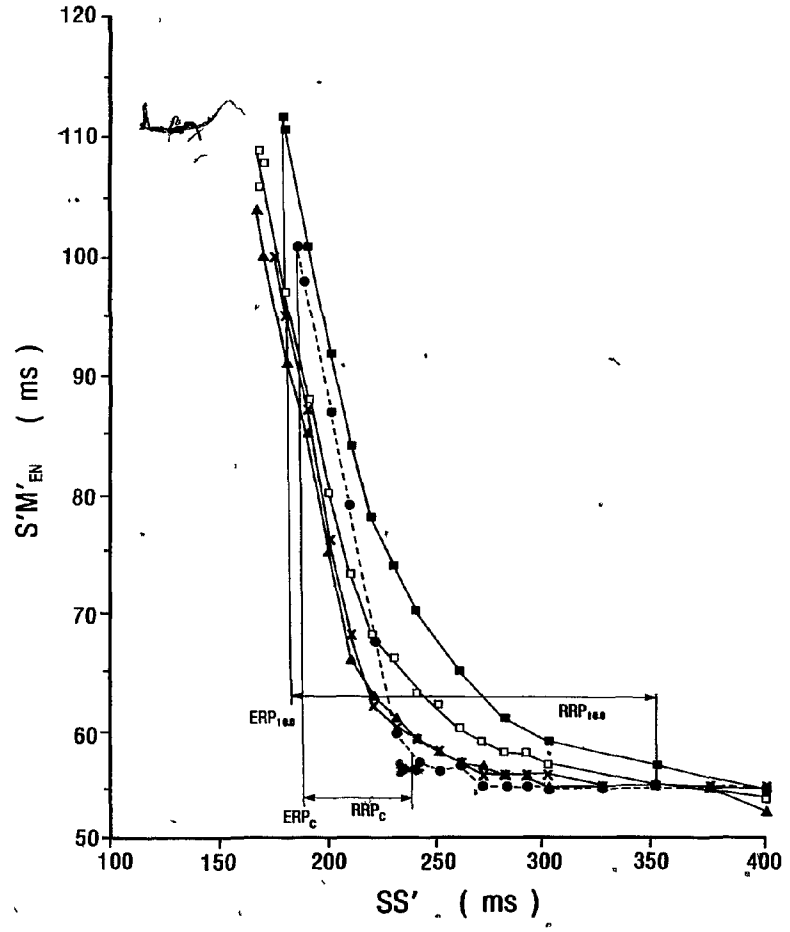


Fig. 10A. The effect of lidocaine on the conduction time of extrasystoles ($S'M'_{en}$) to an endocardial recording electrode from an epicardial stimulating electrode located approximately 3.5 cm away. Basic cycle length = 800 ms. SS' represents the interval between the last normal stimulus and the test stimulus. Control (●), lidocaine 1.25 mg/kg (x), lidocaine 2.5 mg/kg (▲), lidocaine 5.0 mg/kg (□), lidocaine 10.0 mg/kg (■). Also indicated are the relative refractory period, RRP, and effective refractory period, ERP, for the control and lidocaine 10.0 mg/kg.

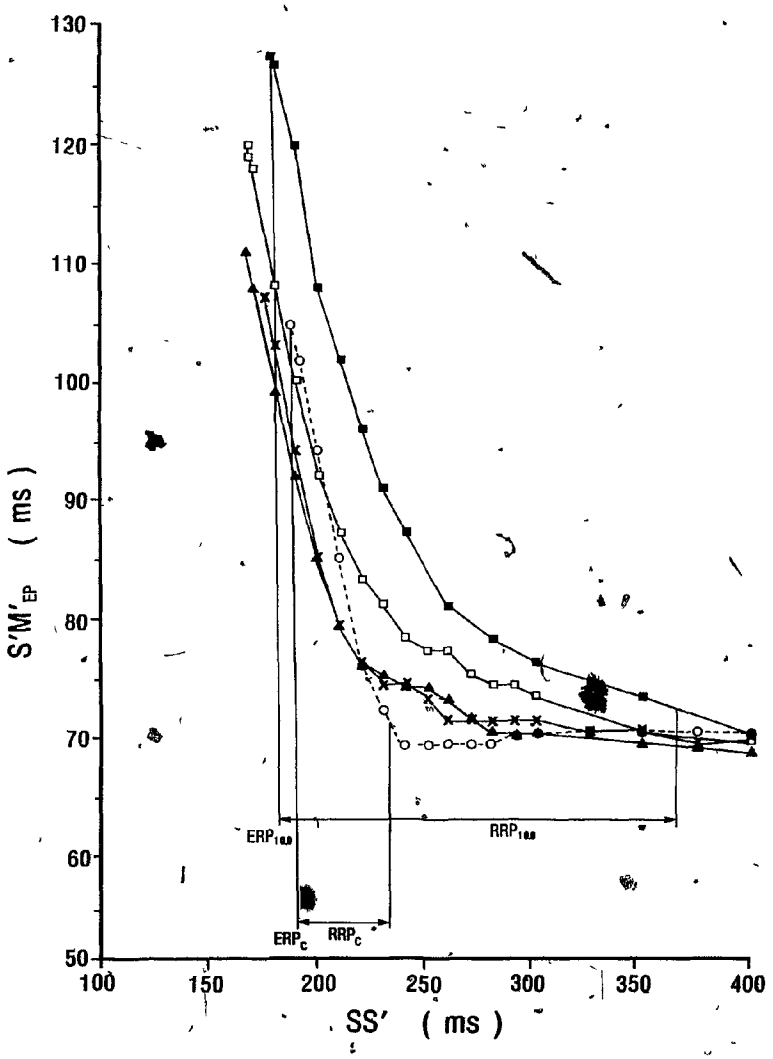


Fig. 10B. The effect of lidocaine on the conduction time of extrasystoles ($S'M'_{ep}$) to an epicardial recording electrode from an epicardial stimulating electrode approximately 3.5 cm away. Basic cycle length = 800 ms. Symbols as in Fig. 10A. Control = (0).

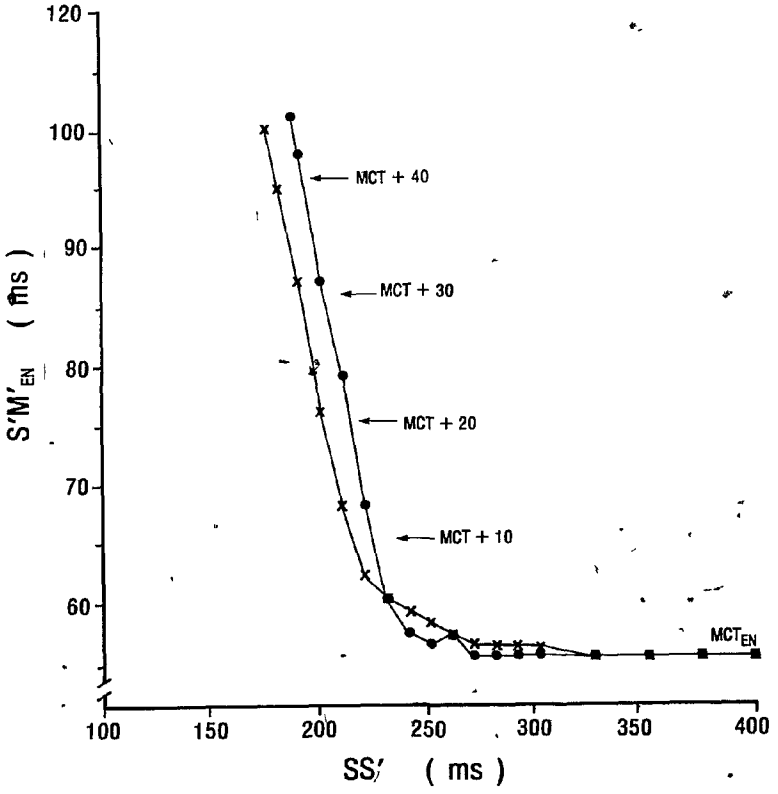


Fig. 11A. Conduction times of extrasystoles to an endocardial electrode under control conditions (●), and after lidocaine 1.25 mg/kg (x). Same as Fig. 10A but containing the curve for the lowest dose of lidocaine only. MCT +10, 20, 30 and 40 represent the points on the control curve where conduction times have increases 10, 20, 30 and 40 ms above the minimum conduction time (MCT_{en}).

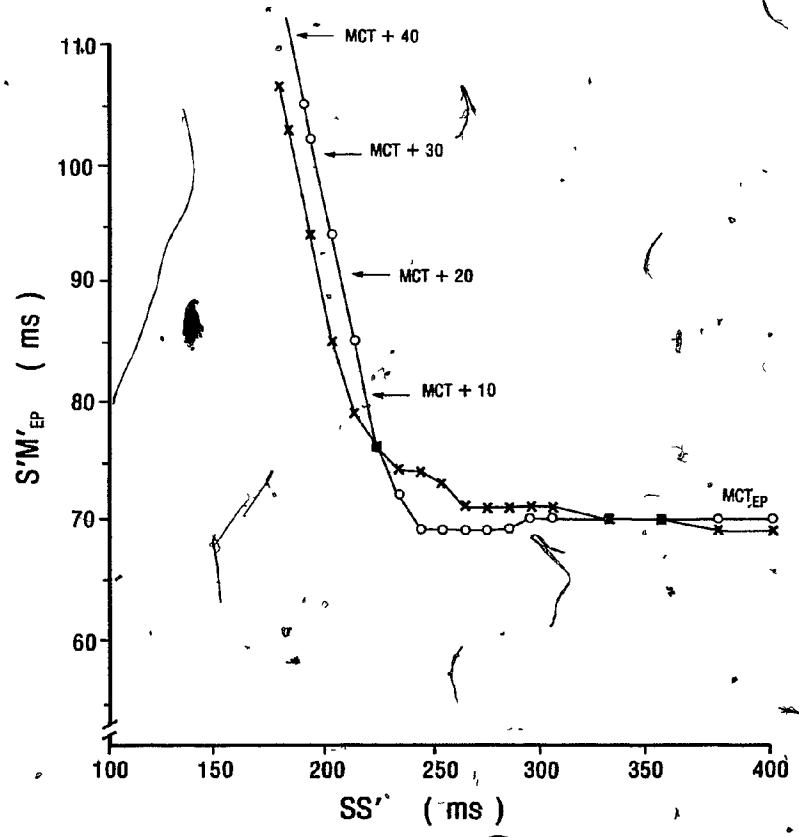


Fig. 11B. Conduction times of extrasystoles to an epicardial electrode under control conditions (0), and after lidocaine 1.25 mg/kg (x). Same as Fig. 10B but containing the curve for the lowest dose of lidocaine only. MCT +10, 20, 30 and 40 represent the points on the control curve where conduction times have increased 10, 20, 30 and 40 ms above the minimum conduction time (MCT_{ep}).

intervals and conduction times (CT) in different dogs varied both on the abscissa and the ordinate. We therefore chose to measure conduction times at arbitrarily defined coupling intervals before and after lidocaine administration. The coupling intervals at which measurements were made were those at which control measurements had shown conduction times to have been increased by 10, 20, 30 and 40 ms above the MCT. These points are indicated in Fig. 11. This allowed statistical comparison between conduction times for control vs lidocaine in the entire group of 8 animals. Table 1 summarizes the analysis at the lowest dose of the drug. Lidocaine caused significant ($p < .01$) speeding of conduction at the coupling intervals at which control CT had been MCT +30 and MCT +40 ms at the endocardial electrode. Speeding of conduction also occurred at 2.5 mg/kg but was not as clear at 5.0 mg/kg and slowing rather than speeding occurred in 6/8 dogs given 10 mg/kg of the drug.

iii) Effect of disopyramide on endocardial conduction of extrasystoles: the effect of disopyramide on the conduction time between an endocardial stimulating electrode and a distal endocardial recording electrode (sites B and C, Fig. 9), was studied. Endocardial conduction times for one experiment are plotted as a function of coupling interval for control conditions and for two doses of disopyramide in Fig. 12A. Disopyramide caused a dose dependent shift to the right of the conduction curves increasing the ERP from a control value of 204 ms to 221 ms at 1.0 mg/kg and to 224 ms

TABLE 1: Effect of lidocaine, 1.25 mg/kg, on conduction times of extrasystoles of short coupling intervals.

Endocardium	MCT +10*	+20	+30	+40
Mean Diff.	-.7	-2.4	-4.1	-4.6
SD_{diff}	2.3	3.9	3.7	4.0
t	.8589	1.736	3.100	3.072
p**	N.S.	N.S.	.01	.01
N = 8				

Epicardium	MCT +10*	+20	+30	+40
Mean Diff.	+.1	-2.7	-4.4	-5.0
SD_{diff}	3.7	4.1	6.0	5.3
t	-.113	1.842	2.100	2.467
p**	N.S.	N.S.	.05	.05

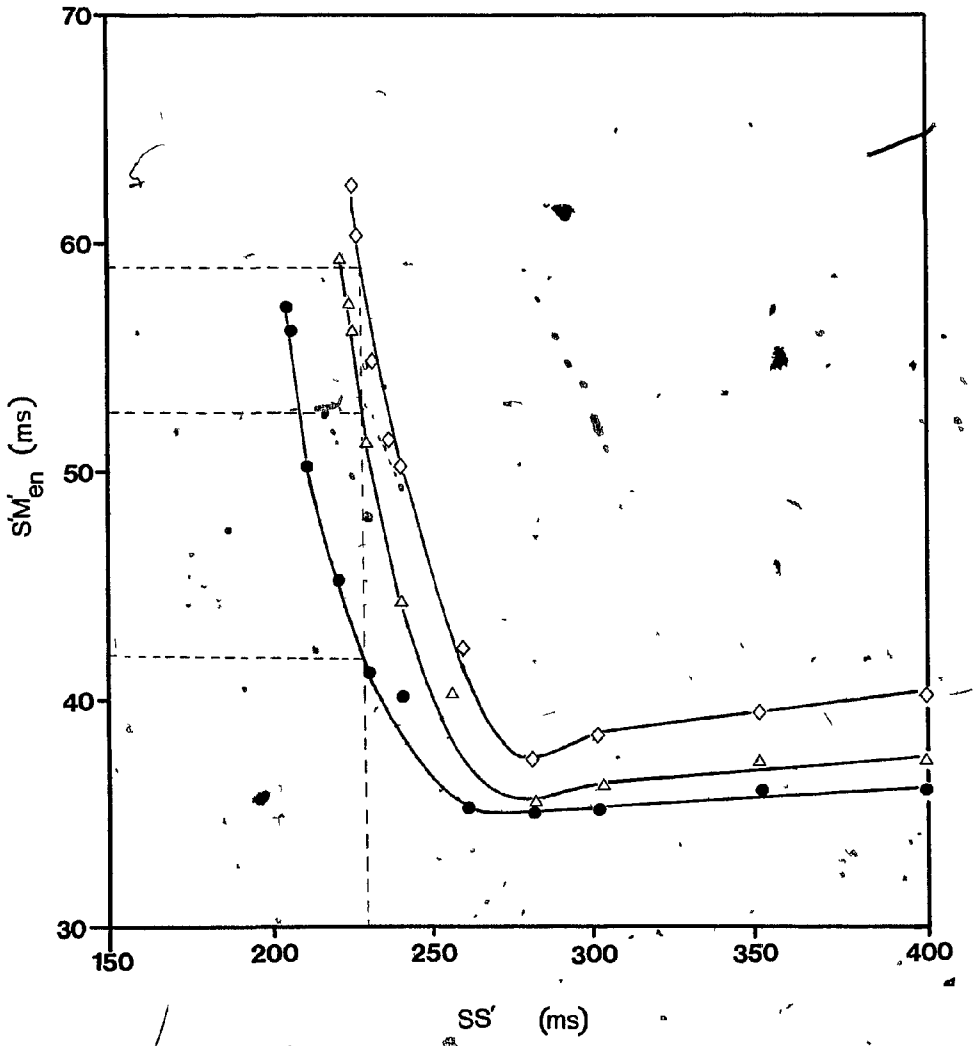


Fig. 12A. Effect of disopyramide on the relationship between conduction time and coupling interval of extrasystoles in a representative experiment. The ordinate S'M'en, represents endocardial conduction times, the abscissa, SS', the interval between the last regular stimulus and the test stimulus. Control (●), disopyramide 1.0 mg/kg (△), disopyramide 3.0 mg/kg (◇). Basic cycle length = 800 ms.

at 3.0 mg/kg. Thus, at any given extrasystole coupling interval that falls within the RRP, the conduction time after the drug is greater than during control. The dashed line in the figure represents a coupling interval within the RRP, 250 ms. At this coupling interval conduction times are 42, 53, and 59 ms for control and disopyramide 1.0 and 3.0 mg/kg respectively. Disopyramide 3.0 mg/kg caused additional slowing of conduction which is not interval related but was also seen at long coupling intervals (greater than 300 ms). This is seen as an increase in the MCT. The increase in MCT due to 1.0 mg/kg disopyramide is within experimental error and not significant.

In order to normalize data between animals, conduction times for each animal were calculated relative to the ERP, a coupling interval which could be accurately defined in each animal. Conduction times were determined at the ERP, ERP +5, +10, +20, +30, +40, +60, +80, and +100 ms. The data averaged for the group of 8 animals at each one of these intervals is presented in Fig. 12B. The average ERP values for control and drug conditions were used as a reference point for plotting. The mean ERP for control was 197 ms. This was increased to 204 ms with disopyramide 1.0 mg/kg and to 211 ms with 3.0 mg/kg. These ERP values are contained in brackets in the figure. Non-interval related slowing of conduction by disopyramide 3.0 mg/kg is evident as an increase in MCT in the figure.

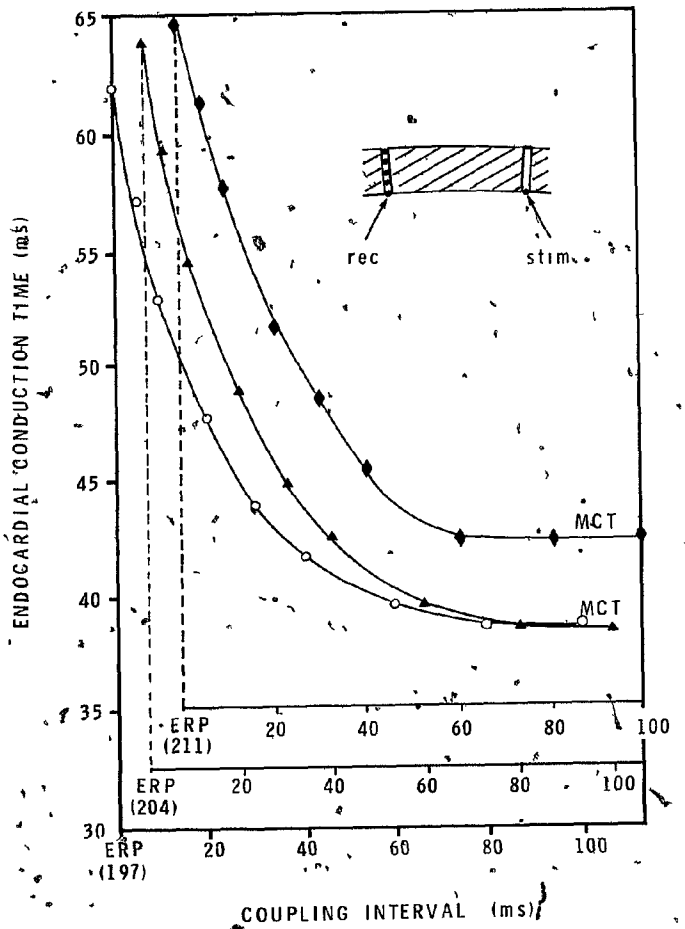
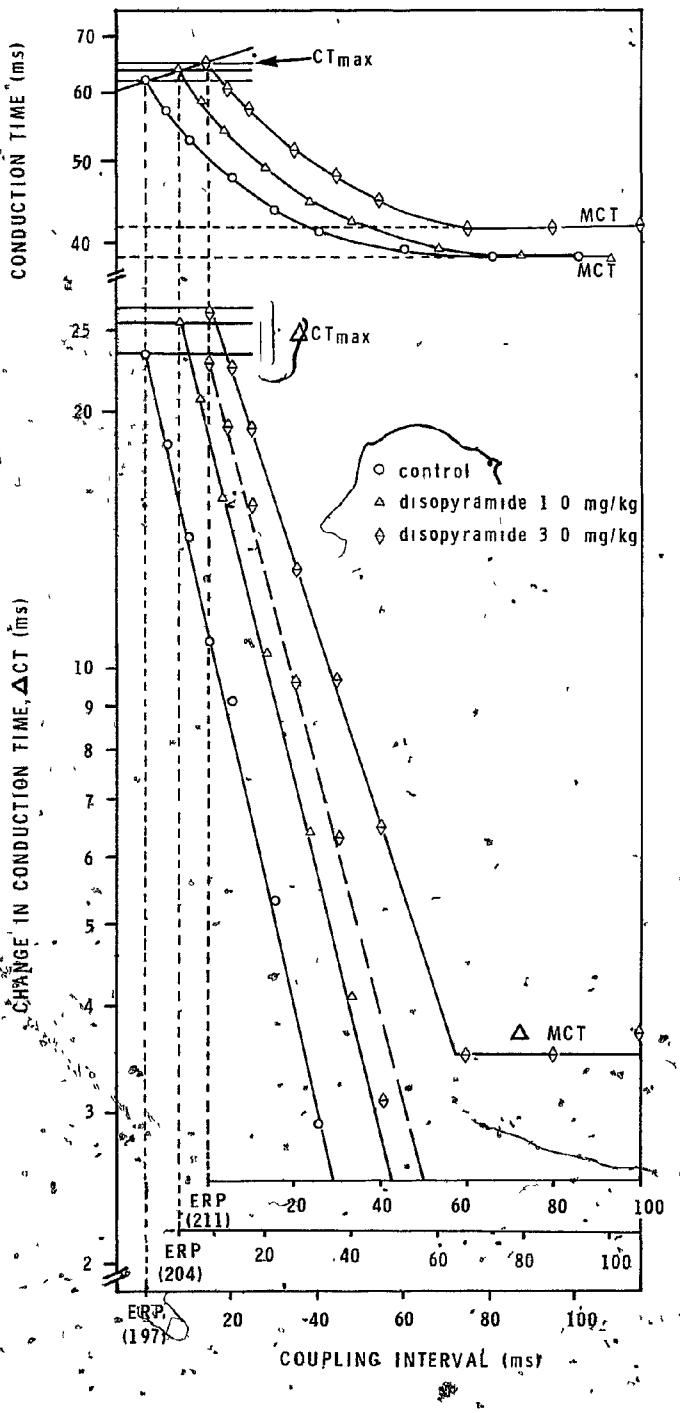


Fig. 12B. Effect of disopyramide on the relationship between conduction time and coupling interval of extrasystoles. Conduction times were measured over a distance of approximately 3.5 cm at the coupling interval which defined the effective refractory period (ERP), and at coupling intervals 5, 10, 20, 30, 40, 60, 80 and 100 ms above the ERP. The curves represent average conduction times for 8 animals. The average ERP values are represented in brackets for control conditions and two doses of disopyramide. Control (○), disopyramide 1.0 mg/kg (▲), disopyramide 3.0 mg/kg (◆). Basic cycle length = 800 ms.

Although disopyramide caused slowed conduction of extrasystoles it did not change the manner in which the heart conducted extrasystoles while it was refractory. This may be concluded from a parallel shift to the right of the curves in figure 12B. (Conduction during refractoriness, CDR, was the same during the drug as it was for control).

The actions of disopyramide on endocardial conduction are more readily appreciated when conduction times are plotted logarithmically as shown in Fig. 13. The upper part of the figure is a replica of Fig. 12B plotted logarithmically. The solid lines in the lower part of Fig. 13 are plots of the change in conduction time (ΔCT) above the minimum conduction time (MCT) determined under control conditions. For any given coupling interval the change in conduction time is greater for disopyramide treatment than for control. This was observed to be a dose dependent phenomenon. The parallel shift to the right by disopyramide of the ΔCT plot without a change in slope indicates that the drug increases the ERP and thus the absolute refractoriness of the heart but does not change conduction during refractoriness (CDR). The drug increased the conduction time at the ERP, so that the maximum conduction time (CTmax) in the Purkinje system was increased in a dose-dependent manner. For disopyramide 3.0 mg/kg the increase in CTmax is equivalent to the increase in MCT indicating the drug not only causes a parallel shift to the right but also upwards of the conduction curves. The

Fig. 13. The upper part of the figure is a logarithmic plot of the effect of disopyramide on the relationship between endocardial conduction time and extrasystole coupling interval. (A logarithmic plot of the data previously presented in Fig. 12B) The solid lines in the lower part of the figure are plots of the change in conduction time. (Δ CT) above the minimum conduction time (MCT) for control conditions. The broken line represents the change in conduction time (Δ CT) observed for disopyramide 3.0 mg/kg above the MCT for disopyramide 3.0 mg/kg, not the MCT of control. CT_{max} = the maximum conduction time achievable, i.e. conduction time at the ERP. Control (0), disopyramide 1.0 mg/kg (Δ), disopyramide 3.0 mg/kg (◇). Basic cycle length = 800 ms. n= 8.


CONDUCTION TIME (ms)
CHANGE IN CONDUCTION TIME, ΔCT (ms)
COUPLING INTERVAL (ms)
CTmax
MCT
MCT
CTmax
control
disopyramide 1 0 mg/kg
disopyramide 3 0 mg/kg
Δ MCT
ERP (211)
ERP (204)
ERP (197)
70
60
50
40
25
20
10
9
8
7
6
5
4
3
2
20
40
60
80
100

increase in minimum conduction time (MCT) by 3.0 mg/kg disopyramide is represented at the horizontal line in the plot of ΔCT in the figure. The broken line in this figure represents the ΔCT for disopyramide 3.0 mg/kg above the MCT for disopyramide 3.0 mg/kg, not the MCT of control.

b) Transmural conduction time (TMCT) of extrasystoles.

Transmural conduction time was determined in two different manners. For distal stimulation, whether epicardial or endocardial, when the distance between stimulating electrode and recording electrodes was greater than 3 cm, TMCT was taken as the time difference in activation of the epicardium and endocardium at the recording electrode. When the heart was driven from the endocardial tip of the recording electrode, proximal stimulation, TMCT was taken as as the time from the stimulus artifact to the activation of the epicardium at a transmural site.

i) Transmural conduction time determined during distal stimulation: effects of lidocaine and disopyramide.

Transmural conduction time was plotted against the coupling interval "seen" at the endocardial electrode, S_1'en, (Fig. 14A). TMCT in this experiment was determined during distal epicardial stimulation (site A, Fig. 9) and

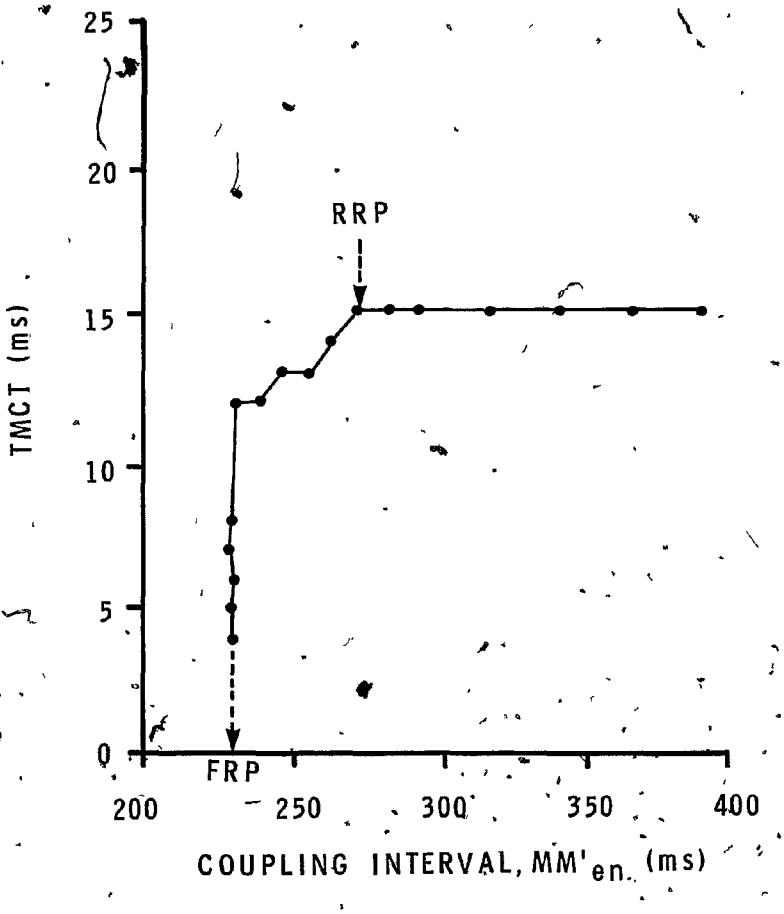


Fig. 14A. Results from a single experiment showing the relationship between transmural conduction time (TMCT) and extrasystoles coupling interval. TMCT was calculated as the difference between endocardial and epicardial activation times and plotted relative to the coupling interval invading the myocardium at the endocardial recording site, MM'_{en}. The heart was stimulated at a site on the left ventricle approximately 3.5 cm from the recording electrodes. FRP = functional refractory period, RRP = the beginning of the relative refractory period (the coupling interval at which conduction times to the endocardial electrode first began to increase above the minimum conduction time). Basic cycle length = 800 ms.

remained constant at 15 ms down to the coupling interval which marked the beginning of the RRP, after which it decreased to 4 ms (73%). Decreases in TMCT indicating apparently supernormal conduction were observed in 6 of the 8 dogs in this series and 21/32 dogs when results from other experiments are included. The maximum decreases in TMCT ranged from 5 to 100%. The very large change in TMCT shown in Fig. 14A represents an extreme case. The decrease in transmural conduction time observed most commonly in (21) dogs was 5 - 7 ms or approximately 30%.

In these experiments the impulse had to travel through a minimum of 3 cm of tissue before reaching the recording sites. Thus, TMCT was plotted as a function of the extrasystole interval reaching the endocardium at the recording site, the MM' interval. The shortest coupled extrasystole entering the myocardium at the recording site was determined by the functional refractory period (FRP) of the Purkinje system. The refractory periods differed from one animal to the next therefore in order to normalize data between animals, TMCT was calculated relative to the FRP, for each animal i.e. at the FRP, FRP +5, +10, +20, +30, +40, +60, +80, and FRP +100 ms. TMCT's were averaged for the group of animals at each of these coupling intervals. Figure 14B shows a plot of TMCT at these defined coupling intervals. Results in this figure are average results from a group of 8 animals in which the hearts were driven from a distal epicardial electrode (site A, Fig. 9). In this group

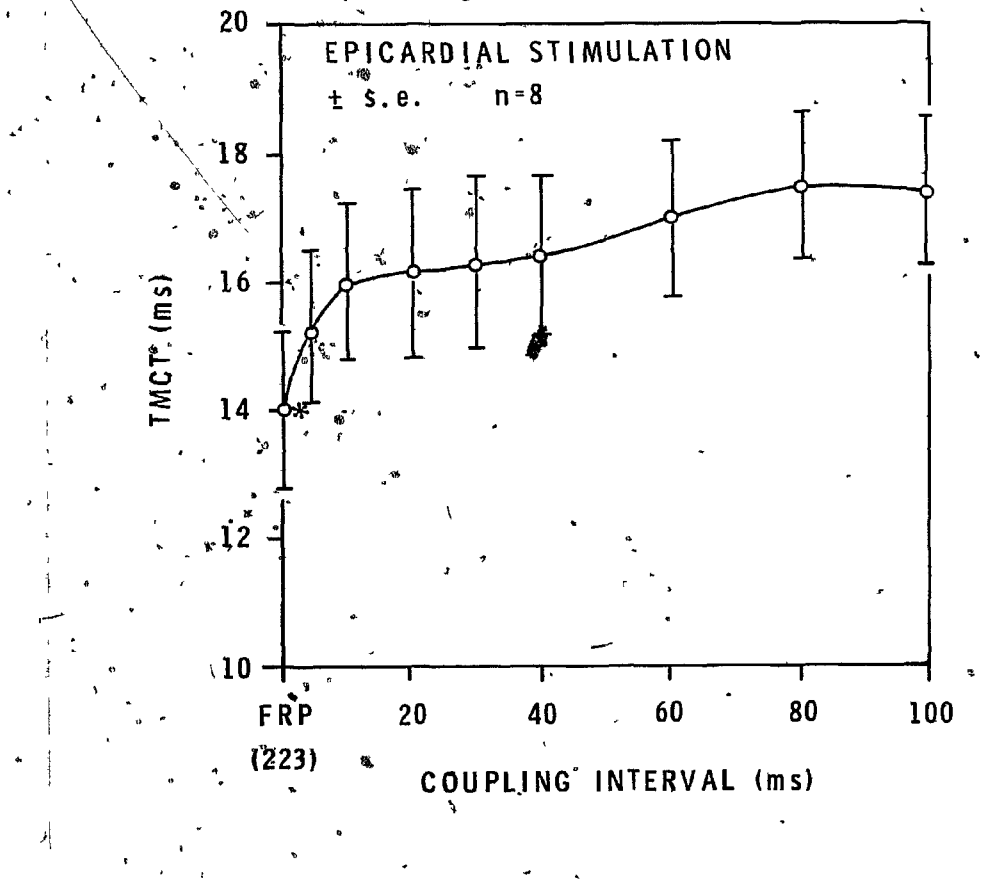


Fig. 14B. Average results from 8 animals showing the relationship between transmural conduction time (TMCT) and coupling interval of extrasystoles. Stimulation was carried out from an epicardial electrode located approximately 3.5 cm from the recording electrodes. MM'_{en} represents the coupling interval invading the myocardium at the endocardial recording site. RRP = relative refractory period, FRP = functional refractory period. Conduction times were calculated at the shortest coupling interval invading the myocardium at the recording site, the FRP, and at coupling intervals 5, 10, 20, 30, 40, 60, 80 and 100 ms above the FRP. Basic cycle length = 800 ms.

TMCT decreased an average of 3.5 ms at the shortest coupling interval. Transmural conduction time at the FRP was compared to TMCT determined at a long coupling interval, 100 ms above the FRP (FRP + 100), using a paired t-test. The decrease in TMCT was found to be statistically significant ($p<.01$).

Effects of lidocaine on transmural conduction: The effects of lidocaine on myocardial conduction are shown in Fig. 15 for one animal for control conditions (data already presented in Fig. 14A) plus curves for 2.5 and 10. mg/kg lidocaine. Lidocaine caused a dose-dependent attenuation of the decrease in TMCT observed at short coupling intervals, and increased TMCT at 10 mg/kg. The drug had little or no effect on myocardial conduction of extrasystoles with long coupling intervals. It is interesting to note that lidocaine did not shift the coupling interval at which TMCT began to decrease.

Effects of disopyramide on transmural conduction time: The effects of disopyramide on transmural conduction time, TMCT, are presented in Fig. 16. Transmural conduction time determined during epicardial stimulation (site A, Fig. 9) is shown in Fig. 16A and TMCT determined during distal endocardial stimulation (site B, Fig. 9) is shown in Fig. 16B. Data are plotted relative to the FRP as discussed above. The mean FRP values for control conditions (circles), for disopyramide 1.0 mg/kg (triangles) and for disopyramide 3.0 mg/kg (diamonds) are indicated in brackets

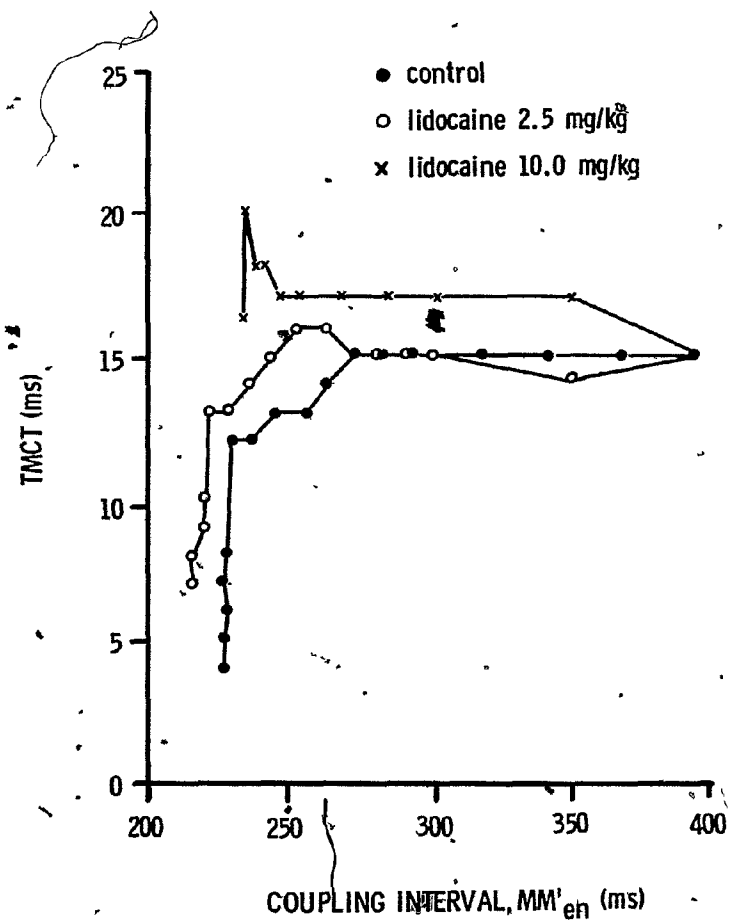


Fig. 15. Effect of lidocaine on the relationship between transmural conduction time and coupling interval of extrasystoles. Shown are results from one animal for control conditions (●) (data previously presented Fig. 14A) and for lidocaine 2.5 mg/kg (o), and lidocaine 10.0 mg/kg (x). Basic cycle length = 800 ms.

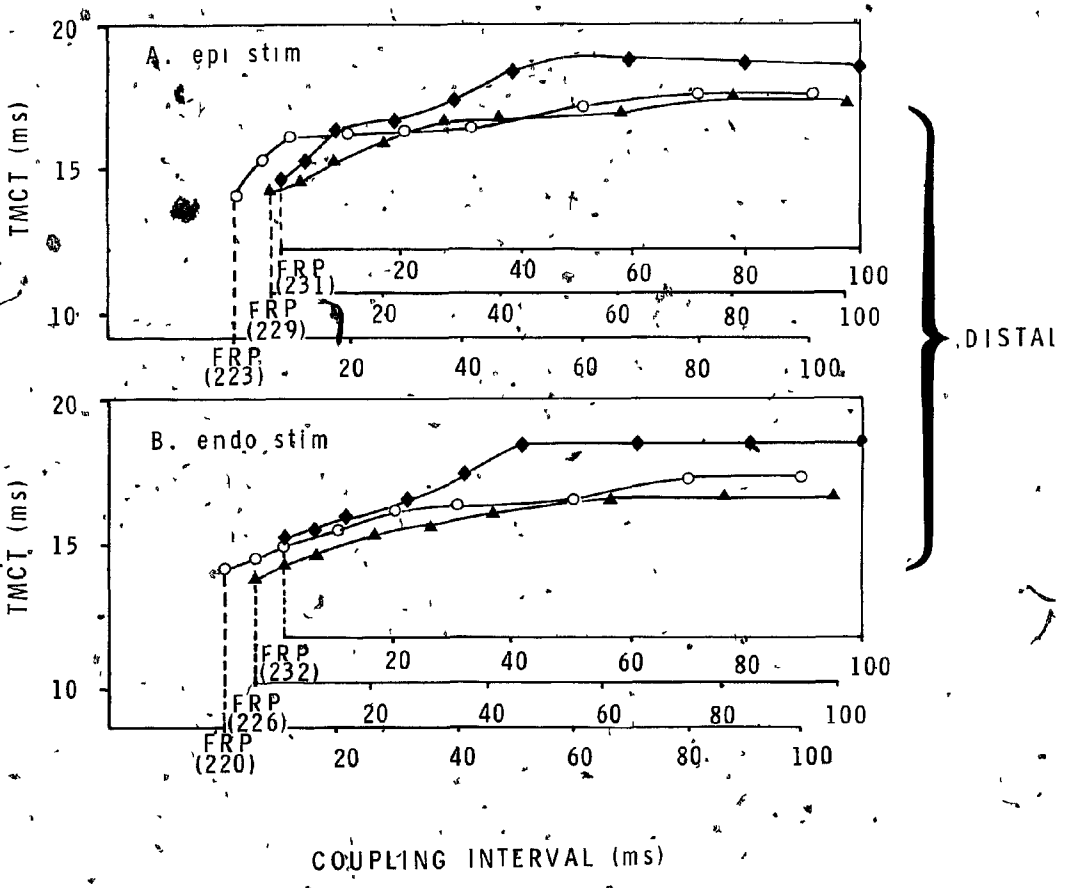


Fig. 16. Effect of disopyramide on the relationship between transmural conduction time (TMCT) and coupling interval of extrasystoles. Panel A represents TMCT calculated during stimulation of the heart from a distal epicardial electrode located approximately 3.5 cm from the recording electrodes.electrodes. Similarly, panel B represents TMCT calculated during stimulation from a distal endocardial electrode located transmurally to the epicardial stimulating electrode. Conduction times are calculated relative to the minimum coupling interval invading the myocardium at the recording site, the FRP of the ventricle. Control (0), disopyramide 1.0 mg/kg (▲), disopyramide 3.0 mg/kg (◆). Basic cycle length = 800 ms. n = 8 (See text for full explanation).

in the figure. The 1.0 mg/kg dose of the drug had no effect on the calculated TMCT. At 3.0 mg/kg however disopyramide caused an increase in TMCT calculated for long coupled extrasystoles, those greater than FRP + 40 ms. The drug did not affect the decrease in TMCT seen at the short coupling intervals. Increases in transmural conduction time produced by disopyramide 3.0 mg/kg were analysed statistically using the students paired t-test at the coupling interval of FRP +100 ms. The drug caused a significant increase in TMCT at this coupling interval during distal endocardial stimulation ($p < .01$) with a somewhat less effect during distal epicardial stimulation ($p<.10$).

ii) Transmural conduction time determined during proximal stimulation: Effects of disopyramide.

For proximal stimulation the extrasystole interval invading the myocardium at the recording site did not first have to transverse the Purkinje system in being conducted from the stimulating electrodes. Therefore the minimum extrasystole interval obtainable at the recording electrode was defined by the effective refractory period (ERP) of the myocardium. Conduction times across the ventricular wall from the stimulating to recording electrodes were calculated for each animal relative to the ERP allowing results to be pooled for the group of animals. Conduction times were determined at the ERP, ERP +5, +10, +20, +30, +40, +60, +80,

and ERP +100 ms. Fig. 17 contains the results for TMCT determined at these coupling intervals for a group of 8 animals (the same 8 animals in which TMCT was determined during distal stimulation, Fig. 14B and Fig. 16A and 16B). The figure contains data determined during control conditions (open circles) and after disopyramide 3.0 mg/kg (diamonds). Conduction times were plotted relative to their corresponding ERP value. Control TMCT's were plotted relative to the mean ERP for control and TMCT's for disopyramide 3.0 mg/kg were plotted relative to the mean ERP for this dosage of the drug. During proximal stimulation a decrease in TMCT, apparent supernormal conduction, was never observed. Rather, an increase in TMCT was observed at short coupling intervals, i.e. ERP +20 ms, as the relative refractory period of the myocardium was entered. This increase in TMCT always occurred at a coupling interval that was shorter than the FRP of the Purkinje system. This phenomenon can be seen by comparing Fig. 17 with panels A or B of Fig. 16. Thus during Purkinje activation of the ventricle the extrasystole interval invading the myocardium is limited by the "gating" function of the Purkinje, such that the myocardium never becomes refractory and never displays slowed conduction. This relationship is unchanged after 3.0 mg/kg disopyramide which caused an increase in ERP of the myocardium (Fig. 17) but caused equivalent increases in the FRP of the Purkinje system (panels A and B, Fig. 16).

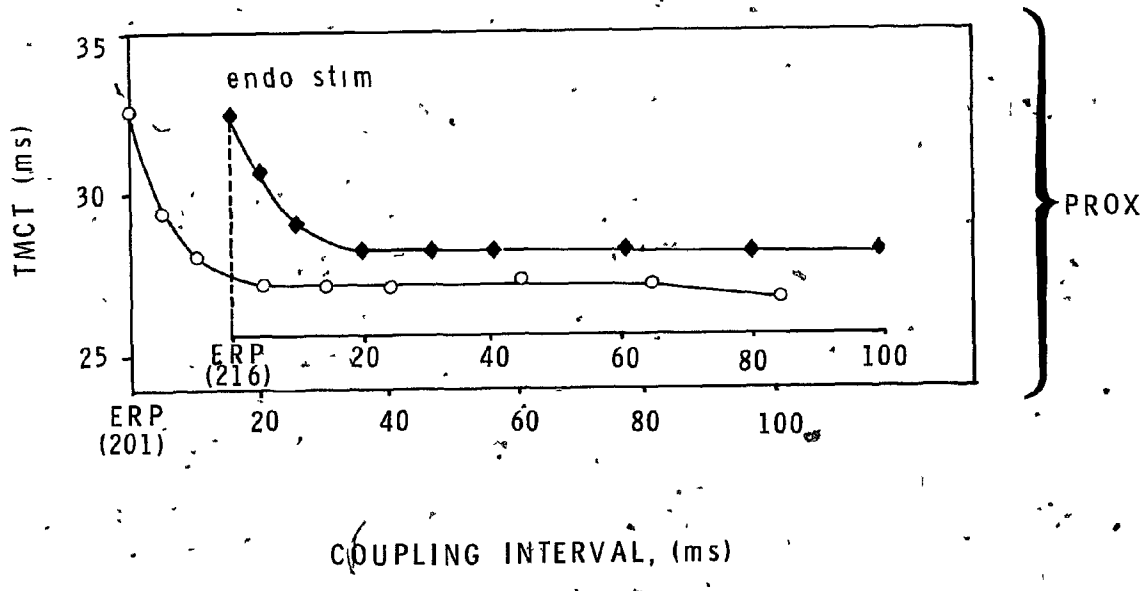


Fig. 17. Effect of disopyramide on the relationship between transmural conduction time (TMCT) calculated during proximal stimulation and coupling interval of extrasystoles. TMCT was calculated as the time required for a stimulus delivered to the endocardium to travel across the heart wall to the epicardial surface. Conduction times were measured at the coupling interval which defined the effective refractory period, ERP, and at coupling intervals 5, 10, 20, 30, 40, 60, 80 and 100 ms above the ERP. The average ERP values for control and disopyramide 3.0 mg/kg are indicated in brackets in the figure. Control (0), disopyramide 3.0 mg/kg (◆). Basic cycle length = 800 ms. n = 8.

Disopyramide, 3.0 mg/kg caused an increase in TMCT at all coupling intervals in addition to the increase it produced in the ERP. The effect of disopyramide on TMCT was assessed at one coupling interval, ERP + 100 ms, using the students paired t-test. At this coupling interval disopyramide caused a increase in TMCT which was significant at the ($p < .05$) level.

The effects of lidocaine on TMCT determined during proximal stimulation were not explored because of the time constraints of this project.

c) Intramural conduction of extrasystoles:

1) Distal epicardial stimulation. In order to try and determine the cause of the decrease in TMCT observed at short coupling intervals a recording electrode with 5 bipolar recording sites was used to observe intramural activation during extrasystoles. The heart was stimulated from the four different locations indicated in Fig. 9 to determine whether Purkinje activation of the heart wall at the recording site was necessary for the observed decrease in TMCT or whether it was a property of the myocardium, proper. Conduction times of extrasystoles to the five recording sites from a distal epicardial stimulating electrode (site A Fig. 9) located at the base of the heart are shown in Fig. 18A in which the conduction times are plotted as a function of coupling interval of the

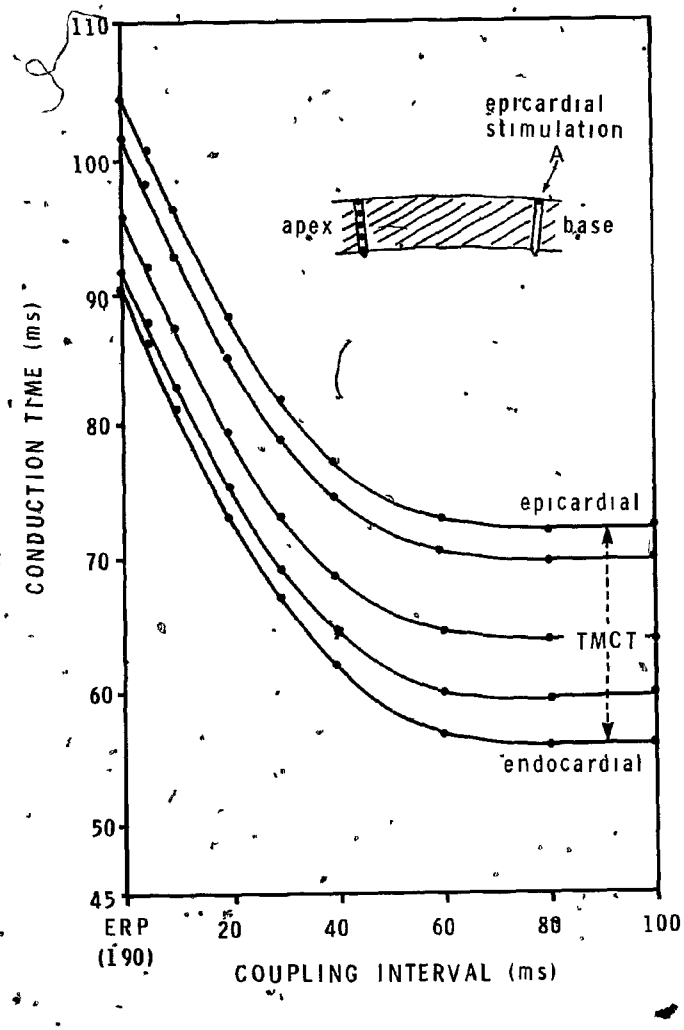


Fig. 18A. Relationship between conduction time and coupling interval of extrasystoles. The five curves represent conduction times to five intramural recording sites from an epicardial stimulating electrode located at a distance of approximately 3.5 cm. The endocardial electrode is the first to be activated with the remainder being activated in a sequential fashion from the endocardium to the epicardium. Conduction times were measured at the coupling interval which defined the effective refractory period, ERP, and at coupling intervals 5, 10, 20, 30, 40, 60, 80 and 100 ms above the ERP. The curves represent results averaged for 8 animals. The average ERP value, indicated in brackets, was 190 ms. Transmural conduction time, TMCT, was calculated as the time difference between activation of the endocardial and epicardial electrodes.

extrasystoles. As the relationship between coupling intervals and conduction time varied both on the abscissa and ordinate between animals, data was normalized for the 8 animals relative to the ERP. Conduction times in each animal were determined at the effective refractory period and at the coupling intervals which corresponded to the ERP + 5, 10, 20, 30, 40, 60, 80 and ERP + 100 ms. Average results for the 8 animals are plotted in the figure. The mean ERP value, was 190 ms for stimulation from the epicardial site A shown in the inset of the figure. (The inset is a reproduction of Fig. 9).

The heart wall was activated sequentially from the endocardium to the epicardium. The difference between epicardial and endocardial activation, the transmural conduction time (TMCT), is indicated in Fig. 18A. The average value for TMCT was 17 ms at long coupling intervals (> ERP + 60) but as the relative refractory period of the ventricle was entered and conduction times to all recording sites increased, the lower two curves in the figure approached each other resulting in a decrease in the measured TMCT value (previously presented in Fig. 16A).

This decrease in TMCT or "apparent supernormal conduction" within the myocardium was due to a disproportionate increase in conduction time to the electrode located at the endocardium and not to any of the others. Note that in Fig. 18A, the conduction time between the endocardial

electrode and the electrode located in the sub-endocardium (the two lower curves) appears to decrease at the short coupling intervals whereas the distance between other curves remains constant. In 2/8 experiments there was a reversal in activation sequence in these electrodes with the more central electrode pair being activated before the endocardial pair. This caused a cross over of their conduction curves as seen in Fig. 18B which shows results from one of these experiment. The conduction times between other electrode sites remains constant at all coupling intervals.

The conduction times between consecutive intramural electrodes, the differences between the curves in Fig. 18A, are plotted as a function of coupling interval in Fig. 19. The solid circles represent the conduction time between the endocardial electrode and the immediately adjacent electrode located intramurally. This conduction time decreases steadily as the ERP in approached. The conduction times between other pairs of electrodes (indicated by the open symbols) do not change (within measurement error) with extrasystole interval indicating that the muscle never became refractory even at the shortest extrasystoles. The differences in conduction times observed between different pairs of electrodes is due to different distances between electrode pairs rather than variations in conduction velocity of the myocardium i.e. the open circles represent conduction time over a 1 mm distance whereas the triangles.

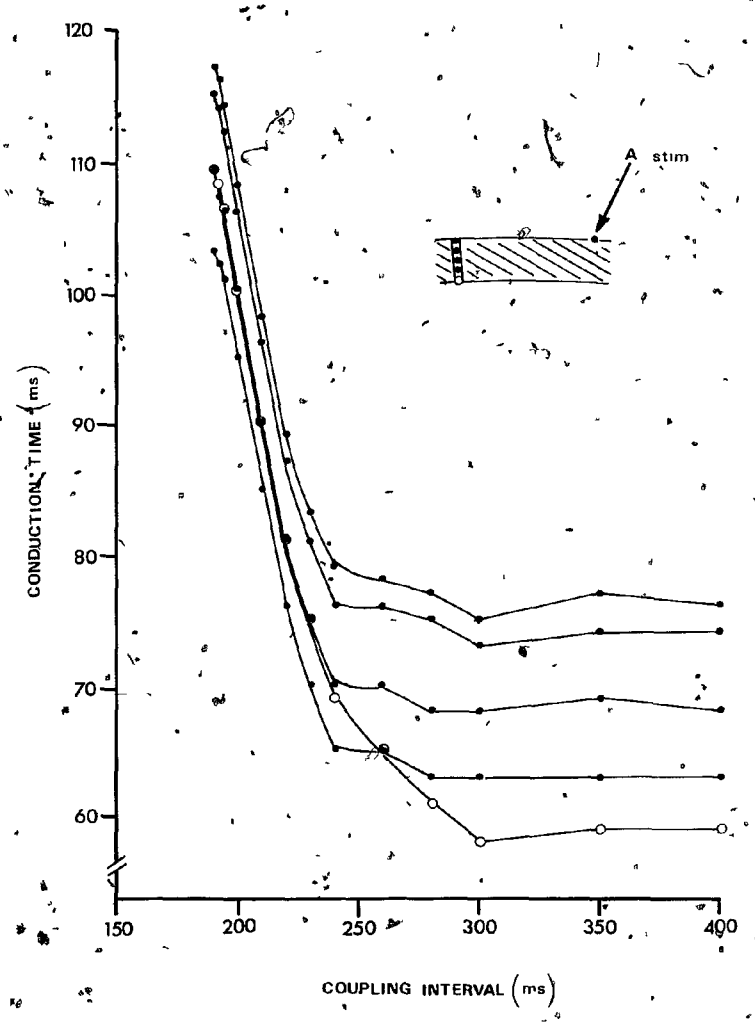


Fig. 18B. A diagram containing similar curves to those presented in Fig. 18A but for a single animal only. Conduction times to five intramural recording sites are plotted as a function of the coupling interval delivered to the heart at an epicardial site located approximately 3.5 cm from the recording electrodes. Conduction time to the endocardial electrode is represented by circles and to all other electrodes by dots. The heart wall was activated in a sequential manner from the endocardium to the epicardium at long coupling intervals but at short coupling intervals the activation of the endocardial electrode followed, and not preceded the activation of the adjacent electrode located in 2 mm away in the sub-endocardium. Basic cycle length = 800 ms.

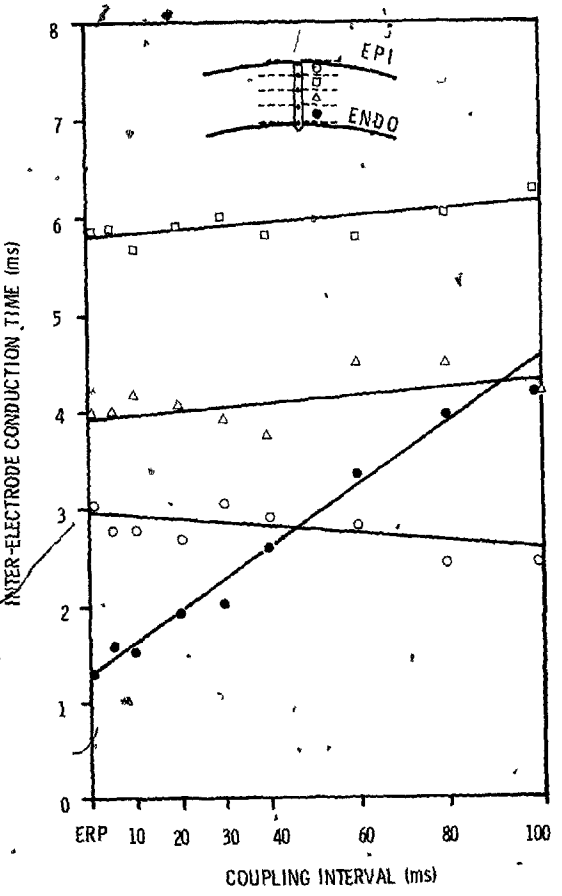


Fig. 19. Conduction times between adjacent electrodes of a multicontact needle electrode as a function of extrasystole coupling interval. Conduction times are those determined over 2 mm segments of the left ventricular wall from the endocardium to the epicardium, i.e. the difference between the curves of Fig. 18A. The heart was stimulated at an epicardial site located approximately 3.5 cm from the multicontact electrode. Basic cycle length = 800 ms. Conduction times were calculated at the coupling interval defining the ERP and at coupling intervals 5, 10, 20, 30, 40, 60, 80 and 100 ms above the ERP. n = 8.

and squares are conduction times over 2 mm sections of myocardium.

ii) Distal endocardial stimulation. The heart was stimulated at an endocardial site located at the base of the heart (site B, Fig. 19). Conduction times to the 5 intramural sites for endocardial stimulation are presented in Fig. 20 which also includes the results for epicardial stimulation previously presented in Fig. 18A. Conduction times from both sites of stimulation are plotted relative to the ERP. The average ERP value for endocardial stimulation was 197 ms vs 190 ms for epicardial stimulation causing a shift to the right of the curves for the former. However, the shapes of the curves for both sites of stimulation are identical indicating extrasystoles were conducted in a similar manner to the recording electrode. The "apparent" supernormal conduction which is due to the disproportionate increase in conduction time to the endocardial electrode at short coupled extrasystoles is seen for stimulation from both distal sites. There are however 2 differences in the curves for endocardial vs epicardial stimulation.

1) The conduction time to any one of the recording sites was 16 ms less during endocardial stimulation. This is to be expected as 16 ms is the value calculated for the transmural conduction time. Thus during epicardial stimulation the signal has first to propagate across the ventricular wall to the endocardium before it is propagated to the distal recording electrode.

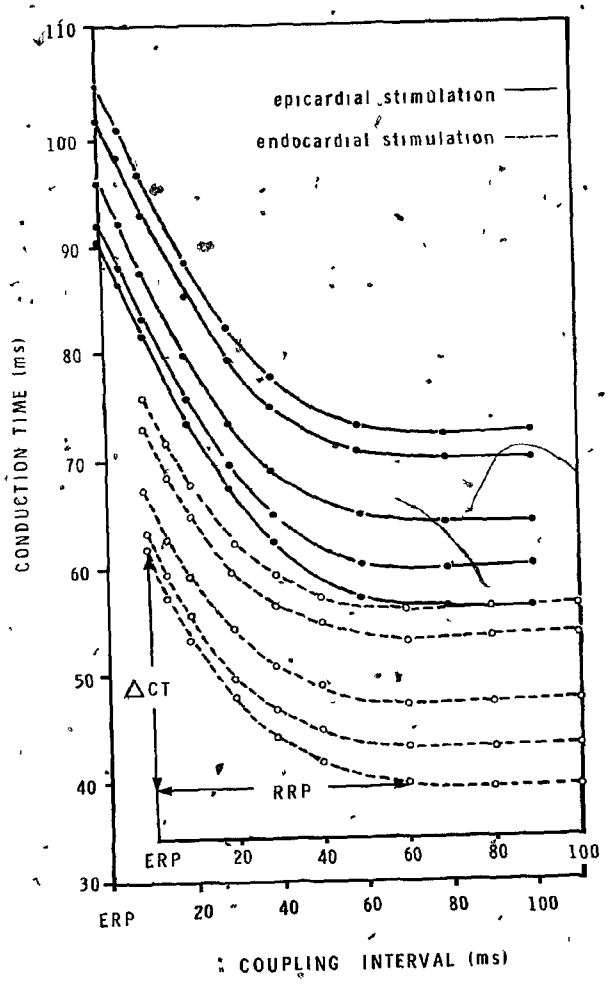


Fig. 20. Relationship between conduction time and coupling interval of extrasystoles. The five curves (broken lines) represent conduction times to 5 intramural recording sites from and endocardial stimulating electrode located at a distance of approximately 3.5 cm from the recording electrode. The five solid curves represent conduction times from an epicardial stimulating electrode located transmurally to the endocardial stimulating electrode (previously presented in Fig. 18A). Conduction times were calculated at the coupling interval defining the effective refractory period, ERP, and at coupling intervals up to 100 ms above the ERP. Results shown are average values determined for 8 animals. The mean ERP for epicardial stimulation was 190 ms and for endocardial stimulation 197 ms. This caused a shift to the right of the plot for endocardial stimulation. RRP = relative refractory period, ΔCT = increase in conduction time during the refractory period. Basic cycle length = 800 ms.

2) Epicardial stimulation resulted in a greater increase in conduction time (ΔCT) above the minimum conduction time (MCT) than occurred during endocardial stimulation. This additional slowing of conduction seen with epicardial stimulation is thought to be due to the differences in ERP shown to exist between the endocardium and epicardium as explained in the discussion.

iii) Proximal endocardial stimulation. In order to study myocardial conduction exclusively, the hearts were stimulated very close to the recording electrodes, i.e. at the endocardial or epicardial end of the multicontact recording electrode (sites C or D, Fig. 9). Conduction time of the wavefront in a direction perpendicular to the epicardial surface (along the length of the recording needle) was determined at distances of approximately 2, 4, 6, and 8 mm from the site of stimulation. A plot of these conduction times as a function of coupling interval for endocardial stimulation (site C-Fig. 9) is shown in Fig. 21. In order to average results coupling intervals are again expressed relative to the ERP. There are only four curves in Fig. 21 because the endocardial-most recording site was used for stimulation. Conduction times between intramural recording sites correspond well to those seen when the heart was activated via the Purkinje system during distal stimulation (shown as shaded areas in the right hand margin of Fig. 21). The lower curve in Fig. 21 represents conduction time between the stimulating electrode and

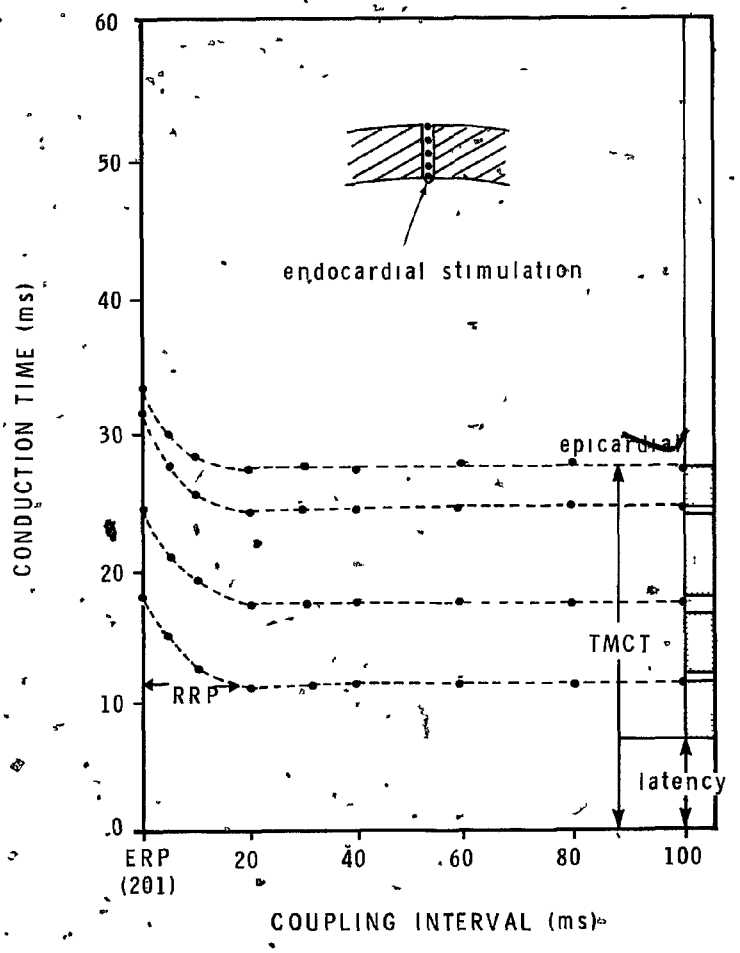


Fig. 21. Intramural conduction times as a function of extrasystole coupling interval. The heart was stimulated from the endocardial tip of a multicontact needle electrode (proximal stimulation) and conduction times of the wave front as it propagated towards the epicardium were determined at four recording sites located at 2 mm intervals along the length of the needle. Transmural conduction time, was measured as the time between the stimulus artifact and epicardial activation. Conduction times between consecutive recording electrodes determined when the heart was stimulated from an electrode located approximately 3.5 cm from the multicontact electrode (distal stimulation) are indicated by the shaded areas at the right of the figure. The calculated value for the latency in propagation of the wavefront is also indicated. Conduction times were calculated relative to the ERP as in previous figures. The curves represent average results from 8 animals. Basic cycle length = 800 ms.

nearest recording electrode located at a distance of 2-3 mm. Because this distance is so small a large percentage of the measured conduction time between the two electrodes will be due to the latency at the site of stimulation. An estimate of the conduction time between these electrodes can be derived from the results obtained when the heart was stimulated from a distal site. For long coupling intervals this conduction time was 4 ms as shown by the solid circles in Fig. 19. This value was transcribed into Fig. 21 and is indicated by the solid line in the lower right hand corner of figure. Thus, the observed conduction time - the known conduction time = latency. The value obtained for latency at the stimulus site is 6 ms. This value is similar to a 3-5 ms latency described by Durrer et al. (30). Under no circumstances were rapid conduction velocities observed in the endocardial layers. This result suggests Purkinje penetration and/or conduction does not extend into the myocardium from the endocardium as originally proposed by Durrer et al. (29, 30).

Conduction times to each electrode site remain constant down to a coupling interval of approximately 20 ms above the ERP. Shorter coupled extrasystoles fell within the RRP of the myocardium and conduction increased in the refractory tissue reaching a maximum at the ERP. The increase in conduction time ($\triangle$ CT) during the RRP had occurred by the time the wavefront reached the first recording electrode (within 3 mm distance) and no further slowing of conduction

occurred as indicated by the parallel slope of the curves in Fig. 21. This fact is shown more clearly in Fig. 22 which is a plot of inter-electrode conduction time, the difference between the curves of Fig. 21, as a function of coupling interval. The only conduction time that increases at short coupled extrasystoles is the conduction time between the stimulating electrode and closest pair of recording electrodes, indicated by the filled circles in the figure. These results are consistent with earlier results of van Dam et al. (105) who demonstrated the slowing of conduction in refractory cardiac muscle is confined to a 3 mm distance surrounding the stimulating electrode. All other inter-electrode conduction times remain constant. The small conduction time of 2 ms indicated by open circle represents conduction time over a 1 mm distance. The 6 - 7 ms values represent conduction times over a 2 mm myocardial distance.

iv) Proximal epicardial stimulation.

Intramyocardial conduction from an epicardial stimulation site was studied in 3 of 8 animals. Conduction time to the four recording sites are presented as the solid lines in Fig. 23; the broken lines represent the corresponding curves for endocardial stimulation that have been previously presented in Fig. 21. Conduction times during epicardial stimulation appear less than those for endocardial stimulation at long coupling intervals but the difference falls within the experimental error. There was however a greater increase in conduction time ($\triangle$CT) above the

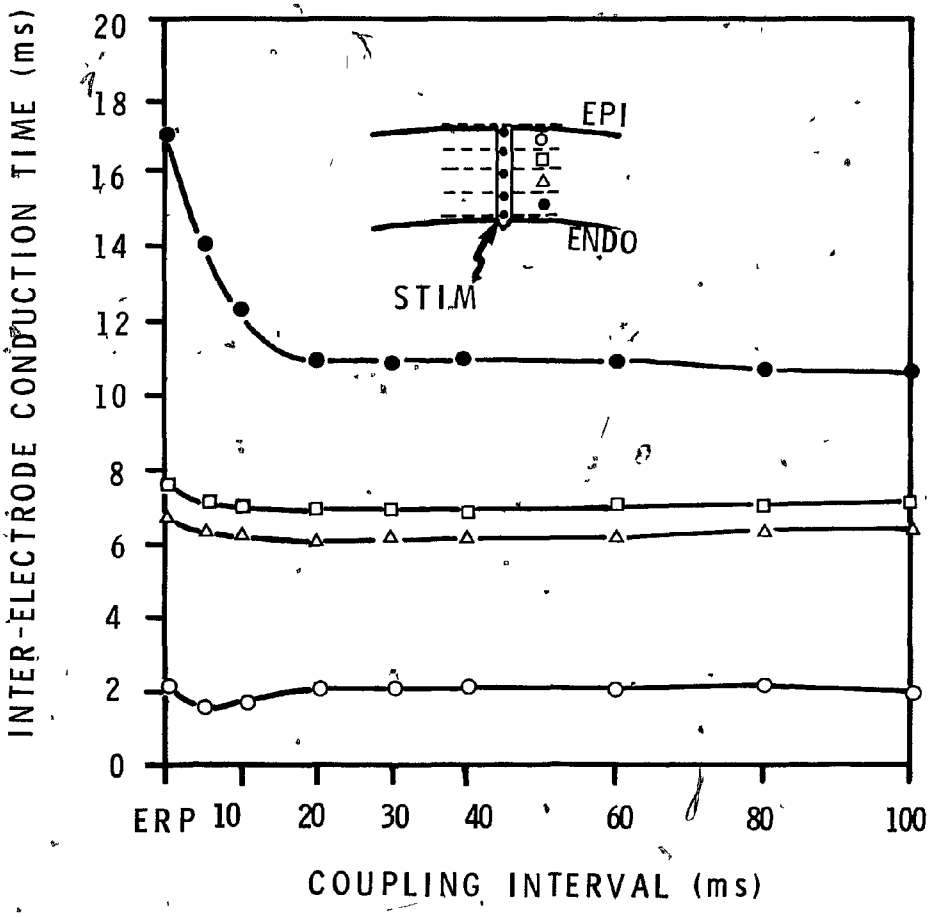


Fig. 22. The curves in this figure represent the time difference between the curves of Fig. 21, i.e. conduction times between consecutive recording sites of a multicontact needle electrode during stimulation of the heart from the endocardial tip of the needle electrode. Conduction times were calculated at the coupling interval defining the effective refractory period, ERP, and coupling intervals up to 100 ms above the ERP. Results shown are average results for 8 animals. Basic cycle length = 800 ms.

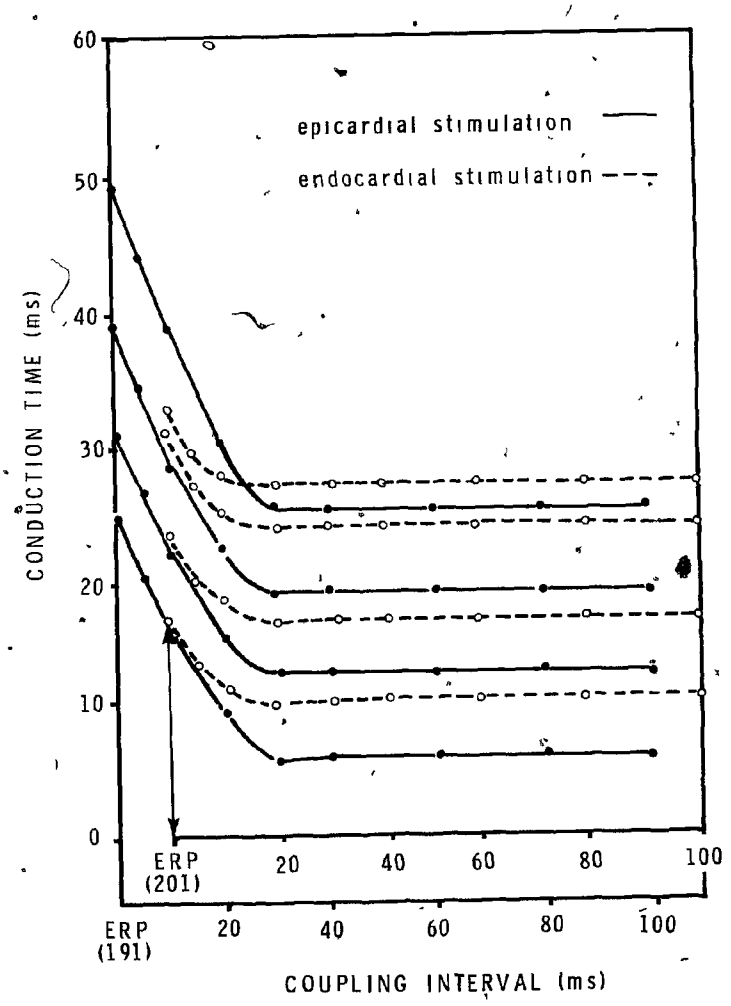


Fig. 23 Conduction times to four intramural recording sites as a function of extrasystole coupling interval. The broken curves represent conduction times during endocardial stimulation previously presented in Fig. 21 and the solid curves represent corresponding conduction times during epicardial stimulation. Conduction times were calculated at the coupling interval defining the ERP and at coupling intervals up to 100 ms above the ERP. The curves represent results averaged for 8 animals. The average ERP for epicardial stimulation was 191 ms and 201 ms for endocardial stimulation causing a shift to the right of the latter. Basic cycle length = 800 ms. (See text for full explanation).

minimum conduction time (MCT) achieved at short coupling intervals during epicardial stimulation. This result is consistant with the results obtained during distal stimulation (Fig. 20).

d) Refractory periods as a function of site of stimulation.

1) Control Conditions: The relative refractory period (RRP). The relative refractory period was calculated as the interval between the ERP and the coupling interval at which the conduction time of extrasystoles first began to exceed the minimum conduction time by more than 2 ms. The relative refractory period determined at an endocardial recording electrode, site C in Fig. 24, was a function of where the heart was stimulated, as is shown in the figure. When the heart was stimulated from a distal electrode, site A or B shown in the inset, the relative refractory period had values of 45 ms for epicardial stimulation and 35 ms for endocardial stimulation. During stimulation through an electrode proximal to the recording electrode, within 2 mm of site C, the relative refractory period had a measured value of 9 ms which was significantly less than the RRP measured during stimulation from either distal sites A or B as determined by ANOVA. In 3 experiments the RRP was determined within a 2 mm distance of an epicardial stimulating electrode (site D). The average RRP determined

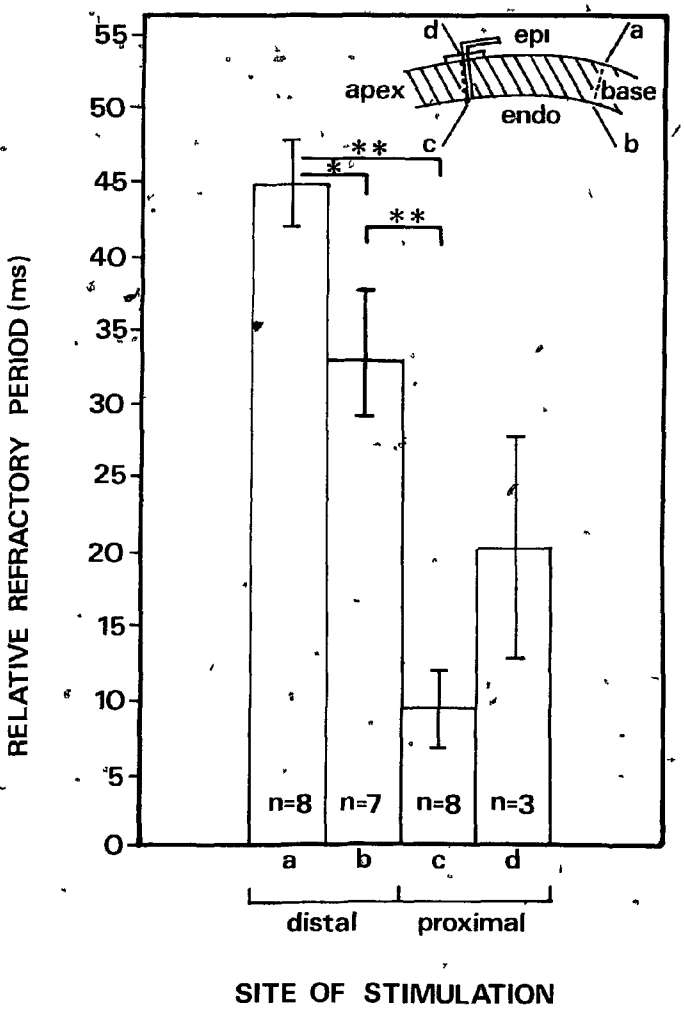


Fig. 24 Relationship between the length of the relative refractory period (RRP) and the distance between stimulating and recording electrodes. The RRP was determined at the endocardial site C when the heart was driven from 3 sites; distal sites A and B located approximately 3.5 cm from site C, and a proximal site within 2 mm of site C. Also in 3 experiments the RRP was measured at the epicardial site D during proximal stimulation.
* = $p < .05$, ** = $p < .01$. Basic cycle length = 800 ms. Bars indicate ± s.e.m.

for these 3 experiments is also presented in Fig. 24 although this value was not compared statistically with the others.

The functional refractory period (FRP). The functional refractory period was defined as the minimum interval achievable between two conducted beats. The data in Fig. 25 are FRP values measured at the endocardium, site C in the inset. When the distance between stimulating and recording electrodes was greater than 3.0 cm., i.e. during distal stimulation from site A or B, the conduction pathway between the two involved the specialized conduction system. The FRP determined during distal stimulation was 223 ms when the heart was driven from the epicardium and 220 ms when driven from the endocardium. These values are significantly different from each other, $p < .05$ as determined by ANOVA. When the heart was driven from the endocardium within 2 mm of the recording electrode (proximal stimulation) the FRP measured was 206 ms which was significantly less ($p < .01$) than either FRP value obtained during distal stimulation (FRP values were compared using ANOVA). The mean FRP value for proximal epicardial stimulation, site D Fig. 25, is that determined within 2 mm of the stimulating electrode. This measurement was made only in 3 experiments. For these three experiments there was no significant difference in the FRP of the myocardium determined at the epicardium vs endocardium.

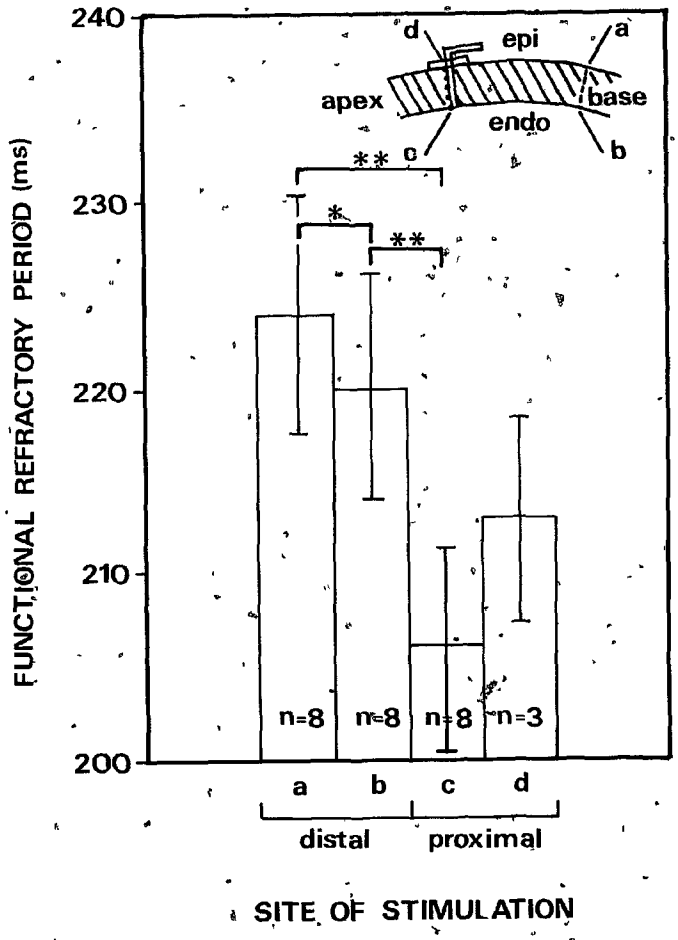


Fig. 25 Relationship between the functional refractory period (FRP) and distance between stimulating and recording electrodes. The FRP was measured in 8 experiments at site C indicated in the inset when the heart was stimulated from distal electrodes, site A, (epicardial stimulation) and site B (endocardial stimulation) and also when the heart was driven from a proximal electrode (located 2 mm from the recording electrode at site C). In 3 experiments the FRP was also determined at the epicardial site D during proximal stimulation. * = $p < .05$, ** = $p < .01$. Basic cycle length = 800 ms. Bars indicate ± s.e.m.

Effective refractory period (ERP). The effective refractory period was calculated for all sites of stimulation. The results are shown in Fig. 26. Endocardial stimultion (sites B or C) resulted in an ERP values which exceeded the ERP for epicardial stimulation (site A) as compared statistically by ANOVA. The mean ERP determined for stimulation at site A was 189.6 ms. This was significantly less than the ERP for site B ($p<.05$) which was 197 ms and site C ($p<.01$) which was 200.8 ms. These differences in ERP values between epicardial and endocardial stimulation are evident in Figs. 20 and 23 where data is plotted relative to the ERP for the site of stimulation.

11) Effect of lidocaine on refractory periods.

The effect of lidocaine on the RRP determined when the heart was driven from a distal epicardial electrode is indicated by horizontal arrows in Fig. 10. Fig. 27 shows the dose-response curve for lidocaine on the mean (± S.E.) duration of the RRP determined at an endocardial site and a transmurally opposed epicardial site. The effect of lidocaine on the RRP was averaged for five experiments. Lidocaine significantly increased the duration of the RRP at all except the lowest dose. The RRP was somewhat more prolonged by lidocaine at the epicardial site indicating a myocardial as well as Purkinje drug effect. Lidocaine did not change the functional refractory period (FRP) or the effective refractory period (ERP) to a statistically significant degree as indicated by the analysis of variance

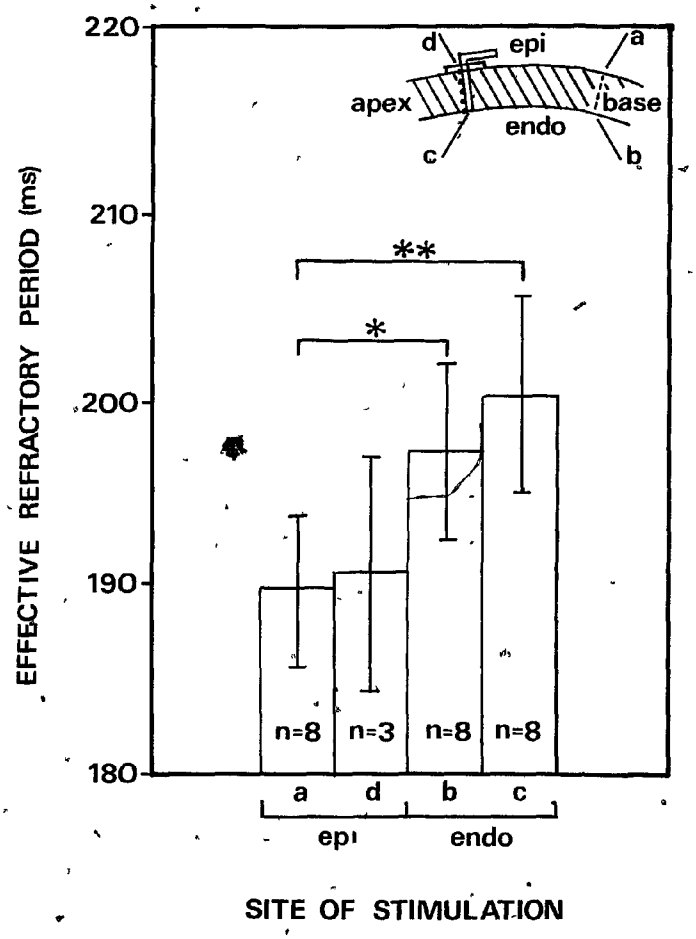


Fig. 26 Relationship between the effective refractory period (ERP) and the site of stimulation. The ERP was determined when the heart was driven from the epicardial sites A and D indicated in the inset and also during stimulation from the endocardial sites B and C. * = $p < .05$, ** = $p < .01$. Basic cycle length = 800 ms. Bars indicate ± s.e.m.

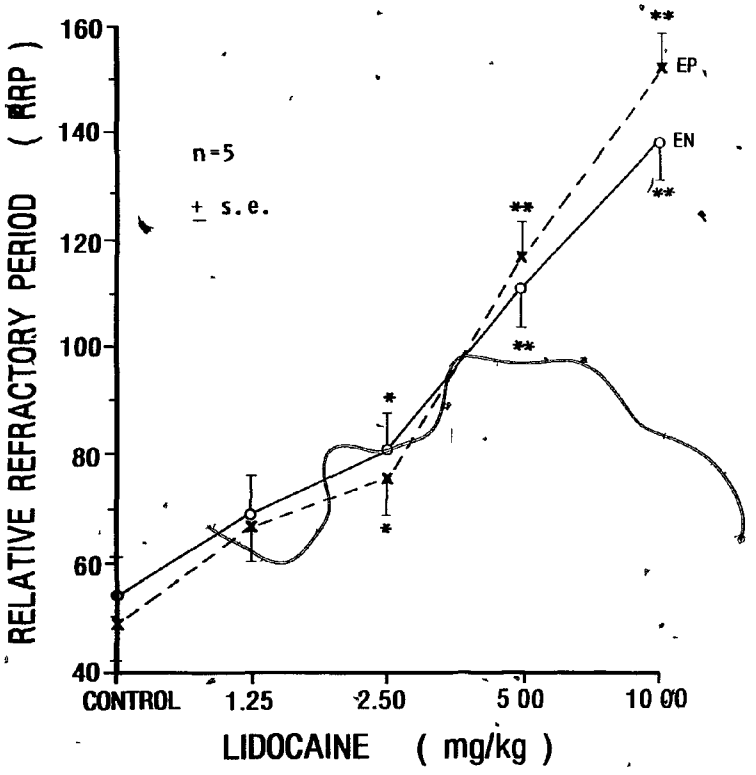


Fig. 27. The effect of lidocaine on the relative refractory period (RRP) determined at an endocardial site (en) and a transmurally apposed epicardial site (ep) during stimulation from an epicardial electrode located approximately 3.5 cm away. Lidocaine, at doses greater than 1.25 mg/kg causes a significant increase in the RRP measured at both sites. * = $p < .05$, ** = $p < .01$. Basic cycle length = 800 ms.

results presented in Table 2. Conduction to the epicardium as measured by the ERP_{ep} was always limited by the ERP_{en}.

iii) Effect of disopyramide on refractory periods.

Disopyramide caused an increase in the effective refractory period (ERP) as shown in Fig. 28. It is evident that the drug produces a dose dependent increase in the ERP for all sites of stimulation both endocardial and epicardial. The significance of the drug's effect was determined using the paired t-test (one-tailed). Statistics were not performed on results of stimulation from site D because of the small number of experiments involved (n = 3 vs n = 7 for other sites of stimulation).

Disopyramide did not significantly alter the relative refractory period (RRP) measured at site C, indicated in the inset of Fig. 29 during stimulation of the heart from any of the three sites A, B, and C. Similarly, disopyramide did not affect the RRP measured within 2 mm of the epicardial stimulating electrode at site D. Results are presented for control conditions and for the two doses of disopyramide. This lack of drug effect on the RRP is in sharp contrast to that of lidocaine which caused a dose dependent increase in the RRP as shown in Fig. 27. Both drugs cause slowing of extrasystoles at longer coupling intervals than for control conditions. Disopyramide, however, increased the ERP by an equivalent amount thus causing no change in the RRP. Lidocaine on the contrary, did not change the ERP therefore caused an increase in the calculated RRP.

TABLE 2: Effect of lidocaine on the FRP and ERP in normal hearts.

	Lidocaine (mg/kg)					
	CONTROL	1.25	2.5	5.0	10.0	S.E.*
MEAN FRP_{ep}	229.7	226.7	225.7	227.0	234.0	2.3
MEAN FRP_{ep}	232.8	229.2	229.0	227.5	230.7	1.8
MEAN ERP_{en}	185.7	184.4	181.6	180.4	182.0	2.3

* SE term from ANOVA

N = 5

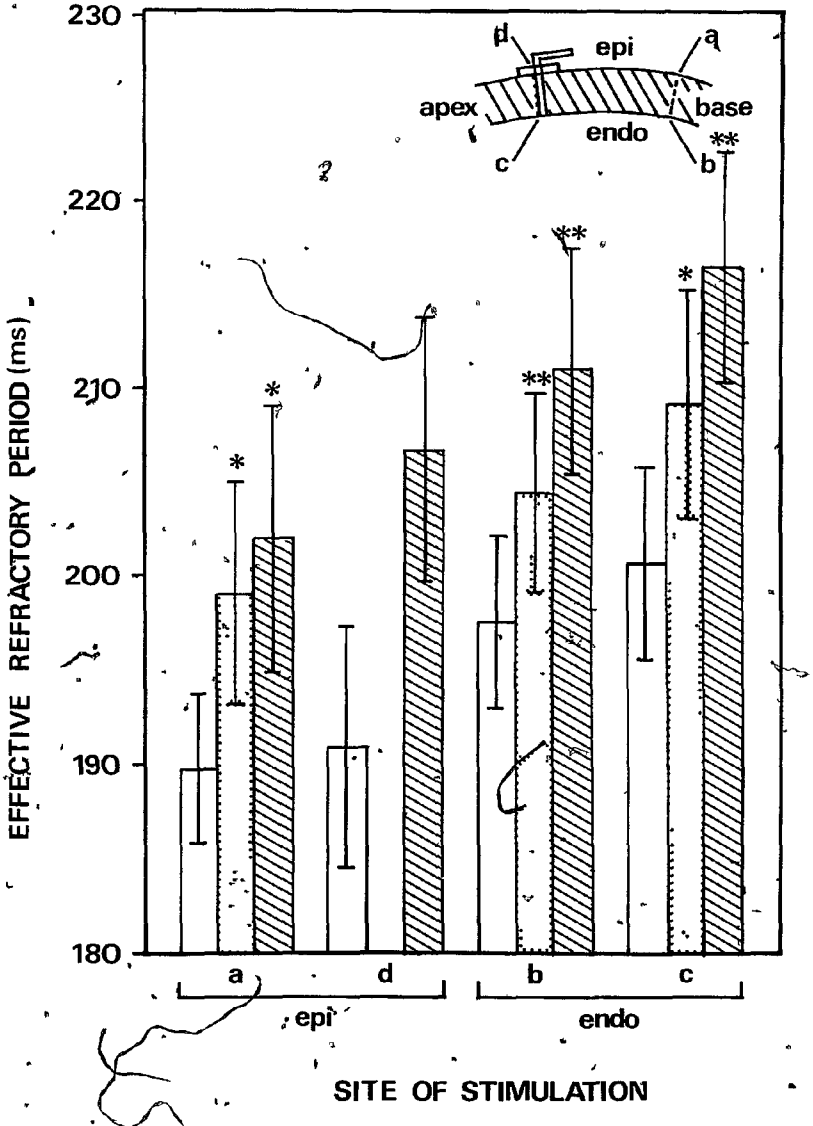


Fig. 28 Effect of disopyramide on the effective refractory period (ERP) determined at 2 epicardial (sites A and D) and 2 endocardial (sites B and C) locations in the left ventricle. Open bars = control, shaded bars = disopyramide 1.0 mg/kg, cross-hatched bars = disopyramide 3.0 mg/kg. Basic cycle length = 800 ms. Errors shown are ± s.e.m. * = $p < .05$, ** = $p < .01$.

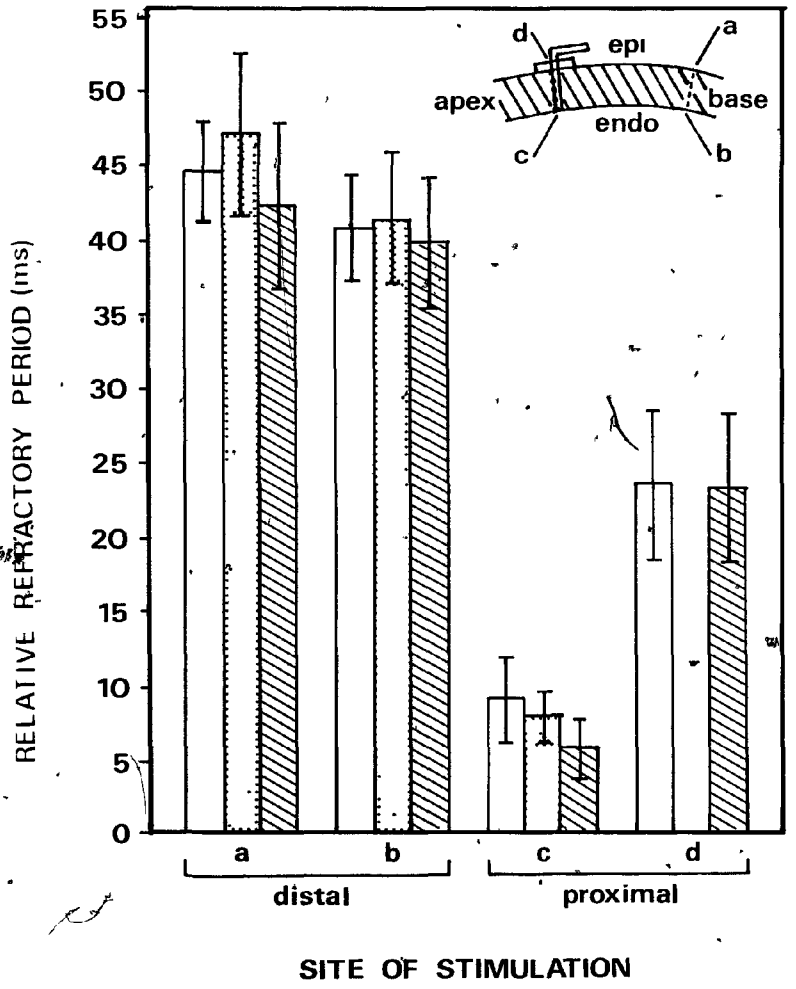


Fig. 29 Effect of disopyramide on the relative refractory period (RRP). The RRP was determined at the endocardial site C during stimulation of the heart from one of three locations; distal sites A and B located approximately 3.5 cm from site C, and a proximal site within 2 mm of site C. Also, in 3 experiments, the RRP was determined within 2 mm of an epicardial stimulating electrode at site D. Open bars = control, shaded bars = disopyramide 1.0 mg/kg, cross-hatched bars = disopyramide 3.0 mg/kg. Basic cycle length = 800 ms. Errors shown are ± s.e.m.

Disopyramide caused a dose dependent increase in the functional refractory period (FRP) determined during stimulation for all four sites as shown in fig. 30.

2. Ventricular conduction as a function of heart rate.

For control conditions there was no increase in either endocardial or transmural conduction times as the heart rate was increased from a basic drive interval (SS) of 800 to 250 ms as shown in Fig. 31. A decrease in transmural conduction time similar to the apparent supernormal conduction of short-coupled extrasystoles was never seen at high drive rates.

B. THE ISCHEMIC HEART

1. Continuous electrical activity in acutely ischemic myocardium (10 dogs).

Electrical recordings were made from large areas of the left ventricle. Composite electrodes were used to make bipolar recordings from a 2 cm^2 area of myocardium in the region supplied by the left anterior descending coronary artery (LAD), the ischemic zone (IZ), and also from a more posterior region, one supplied in part by the circumflex artery, the normal zone (NZ). Fig. 32A contains representative recordings obtained from both composite

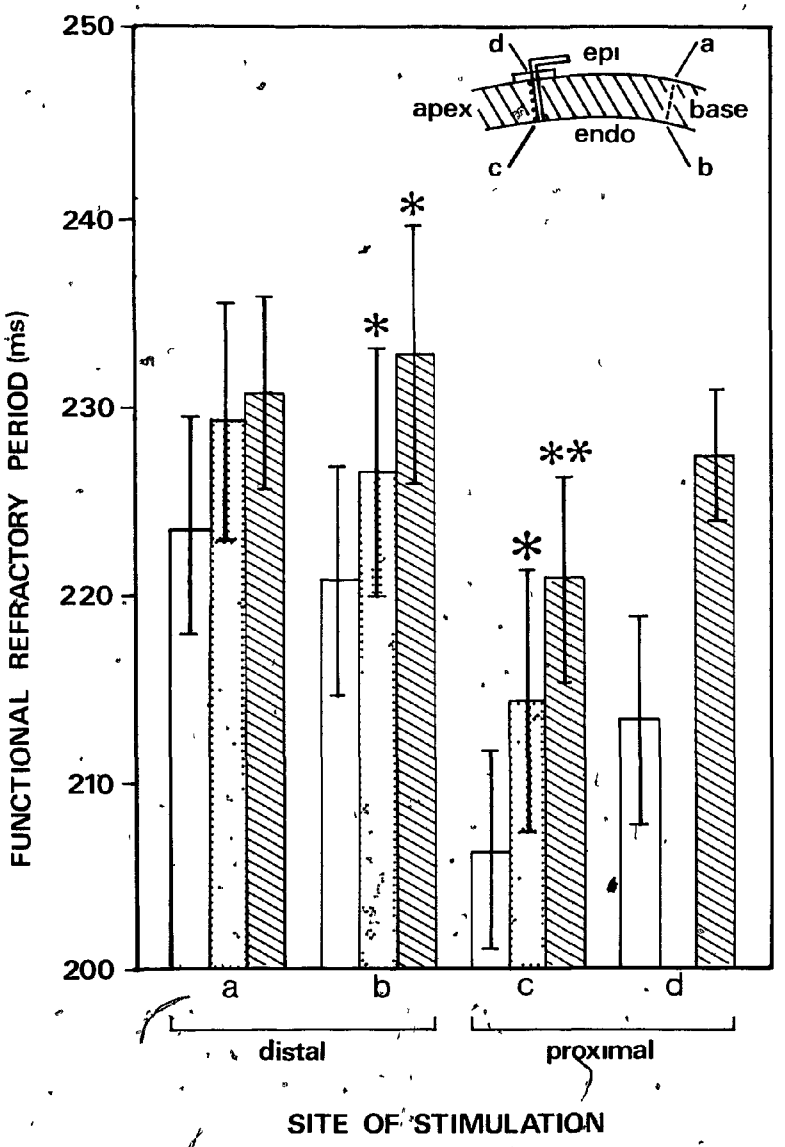


Fig. 30 Effect of disopyramide on the functional refractory period (FRP) determined at an endocardial location in the left ventricle (site C) during stimulation of the heart from one of the three locations A, B and C. Also shown is the effect of disopyramide on the FRP determined within 2 mm of an epicardial stimulating electrode at site D. Stimulation at sites C and D were achieved via an electrode located 2 mm from the recording electrode. Open bars = control, shaded bars = disopyramide 1.0 mg/kg, cross-hatched bars = disopyramide 3.0 mg/kg. Basic cycle length = 800 ms. Errors shown are ± s.e.m. * = $p < .05$, ** = $p < .01$.

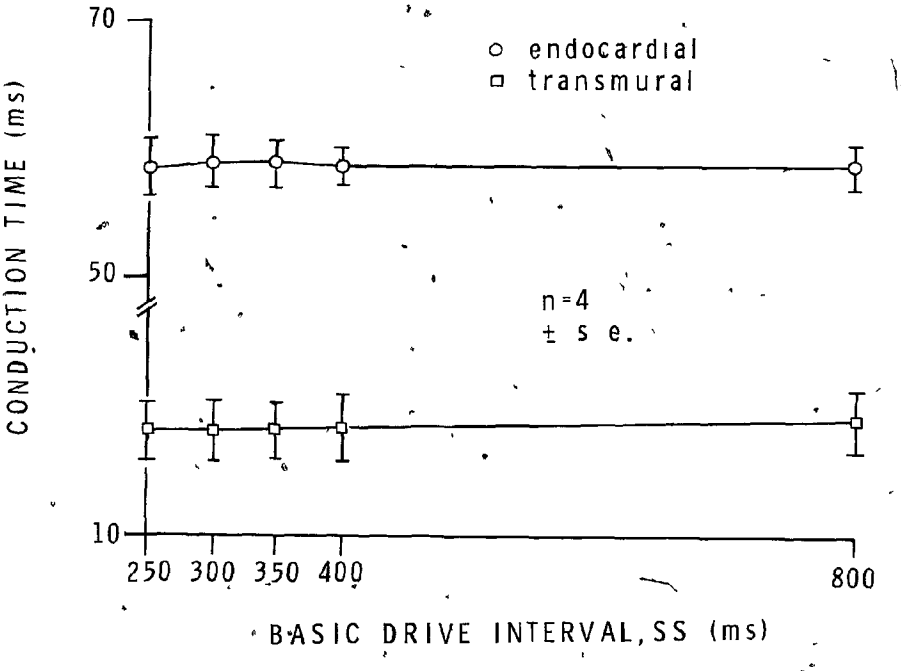


Fig. 31 Relationship between conduction times in the left ventricle and heart rate. Endocardial conduction time (conduction time over a 3.5 cm pathway to an endocardial recording electrode) and transmural conduction time (conduction time across the ventricular wall) were calculated during ventricular pacing at basic drive intervals ranging from 800 ms (75 b.p.m.) down to 250 ms (240 b.p.m.). Ventricular pacing was achieved via an electrode sewn to the base of the left ventricle and recording were made in the mid-anterior portion of the left ventricle. Circles = endocardial conduction time, squares = transmural conduction time.

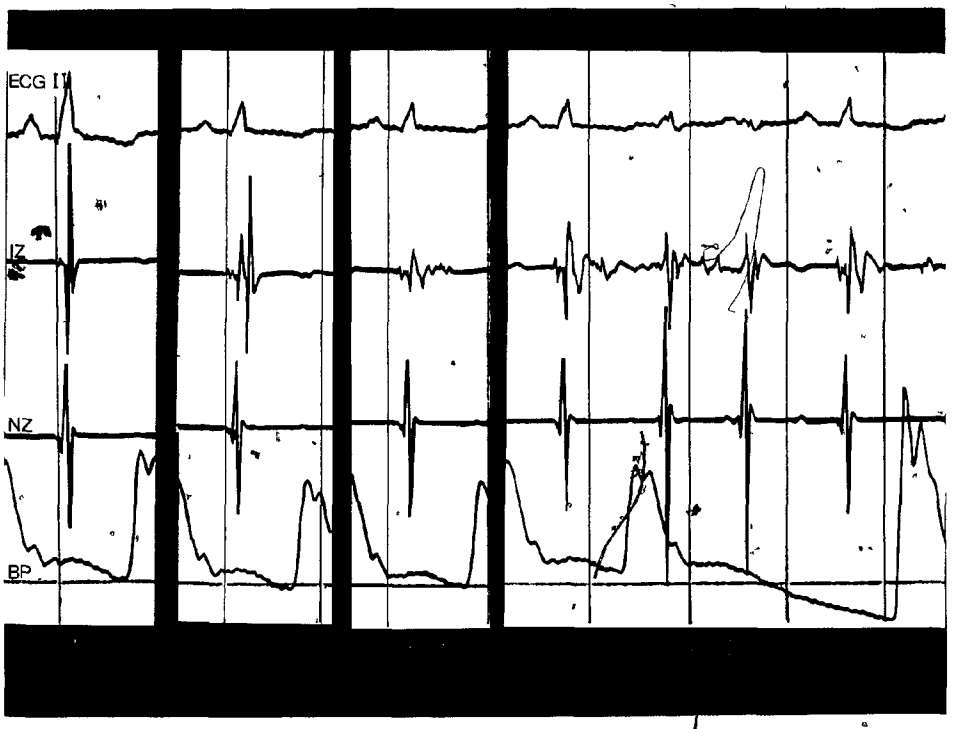


Fig. 32A Effect of ischemia on composite electrograms recorded from two areas of the left ventricle during sinus rhythm. Top tracing = lead II EKG; tracing #2 = composite electrogram recorded from an area of the left ventricle made ischemic by occlusion of the LAD, the ischemic zone (IZ); tracing #3 = composite electrogram recorded from a non-ischemic or normal zone (NZ) of the left ventricle; bottom tracing = blood pressure recorded from the femoral artery. The first panel represents control conditions, the second panel was recorded 2 min after LAD occlusion, the third panel 3 min following LAD occlusion, and the fourth panel 5 min following LAD occlusion.

electrodes in addition to a lead II ECG and blood pressure tracing. Under control conditions recordings obtained from both composite electrodes are simultaneous sharp biphasic deflections that fall within the R wave of the ECG. Occlusion of the left anterior descending coronary artery for 2 min causes fractionation and delayed activity in the electrogram recorded in the IZ. This is more prominent after 2.5 minutes of occlusion and is accompanied by a decrease in amplitude of the signals from the IZ while the signals in the NZ are not changed from control. Five minutes after occlusion of the artery the heart produces two premature ventricular contractions evidenced in the ECG and blood pressure tracings. The period between the last normal and first arrhythmic beat as well as between arrhythmic beats is characterized by continuous electrical activity in the IZ which bridges the diastolic gap while electrical activation in the NZ still occurs as a rapid event. The continuous electrical activity disappears from the IZ prior to resumption of the normal sinus rhythm.

Results from another similar experiment are presented in Fig. 32B. In this experiment a bipolar electrogram was recorded from the endocardium in the IZ (IZ en) by inserting a pair of plunge electrodes into the myocardium through the composite electrode to a depth of approximately 8 mm. Under control conditions the endocardial activation preceded epicardial activiation in the IZ by approximately 20 ms. Occlusion of the coronary artery for 2.5 minutes as

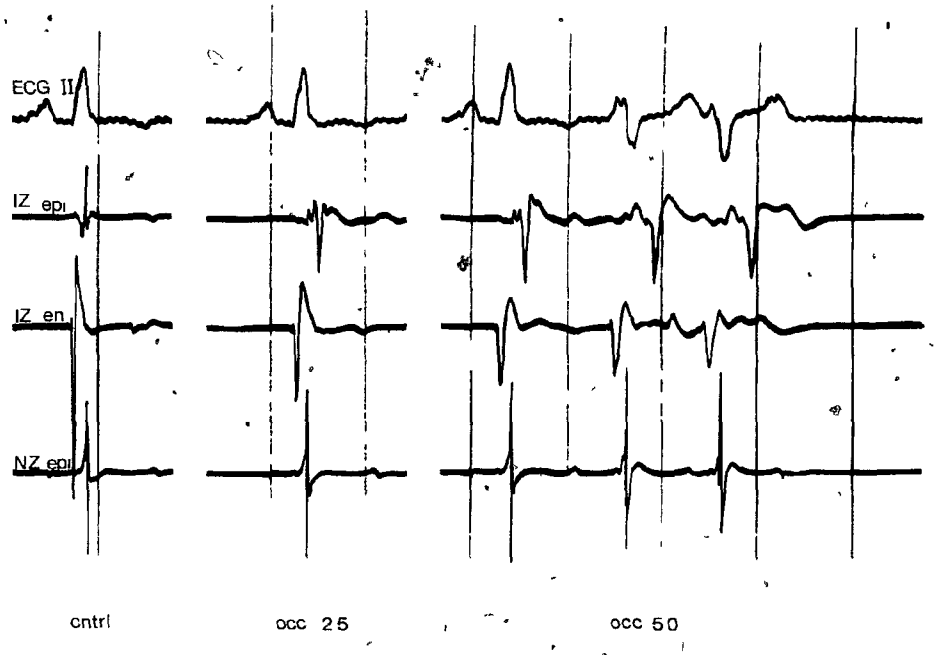


Fig. 32B A figure similar to Fig. 32A but results from another animal and with the blood pressure tracing replaced with an electrogram. Upper tracing = lead II EKG; IZ epi = composite electrogram recorded from the area of the left ventricle made ischemic by occlusion of the LAD, the ischemic zone; IZ_{en} = bipolar recording made from the endocardium within the ischemic zone; NZ_{epi} = composite electrogram recorded from the normal zone of the left ventricle. The first panel represents recordings made under control conditions, the second panel after 2.5 min of LAD occlusion, the third panel after 5 min LAD occlusion.

indicated in the second panel causes an inversion, fractionation, and delay of the electrogram recorded from the myocardium in the IZ (IZ epi) but had less affect on the electrical activation of the endocardium in the IZ and no effect on epicardial activation in the NZ. Six minutes of occlusion resulted in two premature ventricular contractions accompanied by continuous electrical activity recorded on both tracings obtained from the IZ. However, endocardial activation in the IZ still leads all measured epicardial activation during each premature beat. Transmural conduction time (TMCT) in the IZ, the time between endocardial activation and the major deflection in the epicardial composite electrogram increases on each successive premature beat. However the time difference between activation of the endocardium in the IZ and the epicardium in the NZ remains constant during the arrhythmia. This indicates decremental myocardial conduction exists in the infarcted but not normal tissue.

2. Initial changes in TMCT accompanying coronary artery occlusion

In order to get a quantitative assessment of the effects of ischemia on ventricular conduction, conduction times before and after coronary occlusion were determined in paced hearts in which the AV node had been destroyed (a procedure identical to that used to measure ventricular

conduction in the normal heart described above). The effect of up to 90 minutes of ischemia on the two aspects of ventricular conduction, endocardial conduction and transmural conduction, are shown for 4 animals in Fig. 33 (during the basic drive rate of 800 ms). Fig. 33A indicates that endocardial conduction did not change from control values in any of the four animals even up to 90 minutes of ischemia. However, TMCT, shown in Fig. 33B increased dramatically in 2 animals after ligation of the LAD but did not change significantly from control in the other two. In the animals which showed an increase in TMCT the change took place within the first 10 minutes of occlusion and no further increase was observed for the remaining 80 minutes of occlusion. During this 10 minute period electrograms recorded from the ischemic zone decreased in amplitude and increased in duration as reported by others (9, 44, 53, 54, 92, 93, 108, 112). Severe ventricular arrhythmias occassionally leading to fibrillation were observed within this 10 minute interval and then subsided coincidently with an improvement in electrograms in the IZ. In all of the four animals a ventricular tachycardia which exceeded the basic drive interval developed after 40 minutes of ischemia whether or not an increase in TMCT was detected. The arrhythmic periods are indicated by the dashed lines in the figure. It was not possible to determine conduction times accurately during this period because of the arrhythmia.

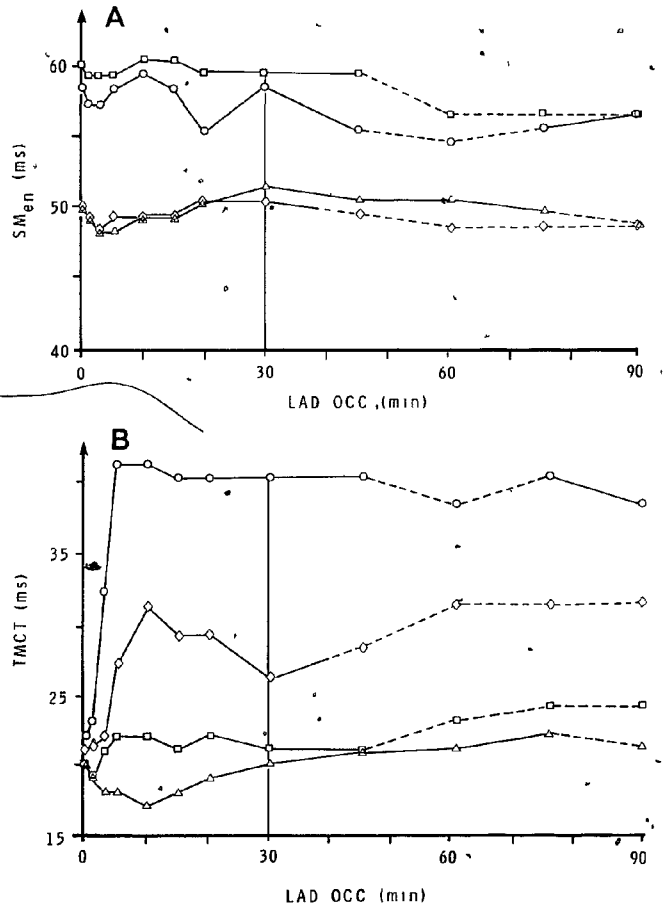


Fig. 33A The effect of ischemia on endocardial conduction time of non-premature stimuli in the left ventricle. Ordinate = conduction time from an epicardial stimulating electrode at the base of the heart to an endocardial recording electrode located approximately 3.5 cm away in the ischemic zone; abscissa = minutes of LAD occlusion. Basic cycle length = 800 ms. Results are presented for 4 animals.

Fig. 33B The effects of ischemia on transmural conduction time of non-premature stimuli in the left ventricle. Ordinate = transmural conduction time in the ischemic zone; abscissa = minutes of LAD occlusion. Basic cycle length = 800 ms. Results are presented for 4 animals.

Transmural conduction time was calculated in a total of 16 animals during basal drive under control conditions and after 30 minutes of ischemia. Results are presented in Table 3. The increase in TMCT due to ischemia varied widely from one animal to the next ranging from 0% to an increase of over 200%. The results presented below the dotted line in Table 3 are from animals which showed less than a 10% increase in TMCT, the limits of experimental error. However, in all animals in which an increase occurred it reached a maximum by 10 minutes of occlusion and had stabilized by 30 minutes of occlusion. Therefore, any changes in ventricular conduction produced by injection of drugs after this 30 minutes period of ischemia were attributed to the effects of the drug.

3. Rate-dependent changes in conduction in ischemic myocardium: potentiation by lidocaine.

The effect of different drive rates on ventricular conduction under ischemic conditions was studied in four animals. Averaged results for endocardial conduction and transmural conduction are presented in Fig. 34 for both control and ischemic conditions. Thirty minutes of ischemia caused little orchange in endocardial conduction at any heart rate. Transmural conduction time however was increased at even the slow heart rates (SS = 800 ms) from 18 to 32 ms. TMCT was further increased at fast heart rates

TABLE 3: Effect of 30 min ischemia on endocardial and transmural conduction time in the left ventricle.

	TMCT			SMen	
Exper. #	control	occlusion	% change	control	occlusion
LC21	9	32	255	63	63
LC01	17	51	200	56	60
LC35	13	37	184	53	51
LC50	22	40	82	62	58
LC43	17	29	71	58	54
LC44	15	23	53	59	58
LC49	21	26	24	50	50
LC29	13	16	23	55	55
LC30	19	22	16	52	52
LC52	15	17	13	52	49
LC33	23	25	9	52	52
LC36	17	18	6	48	46
LC25	18	19	6	66	64
LC46	25	26	4	60	60
LC47	20	20	0	50	51
LC51	21	21	0	60	59

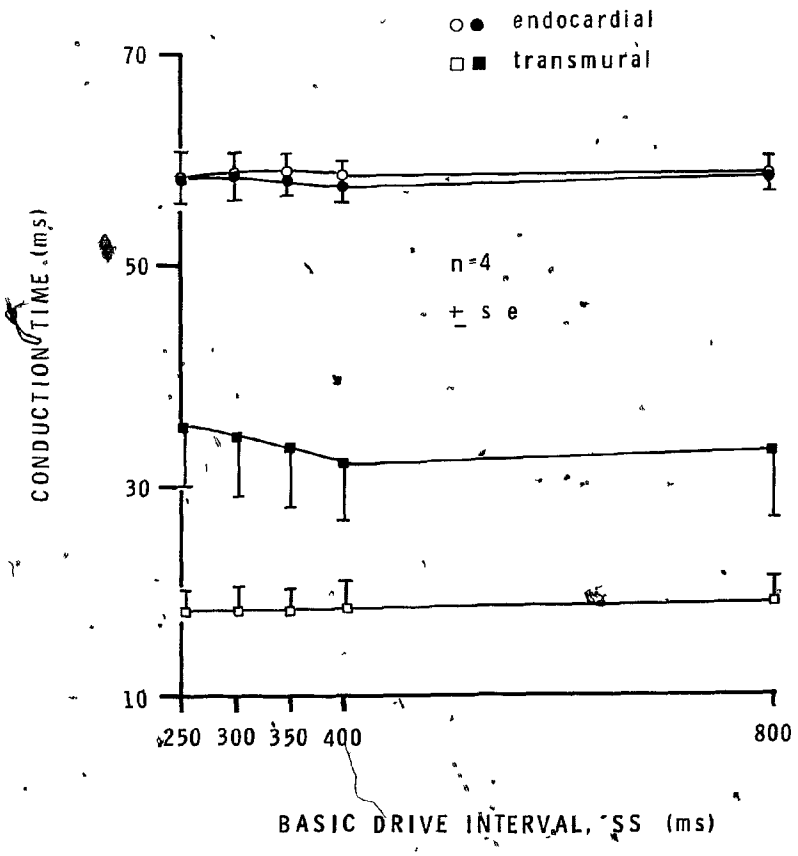


Fig. 34 Effects of 30 min ischemia on the relationship between conduction time in the left ventricle and heart rate. Circles = conduction time from an epicardial stimulating electrode to an endocardial recording electrode approximately 3.5 cm away in the area of the ventricle supplied by the LAD; dots represent conduction time after 30 min LAD occlusion; open squares represented transmural conduction times under control conditions; solid squares represent transmural conduction time in the ischemic zone after 30 min LAD occlusion. The hearts were paced at basic drive intervals ranging from 800 ms (75 b.p.m.) to 250 ms. (240 b.p.m.).

(SS 400 ms) up to a maximum of 35 ms at the drive interval of 200 ms. However this rate-related increase in TMCT was found not to be significant when TMCT values at the 800 ms drive rate were compared to TMCT values at the 250 ms drive rate using the students t-test.

The data in Table 3 suggest that there is a great interanimal variability in the changes observed in myocardial conduction following 30 minutes of coronary artery occlusion. Table 4 shows TMCT values for 12 animals determined 30 minutes following LAD occlusion and after injections of lidocaine given at 15 minute intervals over the following 60 minutes of occlusion. All TMCT calculations were made at the basic drive interval of 800 ms, 5 minutes after each injection of the drug. The effect of lidocaine on TMCT is expressed as % change over the 30 minute TMCT value for each concentration of the drug. These were compared to the % change in TMCT due to ischemia alone presented (column 1). Although lidocaine increased TMCT in ischemic tissue while having little effect on TMCT in normal animals (as shown above), there was no good correlation found between the increase in TMCT due to ischemia alone and further increases in TMCT due to lidocaine. Thus lidocaine slows conduction in ischemic more than in normal myocardium but the degree of slowing does not appear to be a function of the damage to the myocardium produced by ischemia.

Endocardial conduction of normally driven beats was not changed by ischemia (Table 3) and lidocaine had no effect on endocardial conduction under these conditions.

TABLE 4: Effect of lidocaine on transmural conduction time (TMCT) of non-premature stimuli in the ischemic left ventricle. The abbreviations in the table are as follows: OCC 30 = TMCT after 30 min LAD occlusion and % change = % change over TMCT control. The numbers 1.25, 2.5, 5.0 and 10.0 represent the dose of lidocaine given at various times after 30 min LAD occlusion. The % change indicated with each dose of the drug represents the % increase in TMCT observed after drug injection, over TMCT measured after 30 min occlusion. Basic drive interval = 800 ms.

	TMCT									
Ex.	OCC 30	% change	1.25	% change	2.5	% change	5.0	% change	10.0	% change
LC 21	32	255	33	3	35	9	39	22	44	38
LC 01	50	200	50	0	49	-1	50	0	54	8
LC 35	37	184	14	19	57	54	61	65	61	61
LC 43	29	71	36	24	40	37	52	79	54	121
LC 44	23	53	32	39	36	57	38	65	44	91
LC 29	16	23	18	13	18	13	19	19	18	13
LC 30	22	16	22	0	24	9	26	18	34	55
LC 52	17	13	17	0	16	-6	16	-6	18	6
LC 33	25	9	29	16	32	28	33	32	33	32
LC 36	18	6	18	0	22	22	22	22	22	22
LC 25	19	6	20	5	21	11	25	32	26	37
LC 46	26	4	28	8	27	7	28	8	29	10

The effects of lidocaine on the relationship between endocardial conduction time and heart rate are shown in Fig. 35. Ischemia alone did not change endocardial conduction time through the infarcted zone at any heart rate. Lidocaine however caused a rate-related increase in endocardial conduction in the ischemic area of the highest two dosages (Fig. 35A) causing greatest increases in conduction times at the fastest drive rates (short basic drive intervals, SS).

Transmural conduction time was increased in the ischemic zone after 30 minutes of ischemia as discussed above. It was further increased by lidocaine in a dose dependent fashion (Fig. 35B). The depressant action of lidocaine on conduction within the ischemic myocardium was rate-related with the maximum drug effect being observed at the highest heart rates.

4. Interval-dependent changes in conduction in ischemic myocardium: potentiation by lidocaine and disopyramide.

Endocardial conduction of short coupled extrasystoles was increased in the ischemic zone in 5/8 dogs studied. Fig. 36 shows results from one experiment. The greatest increase in endocardial conduction time in this animal was 10 ms (20%) observed with the shortest coupled extrasystole of 180 ms.

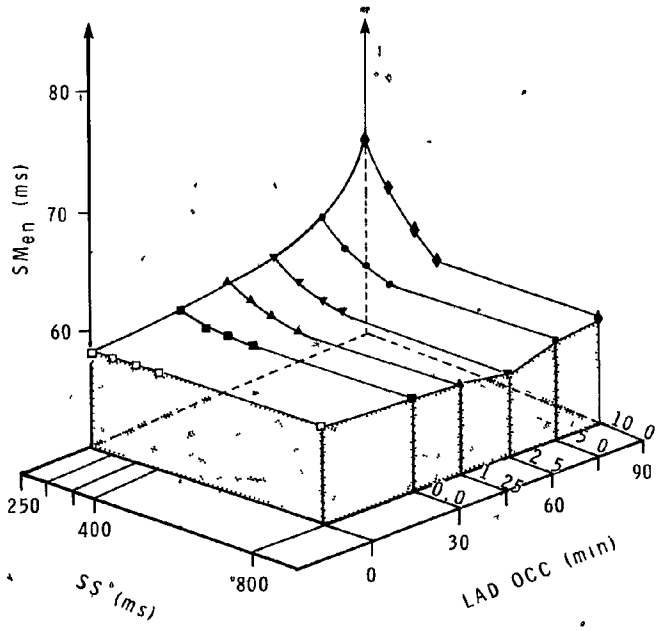


Fig. 35A Effects of lidocaine on the relationship between heart rate and endocardial conduction time in the ischemic left ventricle. SM_{en} = conduction time from a stimulating electrode at the base of the ventricle to an endocardial recording electrode located approximately 3.5 cm away in an area of the ventricle supplied by the LAD coronary artery; SS = basic drive interval; LAD OCC = time after occlusion of the LAD coronary artery; (□) = control conditions; (■) = occlusion 30 min; (▲) occlusion 45 min, lidocaine 1.25 mg/kg; (▼) occlusion 60 min, lidocaine 2.5 mg/kg; (●) occlusion 75 min, lidocaine 5.0 mg/kg; (◆) occlusion 90 min, lidocaine 10.0 mg/kg. n = 4.

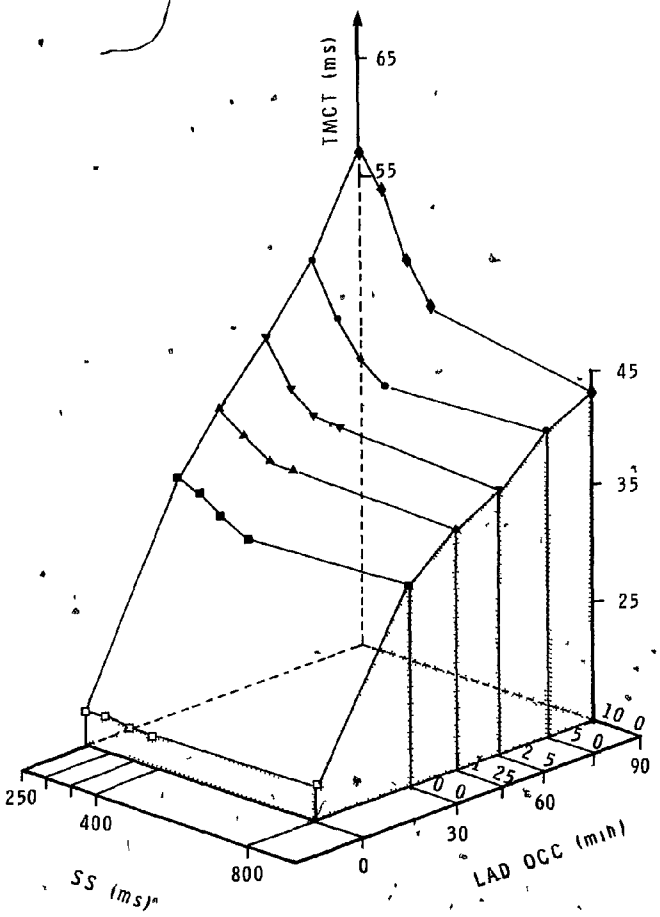


Fig. 35B Effects of lidocaine on the relationship between heart rate and transmural conduction time (TMCT) in the ischemic left ventricle. TMCT was measured in the area of left ventricle supplied by the LAD coronary artery when the heart was paced a different rates from an electrode sewn to the base of the ventricle. SS = basic drive interval; LAD OCC = time in min after occlusion of the LAD coronary artery; (□) = control conditions; (■) occlusion 30 min; (▲) = occlusion 45 min, lidocaine 1.25 mg/kg; (▼) = occlusion 60 min, lidocaine 2.5 mg/kg; (●) = occlusion 75 min, lidocaine 5.0 mg/kg; (◆) = occlusion 90 min, lidocaine 10.0 mg/kg. n = 4.

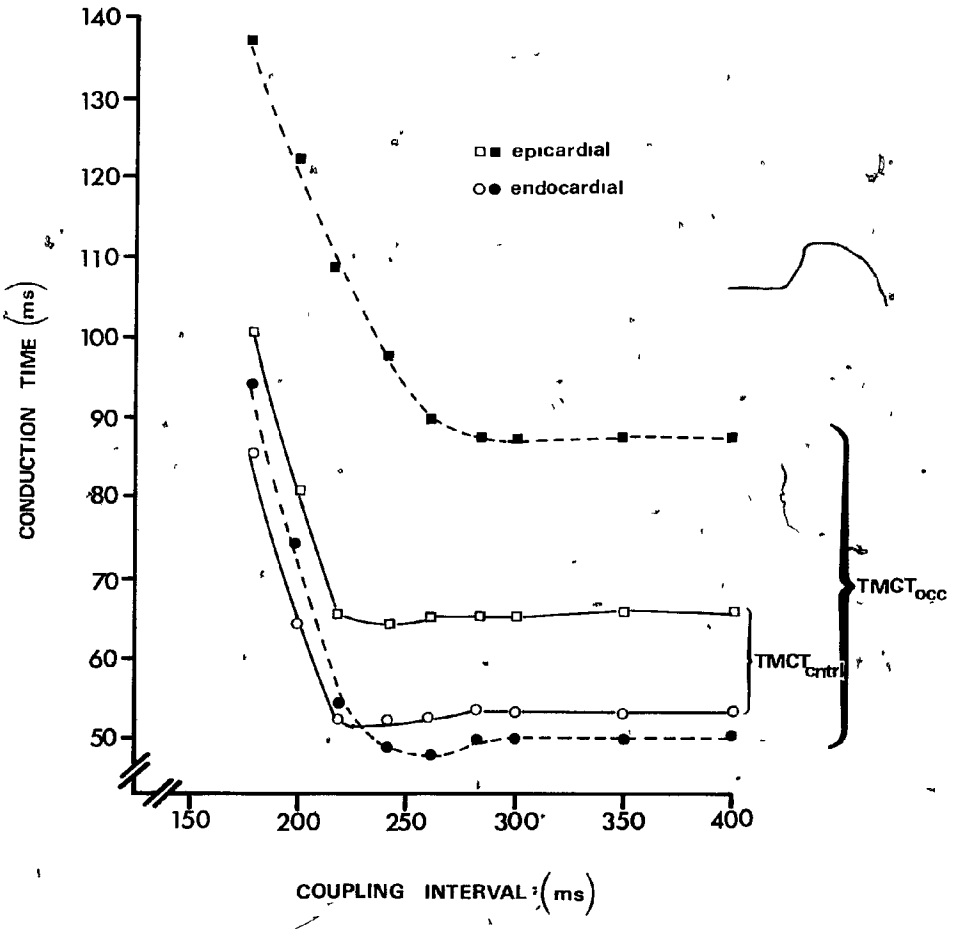


Fig. 36 Effect of ischemia on the relationship between extrasystole coupling interval and ventricular conduction time in a single experiment. Data similar to that previously presented in Fig. 8 but also containing conduction times after 30 min of ischemia. The heart was stimulated at the base of the left ventricle. (○) = conduction time under control conditions to an endocardial electrode located in an area supplied by the LAD coronary artery; (□) = conduction time to a transmurally opposed epicardial electrode; (●) = conduction time to the endocardial electrode 30 min after LAD occlusion; (■) = conduction time to the epicardial electrode 30 min after LAD occlusion.

Transmural conduction time of extrasystoles increased due to ischemia in 5/8 dogs. Unlike the change in endocardial conduction, this was observed at all coupling intervals (Fig. 36). The increase in TMCT in this animal was 30 ms, representing an increase of 100%. The average TMCT observed in the 8 animals is presented in Fig. 37. Ischemia produced a mean increase of 8 ms in TMCT over the entire range of coupling intervals which was statistically significant ($p < .05$). Also shown in Fig. 37 are the average values for endocardial conduction. Ischemia caused slowing of the short coupled extrasystoles in the Purkinje system.

The effect of lidocaine on the conduction of extrasystoles in the ischemic heart was also studied. Fig. 38A is a plot of the average endocardial conduction times for the 8 animals, as a function of coupling interval of extrasystoles. It summarizes conduction times measured under control and ischemic conditions presented previously in Figure 37 as well as after each of the four doses of lidocaine. The 3 lower doses, 1.25, 2.5, and 5.0 mg/kg did not appear to have much effect on endocardial conduction of extra-systoles over those values obtained after 30 minutes of ischemia. However, 10 mg/kg did cause slowing of midrange and short coupled extrasystoles. Results from an ANOVA test done on endocardial conduction indicate the drug caused a significant change in conduction time ($p < .0001$). The results from the ANOVA test are presented in the

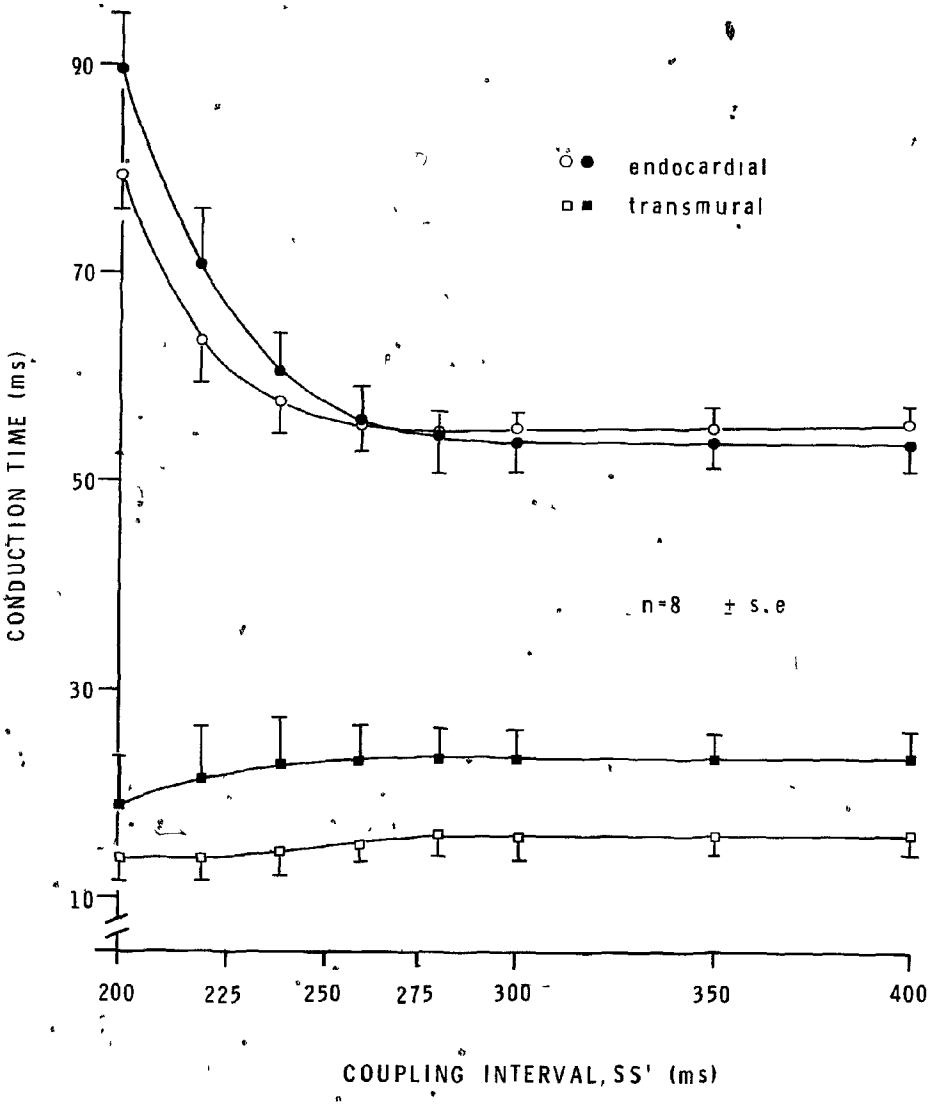


Fig. 37 Effect of ischemia on the relationship between extrasystole coupling interval and conduction time in the left ventricle averaged for 8 animals. (○) = conduction time under control conditions from a stimulating electrode located at the base of the ventricle to an endocardial electrode located in the area of the ventricle supplied by the LAD coronary artery; (□) = transmural conduction time under control conditions in the area of the LAD coronary artery; (●) = endocardial conduction time 30 min after LAD occlusion; (■) = transmural conduction time 30 min after LAD occlusion. Basic cycle length = 800 ms.

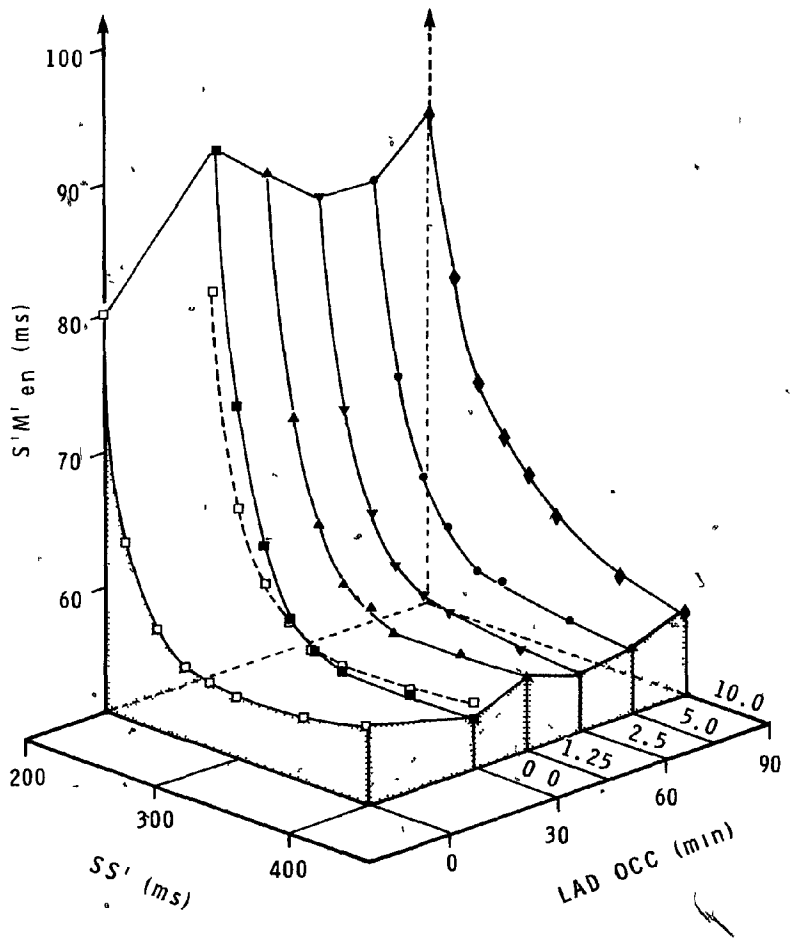


Fig. 38A Effects of lidocaine on the relationship between extrasystole coupling interval and endocardial conduction time in the ischemic left ventricle. $S'M'_{en}$ = conduction time from a stimulating electrode at the base of the ventricle to an endocardial recording electrode approximately 3.5 cm away in an area of the ventricle supplied by the LAD coronary artery; SS' = interval between the last normal and the test stimulus; LAD OCC = time after occlusion of the LAD coronary artery; (□) = control conditions; (■) = occlusion 30 min; (▲) occlusion 45 min, lidocaine 1.25 mg/kg; (▼) = occlusion 60 min, lidocaine 2.5 mg/kg; (●) occlusion 75 min, lidocaine 5.0 mg/kg; (◆) occlusion 90 min, lidocaine 10.0 mg/kg. n = 8.

appendix. This effect of lidocaine on endocardial conduction is similar to that described in normal hearts (Fig. 10A). However the actions of lidocaine on myocardial conduction differs greatly in ischemic vs normal hearts. Lidocaine markedly depressed conduction of extrasystoles within the ischemic myocardium as illustrated in Fig. 38B. In this figure TMCT is plotted for control, ischemic control, and drug conditions. Each dose of lidocaine caused an increase in TMCT over the value of 23 ms seen at 30 minutes of LAD occlusion. These increases in TMCT occurred even at long coupling intervals whereas the increases in TMCT produced by the drug in the normal heart were limited to the short coupled extrasystoles. Also the increases in TMCT produced by lidocaine were much greater than in normal tissue. Analysis of variance done on TMCT determined at each coupling interval and after each dose of lidocaine, showed TMCT to be significantly increased by ischemia, and by lidocaine. These results from ANOVA are presented in the appendix.

The action of lidocaine on myocardial conduction was interval-related as well as being dose-dependent. The drug caused the greatest slowing of conduction at the shortest coupling intervals. Lidocaine at the two higher doses removed the "apparent" supernormal transmural conduction evident at short coupling intervals in the control and ischemic conditions and converted it to subnormal conduction at those coupling intervals.

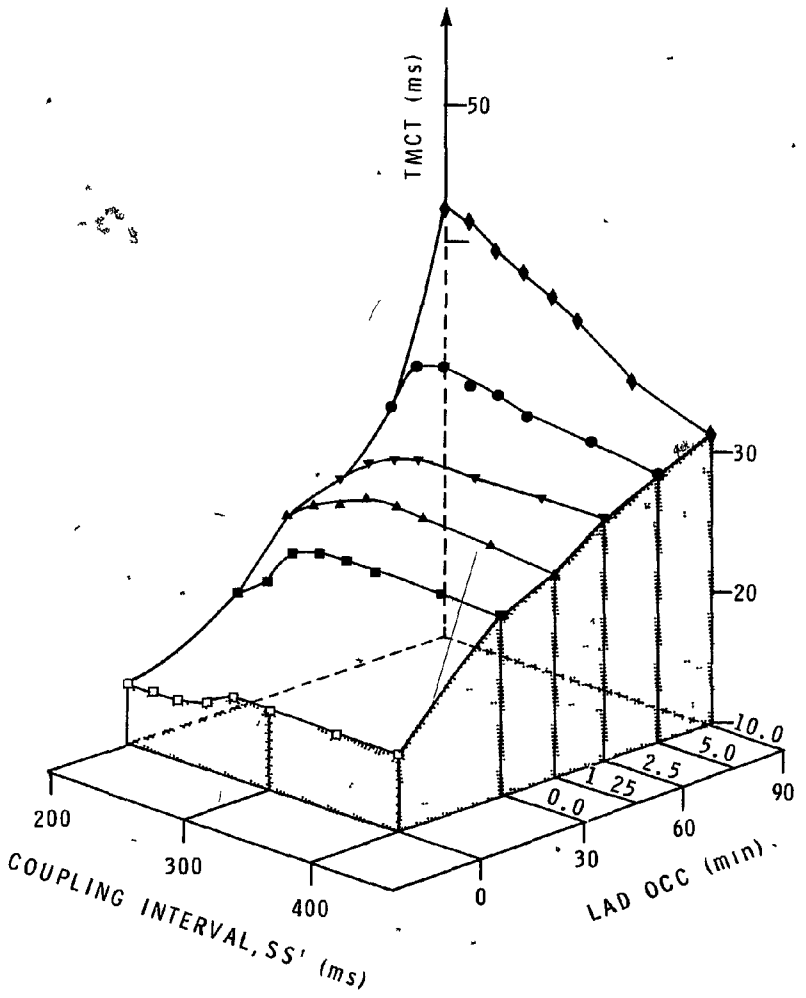


Fig. 38B Effects of lidocaine on the relationship between extrasystole coupling interval and transmural conduction time (TMCT) in the ischemic left ventricle. TMCT was measured in the area of the left ventricle supplied by the LAD coronary artery when the heart was stimulated from an electrode located at the base of the left ventricle. SS' = interval between the last normal and test stimuli; LAD OCC = time after occlusion of the LAD coronary artery; (□) = control conditions; (■) = occlusion 30 min; (▲) occlusion 45 min, lidocaine 1.25 mg/kg, (▼) occlusion 60 min, lidocaine 2.5 mg/kg; (●) = occlusion 75 min, lidocaine 5.0 mg/kg; (◆) occlusion 90 min, lidocaine 10 mg/kg. n = 8.

The effects of disopyramide on conduction within the infarcted heart were studied in one experiment. Disopyramide like lidocaine appears to have a much greater effect in ischemic than normal heart tissue. Fig. 39 shows results from this preliminary experiment. Disopyramide 3.0 mg/kg increased endocardial conduction time (Fig. 39A) over the control conduction time determined after 30 min of occlusion, over the entire range of coupling intervals. Additional slowing of short coupled extrasystoles, less than 250 ms, is also evident representing an interval-related effect of the drug. In this experiment the heart was arrhythmic 30 min following LAD occlusion, therefore it was not possible to determine conduction times of extrasystoles below a coupling interval of 200 ms. Disopyramide given 40 min after the LAD occlusion cleared up the arrhythmia, thus allowing measurement of conduction times during short coupled extrasystoles.

A more striking effect of disopyramide is its effect on myocardial conduction in the ischemic zone (Fig. 39B). Even the lowest dose of the drug 1 mg/kg, causes a significant increase in TMCT during short coupled extrasystoles. This slowing of conduction is extended to longer coupling intervals at the higher dose of 3.0 mg/kg.

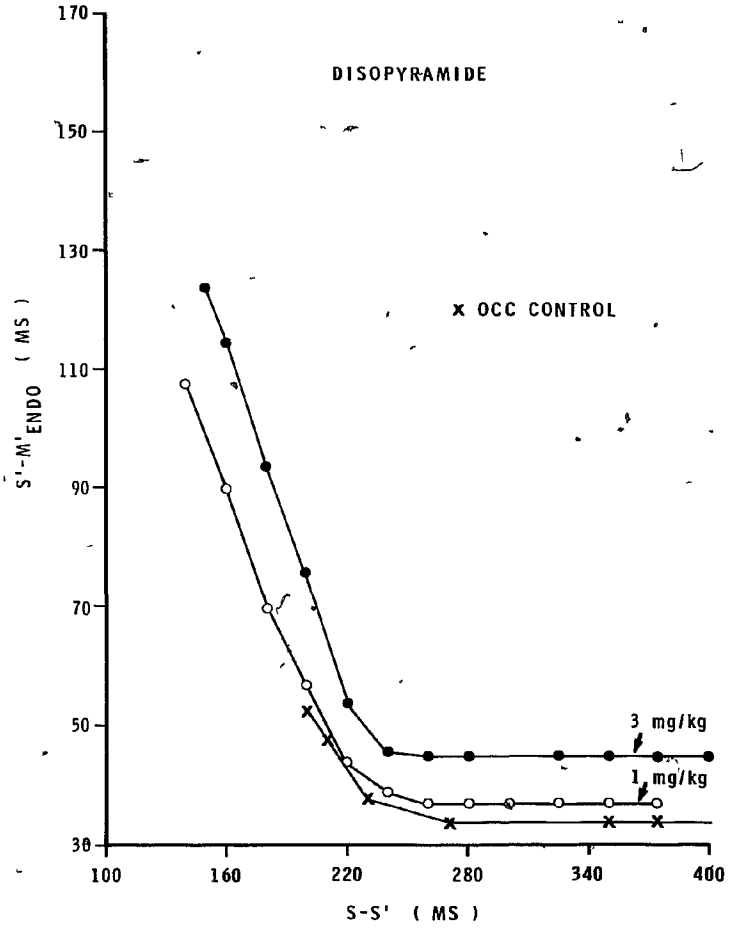


Fig. 39A. Effects of disopyramide on the conduction of extrasystoles within the ischemic zone of the left ventricle in a single experiment. $S'M'_{endo}$ = conduction time from an epicardial stimulating electrode to an endocardial recording in the ischemic zone produced by occlusion of the LAD coronary artery; S-S' = interval between the last normal stimuli and the test stimuli; x = occlusion 30 min; (O) = occlusion 45 min, disopyramide 1.0 mg/kg; (●) = occlusion 60 min, disopyramide 3.0 mg/kg.

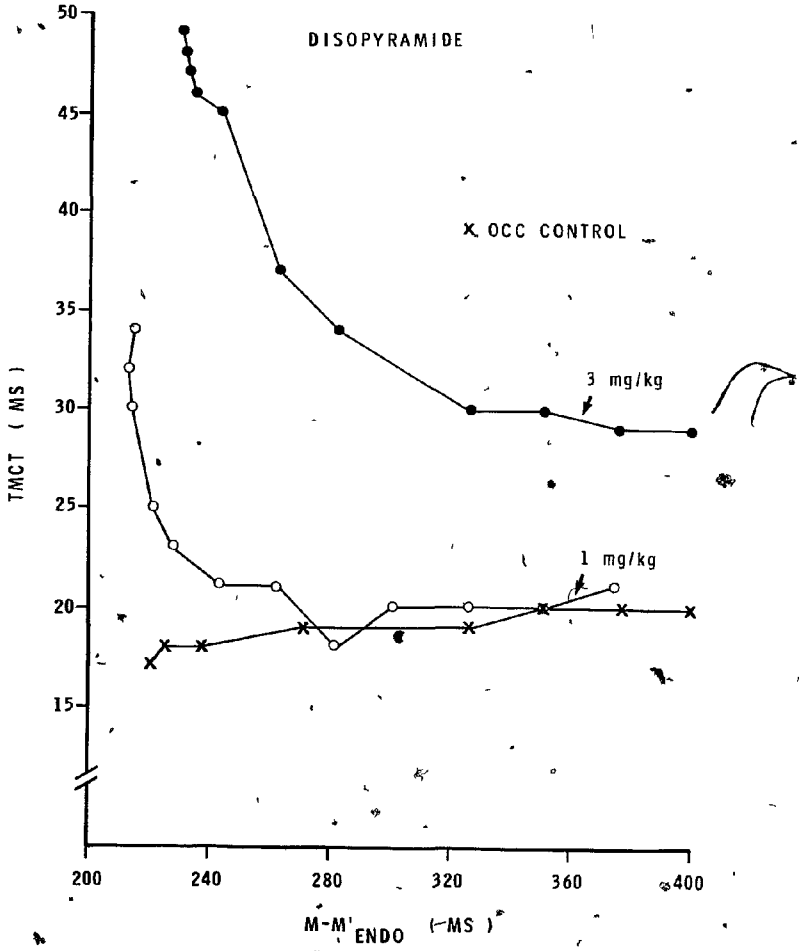


Fig. 39B. Effects of disopyramide on the transmural conduction time (TMCT) of extrasystoles within the ischemic zone of the left ventricle of the same animal as in Fig. 39A. $M\text{-}M'_{endo}$ = the extrasystole interval reaching the recording electrode in the ischemic zone from a stimulating electrode located at the base of the left ventricle. (x) = occlusion 30 min; (o) = occlusion 45 min, disopyramide 1.0 mg/kg; (●) = occlusion 60 min, disopyramide 3.0 mg/kg.

SECTION IV

DISCUSSION

A. THE NORMAL HEART

1. Conduction pathway: Purkinje vs myocardial conduction.

In the results described here, attempts were made to measure two facets of ventricular conduction. 1) endocardial or Purkinje conduction, 2) transmural or muscle conduction, in an *in vivo* preparation. Experiments were designed in which 2 or more recordings were made from the mid-anterior portion of the left ventricle and the distance from the stimulating electrode to the recording electrode was changed. Stimulation from both distal and proximal sites was carried out from an epicardial and endocardial location in order to determine whether the heart was activated in a temporally equivalent manner, when activation originated at the epicardium or endocardium.

Evaluation of the results reported here depends in part on the confidence with which conduction times from a *distal* site to the endocardial recording site may be considered to be a measure of conduction in the Purkinje system. There is good evidence that stimuli were conducted to the endocardial recording electrode and throughout the heart by way of the endocardial Purkinje network. Firstly, the arrival time at the endocardial recording electrode always preceded that of the epicardial electrode by 15-20 ms as it did during sinus rhythm.

Secondly, the classical experiment of Lewis (61) was repeated showing that a 2 mm deep transverse cut at the epicardial surface between stimulating and recording electrodes did not change the appearance of the electrograms.

Thirdly, the recording sites were always more than 3 cm from the site of stimulation, a distance which has repeatedly been shown by others (61, 64, 63, 100, 106) to be sufficient to assure a major contribution of the Purkinje system to conduction. Lewis and Rothschild (61) were first to suggest that the conduction pathway between an epicardial stimulating electrode and an epicardial recording electrode involved a Purkinje as well as muscle component if the two were separated by a distance greater than 2X the thickness of the ventricular wall. The left ventricular wall in the canine heart has a maximum thickness of 10 mm. We therefore always established a distance of greater than 20 mm, in fact greater than 35 mm between epicardial stimulating and recording electrodes. If the hypothesis were correct the conduction time between two epicardial electrodes should be equal to the conduction time between two transmurally opposed endocardial electrodes plus 2X the conduction time required for the impulse to cross the ventricular wall (i.e. the transmural conduction time, TMCT). Referring to Fig. 9 we can make the following approximations. The conduction time from points A to D, CT_{ad}, equals the endocardial conduction CT_{bc} plus the TMCTs' CT_{ab} and CT_{cd}.

i.e. $CT_{ad} = CT_{bc} + (CT_{ab} + CT_{cd})$ equation 1

By making the second approxrmation that the distance AB=DC i.e. the wall thickness is equal of the two locations in the heart then

$CT_{ad} = CT_{bc} + (2 \times CT_{cd})$ equation 2

CT_{cd} was the transmural conduction time calculated in all of the animals. Using this value for the TMCT, the relationship expressed by equation 2 holds true. Results averaged for seven animals are presented in Fig. 40. The upper curve in the figure are conduction times between two epicardial electrodes A and D as a function of extrasystole coupling interval. The lower curve indicated by the broken line is an equivalent plot for the conduction time between the two endocardial electrodes, B and C. Data are plotted relative to the ERP for the site of stimulation as explained in the results. The time difference between the curves is roughly 35 ms which is approximately 2 times the average TMCT presented in Fig. 16, and in agreement with the prediction in equation 2.

The fourth point suggesting ventricular activation via the Purkinje system is evident in Fig. 20. The curves of conduction times to five intramural recording sites during endocardial stimulation (dashed lines) have a parallel slope

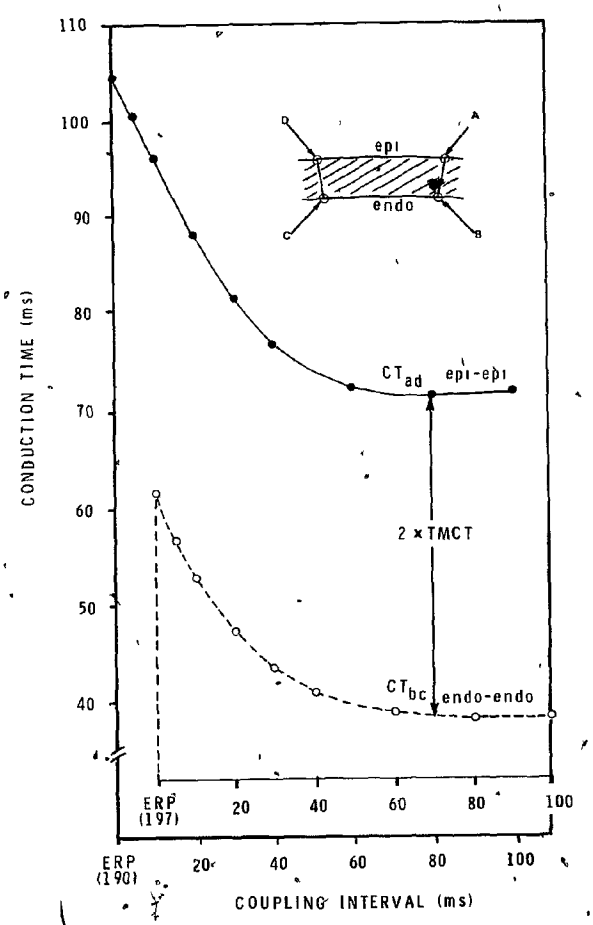


Fig. 40. Relationship between conduction time and conduction pathway. The upper solid curve represents the conduction time from an epicardial stimulating electrode located at A to a second epicardial electrode, D, located approximately 3.5 cm away as a function of extrasystole coupling interval. The lower broken curve represents the conduction time from the endocardial stimulating electrode, B, to a second endocardial electrode C. Electrodes A and D are located transmurally to B and C respectively. Conduction times are plotted at the coupling interval defining the ERP for each site of stimulation and at coupling intervals 5, 10, 20, 30, 40, 60, 80, and 100 ms above the ERP. ERP for epicardial stimulation = 190 ms, ERP for endocardial stimulation = 197 ms. n = 8.

to those obtained during epicardial stimulation (solid lines) suggesting the impulse reached the recording electrode via the same conduction pathway.

Fifth, in 10-20% of the animals rapid low amplitude deflections characteristic of Purkinje cells (28, 29, 30, 92, 95, 19), were detected at the endocardial recording site which preceded the main muscle potential by 5-10 ms. As these Purkinje "spikes" were not seen in all experiments the muscle potential recorded at the endocardium was used as an approximation of Purkinje activation.

2. Transmural conduction: absence of supernormal conduction.

Supernormal conduction has been shown to exist in the dog ventricle by Arbel et al. (4) as well as Ferrier and Dresel (33). Spear and Moore (99) have shown this period of supernormal conduction to exist within the His-Purkinje system of the heart and have correlated the supernormal conduction with the period of supernormal excitability in an in vitro Purkinje fibre preparation. This phenomenon was apparent in a small percentage of the experiments reported here and is illustrated as the shaded area in the upper panel of Fig. 41 for one animal. The supernormal period of Purkinje conduction occurred outside the relative refractory period and had a duration of approximately 50 ms. This supernormal conduction was observed as a decrease in

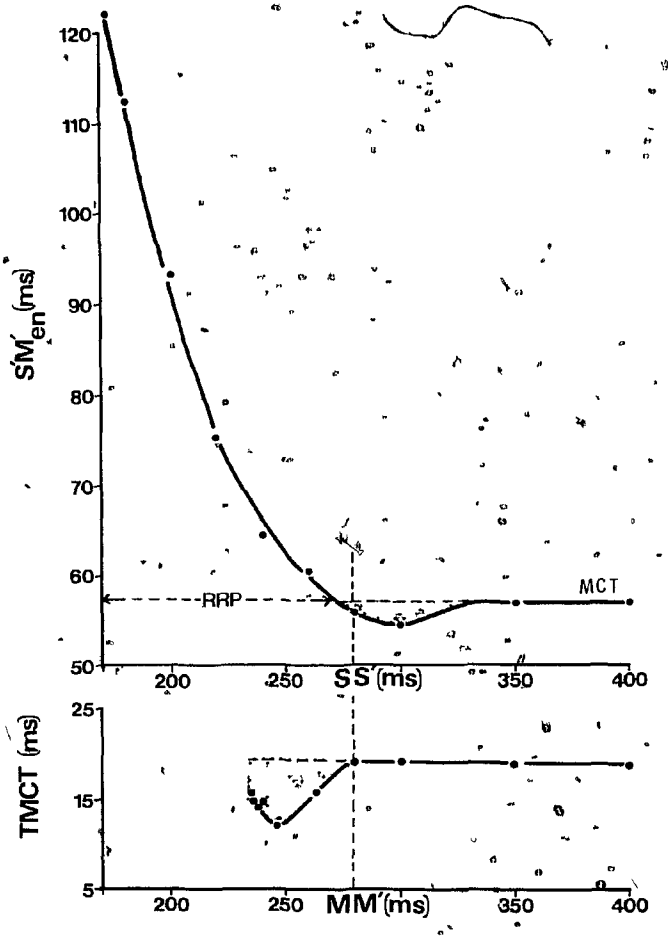


Fig. 41. Results from one experiment showing the relationship between supernormal Purkinje conduction and the "apparent" supernormal transmural conduction. In the upper panel $S'M'_{en}$ = the conduction time between an epicardial stimulating electrode and an endocardial recording electrode approximately 3.5 cm away; SS' = interval between last normal stimuli and test stimuli delivered by the stimulator. Supernormal conduction within the His-Purkinje system falls outside the RRP and is indicated by the shaded zone where conduction time falls below the MCT. In the lower panel TMCT = transmural conduction time; MM' = the effective extrasystole coupling interval reaching the endocardial recording electrode. Supernormal transmural conduction, also indicated by the shaded area, falls within the RRP. Basic cycle length = 800 ms.

conduction time below the MCT at the endocardial electrode and was reflected at the epicardial electrode. The conduction curve for the epicardial electrode is not shown in the figure. Although supernormal Purkinje conduction was observed in some animals it was not the prime interest of this study and therefore was not examined in detail.

Supernormal conduction has also been discovered in the dog atrium by Peuch et al. (76) but has never been shown to exist in the myocardium of the ventricle. Transmural conduction time was used as an indication of the time required for the cardiac impulse to travel a 1 cm distance (thickness of the heart wall at the point of recording) of myocardium. Early results of Durrer et al. (29, 30) suggested simultaneous activation of the inner layers of heart wall which led them to theorize Purkinje penetration into the inner 1/3 of the left ventricular wall. However, convincing histological evidence to support this idea is lacking. Our results are more consistent with those of Scher and Young (88, 91) who found little electrophysiological evidence for intramural penetration of Purkinje fibers. In our experiments, the left ventricular wall was always activated sequentially from the endocardium to the epicardium during sinus rhythm and when the heart was driven at a constant rate. Rapid conduction in the subendocardial layers was never observed, suggesting rapidly conducting Purkinje tissue was absent from this area, contrary to the early work of Durrer et al. (28, 29, 30).

Thus, transmural conduction time was assumed to be a measure of purely muscle conduction and not a composite measure of Purkinje plus muscle conduction. Transmural conduction time had an average value of 17 ms when the stimulating electode was located at a distance of several cm from the recording electrode (distal stimulation). Allowing for an average wall thickness of 10 mm at the point of recording, gives a calculated myocardial conduction velocity of 588 mm/s. This value is slightly higher than that determined by Durrer et al. (30) or by Scher and Young (88) who estimated intramural conduction velocity to be approximately 500 mm/s and 400 mm/s respectively in a similar preparation.

During distal stimulation transmural conduction time remained constant at long coupling intervals but decreased at extrasystoles of short coupling intervals. This appeared to be a phase of supernormal conduction in cardiac muscle similar to the one that is known to exist for Purkinje system. Unlike the phenomenon in the Purkinje system the period of supernormal myocardial conduction fell inside not outside the relative refractory period of the ventricle as shown in the lower panel of Fig. 41.

A series of experiments, in which five electrograms recorded intramurally at 2 mm intervals from the endocardium to the epicardium, were carried out to investigate the posibility of supernormal conduction in the heart wall. During extrasystoles from a distal stimulating electrode

there was a disproportionate increase in conduction time to the electrode located at the endocardium as the relative refractory period was entered. In two experiments this caused a reversal in activation sequence of this electrode and the electrode located 2 mm away in the subendocardium. However conduction times between all other intramural sites remained constant at all coupling intervals. Thus the "apparent" supernormal transmural conduction was in fact due to a greater increase in conduction time to the endocardium relative to the other electrode sites. This effectively decreased the time difference in activation between the epicardium and endocardium and thus the transmural conduction time as we had calculated it.

This peculiarity in endocardial activation during premature excitation is hard to explain in light of the present evidence. One possibility may be that there is a different conduction pathway that becomes functional during short extrasystoles, i.e. while the heart is refractory, resulting in an epicardial to endocardial activation of the inner layers of the heart wall. This idea is supported by the fact that a change in shape and/or polarity of the endocardial electrogram was often seen during the relative refractory period while intramural and epicardial electrograms maintained the same configuration from normal to extrasystolic beats. An epicardial to endocardial direction of activation in the heart wall has been reported

by others and has been dubbed a "reversal phenomenon" (30) or "bidirectional intramural activation" (11, 20). However, these workers observed this phenomenon during normal ventricular activation whereas in our experiments it was only uncovered by extrastimulus techniques.

An alternate explanation is based on mechanical rather than electrical events in the heart. Rushmer and Thal (83) have shown an increase of 50% in wall thickness to occur in the heart during systole. Durrer et al. (30) have estimated this to represent an increase in wall thickness of 3-4 mm. As the recording electrode in our experiments was fastened to the epicardium it remained stationary relative to the heart muscle during systole. However, as the myocardium contracted and the heart wall thickened, this would necessitate the muscle fibers in contact with the endocardial recording site(s) to move along the electrode. During regular heart beats, this is irrelevant to the recording as electrical systole preceeds the mechanical systole (the ejection phase of contraction; as little change in heart geometry occurs during isovolumic contraction) by some 70-90 ms (10). However, during short coupled extrasystoles the heart is still in a contracted state from the previous normal beat, i.e. electrical systole occurs without the corresponding mechanical systole. This was evident in our experiments during short coupled extrasystoles which appeared in the electrocardiogram but were not seen in the arterial blood presure recording. This indicated the heart

had been activated electrically but had not contracted sufficiently enough to cause opening of the aortic valves (intraventricular pressure was not recorded and therefore we had no measure of isovolumetric contraction if in fact it did occur). Thus, we suspect the wall thickness was greater during short coupled extrasystoles than during normal beats. Therefore the activation recorded by the endocardial electrode may have been of a different muscle fibers during the two beats thereby accounting for the differences observed in the electrograms and transmural conduction times.

The task of resolving which of these two explanations is the more probable is a difficult if not impossible one due to the inseparable coupling that exists between the electrical and mechanical events in the heart. Theoretically, if the decrease in transmural conduction time were due to the geometrical change in the heart during systole one should be able to change the coupling interval at which the decrease occurred by changing the heart rate. At a higher heart rate the ejection phase of contraction is considerably shortened (10). Therefore, the coupling interval which excites the heart while still in a contracted state should occur at a shorter coupling inteval. i.e. cause a shift to the left of the dip observed in the TMCT plot. However, electrical alterations in the heart accompanying an increase in rate should produce the same effect. Mendez et

al. (63) and Janse et al. (52) have shown that the functional refractory period of the ventricle decreases at increasing heart rates. The dip observed in TMCT was maximal at the functional refractory period as was evident when TMCT was plotted against the extrasystolic interval "seen" at the recording site (MM') as shown in Figs. 14A and B. Thus, the dip in TMCT would also be shifted to the left by an increase in heart rate if it were an electrical phenomemon associated with the refractory period of the heart. This was observed in a rather reverse fashion in our experiments. Disopyramide caused an increase in the functional refractory of the heart and caused a shift to the right of the dip in the TMCT plot (Fig. 16A and B). It was not determined from our experiments whether disapyramide increases the duration of mechanical systole concurrently with the electrophysiological changes it produces FRP. If it does not, this would be evidence to support the idea that the changes in endocardial conduction times on short extrasystoles are due to a change in conduction pathway in refractory tissue rather than a change in geometry associated with contraction of heart muscle.

3. Gating function of the Purkinje system.

Myerburg et al. (68, 69) have put forth the theory that cells in the distal Purkinje system, by nature of their long action potential duration, serve as gates limiting the

propagation of very premature extrasystoles to the myocardium. If the conduction distance between a stimulating and recording electrodes is greater than a few centimeters (distal stimulation) it can be assumed that the Purkinje system will be involved in conduction as discussed above. Thus the extrasystole interval arriving at the recording electrode will first be gated by the specialized conducting tissue. This was proven to be so in the experimental results. During distal stimulation the myocardium at the recording site never became refractory as conduction time within the myocardium (between intramural sites) did not increase even at the shortest coupled extrasystoles (Fig. 19). The minimum coupling interval reaching the recording site was determined by the FRP of the endocardial Purkinje system. Referring to Fig. 16A or B this represents a coupling interval of approximately 220 ms averaged for 8 dogs. However, when the heart was stimulated from the endocardial tip of the recording electrodes (proximal stimulation) the extrasystole interval invading the myocardium was delivered directly from the stimulator and was not first gated through the Purkinje system. Under these circumstances, the minimum extrasystole interval obtainable in the myocardium at the recording electrode was defined by the ERP of the myocardium. This value was 200 ms averaged for the same 8 animals - see Fig. 17. Thus during proximal stimulation it was possible to visualize the

refractory period of the myocardium, and conduction time within the myocardium increased at the short coupling intervals. The total sum of this slowing occurred only over the 2 mm distance between the stimulating electrode and first recording electrode as is indicated in Fig. 22. van Dam et al. (105, 106) have also shown slowed conduction of extrasystoles to be confined to the immediate vicinity of the stimulating electrode in cardiac muscle. Thus, it can be seen that it is possible to achieve extrasystoles with very short coupling intervals within a localized area of the myocardium around a stimulus site (or possibly an ectopic foci). However, the minimum coupling interval obtainable as extrasystoles propagate to other areas of the heart will be limited by the FRP of the endocardial Purkinje network.

4. Refractory periods.

Three measures of refractoriness were derived in these studies, the relative refractory period, functional refractory period, and the effective refractory period. All three refractory periods changed with changing sites of stimulation and were therefore plotted separately. The effective refractory period (ERP) varied between epicardial and endocardial stimulation at the same location in the heart. It was consistently found that the heart would follow an extrasystole with a much shorter coupling interval during epicardial stimulation than during endocardial stimulation

even though the strength and stimulation at both locations was 2X threshold (sometimes 4X threshold at the endocardium). In other words, the ERP for epicardial stimulation was less than the ERP for endocardial stimulation. If endocardial stimulation can be assumed to reflect the electrophysiological properties of the endocardial Purkinje system and epicardial stimulation those of the myocardium then these results are not unexpected as Gettes and Surawicz (35) and Moore et al. (65) have shown from in vitro studies the action potential duration, and effective refractory period to be greater in Purkinje than muscle tissue. Alternately, these results may reflect differences in refractory characteristic between endocardial an epicardial muscle as we had no way of determining whether endocardial stimulation was of Purkinje or muscle tissue.

As Purkinje and myocardium show different conduction characteristics so should they show different relative and functional refractory periods as both are determined by measurements made on conduction. The relative refractory period (RRP) was defined as the range (in ms) of coupling intervals over which the heart displayed slowed conduction. This represented the coupling interval at which conduction time first exceeded the minimum conduction time (MCT) by 2 ms to the coupling interval of the effective refractory period. From Fig. 20 it is apparent that when conduction times were determined from a distal stimulation site the

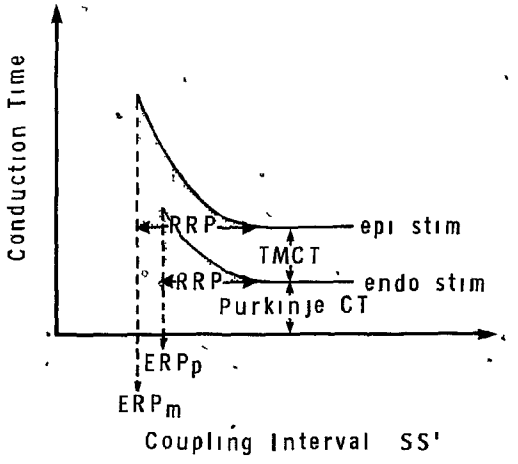
coupling interval at which conduction time began to increase was approximately the same for endocardial and epicardial stimulation. However, the effective refractory period for the two sites differed as mentioned above, resulting in a difference in the relative refractory period calculated for epicardial vs endocardial stimulation. This concept is presented schematically in Fig. 42A. The average difference in the RRP calculated in 8 animals for the two distal sites of stimulation is 45-33 = 12 ms (Fig. 24) which is approximately equal to the difference in the ERP for the two 197-190 = 7 ms (Fig. 26).

The greater increase in conduction time (Δ CT) above the minimum conduction time (MCT) obtainable during epicardial stimulation, evident in Figs. 20 and 23 can also be attributed to the difference in the ERP that exists between the endocardium and the epicardium. As the electrical activation of the heart occurs via the Purkinje system and is an all or nothing phenomenon, the minimum interval obtainable between two stimuli delivered to the endocardium which results in conducted impulses is the ERP of the Purkinje by definition. However, extrasystoles of shorter coupling intervals delivered to the epicardium can still result in conducted beats. This is presumably due to slowing of conduction within the myocardium near the site of stimulation so that the coupling interval that reaches the Purkinje after travelling across the heart wall now falls

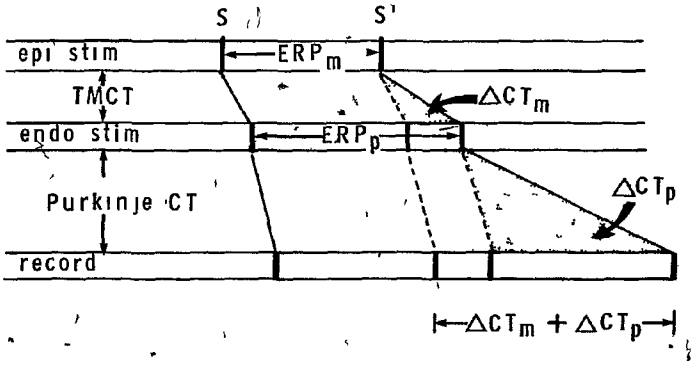
Fig. 42A. A theoretical diagram showing the relative refractory period (RRP) and effective refractory period (ERP) determined during epicardial and endocardial stimulation. The upper curve represents the conduction time from an epicardial stimulating electrode to a distal recording electrode. The lower curve represents the conduction time from an endocardial stimulating electrode (located transmurally to the epicardial stimulating electrode) to the same recording electrode. ERP_m = effective refractory period of the myocardium. ERP_p = effective refractory period of the Purkinje system; Purkinje CT = conduction time in the Purkinje system; TMCT = transmural conduction time.

Fig. 42B. A theoretical diagram showing the relationship between site of stimulation and slowing of conduction that occurs at the effective refractory period (ERP). The conduction of a nonpremature stimulus, S, is shown in the left hand of the figure and the conduction of the extrasystole on the right. S' ΔCT_m = increase in TMCT that occurs during the extrasystole; ΔCT_p = increase in Purkinje conduction time that occurs during the extrasystole; record = recording electrode located at a distance from the stimulating electrodes sufficient enough to ensure a Purkinje component in the conduction pathway. Other symbols are the same as those used in Fig. 42A.

A.


Conduction Time
RRP
epi stim
TMCT
RRP
endo stim
Purkinje CT
ERPp
ERPm
Coupling Interval SS'

B.


S
S'
epi stim
ERPm
TMCT
ΔCTm
endo stim
ERPp
Purkinje CT
ΔCTp
record
ΔCTm + ΔCTp

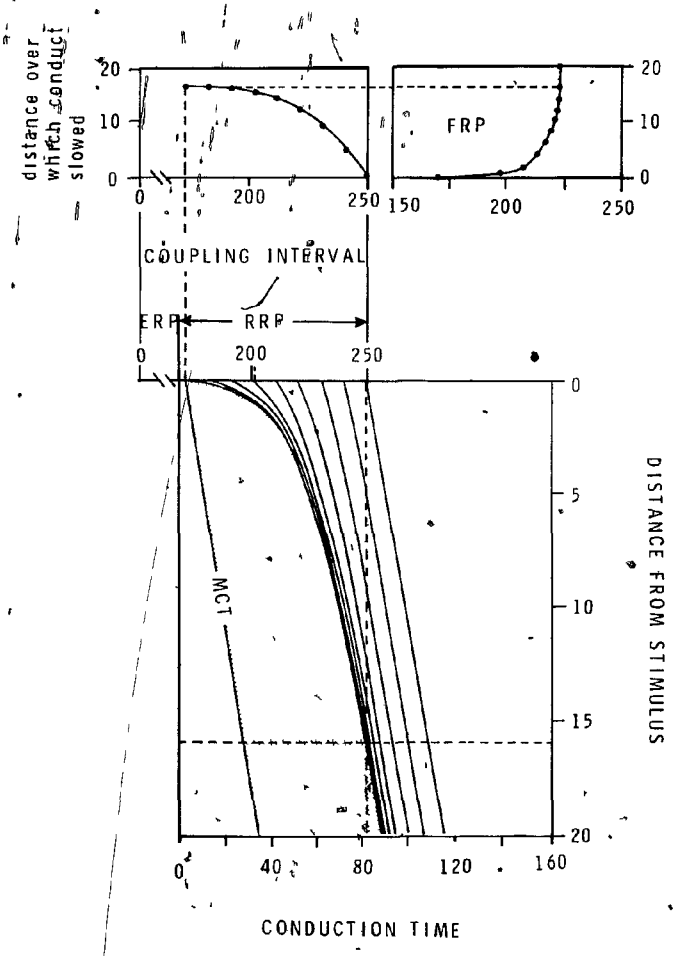
outside the ERP of the Purkinje and thus is capable of activating the ventricle. This concept is presented schematically in Fig. 42B. The total slowing of conduction observed for a short coupled extrasystole is the slowing which occurs in the myocardium as the extrasystole journeys towards the Purkinje system, plus the additional slowing of conduction that occurs once the extrasystole invades the Purkinje. Thus, the total slowing of conduction during epicardial stimulation is greater than that which occurs during endocardial stimulation and is manifest by a larger ΔCT value.

The functional refractory period (FRP) was defined as the minimum interval obtainable between two conducted beats. The functional refractory period at the site of stimulation is equal to the effective refractory period plus the increase in latency in propagation of the cardiac impulse from normal to extrasystolic beats (63, 82). The FRP increases in length however, as the distance between the stimulating and recording electrode increases. The FRP will continue to increase until that distance from the stimulating electrode at which the extrasystole has been slowed sufficiently to allow complete recovery of the tissue from the previous beat (i.e. non refractory tissue). This point is represented by the horizontal broken line in Fig. 43, a schematic representation of the relationship that exists between the measured FRP and the distance from a

Fig. 43. A theoretical diagram indicating the relationship between the effective refractory period (ERP), functional refractory period (FRP), and the relative refractory period (RRP). The main panel of the figure represents the conduction of an impulse in a homogenous medium as a function of extrasystole coupling interval. The diagonal line at the left hand side of the panel represents the conduction of non-premature stimuli. With increasing distance from the stimulus point, conduction time increases in a linear fashion. However for premature stimuli with coupling intervals less than 250 ms, conduction away from the stimulus point occurs in a non linear fashion, rather in an exponential fashion with the slowest conduction occuring nearest the stimulus. On the coupling intervals axis there are broken lines and solid lines. The solid lines indicate the time the stimulus is applied; the broken lines, the time at which conduction of the impulse commences. The difference between the two represents the latency of stimulation which changes with coupling interval. For clarity sake it is shown for 2 stimuli only.

The most premature extrasystole the heart conducts is defined as the ERP. In this figure the ERP is approximately 170 ms. The time between the ERP and the coupling interval at which conduction first becomes slowed, 250 ms, represents the RRP. The FRP, the minimum interval obtainable between two conducted beats is equal to the ERP plus the increase in conduction time over the minimum conduction time (MCT) that occurs with extrasystoles that fall within the RRP (indicated by the shaded area in the figure). The FRP increases with increasing distance from the stimulus up to a distance of 16 arbitrary units. This point indicated by the broken horizontal line represents the border between refractory and non-refractory tissue at the ERP. For all other coupling intervals the border is located at the point where the curves of conduction time intersects the vertical broken line. At distances greater than 16 units from the stimulus, the conduction time is sufficiently long to allow full recovery of the tissue from the previous stimuli before the arrival of the extrasystole (i.e. is non-refractory). From this point onward the impulse is conducted normally and the FRP assumes a constant value.

The upper right hand panel of the figure is a plot of the relationship between the FRP and the



distance from the stimulus site. The FRP at the stimulus site = ERP and latency associated with the premature stimulus. The horizontal broken line in both upper panels represents the border line refractory and non-refractory tissue (16 units) at the ERP. The upper left hand panel shows the relationship between coupling interval and distance from the stimulus over which conduction is slowed. For non-premature stimuli, coupling intervals greater than 250 ms, no slowed conduction occurs. At the shortest coupling interval (ERP), maximum slowing of conduction occurs and extends to a distance of 16 units from the stimulus.

stimulus site in a homogenous tissue medium (a modification of a diagram by Rosenblueth (82). At any distance from a stimulating site, the FRP is equal to the ERP plus the increase in conduction time that ocurs at the ERP indicated by the shaded zone in the figure. For extrasystoles which fall within the RRP the FRP will appear to increase up to a distance of 16 arbitrary units from the stimulus. At greater distance, the FRP will assume a constant value, i.e. that measured at the dotted line which is the border zone between refractory and non refractory tissue.

Stimulation of the heart from the endocardial tip of the recording electrode (proximal stimulation) allowed determination of the FRP of the myocardium. As all slowing of conduction of premature beats occurred within the 2 mm distance between the stimulating and first recording electrode (Fig. 22), the FRP value measured at this distance was identical to the FRP measured at a more distant site, such as at the epicardial surface at a distance of 10 mm. The FRP of the myocardium had an average value of 206 ms (n = 8) for endocardial stimulation and 213 ms (n = 3) for epicardial stimulation as indicated in Fig. 25.

However, when the heart was driven from an electrode several cm from the recording electrode (distal stimulation) it was not possible to determine the distance over which the slowing of conduction occurred. The FRP therefore calculated was the FRP of the conduction pathway between

electrodes which involved both Purkinje and muscle tissue. It may have been less than the FRP of the ventricle as a whole. The FRP measured during distal stimulation was 223 ms (n = 8) for epicardial stimulation and 220 ms (n= 8) for endocardial stimulation as shown in Fig. 25. These values are significantly different from the FRP determined during proximal stimulation ($p < .01$), and it is believed that they represent the FRP of the Purkinje component of the conduction pathway.

5. Drug actions

a) Endocardial conduction and refractory periods:

1) Lidocaine. The effects of lidocaine in the normal heart are subtle but not easily interpreted. At low doses of 1.25 and 2.5 mg/kg the drug can cause both speeding and slowing of conduction within the Purkinje system with little effect on myocardial conduction. At higher doses of 5.0 and 10.0 mg/kg, lidocaine causes only slowing of conduction and this is seen in both the Purkinje and myocardium. In order to explain lidocaine's ability to alter the conduction characteristics of the heart, it is first necessary to consider its actions at the cellular level as described by others.

Conduction velocity is generally considered to be highly correlated with Vmax (47), the maximum rate of rise of the upstroke of the action potential. Although it has been established that this correlation need not hold under all conditions or when examined carefully (75, 79) it seems reasonable to discuss the results in relation to the effect of the drug on Vmax and on the duration of the action potential. Lidocaine has been shown to affect the steady-state voltage dependence of Vmax (7, 8, 14, 21, 73, 109) causing a decrease in Vmax for any given resting membrane potential. However, this effect is less than the shift the drug produces in the "membrane responsiveness curve" (14) the difference probably being due to its actions to decrease the rate of recovery from inactivation of the fast sodium channel. Both of these drug effects are accentuated at lower (more positive) resting membrane potentials. A detailed hypothesis for the interaction of antiarrhythmic drugs with the sodium channel has been provided by Hondeghem and Katzung (49, 50) and recently by Courtney (18). Earlier work also established that lidocaine decreases the duration of the action potential (APD) and increases the ratio of refractoriness to APD (8). Also Wittig et al. (113) have shown lidocaine to cause preferential shortening of the APD in the distal Purkinje fibres of the canine heart, the so-called "gate" cells. Thus, if in vitro results can be extrapolated to the in vivo

situation it might be expected that lidocaine could cause speeding of the conduction of extrasystoles by its ability to shorten APD and/or cause slowing of conduction by its ability to decrease Vmax.

The results described here for lidocaine support this assumption. While the drug did not have any effect on the conduction of extrasystoles with coupling intervals longer than 400 ms, it had a biphasic action on more premature extrasystoles. 1) It slowed conduction of mid-range extrasystoles (MREs: 250-400 ms) in a dose dependent fashion, and this resulted in an increase in the measured RRP; 2) low doses caused speeding of conduction of early (< 225 ms) extrasystoles.

The effect of lidocaine to slow the conduction of MREs may be explained by the drugs effect on time dependence of Vmax. It seems clear that whatever degree of inactivation of the sodium channel may remain 400 ms after an action potential elicited with an 800 ms basic driving interval, it is not sufficient to affect conduction time over a 3-4 cm long conduction pathway between the stimulating and recording electrodes. The increase in conduction time of MREs was manifested by a lengthening of the RRP in the absence of a change in ERP. The absence of any drug effect on extrasystoles with long coupling intervals (< 400 ms) might have been predicted for two reasons: a) the concentrations of lidocaine used do not have any effect to

decrease Vmax at the normal resting membrane potential (14), and b) the effects of lidocaine on the fast sodium channel are transient. It has been hypothesized (18) lidocaine binds to and blocks only the open sodium channel and rapidly dissociates from the closed channel so that during diastole the effects of lidocaine rapidly declines.

The speeding of conduction by lidocaine is more difficult to explain especially in light of the data of Hondeghem and Katzung (50) or Chen et al. (14) which predicts lidocaine to cause the greatest slowing of conduction at the shortest coupled extrasystoles i.e. interval-related slowing. At low doses the opposite effect was observed. In order to explain this discrepancy one would have to assume that, at these low doses, the effect of the drug on APD exceeds its effect on refractoriness, or that the correlation of Vmax with conduction velocity no longer holds true, as suggested by Peon et al. (75) and Reynolds et al. (79). The first of these possibilities would be supported by the observations of Wittig et al. (113) who showed a decrease in FRP accompanying the decrease in APD of gate cells of the distal Purkinje system. This result suggests less slowing of extrasystoles propagated through the Purkinje system in the presence of lidocaine than would occur during control conditions. This would be observed as a speeding effect of lidocaine on ventricular conduction as was seen in our experiments.

ii) Disopyramide. Disopyramide is similar to lidocaine in the respect that it does not produce dramatic changes in conduction characteristics of the "normal" heart. However, the electrophysiological effects that are produced by disopyramide differ quite considerably from those of lidocaine.

The most striking effect of disopyramide was the increase it produced in the effective refractory period (ERP). Disopyramide caused dose-dependent increase in ERP at all sites of stimulation as shown in Fig. 28. Increases in minimum conduction time accompanied increases in ERP at 3.0 mg/kg but not at 1 mg/kg. Lidocaine, on the other hand increased conduction times of extrasystoles without altering the ERP. Kus and Sasniuk (57) have found similar results for disopyramide in in vitro studies on canine ventricular muscle and Purkinje fibers. They reported disopyramide caused an increase of 10% in ERP of Purkinje fibers in the region of the "gate" cells at a concentration of 5 mg/ml. This was accompanied by a somewhat smaller increase in conduction time of 5% in the same tissue for non-premature stimuli. In our experiments, disopyramide 1.0 mg/kg increased the ERP by 3.6% (197-204 ms) with no change in endocardial conduction time of nonpremature beats or extrasystoles with long coupling intervals as shown in Fig. 12B. The 3.0 mg/kg dose caused 7.0% increase in ERP (197 to 211 ms) but associated with a 9.4% increase in conduction

(38.4 ms to 42 ms). This slowing of conduction has been attributed to the drug's ability to block the fast sodium channel (57), thus causing a decrease in action potential amplitude and maximum rate of rise of the action potential upstroke, Vmax.

The effect of disopyramide on the endocardial conduction of extrasystoles was such that for any given extrasystole that fell within the relative refractory period (RRP), the conduction time was greater in the presence of the drug than during the control. The drug caused a parallel shift to the right of the curve of extrasystole conduction time by an amount equivalent to the ERP at the 1.0 mg/kg dosage. This indicates the heart does not conduct differently from control while refractory, but merely becomes refractory at longer coupling intervals. Conduction during refractoriness (CDR) was the same during drug treatment as it was for control. In accordance with this concept, disopyramide did not alter the duration of the relative refractory period, whereas lidocaine changed the manner in which the heart conducted extrasystoles while refractory and increased the relative refractory period. This may be taken to suggest disopyramide does not alter the time dependence of reactivation of the fast sodium channels. Again, these results are consistent with those of Kus and Sasyniuk (57) who showed disopyramide to cause a decrease in maximum action potential upstroke velocity and a

parallel shift to the right of the membrane responsiveness curve. This action of disopyramide is similar to that described for quinidine by Chen et al. (14) who showed that the parallel shift in the membrane responsiveness curve was associated with a parallel shift in the steady state relationship between the membrane potential and Vmax. This suggested to them that quinidine did not have any effect on the recovery kinetics of Vmax at any level of membrane potential.

An additional effect of disopyramide was seen at the higher dose of 3.0 mg/kg. At this dose disopyramide caused an increase in the MCT, i.e. conduction time of extrasystoles with long coupling intervals. This action of disopyramide resembles that of quinidine (14). In contrast to lidocaine the block of Na+ channels produced by quinidine is not reversed during diastole (50) therefore accounting for the non discriminant slowing of both premature and non-premature impulses observed for the drug.

The functional refractory period (FRP) can be defined as a single point on the curve representing conduction time as a function of extrasystole coupling interval. This has been demonstrated for AV nodal conduction by Ferrier and Bresel (34) and Simson et al. (94) but can be extrapolated to ventricular conduction times during ventricular pacing. The FRP is that point on the curve of conduction time where the slope has a value of -1. As disopyramide did not change

the slope of the curve it should have increased the FRP by an amount equivalent to the increase in the ERP. This was found to be the case.

b) Transmural conduction time: effects of lidocaine and disopyramide on apparently supernormal conduction.

Lidocaine did not alter conduction times of extrasystoles of long coupling intervals (< 400 ms) in either Purkinje or myocardial tissue. It did however cause slowing of extrasystoles in both tissues at doses of 2.5, 5.0 and 10.0 mg/kg. The effect of lidocaine on Purkinje conduction was seen at the endocardial electrode (Fig. 10. A). The drug caused additional slowing of conduction transmurally as indicated in Fig. 15. However, lidocaine failed to cause speeding of conduction in the myocardium as it did in the Purkinje system. Conversely, lidocaine removed the "dip" observed in the TMCT curve, the apparent supernormal myocardial conduction. As it was postulated that the dip is due to discrepancies that exist between endocardial and intramural conduction of extrasystoles, lidocaine must have differentially affected the conduction characteristics of either the endocardial Purkinje system or the myocardium in order to remove this "apparently" supernormal conduction. The dip observed in TMCT was an interval-related phenomemon, occuring only at short coupling intervals. In vitro studies in cardiac muscle have

indicated that lidocaine causes more slowing of premature extrasystoles than those that fall later in diastole (14, 50). Our in vivo results indicate lidocaine causes preferential slowing of mid-range extrasystoles in the Purkinje system. Therefore it is postulated that lidocaine removes the measured dip in TMCT by causing greater slowing of myocardial vs Purkinje conduction on short coupled extrasystoles, thereby eliminating the disproportionate increase in conduction time to the endocardial electrode observed under control conditions.

Disopyramide had little effect on the transmural conduction time of extrasystoles at the dosage of 1.0 mg/kg. However for the higher dosage of 3.0 mg/kg there was a slowing in myocardial conduction of extrasystoles with long coupling intervals. For distal stimulation, TMCT was increased by disopyramide from 17 to 19 ms at coupling intervals greater than 40 ms above the FRP of the endocardium. (Fig. 16A and B). By nature of its effect to decrease the steady state voltage dependence of Vmax one might anticipate disopyramide to cause a parallel increase in TMCT at all coupling intervals. However, unlike lidocaine, disopyramide, at the dosages tested, did not appear to effect the decrease in TMCT that occurred at short coupling intervals, and the apparent supernormal conduction in the myocardium was maintained after a total of 3 mg/kg of the drug.

The conduction characteristics of the myocardium were examined more closely during stimulation of the heart from the tip of the recording electrode (proximal stimulation, Fig. 17). As was seen for endocardial conduction, disopyramide caused a parallel shift to the right and upwards of the curve of extrasystole conduction times. The drug effect on TMCT was not as great as that seen for endocardial conduction because of the shorter conduction pathway involved, 1 cm vs 3-4 cm. However the relative amount of slowing by disopyramide was approximately equivalent in the two tissue types.

B. THE ISCHEMIC HEART

1. Initial electrophysiological alterations following coronary occlusion.

Our experiments in infarcted hearts were designed to 1) examine the electrophysiological changes that occurred within the ischemic myocardium during the initial periods of ischemia 2) to compare these changes with any changes that occurred in Purkinje conduction and 3) to determine the site of action of antiarrhythmic drugs in the ischemic zone. In preliminary experiments recording were made from a large area of the ventricle using a composite electrode similar to that of Williams et al. (112). Composite electrograms recorded during sinus rhythm from the anterior and posterior areas of the left ventricle under control conditions showed rapid sharp deflections that corresponded with the R wave of

the electrocardiogram indicating synchronous activation of the ventricular epicardium. However, within minutes of occlusion of the LAD, electrograms recorded from the composite electrode overlying the area supplied by the LAD began to degenerate while those recorded from the normal zone on the posterior surface of the ventricle maintained the configuration seen under control conditions. Decreases in amplitude and increases in duration of electrograms similar to those observed by others (9, 53, 54, 55, 74, 108, 112) were seen within the first 10 minutes of occlusion suggestive of slowed and asynchronous conduction through the ischemic area. Also, continuous electrical activity bridging the diastolic gap between normal and arrhythmic beats, and between consecutive arrhythmic beats was observed in the ischemic but not normal areas, consistent with the results of others described above.

In some experiments bipolar electrograms were recorded from the endocardium in addition to the composite epicardial electrograms. These indicated that the normal 15-20 ms time difference between endocardial and epicardial activation (TMCT) was increased in the ischemic zone. This increase in conduction time was associated with the loss of integrity of the ischemic zone electrograms. No changes in conduction time were observed in the normal zone. Transmural conduction time in the ischemic zone was further increased during spontaneous premature beats suggestive of increased refractoriness in the damaged muscle. Occasionally a total loss of epicardial activity occurred in the ischemic zone without losses in endocardial activation. The loss of

epicardial potentials occurred within the first ten minutes of occlusion but gradually returned as ischemia progressed.

The effect of ischemia on the two aspects of ventricular conduction, Purkinje conduction and myocardial conduction, was examined in more detail in a further 17 experiments. In these experiments hearts with an A-V block were driven from an electrode located at the base of the left ventricle and conduction times were measured to two electrodes located in the ischemic zone. The effects of prolonged ischemia up to ninety minutes duration were examined in 4/17 of these experiments. Transmural conduction time increased dramatically in 2/4 animals within the first 10 minutes of occlusion of the LAD, the time period consistantly shown by others (5, 22, 42, 44, 53, 17) to be associated with serious conduction disturbances and fibrillation. During this 10 minute period there was a decrease in amplitude or complete loss of bipolar electrograms recorded at the epicardial surface in the infarcted zone. However there were very few instances of severe ventricular arrhythmias or fibrillation during the early periods of ischemia possibly because the hearts were driven at a very slow rate (75 to 100 bpm). This is in agreement with the work of Scherlag et al. (92) who have shown the incidence of arrhythmias associated with acute ischemia to be increased at increasing heart rates. Following this intial 10 minute period electrograms regained amplitude, approaching control values and arrhythmias

subsided. This phenomenon has also been reported by Scherlag et al. (92), Hill and Gettes (45) and Murdock et al. (67). However this recovery of signal amplitude was not accompanied by a recovery of conduction times and TMCT remained elevated during the entire 90 minutes of ischemia. No changes in endocardial conduction time were observed during this period.

A second phase of arrhythmic activity developed at some time after 45 minutes of ischemia in all four of these animals without any further increases in conduction time. In 3/4 animals the arrhythmias persisted until the conclusion of the experiments after 90 minutes of LAD occlusion. However it should be noted that during this period it was not possible to determine conduction times accurately because the ventricular tachydysrhythmias that developed exceeded the ventricular drive rate. Two phases of ventricular arrhythmias have also been documented by Kaplinsky et al. (53) and Ogawa et al. (74) within the first hour of coronary occlusion.

As maximum increases in TMCT occurred within 10 minutes of the onset of LAD occlusion and had stabilized by 30 minutes, the effects of ischemia on myocardial conduction were determined by comparing TMCT values taken at the 30 minutes mark to those of control. Results from the 17 animals (Table 3) indicate an average TMCT of 17.8 $\pm$ 1.0 (S.E.) ms for control conditions. Assuming an average wall thickness of 10 mm at the recording needle this represents

an average conduction velocity of 562 mm/s. Ischemia caused an increase in TMCT time to 26.1 ± 2.3 (S.E.) ms, which is equivalent to a conduction velocity of 383 mm/s. There was a large inter-animal variability in the changes observed in TMCT with some animals showing no change during ischemia and others showing a dramatic increase. In one animal in which the effects of ischemia were particularly pronounced TMCT increased to 51 ms from a control value of 17 ms giving an estimated value of conduction velocity in ischemic myocardium of 196 mm/s. The variations between animals in response to ischemia may be accounted for by anatomical differences in collateral coronary circulation known to exist between animals, which can greatly influence the hearts tolerance to ischemia (101).

The above discussion has focused on the effects of ischemia on cardiac conduction both during sinus rhythm and during a slow heart rate imposed by a ventricular pacing electrode. The behavior of the ischemic heart during artifically imposed extrasystoles and increasing heart rates was also studied. TMCT measured during the basic drive interval of 800 ms was increased during ischemia and no further increases in TMCT could be achieved on premature beats (Fig. 37), that is to say the increase in TMCT observed after 30 minutes of ischemia was uniform at all coupling intervals. Also, the apparent supernormal phase of myocardial conduction was still evident at the short coupling intervals. These results indicate that the

Purkinje system of the ventricle is still acting as an effective gating mechanism, such that the minimum extrasystole interval reaching the ischemic myocardium still falls outside the refractory period of the muscle even though its refractory period may be increased by ischemia (22, 23, 39). However, this gating function of the Purkinje system may not be effective during multiple premature beats that follow one after the other as is evident in Fig. 32B. In this figure, TMCT increased on each successive spontaneously occurring extrasystoles, results consistent with those of Williams et al. (112). This hypothesis was never tested however, as in experiments in which hearts were electrically stimulated never more than a single extrasystole was delivered to the heart.

Conduction times were measured during increasing heart rates in 4 of 17 animals (Fig. 34). TMCT showed slight increases at higher heart rates after 30 minutes of ischemia when no interval-related increases in TMCT were observed. Thus there appears to be a fatigue effect in the conduction characteristics of the ischemic myocardium such that a single premature beat is not slowed but conduction during a train of rapid stimuli is impaired. It is interesting to note that applied extrasystoles failed to provoke ventricular fibrillation in 8 experiments. However ventricular fibrillation developed in 1 of 4 animals at a high drive rate of 240 bpm, in the presence of lidocaine 10.0 mg/kg.

Endocardial conduction time, unlike TMCT, was relatively unaffected by ischemia. Only minimal slowing of conduction occurred at the shortest coupled extrasystoles and no slowing at any of the heart rates (Figs. 37 and 34). Conduction velocity in the Purkinje could not be calculated per se in this series of experiments because stimulation of the heart was carried out through an epicardial electrode, and the contribution of Purkinje conduction to the total conduction time could not be calculated. However, it is sufficient to say Purkinje conduction was relatively unaffected by acute ischemia as conduction times to the endocardial electrode located within the infarcted zone remained essentially unchanged from control values after occlusion.

Explanations for the bizarre electrical patterns that occur during acute episodes of ischemia have been proposed by many. Harris (43) and Russell et al. (84) have observed a release of potassium ions (K^+) from ischemic hearts and have suggested that resultant rise in extracellular K^+ plays an important role in the genesis of cardiac arrhythmias that occur during infarction. The electrical changes observed in myocardium shortly after occlusion of the LAD may be due in part to this increase in extracellular potassium. Ettinger et al. (31, 32), artificially raised potassium levels in the heart by infusing a potassium solution into the LAD and found electrophysiological changes similar to

those produced by coronary artery ligation. Among these were increases in transmural conduction time often with 2:1 or higher intramural block. Also, an epicardial to endocardial activation pattern was observed in the perfused region during spontaneous extrasystoles suggestive of reentrant activity. This last result differs from ours as we always observed endocardial activity preceding epicardial activity in the ischemic zone on normal and arrhythmic beats. Hill and Gettes (45) measured a rise in a extracellular K^+ that began within seconds of coronary artery occlusion and extended throughout 60 minutes of occlusion. The most rapid rise in extracellular potassium occurred within the first 5 - 15 minutes of occlusion during which time there was a delay in activation in the ischemic zone accompanied by a decrease in amplitude of bipolar electrograms. Although electrograms regained amplitude following this period the extracellular K^+ continued to rise (but not as rapidly) and conduction times to the electrode within the ischemic zone remained elevated. On the basis of this fact, and their observation that artificially raising K^+ levels to those achieved during ischemia did not produce equivalent electrophysiological changes to those seen during ischemia, Hill and Gettes concluded that K+ was not the only factor causing the electrical abnormalities seen during ischemia in the myocardium. Their view is supported by

Downar et al. (22) who found that coronary venous blood taken from a heart in which the LAD had been occluded could cause profound changes in the transmembrane potential and refractoriness in otherwise "normal" myocardial tissue. These changes could be mimicked by elevating K^+ levels in the tissue bath but only at concentrations twice those found in the venous outflow from the ischemic zone. They considered the possibility that moderately elevated potassium in combination with other chemical and/or biochemical changes occurring during ischemia produced the electrophysiological changes observed. However, it was found that the effects of ischemic blood could not be accounted for by the combination of hyperkalemia, acidosis, hypoxia, and hypoglycemia. Therefore it was postulated that some as of yet undetermined metabolic factor(s) were responsible for the depression of electrical activity in ischemic myocardium. It is interesting to note that these factors were released within the first 10 minutes of ischemia, as blood taken after 15 minutes of LAD occlusion produced the same effect as the sample collected after 7½ minutes and longer periods of ischemia of up to one hour did not produce more marked effects. Bagdonas et al. (5) used an in vivo dog model to compare the differences in cardiac electrical activity brought about by periods of ischemia vs hypoxia. These workers reported fibrillation occurred in all of their animals within the initial 5 - 13 minutes of

ischemia. During this period conduction times recorded in the His-Purkinje system remained constant but the time interval between left bundle branch and left ventricular epicardial activation increased. Conversely, hypoxia caused increases in conduction time but never fibrillation, even up to a period of 120 minutes. The arrhythmias that occurred during ischemia, but not hypoxia, were suggested as being due to accumulation of metabolites, changes in blood pH and electrolyte concentrations, and could not be accounted for by a lack of oxygen alone.

More recent work by Morena et al. (66) in the isolated porcine heart has attempted to define accurately the metabolic changes during ischemia that are responsible for the electrical changes observed. By comparing the changes produced in DC electrograms, with metabolic changes during ischemia (produced by LAD occlusion) and hypoxia (produced by perfusion of the LAD with an oxygen deficient Tyrode solution) they concluded no simple direct relationship exists between electrophysiological changes and the metabolic state. Ischemia and hypoxia both elevated tissue content of creatine phosphate and ATP but produced different electrical changes. This group reported few incidences of arrhythmias during hypoxia with LAD perfusion whereas LAD occlusion produced fibrillation in 50% of the hearts within 3-8 minutes. They attributed this difference to inhomogeneity of resting membrane potentials and

refractoriness shown to exist among ischemic cells during the latter but not the former. Thus it was suggested the lack of oxygen and substrate, plus the lack of washout from the infarcted area, are necessary cofactors in the genesis of arrhythmias during acute ischemia.

Although these results provide explanations for the arrhythmias seen during the initial phase of acute ischemia (i.e. the first 10-15 minutes) they cannot explain the recovery of electrograms within the ischemic zone reported here and by others (92, 45, 67), nor do they account for the remission of arrhythmias we observed after this initial ischemic period. Murdock et al. (67) noted a similar quiescent arrhythmia free period following the initial 10 minutes of ischemia, but unlike our results they reported a progressive loss of electrical activity from the ischemic zone after this 10 minute period.

Corr et al. (17) have measured cyclic AMP levels during acute ischemia in the feline heart. They too observed an arrhythmic phase beginning within minutes of occlusion of the LAD and subsiding within thirty minutes of occlusion. During this time there was a build up of cyclic AMP in the ischemic zone which was significantly greater than that in the non-ischemic zone. The levels of cyclic AMP were shown to fall off concurrently with the dissappearance of arrhythmias. In the hearts that fibrillated cyclic AMP levels were found to be higher than those in non-fibrilla-

ting hearts. It was postulated that "cyclic AMP or processes responsible for its accumulation such as regionally enhanced adrenergic activity in ischemic zones, contribute to the maintenance of ventricular arrhythmias after myocardial ischemia". Thus, this is the only bit of evidence to suggest a direct correlation between a biochemical factor and the disparate electrical events that occur during ischemia.

The apparent resistance of the Purkinje system to ischemia reported here is in agreement with the work of others (5, 19, 20, 92) and may be attributed to a number of factors. a) The Purkinje cells within the ischemic zone are bathed by cavity blood and are not as dependent on coronary blood flow for oxygen as the myocardial cells and b) Purkinje cells unlike myocardial cells, are not working cells, thus require less oxygen and are better able to cope with an environment of low oxygen.

2. Effect of lidocaine on conduction: Preferential slowing of conduction in ischemic myocardium.

As stated above lidocaine had little effect on conduction in the normal heart. Only at high doses of 2.5 to 10.0 mg/kg did lidocaine increase the conduction times of extrasystoles, and no effect of the drug was observed for non-premature beats. However in the acutely ischemic heart

lidocaine had a much more pronounced effect. Transmural conduction time in the ischemic zone was increased by even the lowest dose of 1.25 mg/kg and this slowing of conduction was observed for non-premature beats during the basic drive interval of 800 ms (Fig. 35B). This represents a preferential slowing of conduction in ischemic tissue by lidocaine, an observation also made by Kupersmith et al. (56). This preferential action of the drug was limited to the myocardium, as endocardial (Purkinje) conduction was changed to the same extent in both normal and ischemic hearts by the drug. Because of this preferential slowing of conduction in ischemic myocardium, attempts were made to try and correlate the ischemia-induced increases in TMCT by 30 minutes ischemia to the further changes in TMCT produced by lidocaine given after the 30 minute mark. However no adequate correlation was found to exist between the effects of ischemia and the effects of the drug on myocardial conduction.

Lidocaine not only had a greater effect in ischemic myocardium but appeared to have an additional mode of action in ischemic over that in the normal heart. The effects on lidocaine on TMCT in the ischemic zone were 3 fold.

a) The drug increased TMCT during the basic drive interval of 800 ms (Fig. 34B) and extrasystoles of long coupling intervals (Fig. 37B). This action is different from its action in normal myocardium where it only slowed

conduction of extrasystoles introduced early in diastole. This result indicates lidocaine may change the steady-state relationship between resting membrane potential and Vmax in damaged muscle fibers. Why the drug should have this effect in ischemic but not normal cardiac muscle has led to much speculation. It is known from in vitro studies that lidocaine has a depressant action on Vmax at lower resting membrane potentials (more positive) (50, 73, 85) and does not decrease Vmax at normal membrane potentials. Also it is known that K+ is released from the ischemic myocardium (43, 45, 84) in sufficiently high concentrations to cause a loss in resting membrane potential (85). Therefore it seems reasonable to assume that lidocaine's preferential action in ischemic vs normal myocardium is due to the depolarization produced by the increased extracellular K^+ found there. Saito et al. (85) have explored this possibility and have shown in dogs that lidocaine has little effect on cardiac conduction under control conditions (K^+ 2.6 - 5.4 mM), but increases ventricular conduction time when plasma K^+ levels are raised to 8.0 mM or higher. Hill and Gettes (45) found K^+ levels to reach upwards to 15 mM during acute ischemia; Downar et al. (22) likewise found levels of K+ to range from 4.6 to 16.2 mM in the venous effluent from the ischemic myocardium of the pig. Similar results were found by Ettinger et al. (32) who infused an isotonic KCl solution into the LAD of the dog. They found lidocaine caused

prolongation of epicardial activation during normal sinus rhythm in the perfused zone and concurrently increased the survival rate (by preventing ventricular fibrillation) from 9 to 75%. Thus, both the studies of Saito and Ettinger indicate lidocaine's action in an environment of high extracellular K+ to be due in part to its influence on the steady-state, voltage dependence of Vmax, as increases in conduction time were observed during normal sinus rhythm i.e. non premature beats.

b) Lidocaine also caused an interval related slowing of TMCT because the greatest slowing of conduction by the drug occurred at the shortest-coupled (most premature) extrasystoles as shown in Fig. 38B, converting the dip in TMCT to an increase. This effect was also seen in the normal hearts (Fig. 15), but much more pronounced in the ischemic hearts.

Saito et al. (85) have also shown lidocaine to cause a time dependent slowing of conduction in the canine heart, in addition to its steady-state slowing, during hyperkalemia. They demonstrated lidocaine slowed conduction of extrasystoles which were introduced after the end of the T-wave of the ECG. This time-dependent effect of lidocaine has been attributed to the drugs' ability to increase the time constant of recovery of reactivation of the fast sodium channel (14, 85, 109) as described above, so that the sodium channel has not recovered from inactivation by the time the

membrane has returned to normal resting potential i.e. remains inactivated in the diastolic period.

c) Lidocaine also caused a rate-related or frequency dependent slowing of TMCT. Under control conditions TMCT was unchanged at all drive rates and increased slightly during fast drive rates following 30 minutes of ischemia. However lidocaine caused a dose-dependent increase in TMCT in the ischemic zone which was greatest of the highest rates (shortest drive interval, Fig. 35B). It was not determined whether lidocaine had similar rate-related actions in normal myocardium although it has been demonstrated by Tritthart et al. (103) and Courtney (18) in "in vitro" myocardial fibers and by Carmeliet and Zaman (16) in the isolated guine-pig heart. It might be anticipated that the rate-related effect of lidocaine would be less in normal than ischemic myocardium, as was its interval-rated action, because Hondeghem and Katzung (50) have shown the rate-related effects of lidocaine are accentuated by depolarization of the cardiac membrane and attenuated by hyperpolarization.

Tritthart et al. (103) have suggested the rate-related action of lidocaine, like its interval-related action is due to the drug's ability to increase the time constant of recovery of the sodium influx system. In their words "this means that with higher frequencies - as the intervals between action potential becomes smaller - the upstroke velocity is reduced more and more".

Thus in ischemic myocardium, lidocaine causes greater slowing of conduction during early premature beats and fast heart rates. This may explain its antiarrhythmic actions in infarcted hearts where it is believed that arrhythmias originate from sustained electrical activity in the ischemic myocardium which re-enters into normal tissue producing premature ventricular contractions. Lidocaine's "arrhythmocidal" action during the early phases of ischemia may be due to its ability to cause sufficient slowing on conduction in the ischemic myocardium to prevent re-entrant beats from emerging into normal tissue.

The fact that lidocaine causes preferential slowing of conduction in ischemic myocardium can be explained in part by the increased extracellular K+ and loss of membrane potential found in infarcted tissue as discussed above. However, there are other biochemical changes associated with ischemia that may modify the manner in which the lidocaine molecule interacts with the cardiac membrane. One of these is a change in pH. Neely et al. (72) have found the pH in the ischemic zone to be lower than surrounding normal tissue because of lactic acidosis. Lidocaine is a weak base with a pKa value of 7.88, and therefore slight changes in tissue pH would alter the ratio of charged to uncharged forms of the drug. Acidic conditions would favour the charged form of lidocaine, causing protonation of the nitrogen atoms in the molecule. The observations of

Glicklich and Hoffman (36), as well as Narahashi et al. (70), have indicated it is the charged form of lidocaine which acts at an intracellular site to block the fast sodium channel in cardiac Purkinje cells and nerve cells respectively. However, Ritchie and Greengard (80) showed lidocaine to cause greater conduction block in nerves in a basic pH environment. Therefore, it has been suggested that local anesthetics cross the cell membrane in the uncharged form and act to block the Na+ channel in the charged form. These experiments were all done on normal tissue in which diffusion of the drug through the cell membrane may have been the limiting factor. It is well known that ischemia produces damage of the cardiac cell membrane so that the cells become leaky and permeable to enzymes and ions. It is reasonable to assume that under these conditions lidocaine in the charged form could readily transverse the cell wall, and thus the greater the ratio of charged/uncharged form of the drug, the greater would be the drug's effect. Recent work by Grant et al. (37) has confirmed the importance of pH in determining lidocaine's effect to increase the recovery kinetics of the fast sodium channel in ventricular myocardial cells. They showed the recovery time constant of Vmax was increased when extracellular pH was lowered, and was further increased by addition of lidocaine. Similarly Nattel et al. (71) suggest extracellular pH may modify the effects of antiarrhythmic drugs. They demonstrated in

canine Purkinje fibers, lidocaine caused a greater reduction of Vmax at pH 6.9 than at pH 7.3, and believe it was due to a reduction in resting membrane potential by lidocaine at the lower pH.

Future work:

The results contained in this thesis are, hopefully, a contribution to our knowledge of the characteristics of ventricular conduction, under normal and pathological conditions, and how it is altered by antiarrhythmic drugs. They raise certain questions which will require further work to elucidate.

Firstly, the reason for the decrease observed in TMCT during early extrasystoles is not clear. It was proposed that this "apparent" supernormal myocardial conduction was due to a mechanical phenomenon associated with the contraction of the heart and/or and electrical phenomenon involving a change in conduction pathway during extrasystoles. Previously, blood pressure tracings made from the femoral artery were used to assess the mechanical state of the heart, i.e. whether it was in a contracted state or in diastole. However, a more direct measure of the mechanical state of the heart during early extrasystoles could be made in future experiments by monitoring the contraction of the heart either by the use of strain gauge sewn to the surface of the heart or by an echocardiogram

recorded simultaneous with the electrograms. This would allow one to determine whether or not the heart was in a contracted state, during the propagation of early extrasystoles, thus having a different wall thickness than during extrasystoles introduced in diastole. Also, it was reported that disopyramide increases the functional refractory period of the ventricle and concurrently changes the coupling interval at which the decrease in TMCT occurs. This suggests the decrease in TMCT may be associated with the electrical spread of the cardiac impulse. Future work might envolve testing the effects of other drugs, known to change the FRP of the ventricle, on the occurrance of the decrease in TMCT and/or the coupling interval at which it occurs.

Under normal circumstances, the Purkinje system serves as a protective mechanism in the ventricles; i.e., due to the long refractory period of the Purkinje system extrasystoles are slowed sufficiently so that the extrasystole interval invading the myocardium falls outside the refractory period of the myocardium (the gate theory (68)). This ensures that no slowed conduction and/or reentrant circuits can occur in the myocardium. This gating phenomenon of the Purkinje system was evident in our experiments by the fact that all the increase in conduction time observed during extrasystoles was observed in endocardial conduction time, myocardial or transmural

conduction time remained constant (or decreased) during extrasystoles. Myerburg et al. (68), from in vitro experiments, have suggested that the gating function of the Purkinje system may be lost at high heart rates. In agreement with this suggestion are the results of Moore et al. (65) which demonstrate differences in FRP and action potential duration normally evident between Purkinje and myocardial tissue are lost at high drive rates. Future in vivo work might test this hypothesis by measuring endocardial and transmural conduction times of extrasystoles during ventricular pacing at a slow drive rate and then during drive rates of increasing frequency. If the gate function of the Purkinje system breaks down at high drive rates one should observe an increase in transmural as well as endocardial conduction time during early extrasystoles at high heart rates.

There is also much work to be completed in the study of antiarrhythmic drugs in ischemic tissue. We have shown, as have others (56), that lidocaine has a much more depressant effect in ischemic than normal tissue. Preliminary experiments have indicated that the same may be true for disopyramide and more experiments are necessary to confirm these results.

Corr et al. have suggested cyclic-AMP may be one of the causative factors in the genesis of arrhythmias in ischemic hearts. Future research into the mechanisms of arrhythmias

associated with myocardial infarction might involve infusing dibuteryl cyclic-AMP into a coronary artery and observing the changes, if any, in the conduction characteristics of the myocardium in the affected area. Alternately, one could treat a series of animals with theophylline, a phosphodiesterase inhibitor, to prevent the breakdown of cyclic-AMP before occluding a coronary artery and compare the incidence and severity of arrhythmias in this group of animals with those in a non-treated group.

Finally, one might look at the changes induced in the electrical activity in the myocardium following anoxia and compare to those produced by ischemia. Several workers (5, 66) have reported that anoxia seldom results in severe arrhythmias and fibrillation, as is so often the case with ischemia. A greater understanding of the electrical events associated with anoxia might provide some clues to the treatment of ischemia and the control of arrhythmias associated with myocardial infarction.

SECTION V

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SECTION VI

APPENDIX

List of Computer Program "CARDOA"

```
CARDOA                  00:32:00

 10 REM .... PROGRAM CARDOA.BAS
 15 REM .... INTENDED TO RUN IN PSIMON
 20 REM .... SAMPLE FROM CH1 & CH2 & CH3 THEN PLOT
 30 DIM #1,X(4096)
 40 OPEN "SISTOR" FOR OUTPUT AS FILE #1
 50 L=4096
 60 CALL BUFF(L)
 70 CALL CLOK(4,4)
 80 CALL SAM(1,1,3,L/3)
 82 K=0
 85 CALL 'DIS'(1,L,K)
 90 IF K=66 THEN 80 \ REM          B FOR BAD EVENT
 95 IF K=69 THEN 560 \ REM         E FOR END
100 FOR J=1 TO L/3
110 CALL GET(J,P)
120 X(J)=P
130 NEXT J
140 FOR J=L/3+1 TO 2*L/3
150 CALL GET(J,P)
160 X(J)=P
170 NEXT J
180 FOR J=2*L/3+1 TO L
190 CALL GET(J,P)
200 X(J)=P
210 NEXT J
240 PRINT  \ PRINT "ENTER THE TWO LABELS FOR DATA STRIPS"
250 FOR T=0 TO 1 \ INPUT D$(T) \ NEXT T
270 CALL 'PLT'(0%,0%,-3%)
280 C=3100
283 U$="LC4779 CNTRL C=3100"
284 Q%=LEN(U$)
284 CALL 'CHR'(0%,1860%,8%,U$,0,Q%)
288 V$="S-S'  P-P'  M-M'(EN)  M-M'(EP)"
289 B%=LEN(V$)
290 CALL 'CHR'(0%,1660%,8%,V$,0,B%)
293 Z$="S'-P'   S'-M'   P'-M'"
294 B%=LEN(Z$)
296 CALL 'CHR'(0%,1460%,8%,Z$,0,B%)
300 E=450
305 D1%=X(1)*C-E
310 CALL 'PLT'(0%,D1%,3%)
330 FOR A=1 TO L/3
335 A%=A
340 K%=X(A)*C-E
345 A%=A%*3
350 CALL 'PLT'(A%,K%,2%)
360 NEXT A
365 D1%=X(L/3+1)*C
370 F=1000
380 CALL 'PLT'(0%,D1%,3%)
390 FOR A=L/3+1 TO 2*L/3
400 K%=X(A)*C-F
410 A%=A-L/3
415 A%=A%*3
420 CALL 'PLT'(A%,K%,2%)
430 NEXT A
435 G=1050
440 D1%=X(2*L/3+1)*C-G
450 CALL 'PLT'(0%,D1%,3%)
460 FOR A=2*L/3+300 TO 2*L/3+1030
470 K%=X(A)*C-G
480 A%=A-2*L/3
490 A%=A%*3
500 CALL 'PLT'(A%,K%,2%)
510 NEXT A
540 A2%=A%+2013%
548 K2%=0%
550 CALL 'PLT'(A2%,K%,-3%)
560 CLOSE #1
570 PRINT  \ PRINT
580 END

READY
```

ANOVA results on endocardial ($S'M'_{en}$) and transmural (TMCT) conduction time of extrasystoles in the left ventricle- effect of ischemia and lidocaine.

List of variables:

V1 = animal number (1 to 8)

V2 = coupling interval of extrasystoles (1 to 8) 1 = 400 ms
2 = 350 ms
3 = 300 ms
4 = 280 ms
5 = 260 ms
6 = 240 ms
7 = 220 ms
8 = 200 ms

V3 = treatment (1 to 6). 1 = control
2 = occlusion 30 min
3 = occlusion 45 min, lidocaine 1.25 mg/kg
4 = occlusion 60 min, lidocaine 2.5 mg/kg
5 = occlusion 75 min, lidocaine 5.0 mg/kg
6 = occlusion 90 min, lidocaine 10.0 mg/kg

V5 = endocardial conduction time, $S'M'_{en}$

V6 = transmural conduction time, TMCT

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                        THE SUBFILES ARE..
                                           N OF
                        NAME              CASES
                        HEARTJ             384

              MANOVA          V4 BY V1(1,8),V2(1,8),V3(1,6)/
                              DESIGN=CONSTANT,V1,V2,V1 BY V2,V3,V1 BY V3,V2 BY V3/
              OPTION          4,6
0533000 WORDS NEEDED TO READ DATA IN MANOVA.
227000 WORDS MAXIMUM NEEDED FOR MANOVA EXECUTION.

            OPTION - 1
            IGNORE MISSING VALUE INDICATORS
            (NO MISSING VALUES DEFINED...OPTION 1 WAS FORCED)

            OPTION - 4
            OMIT CONSTANT TERM FROM DESIGNS

            OPTION - 6
            PRINT NEGATIVE SUM OF PARAMETERS FOR EACH EFFECT


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                                                                                  81/07/22.    16.42.36.    PAGE  2
FILE   HEARTJ   (CREATION DATE =  81/07/21.)
* * * * * * * * * * * * * * * * * * * * A N A L Y S I S   O F   V A R I A N C E * * * * * * * * * * * * * * * * * *

     384 OBSERVATIONS ACCEPTED
       0 OBSERVATIONS REJECTED BECAUSE OF OUT-OF-RANGE FACTOR VALUES
       0 OBSERVATIONS REJECTED BECAUSE OF MISSING DATA
     384 NON-EMPTY CELLS

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CORRESPONDENCE BETWEEN NAMED EFFECTS AND DESIGN PARAMETERS

 STARTING  ENDING
  COLUMN   COLUMN    EFFECT NAME

     1        1      CONSTANT
     2        8      V1
     9       15      V2
    16       64      V1 BY V2
    65       69      V3
    70      104      V1 BY V3
   105      139      V2 BY V3

---------------------------------------------------------------------------------------------------------
```

11	-3.92708	.72799	-5.39441	.00000
12	-4.31771	.72799	-5.93049	.00000
13	-2.50521	.72799	-3.44126	.00088
14	.71354	.72799	.98015	.32798
15	1.77604	.72799	2.43965	.01541
16	-1.57292	.72799	-2.16063	.03169
17	1.16146	.72799	1.59543	.11191
18	.84896	.72799	1.16617	.24488
19	-.18229	.72799	-.25040	.80248
20	1.13021	.72799	1.55250	.12183
21	2.34375	.72799	3.21948	.00166
22	-.29688	.72799	-.40780	.68378
23	1.64062	.72799	2.25363	.02510
24	.48437	.72799	.66536	.50645
25	-1.57812	.72799	-2.16776	.03114
26	3.05208	.72799	4.19247	.00004
27	.53646	.72799	.73690	.46189
28	.97396	.72799	1.33787	.18216
29	.31771	.72799	.43642	.66292
30	-1.11979	.72799	-1.53819	.12529
31	3.38542	.72799	4.65035	.00001
32	-1.13021	.72799	-1.55250	.12183
33	-1.06771	.72799	-1.46665	.14375
34	-.47396	.72799	-.65105	.51562
35	.08854	.72799	.12162	.90330
36	-4.23958	.72799	-5.82367	.00000

81/07/22. 16.42.36. PAGE 6

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ESTIMATES FOR V4 TIMEN
(CONT.)

V2 BY V3

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	2.73958	.72799	3.76321	.00021
2	-.65104	.72799	-.89430	.37204
3	.53646	.72799	.73690	.46189
4	.25521	.72799	.35057	.72622
5	.06771	.72799	.09301	.92597
6	2.05208	.72799	2.81883	.00521
7	-.83854	.72799	-1.15186	.25050
8	.09896	.72799	.13593	.89199
9	.44271	.72799	.60812	.54367
10	.13021	.72799	.17886	.85820
11	1.23958	.72799	1.70274	.08988
12	-1.77604	.72799	-2.43965	.01541
13	-.46354	.72799	-.63674	.52489
14	.38021	.72799	.52227	.60195
15	.56771	.72799	.77983	.43624
16	.48958	.72799	.67251	.50189
17	-1.65139	.72799	-2.26749	.02420
18	-.33854	.72799	-.46509	.64232
19	.25521	.72799	.35057	.72622
20	-.05729	.72799	-.07870	.93734
21	-.69792	.72799	-.95869	.33869
22	-1.71354	.72799	-2.35379	.01937
23	-.65104	.72799	-.89430	.37204
24	.31771	.72799	.43642	.66292
25	1.00521	.72799	1.38080	.16860
26	-1.84375	.72799	-2.53265	.01195
27	-.48438	.72799	-.66536	.50645
28	-.17187	.72799	-.23609	.81356
29	.17188	.72799	.23609	.81356
30	.35938	.72799	.49365	.62199
31	-3.03125	.72799	-4.16386	.00004
32	2.07812	.72799	2.85460	.00468
33	-.35937	.72799	-.49365	.62199
34	-.51562	.72799	-.70828	.47944
35	.04688	.72799	.06439	.94871
36	2.01042	.72799	2.76159	.00619

TMCT

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                        NAME          CASES

                        HEARTJ          384

            MANOVA          V5 BY V1(1,8),V2(1,8),V3(1,6)/
                            DESIGN=CONSTANT,V1,V2,V1 BY V2,V3,V1 BY V3,V2 BY V3/
            OPTION          4,6
053300B WORDS NEEDED TO READ DATA IN MANOVA.
227000B WORDS MAXIMUM NEEDED FOR MANOVA EXECUTION.

        OPTION - 1
        IGNORE MISSING VALUE INDICATORS
        (NO MISSING VALUES DEFINED...OPTION 1 WAS FORCED)

        OPTION - 4
        OMIT CONSTANT TERM FROM DESIGNS

        OPTION - 6
        PRINT NEGATIVE SUM OF PARAMETERS FOR EACH EFFECT

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

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FILE HEARTJ   (CREATION DATE =  81/07/21.)
* * * * * * * * * * * * * * * * * * * * A N A L Y S I S   O F   V A R I A N C E * * * * * * * * * * * * * * * * * * * * *

     384 OBSERVATIONS ACCEPTED
       0 OBSERVATIONS REJECTED BECAUSE OF OUT-OF-RANGE FACTOR VALUES
       0 OBSERVATIONS REJECTED BECAUSE OF MISSING DATA
     384 NON-EMPTY CELLS

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

CORRESPONDENCE BETWEEN NAMED EFFECTS AND DESIGN PARAMETERS

 STARTING   ENDING
  COLUMN    COLUMN    EFFECT NAME

      1         1     CONSTANT
      2         8     V1
      9        15     V2
     16        64     V1 BY V2
     65        69     V3
     70       104     V1 BY V3
    105       139     V2 BY V3

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ANALYSIS OF VARIANCE

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGNIF. OF F
RESIDUAL	1414.06510	245	5.76353		
CONSTANT	273013.33594	1	273013.33594	47369.11004	.00001
V1	38251.93490	7	5464.56213	948.12747	.00001
V2	255.18490	7	36.45499	6.32511	.00001
V1 BY V2	1042.04427	49	21.26621	3.68979	.00001
V3	19896.52344	5	3979.70469	690.49766	.00001
V1 BY V3	15629.08073	35	446.54516	77.47771	.00001
V2 BY V3	1076.83073	35	30.82374	5.34806	.00001

ESTIMATES FOR V5 TMCT

CONSTANT

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	26.66406	.12251	217.64446	.00000

V1

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	4.66927	.32414	14.40527	.00000
2	-11.08073	.32414	-34.18540	.00000
3	1.00260	.32414	3.09316	.00221
4	1.66927	.32414	5.14980	.00000
5	22.66927	.32414	69.93746	.00000
6	-6.66406	.32414	-20.55944	.00000
7	-8.87240	.32414	-27.37242	.00000
8	-3.39323	.32414	-10.46852	.00000

V2

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	-.91406	.32414	-2.81999	.00520
2	-.33073	.32414	-1.02044	.30857
3	.46094	.32414	1.42205	.15628
4	.87760	.32414	2.70752	.00726
5	.83594	.32414	2.57897	.01049
6	.56510	.32414	1.74342	.08256
7	.04427	.32414	.13658	.89147
8	-1.53906	.32414	-4.74819	.00000

ANALYSIS OF VARIANCE

ESTIMATES FOR V5 TMCT (CONT.)

V1 BY V2

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	1.58073	.85758	1.84324	.06650
2	.66406	.85758	.77434	.43946
3	.37240	.85758	.43424	.66450

4	.28906	.85758	.33707	.73636
5	.16406	.85758	.19131	.84844
6	-1.39844	.85758	-1.63067	.10424
7	-1.04427	.85758	-1.21769	.22451
8	2.33073	.85758	2.71778	.00704
9	1.74740	.85758	2.03758	.04267
10	.62240	.85758	.72575	.46888
11	.70573	.85758	.82293	.41135
12	.08073	.85758	.09414	.92508
13	-1.14844	.85758	-1.33915	.18176
14	-.79427	.85758	-.92617	.35527
15	-2.25260	.85758	-2.62669	.00917
16	-1.16927	.85758	-1.36345	.17394
17	.70573	.85758	.82293	.41135
18	.12240	.85758	.14272	.88663
19	.99740	.85758	1.16303	.24595
20	1.93490	.85758	2.25622	.02494
21	.78906	.85758	.92010	.35843
22	1.74740	.85758	2.03758	.04267
23	1.83073	.85758	2.13475	.03377
24	2.20573	.85758	2.57203	.01070
25	1.78906	.85758	2.08617	.03800
26	-.16927	.85758	-.19738	.84369
27	-.39844	.85758	-.46460	.64263
28	-2.37760	.85758	-2.77244	.00599
29	-2.91927	.85758	-3.40406	.00078
30	-2.50260	.85758	-2.91820	.00385
31	-2.29427	.85758	-2.67527	.00797
32	-1.87760	.85758	-2.18941	.02951
33	-.83594	.85758	-.97476	.33064
34	1.76823	.85758	2.06187	.04027
35	2.95573	.85758	3.44656	.00067
36	.74740	.85758	.87151	.38433
37	.33073	.85758	.38565	.70009
38	.03906	.85758	.04555	.96371
39	.12240	.85758	.14272	.88663
40	.16406	.85758	.19131	.84844
41	-.23177	.85758	-.27026	.78719
42	-.71094	.85758	-.82900	.40791
43	-.37760	.85758	-.44031	.66010
44	.03906	.85758	.04555	.96371
45	-.75260	.85758	-.87759	.38103
46	-1.50260	.85758	-1.75214	.08100
47	.03906	.85758	.04555	.96371
48	-.52344	.85758	-.61036	.54219
49	.66406	.85758	.77434	.43948
50	-2.26823	.85758	-2.64491	.00870

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* A N A L Y S I S O F V A R I A N C E *

ESTIMATES FOR V5 TACT
(CONT.)

V3

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	-11.46094	.27395	-41.83661	.00000
2	-4.27344	.27395	-15.59961	.00000
3	-1.38281	.27395	-5.04777	.00000
4	.69531	.27395	2.53814	.01176
5	4.74219	.27395	17.31072	.00000
6	11.67969	.27395	42.63512	.00000

V1 BY V3

D. F.	COEFF.	STANDARD ERROR	T-VALUE	SIGNIF. OF T
1	-11.37240	.72479	-15.69059	.00000
2	.94010	.72479	1.29707	.19583
3	1.04948	.72479	1.44798	.14890
4	.84635	.72479	1.16772	.24405
5	4.42448	.72479	6.10449	.00000
6	5.37760	.72479	7.41953	.00000
7	1.69010	.72479	2.33185	.02052
8	2.54948	.72479	3.51754	.00052
9	-.02865	.72479	-.03952	.96851
10	-1.95052	.72479	-2.69115	.00761