# Coupling Interval-Related Effects of Class I Antiarrhythmic Drugs, Mexiletine, Cibenzoline and Disopyramide, on Ventricular Activation in Canine Myocardial Infarction

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ABSTRACT — Time-dependent inhibition of sodium channels by class I antiarrhythmic drugs has been observed in isolated cardiac muscles or cells. We examined coupling interval-related effects of class I antiarrhythmic drugs, mexiletine, cibenzoline and disopyramide, on ventricular activation in canine infarcted myocardium. A ventricular stimulation with various coupling intervals was applied to the right ventricle, and activation delays (time intervals between the initiation of a deflection and the final rapid deflection of a bipolar electrocardiogram) of infarcted and normal zones were measured. The premature stimulation produced a delayed activation and in some animals, caused reentrant beats. Mexiletine (3 and 10 mg/kg), cibenzoline (1 and 4 mg/kg) and disopyramide (1 and 4 mg/kg) further enhanced or blocked the delayed activation. The effects of these drugs were more marked at shorter coupling intervals, although cibenzoline and disopyramide showed significant effects also at long coupling intervals. The effect of these drugs on the activation in the normal zone was less than that in the infarcted zone. In conclusion, mexiletine, cibenzoline and disopyramide showed a coupling interval-related depression of delayed activation in infarcted myocardium, which may be a reflection of their time-dependent inhibition of sodium channels.

Several class I antiarrhythmic drugs are now available for the treatment of ventricular as well as atrial arrhythmias. These drugs are classified into three groups, i.e., Ia, Ib and Ic, according to their effects on action potential duration (1, 2). These drugs are also classified into three groups on the basis of a kinetics of their interactions with cardiac sodium channels, i.e., fast, intermediate and slow kinetic drugs (2, 3–8). Many investigators have examined the effects of these drugs on the sodium channels in isolated cardiac muscles or myocardial cells. However, their effects on intraventricular conduction have not been fully examined in myocardial infarction models. Previously we studied the effects of lidocaine, bepridil and SUN-1165 on intraventricular conduction in a canine model of myocardial infarction (9, 10). In the present study, we investigated coupling interval-related effects of class I antiarrhythmic drugs, mexiletine, cibenzoline and disopyramide (1, 2, 11–13), a fast, an intermediate and a slow kinetic drug (2, 3, 7, 8), respectively, on ventricular activation in a canine model of myocardial infarction.

## MATERIALS AND METHODS

*Preparation of the myocardial infarction model*

Mongrel dogs weighing 8.5 to 12.0 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). The animal was intubated and ventilated with room air using a positive pressure respirator. A left thoracotomy was performed in the fourth intercostal space, and the heart was exposed. After opening the pericardium, the left anterior descending coronary artery (LAD) was ligated according to Harris (14) and then several branches of LAD were also ligated. The chest was closed after the complete ligation, and routine postoperative care was performed including prophylactic antibiotic therapy, i.e., intramuscular administration of ceftizoxime everyday, during post-infarction convalescence. The animals were studied five to seven days after LAD ligation.

*Measurement of the ventricular activation delay*

Thirty animals were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Ventilation was performed as described above. The body temperature of the animal was maintained at 35–37°C. A left thoracotomy was performed and the pericardium was opened. After the heart was placed in a pericardial cradle, bipolar stimulating electrodes were sutured on the left atrial appendage and the right ventricle for atrial pacing and applying a vetricular stimulation, respectively. Several bipolar electrodes (the distance of the two polars was 2 mm, and the length of each was 5 mm) were also sutured on the epicardial surface of the left or the right ventricule for recording ventricular excitation: One in the normal and two in the infarct zone. The bipolar electrogram was amplified with a filter frequency between 40 and 1000 Hz. The sinus node was destroyed by the injection of 0.1 ml formalin, and atrial pacing at a cycle length between 400 and 500 msec was performed and the rate was fixed throughout the experiment. For the electrical stimulation of the right ventricle, a stimulus triggered by a preceeding excitation of the normal zone was delivered as a 5-msec rectangular pulse with stimulus strength of the triple diastolic threshold using an electronic stimulator (SEN-7203, Nihon Kohden, Tokyo, Japan). To study the effect of the drug on ventricular activation, activation delay of the stimulation-induced ventricular exciatation was measured in both normal and infarcted zones of the ventricle. The time interval between the initiation of a deflection and the final rapid deflection of the epicardial bipolar electrocardiograms was measured, and this value was defined as the activation delay. In the infarcted zone, the measurement was performed in either of two electrocardiograms obtained in the infarcted zone. The coupling interval of the ventricular stimulation was changed between 150 and 1000 msec. When further longer coupling intervals than the basic cycle length was applied, atrial pacing was interrupted. Lead-II ECG, femoral arterial pressure and the epicardial bipolar electrocardiograms were recorded on a 8-channel polygraphic recorder (Nihon Kohden, Tokyo, Japan) at a paper speed of 100 mm/sec.

*Drug administration*

After stabilization of about one hour, control measurements were obtained, and then the drug was administered intravenously at 7-min intervals in cumulative dosages of 3 and 10 mg/kg of mexiletine, 1 and 4 mg/kg of cibenzoline and 1 and 4 mg/kg of disopyramide. The lower dose of each drug was injected within one minute, and the higher dose was injected within two minutes. Five to seven minutes after each administration, the measurements were repeated. In each animal, the effect of one drug was examined.

*Determination of the myocardial infarction size*

Six animals used for the study of ventricular activation were sacrificed by the injection of a pentobarbital overdose at the end of the experiment. The heart was rapidly removed and the ventricle sectioned into transverse rings with 1.0-mm thickness from the apex to the base. The tissue slices were washed with cold saline and then incubated in a phosphate-buf-

fered solution of triphenyltetrazolium at 38°C for 20 min. The incubation produced a bright red coloration in the noninfarcted areas, whereas the infarcted areas remained unstained (15, 16). The areas of the ventricle and infarction were quantified by weighing.

*Statistical analysis*

All data were expressed as arithmetic means ± S.E.M. Comparison between the control and postdrug values of activation delay were performed by analysis of variance followed by Dunnett's test for multiple comparison. The criterion for statistical significance was $P < 0.05$.

*Drugs*

The following drugs were used: mexiletine hydrochloride (Boehringer Tokyo, Japan), cibenzoline succinate (Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan), and disopyramide phosphate (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan). The drugs were dissolved in saline to the appropriate concentration.

RESULTS

*Effects of mexiletine, cibenzoline and disopyramide on the activation delay*

Typical electrocardiograms recorded from normal and infarcted zones are shown in Fig. 1 (control). During atrial pacing at a cycle length of 400 msec, the electrocardiogram recorded from the normal zone consisted of biphasic deflections with a duration of less than 30 msec, whereas the electrocardiogram recorded from the infarcted zone consisted of fractionated potentials, suggesting that the activation in the infarcted zone was delayed. The delayed activation (downward arrow) was further delayed in the premature excitation induced by the ventricular stimulation (upward arrow). The premature stimulation produced a seriously delayed activation, resulting in a reentrant beat in eleven of thirty animals examined.

A typical effect of mexiletine is shown in Fig. 2. Mexiletine at 3 mg/kg slightly pro-

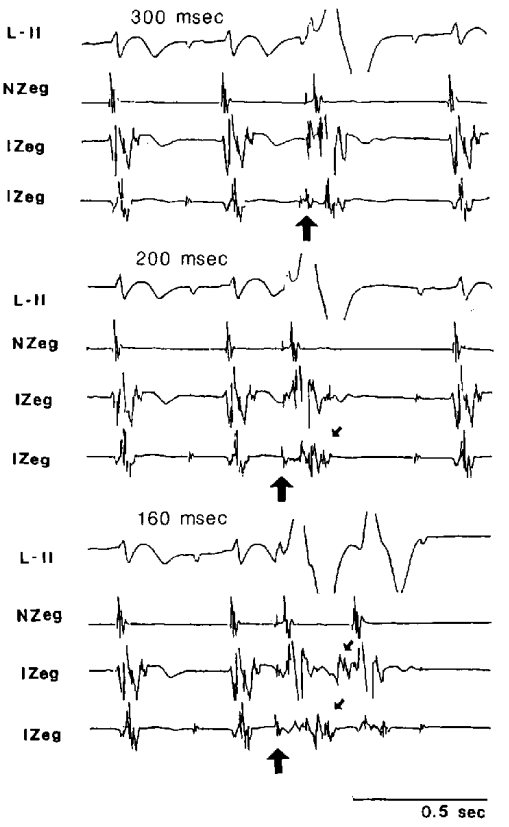


**Fig. 1.** Bipolar electrocardiograms of premature stimulation-induced excitation with coupling intervals of 300, 200 and 160 msec recorded from the normal (NZeg) and the infarcted zone (IZeg) in canine myocardial infarction. L-II: standard limb lead II. The upward and the downward arrows indicate the premature stimulations and the delayed activations, respectively. Basic cycle length: 400 msec.

longed the activation delay of the premature excitation in the infarcted zone. At 10 mg/kg, mexiletine markedly prolonged the activation delay both at the basic cycle length of 450 msec and following a premature excitation in the infarcted zone, and the effect was greater in the premature excitation. The effect on the activation delay of the premature excitation in the normal zone was small. Figure 3 shows the effect of mexiletine on the delayed activation with prolongation of the coupling interval.

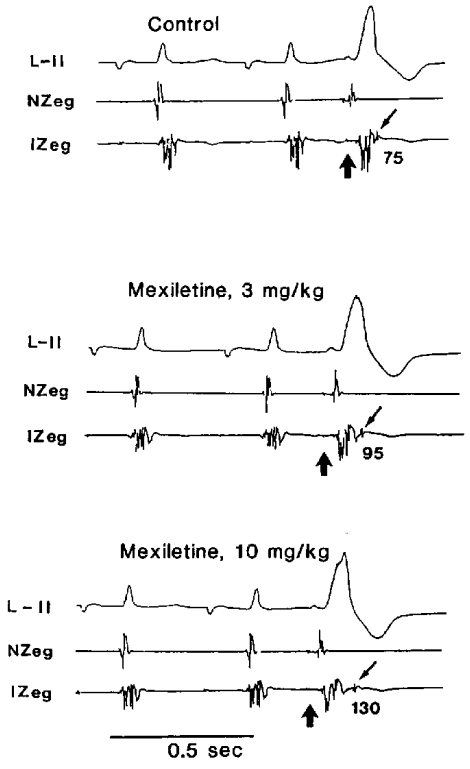


**Fig. 2.** Effect of mexiletine on the ventricular activation in the dog heart with myocardial infarction. L-II: standard limb lead II; NZeg, IZeg: electrocardiograms of normal and infarcted zones. The upward and the downward arrows indicate the premature stimulations and the delayed activations, respectively. Basic cycle length: 450 msec. Coupling interval of the premature stimulation: 200 msec. The numbers under IZeg are the activation delay (msec).

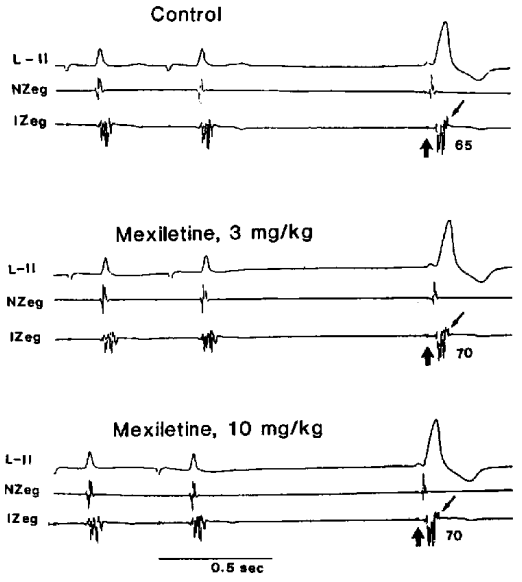


**Fig. 3.** Effect of mexiletine on the ventricular activation at a prolonged coupling interval of 1000 msec in the dog heart with myocardial infarction. L-II: standard limb lead II; NZeg, IZeg: electrocardiograms of normal and infarcted zones. The upward and the downward arrows indicate the stimulation and delayed activation, respectively. Basic cycle length: 450 msec. The numbers under IZeg are the activation delay (msec).

Mexiletine at 3 mg/kg produced a negligible effect at a coupling interval of 1000 msec; and even at 10 mg/kg, it produced only a slight prolongation of the activation delay, whereas it produced a marked effect on the activation at the basic cycle length of 450 msec. Figure 4 summarizes the effects of mexiletine on activation delay in seven animals. Mexiletine at 10 mg/kg produced a marked prolongation of the activation delay at a coupling interval of 200 msec, whereas it produced only a slight effect at a coupling interval of 1000 msec. The effect of mexiletine was obviously coupling interval-related and also dose-dependent. The effect of mexiletine on the activation in the normal zone was small compared with that in the infarcted zone, and the effect was statistically significant only at the shortest coupling interval and at the higher dose.

The effect of cibenzoline on the activation delay in seven animals are summarized in Fig. 5. Cibenzoline at 1 and 4 mg/kg dose-dependently increased the activation delay in the infarcted zone. The effect of the drug was also coupling interval-related. However, the drug increased the activation delay over a wide range of the coupling interval. The effect of cibenzoline on the activation delay in the normal zone was small, but at a dose of 4 mg/kg, the effect was statistically significant at the shortest coupling interval.

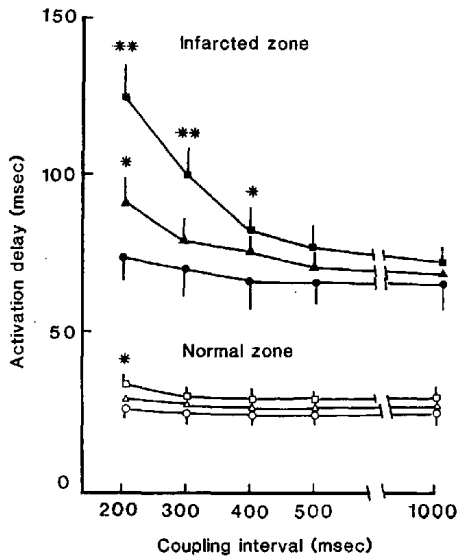


**Fig. 4.** Effect of mexiletine on the activation delay induced by ventricular stimulations with various coupling intervals in seven animals. ○, ●: control; △, ▲: mexiletine, 3 mg/kg; □, ■: mexiletine, 10 mg/kg. *, **: $P < 0.05$ and 0.01 vs. control, respectively.

The effects of disopyramide on the activation delay in seven animals are shown in Fig. 6. Disopyramide at 1 and 4 mg/kg increased the activation delay in the infarcted zone in a dose-dependent fashion. The effect of disopyramide also was coupling interval-related, but differing from that of mexiletine, it significantly increased the activation delay at a coupling interval of 1000 msec. The effect on the activation delay in the normal zone was small. A significant increase was observed only at the shortest coupling interval of 200 msec. None of the three drugs significantly affected the arterial blood pressure (data not shown).

Mexiletine at 10 mg/kg produced abbreviation of a delayed activation in the infarcted zone (Fig. 7). This abbreviation of activation delay indicates that conduction block occurred in the infarcted myocardium. In the control, the premature stimulation produced a seriously delayed activation in the infarcted zone. Mexiletine at 3 mg/kg further delayed the activation, but blocked it at 10 mg/kg. As

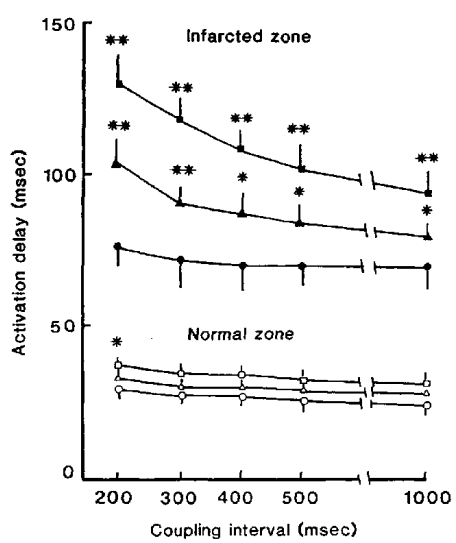


**Fig. 5.** Effect of cibenzoline on the activation delay induced by ventricular stimulation with various coupling intervals in seven animals. ○, ●: control; △, ▲: cibenzoline, 1 mg/kg; □, ■: cibenzoline, 4 mg/kg. *, **: $P < 0.05$ and 0.01 vs. control, respectively.

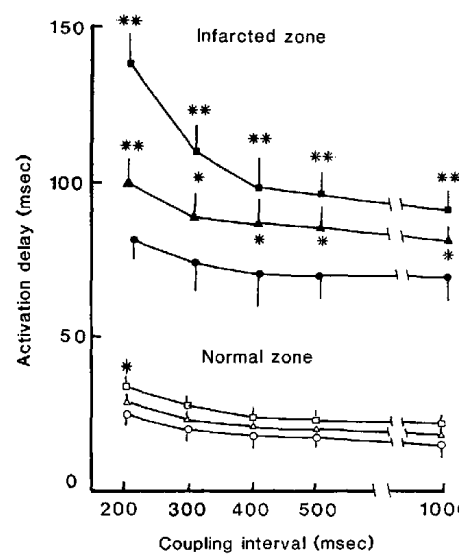


**Fig. 6.** Effect of disopyramide on the activation delay induced by ventricular stimulations with various coupling intervals in seven animals. ○, ●: control; △, ▲: disopyramide, 1 mg/kg; □, ■: disopyramide, 4 mg/kg. *, **: $P < 0.05$ and 0.01 vs. control, respectively.

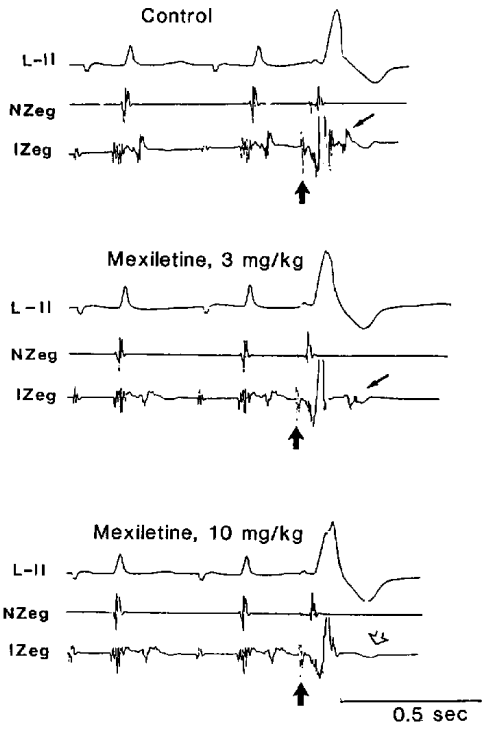


**Fig. 7.** Mexiletine-induced block of the delayed activation in the infarcted zone. L-II: standard limb lead II; NZeg, IZeg: electrocardiograms in normal and infarcted zones. The upward and the downward arrows indicate the premature stimulation and the delayed activations, respectively. Basic cycle length: 450 msec. Coupling interval of the premature stimulation: 200 msec. The open downward arrow indicates block of the delayed conduction.

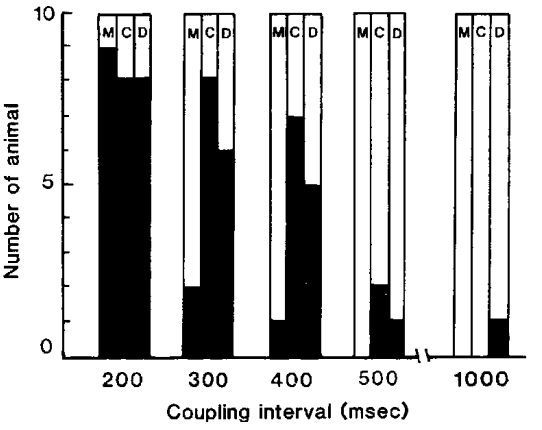


**Fig. 8.** Occurrence of block of the delayed activation at various coupling intervals in the presence of mexiletine, cibenzoline or disopyramide in ten animals. M: mexiletine, 10 mg/kg; C: cibenzoline, 4 mg/kg; D: disopyramide, 4 mg/kg. The filled columns are the numbers of animal which showed block, and the total of each column is the total number of animals examined.

shown in Fig. 8, the development of block was also coupling interval-related. All three drugs at higher doses produced the block of delayed activation in the infarcted zone more frequently at short coupling intervals than at long coupling intervals. However, cibenzoline and disopyramide produced block at longer coupling intervals compared with mexiletine. In these animals, there was no block of any degree at coupling intervals longer than 200 msec in the control state. In Figs. 2–6, the activations which were blocked by the drug were not included.

A premature stimulation at coupling intervals less than 200 msec produced reentrant beats in eleven of thirty animals. A typical example is shown in Fig. 9. In the control state, a premature excitation produced seriously delayed activation in infarcted zones, which resulted in another ventricular beat. Mexiletine at 10 mg/kg blocked the delayed activation and prevented the occurrence of a reentrant ventricular beat. Mexiletine at 10 mg/kg effectively suppressed the reentrant beat in the other three dogs which expressed it. Both of cibenzoline and disopyramide at the higher dose 4 mg/kg suppressed the reentrant beat triggered by premature beats in all dogs in which the reentrant beats were induced by premature ventricular stimulation (4/10 for cibenzoline group, 3/10 for disopyramide group). Mexiletine at 3 mg/kg, cibenzoline at 1 mg/kg or disopyramide at 1 mg/kg neither blocked the delayed activation nor suppressed the reentrant beat.

*The size of infarction*

The size of infarction induced in the present animals was 30 ± 3% of the left ventricle (range 22–35%, n = 6).

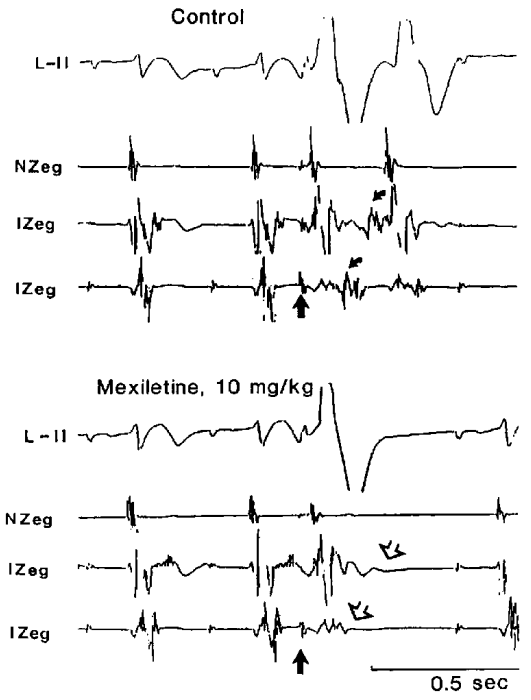


**Fig. 9.** Effect of mexiletine on a premature stimulation-induced ventricular ectopic beat. L-II: standard limb lead II; NZeg, IZeg: electrocardiograms in the normal and the infarcted zones. The upward and the downward arrows indicate the premature stimulation and the delayed activation, respectively. Basic cycle length: 400 msec. Coupling interval of the premature stimulation: 160 msec. The open downward arrows indicate block of the delayed activation.

## DISCUSSION

Mexiletine, cibenzoline and disopyramide are now frequently used for treatment of ventricular arrhythmias. The antiarrhythmic effects of these drugs are mainly due to their inhibitory effects on sodium channels; i.e., these drugs are class I antiarrhythmic drugs (1, 2, 11–13). Sodium channels inhibition by these drugs has been demonstrated by many investigators in isolated cardiac tissues (2, 3, 7, 17).

We examined coupling interval-related effects of these drugs on ventricular activation in the canine myocardial infarction model. In the present model, markedly delayed activation was observed in the infarcted zone. The activation further delayed a premature excitation. According to previous reports, a thin layer of surviving cells exists in the subepicardium of the infarcted zone, and conduction in these tissues is slow (18). As shown in Fig. 1, a premature stimulation produced seriously delayed activations resulted in ventricular ectopic beats, which seemed to be reentrant beats. Similar observations have been reported by other investigators (18–20). Because we did not perform a mapping study in the present study, it could not be denied that other mechanisms such as the triggered activity may also be involved in these arrhythmias.

Several investigators have studied the effects of drugs on ventricular conduction or activation delay in the same model as described in the present study (21, 22). In their studies, "conduction time" was the time interval between the initiation of the QRS complex of standard limb lead II and the largest deflection of a bipolar electrogram, and an "activation delay" was the time interval between the initiation of a deflection and the final rapid deflection of the electrocardiogram. We determined the activation delay, because the activation delay seems to be important for manifestation of arrhythmias. The delayed activation might construct a reentrant beat as will be mentioned later.

In the present study, all three drugs markedly prolonged the activation delay at short coupling intervals in the infarcted zone. In the normal zone, these drugs showed a significant effect only at their higher doses and the shortest coupling interval of 200 msec. In other words, these drugs selectively depressed the activation in the infarcted zone. A similar effect was also observed with other class I antiarrhythmic drugs, lidocaine and SUN-1165 (9, 10). In in vitro studies, several class I antiarrhythmic drugs such as lidocaine, mexiletine and pirmenol depressed more markedly the maximum rate of depolarization in depressed action potentials than in normal action potentials (7, 8). Surviving cells in the infarcted

zone may be slightly depolarized and thus the action potentials may be partly depressed (18, 23), which may be one of reasons for the marked inhibition of the activation by the class I antiarrhythmic drugs in the infarcted zone. In the present study, the doses of the drugs were 3 and 10 mg/kg for mexiletine and 1 and 4 mg/kg for cibenzoline and disopyramide. It has been reported that mexiletine at 4 to 8 mg/kg (24, 25), cibenzoline at 2 to 8 mg/kg (26, 27) and disopyramide at 2.5 to 5 mg/kg (28, 29) showed antiarrhythmic effects on canine ventricular arrhythmias. Thus, the depression of the delayed activation by these drugs indicates that this mechanism may be involved in their antiarrhythmic effects, even if only partially.

The depression of delayed activation in the infarcted zone by the three drugs was coupling interval-related. However, the extents of depression at long coupling intervals were different among the three drugs: Mexiletine caused only a slight depression, whereas cibenzoline and disopyramide produced a marked depression. According to an in vitro study using microelectrode techniques, recovery of sodium channels from inhibition by mexiletine is fast with a time constant of 350 msec (7). Therefore, mexiletine markedly increased the activation delay at short coupling intervals with a slight effect at long coupling intervals in the infarcted zone. In contrast, the interaction of cibenzoline and disopyramide with sodium channels is slow with a time constant of far longer than 1 sec (7, 17, 30), which may be consistent with the result that these drugs prolonged the activation delay at long coupling intervals.

The delayed activation was associated with ventricular ectopic beats in some animals, suggesting that the delayed activation might construct a reentrant pathway. A similar idea has also been suggested by other investigators (18–20). In most cases, the three drugs produced a block of delayed activation in the infarcted zone. As shown in Fig. 9, mexiletine at 10 mg/kg blocked delayed activation, which prevented the occurence of ventricular ectopic beats. Cibenzoline and disopyramide at 4 mg/kg also had a similar effect. Lower doses of these drugs neither blocked the delayed activation nor prevented the reentrant beat. Thus, it seems that the block of delayed conduction is important for the antiarrhythmic effects of these drugs. The block of delayed conduction by these drugs was also coupling interval-related. Mexiletine produced a block at coupling intervals less than 300 msec in most animals, while cibenzoline and disopyramide produced it at a coupling interval of 400 msec in most animals. Therefore, it can be assumed that cibenzoline and disopyramide may prevent reentrant beats with longer coupling intervals in comparison with the case of mexiletine, which may be an advantage of cibenzoline or disopyramide. However, cibenzoline and disopyramide prolonged the activation delay in infarcted zones at a coupling interval of 1000 msec. Coupling intervals longer than 500 msec correspond to a heart rate less than 120 beats/min, which is close to the normal sinus rate. Therefore, it also should be kept in mind that these effects of the two drugs may be arrhythmogenic.

In conclusion, mexiletine, cibenzoline and disopyramide showed a coupling interval-related depression of delayed activation in the infarcted myocardium, which may be caused by a time-dependent inhibition of sodium channels by these drugs.

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