Abstract—Effects of calcium antagonists and lidocaine on the conduction delay observed in the ischemic myocardium were studied in 24 open-chest anesthetized dogs. Acute myocardial ischemia was produced by complete occlusion of the left anterior descending coronary artery (LAD) for 5 or 10 minutes. The conduction time was measured from the initial deflection of V waves on the His bundle electrograms to the major deflection of the bipolar electrograms recorded from the ischemic and non-ischemic subepicardium under a constant atrial pacing. LAD occlusion produced conduction delay in the ischemic zone (14.3 ± 2.3 msec, p < 0.001) with no effect on the normal zone. This ischemia-induced conduction delay was reversible and rate-dependently increased. Administration of lidocaine (2 mg/kg bolus, 4.3 mg/kg/hr constant infusion) prior to the second occlusion increased conduction delay by 12.9 ± 1.9 msec (p < 0.001) whereas diltiazem (0.4 mg/kg i.v.) and verapamil (0.3 mg/kg i.v.) reduced the ischemia-induced conduction delay by 12.7 ± 4.9 msec (p < 0.05) and 8.4 ± 1.8 msec (p < 0.001), respectively. These results indicate that slow channel blocking agents reduce the conduction delay induced by the myocardial ischemia, in contrast with the prolonging effect of lidocaine.

Electrophysiological studies on the ischemic myocardium have shown that ventricular arrhythmias of the early phase are due to the re-entrant mechanism (1, 2). Delayed activation (3–5) associated with electrical inhomogeneity (6, 7) observed in the ischemic myocardium appears to play an essential role in generating the re-entrant circuit. Continuous electrical activities recorded within the ischemic region and which were associated with ventricular extrasystoles, provide supporting evidence for this concept (3, 4). Although precise information relating to the localization of the delay and the existence of re-entry is not available, Scherlag et al. (5) found the greatest delay in the superficial subepicardial layers and inferred that re-entry occurs in that region.

Coincidental disappearance of ventricular arrhythmias of the early phase with the improvement of epicardial electrograms (5) is indicative of the possibility that pharmacological interventions capable of decreasing the extent of conduction delay produced by myocardial ischemia, may alter the incidence or time to the onset of ventricular arrhythmias.

The effects of various antiarrhythmic agents such as lidocaine (8, 9), procainamide (8),
Aprindine (10), propranolol (8, 11) and verapamil (10, 12) on the ischemia-induced conduction delay have been studied in canine experimental models of acute myocardial infarction. Drugs possessing a fast channel blocking property have been shown to increase the ischemia-induced conduction delay (8–10). Verapamil has been found to reduce the conduction delay in ischemic myocardium (10). However, Kupersmith et al. reported contradictory results with application of this drug (12).

The present work was undertaken to examine the effect of verapamil and to determine the effects of diltiazem, which is chemically different from verapamil but possesses a calcium antagonistic property in the cardiac ventricular muscle cells (13, 14), on the delayed activation observed in the ischemic myocardium. We also evaluated the effect of lidocaine in comparison with these slow channel blocking agents.

MATERIALS AND METHODS

The experiments were performed in mongrel dogs weighing 6 to 25 kg anesthetized with pentobarbital sodium (30 mg/kg i.v.). After intubation and ventilation with a respirator (Aika R-60), the heart was exposed through a median sternotomy and suspended in a pericardial cradle. A vinyl cover was placed over the thorax to maintain the epicardial surface within a physiological temperature throughout the experiment. A standard II electrocardiogram and femoral arterial pressure were continuously monitored during experiments.

Acute myocardial ischemia was produced by a single stage complete occlusion of the left anterior descending coronary artery (LAD) distal to the first diagonal branch, using an arterial clamp. The occlusion lasting for 5 to 10 min was repeated two or three times on each dog and a pause of one hour was allowed between these successive occlusions.

The bipolar subepicardial electrodes, each consisting of two enamel-coated stainless steel wires (diameter 0.1 mm), were inserted into the myocardium by a 23-gauge needle to record subepicardial electric activity. The interelectrode distance was 1–2 mm. One subepicardial bipolar plunge wire electrode was placed in the non-ischemic zone (NZ) supplied by the circumflex artery and the other two were placed in the ischemic zone (IZ) which was specified by discoloration following short-term trial occlusion of LAD. Bipolar subepicardial electrograms taken from the normal and ischemic zone were amplified at a time constant of 0.001 sec (San-ei polygraph 142–8) and displayed on a memory oscilloscope (San-ei 2G56) along with His bundle electrogram (HBE) recorded by a bipolar electrode catheter (6 French with ring electrodes 10 mm apart) positioned in the right side of the heart across the tricuspid valve through the right femoral vein. Attempts were made to obtain a His bundle electrogram which showed ventricular waves with sharp initial deflections. These recordings were stored on a four-channel magnetic tape recorder (SONY DFR-3515) at a tape speed of 19 cm/sec and replayed at a speed of 1.9 cm/sec for detailed analysis and transfer to a photographic recorder (San-ei visigraph 5L). The time intervals from the initial deflection of V wave on HBE (HBE-V) to the major deflection of the bipolar electrograms recorded from the ischemic and non-ischemic areas were measured and designated as the conduction time. Accuracy in measurement was in a range of ±0.2 msec.
The sinoatrial node was destroyed by injecting 0.1–0.2 ml of formaldehyde solution and atrial pacing was achieved through a bipolar electrode catheter inserted via the right jugular vein and placed in the high right atrium at a cycle length of 500 msec. Pacing stimuli were rectangular pulses of 2 msec duration and a two fold diastolic threshold strength delivered from an electronic stimulator (Nihon Kohden SEN-3101) and isolation unit (Nihon Kohden SS-101J). To study the influence of the heart rate on the conduction time during the myocardial ischemia, the pacing rate was stepwisely increased from 120 beats/min to 180 beats/min by a step of 20 beats/min for 1.5 minutes.

Effects of the following drugs on ischemia-induced conduction delay were examined: diltiazem (0.4 mg/kg i.v., n=8), verapamil (0.3 mg/kg i.v., n=8), and lidocaine (an i.v. bolus administration of 2 mg/kg followed by a constant-rate infusion of 4.3 mg/kg/hr, n=8). The doses of verapamil and diltiazem were chosen so as to prolong the atrioventricular conduction time to nearly the same extent and the infusion dose of lidocaine was used in order to keep the serum lidocaine concentration within a range of 2 μg/ml to 5 μg/ml, the therapeutic range in human beings (9). Drugs were administered 3 to 5 min before the start of the second occlusion after confirming that the electrograms recorded from LAD area had recovered from the first occlusion. To assess the reproducibility of ischemia-induced conduction delay, control occlusions were carried out twice in another four dogs. Analyses of data were performed using the paired t-test.

RESULTS

Delayed activation in the ischemic myocardium: Within a few minutes after the occlusion of the left anterior descending coronary artery, subepicardial electrograms recorded from the ischemic myocardium began to show a decrease in the amplitude and an increase in the duration and delay in activation. These changes progressed gradually with elapse of time. No significant alterations in the bipolar electrograms recorded from the normal zone were seen after the coronary occlusion (Fig. 1). In this dog, the conduction time measured from the initial deflection of V wave of HBE to the main deflection of the bipolar electrograms recorded from the ischemic myocardium increased from 15.6 msec of pre-occlusion value to 22.4 msec 5 min after the coronary occlusion for one electrogram (IZ1) and from 10.7 msec to 111.5 msec for the other (IZ2) without any change at non-ischemic zone electrogram (NZ). The time course changes of conduction time in this case are depicted in the lower graph of Fig. 1. The deterioration seen on the bipolar electrograms recorded from the ischemic zone showed a rapid improvement and the conduction time returned to the pre-occlusion value within a few minutes after releasing the occlusion.

The conduction delay, defined as an increase in conduction time, observed in the ischemic zone at 5 or 10 min after the control occlusion varied among the animals and sites of electrodes, as shown in Fig. 6. The mean value and its S.E. calculated from 48 sites of 24 dogs was 14.3 ± 2.3 msec (Table 1).

In order to observe the reproducibility of the ischemia-induced conduction delay, the occlusion was repeated twice in another four dogs. No significant difference of the ischemia-
FIG. 1. Progressive delayed activation of the ischemic myocardium. Upper panel depicts actual recordings of subepicardial electrograms obtained from non-ischemic (NZ) and ischemic (IZ1 and IZ2) area before (Pre) and 3, 4 and 5 min after occlusion of the coronary artery with recordings 5 min after release of the occlusion. Conduction time was measured from the initial deflection of ventricular wave of His bundle electrogram (HBE-V), indicated by the vertical broken line, to the major deflection of each bipolar electrogram. Atrial pacing at a cycle length (CL) of 500 msec was maintained throughout the experiment. Horizontal lines at the bottom of each set of electrograms are on a time scale of 20 msec. Lower graph illustrates the time course of changes in conduction time during ischemia. Conduction time is plotted on the ordinate and the elapse of time after occlusion or release of the occlusion on the abscissa.

### TABLE 1. Effects of calcium antagonists and lidocaine on change in the conduction time in non-ischemic and ischemic myocardium after coronary occlusion

|                  | 1st control occlusion | 2nd occlusion after pretreatment | SV interval prolongation (msec) |
|------------------|-----------------------|---------------------------------|---------------------------------|
|                  | NZ delay\(^{a)}\) (msec) | IZ delay\(^{b)}\) (msec) | NZ delay\(^{c)}\) (msec) | IZ delay\(^{d)}\) (msec) |  |
| Diltiazem (n=8)  | 0.0±0.1               | 21.2±5.7                        | 0.2±0.2                        | 8.5±1.5\(^*\)             | 57.9±6.2 |
| Verapamil (n=8)  | 0.1±0.1               | 12.2±2.3                        | 0.5±0.3                        | 3.8±1.1\(^{**}\)          | 67.1±11.5 |
| Lidocaine (n=8)  | -0.2±0.2              | 9.6±2.9                         | 0.0±0.3                        | 22.5±4.4\(^{***}\)        | 5.0±1.1  |
| Total (n=24)     | 0.0±0.1               | 14.3±2.3                        |                                 |                               |          |

\(^{a)}\) increase in the conduction time in the non-ischemic myocardium after coronary occlusion
\(^{b)}\) increase in the conduction time in the ischemic myocardium after coronary occlusion
\(^{c)}\) increase in the time interval from the stimulus artifact to the onset of V wave in the His bundle electrogram after drug administration

Results are expressed as mean±SE. In each group the statistical significance of the difference between the results in the control period and after drug treatment is indicated as follows, \(^*\)p<0.05, \(^{**}\)p<0.01, \(^{***}\)p<0.001.
induced conduction delay was found between the first and the successive occlusions (5.3±1.7 msec and 4.9±1.3 msec, respectively) (Fig. 6, closed circles).

When heart rates were increased by atrial pacing from a basal rate of 120 beats/min to 180 beats/min stepwisely, the conduction delay in the ischemic myocardium increased rate-dependently with no change in the conduction time in the non-ischemic area, as shown in Fig. 2.

**Effects of calcium antagonists:** Figure 3 shows the effect of diltiazem (0.4 mg/kg i.v.) on conduction delay produced by a 5 min occlusion of the left anterior descending coronary artery during pacing at a cycle length of 500 msec. In this case, the delay of conduction time in the ischemic myocardium after the first control occlusion was 6.8 msec for IZ₁ and 100.8 msec for IZ₂. Pretreatment with diltiazem reduced the conduction delay induced by the second occlusion to 3.4 msec and 18.5 msec for IZ₁ and IZ₂, respectively. The results obtained in 8 dogs are shown in Fig. 6 and Table 1. Administration of diltiazem significantly reduced the ischemia-induced conduction delay from a mean value of 21.2 to 8.5 msec (p < 0.05) without influencing the conduction time in the non-ischemic zone. Diltiazem prolonged the SV interval (the interval from the stimulus artifact to the initial deflection of V wave on HBE) by 57.9±6.2 msec.

Verapamal also prevented the conduction delay which was observed in the ischemic myocardium. As shown in Fig. 4, the intravenous administration of verapamal (0.3 mg/kg) prior to the second occlusion reduced the conduction delay and improved the subepicardial electrogram recorded from the ischemic zone. In 8 dogs treated with verapamal, the ischemia-induced conduction delay decreased from 12.2±2.3 msec to 3.8±1.1 msec (p < 0.001) and the SV interval was prolonged to the same extent as diltiazem (Fig. 6 and Table 1).

Low incidence of ventricular extrasystoles during the first occlusion in these dogs made it difficult to correlate the effect on the conduction delay with the incidence of arrhythmias. In two dogs with evidence of ventricular extrasystoles during the control occlusion, diltiazem...
**FIG. 3.** Effect of diltiazem on conduction delay produced by a 5 min occlusion of the left anterior descending coronary artery during pacing at a cycle length (CL) of 500 msec. This case is the same as shown in Fig. 1. HBE-V, NZ, IZ1, IZ2, CL and vertical broken lines are the same as defined in the legend of Fig. 1. The left (Control) and right (Occlusion) panels were recorded before and after 5 min of occlusion, before (A) and 5 min after (B) administration of diltiazem (0.4 mg/kg i.v.). Horizontal lines are on a time scale of 20 msec.

**FIG. 4.** Effect of verapamil on ischemia-induced conduction delay. Panels A and B show electrograms before and after the first trial of coronary occlusion. Panel C shows electrograms recorded after the second occlusion following the administration of verapamil (0.3 mg/kg i.v.). HBE-V, NZ, IZ1, IZ2, CL and vertical broken lines are the same as defined in the legend of Fig. 1. Note that conduction delay produced by a 5 min occlusion at the first trial of the occlusion was reduced with the pretreatment of verapamil.
reduced the frequency of arrhythmias with an improvement in the conduction delay.

*Effect of lidocaine:* In contrast to diltiazem and verapamil, lidocaine increased the

**Fig. 5.** Effect of lidocaine on ischemia-induced conduction delay. HBE-V, NZ, IZ₁, IZ₂, CL and vertical broken lines are the same as described in the legend on Fig. 1. Panels A and B show electrograms before and after the first trial of the coronary occlusion. Panel C shows electrograms recorded from non-ischemic and ischemic myocardium in the presence of lidocaine 10 min after the second trial of the occlusion. One hour was allowed to elapse between the first and the second trial of the coronary occlusion. Note that a further decrease in amplitude and increased delay in conduction time were observed in IZ₁ and IZ₂.

**Fig. 6.** Relation of ischemia-induced conduction delay before and after the administration of drugs. Delays in conduction time observed at the first trial of occlusion of coronary artery are expressed on the abscissa and those at the second trial of occlusion after the pretreatment with drugs or saline on the ordinate. In order to assess the reproducibility of the ischemia-induced conduction delay, saline instead of drugs was administered before the second occlusion (○). The closed circles are positioned nearly on the line of identity indicating the high reproducibility. Note that all plots of diltiazem (△) and verapamil group (■) are below the identity line in contrast with lidocaine group (○) above the line.
ischemia-induced conduction delay. In the experiment shown in Fig. 5, 10 min of coronary occlusion in the control produced a conduction delay of 3.4 msec and 4.2 msec for IZ1 and IZ2, respectively. A second occlusion during lidocaine infusion prolonged the conduction time to 13.7 msec and 17.6 msec for each. In 8 dogs given lidocaine, the extent of the conduction delay observed in the ischemic myocardium increased significantly from a mean value of 9.6 msec to 22.5 msec (p<0.001) as shown in Fig. 6 and Table 1. Lidocaine did not significantly affect the SV interval and the conduction in the non-ischemic area. In one dog, a second coronary occlusion during lidocaine administration resulted in ventricular fibrillation after 6 min.

DISCUSSION

Electrophysiological studies of experimental ischemic myocardium revealed that delayed activation (3–5), dispersion of refractoriness (7) and changes in excitability (6) occurred immediately after acute coronary occlusion. These electrophysiological alterations would provide a situation in which ventricular arrhythmias of reentrant type are prone to occur (1, 2).

The present study confirmed the delayed activation in the ischemic myocardium after the total occlusion of the left anterior descending coronary artery in dogs. It also demonstrated that diltiazem as well as verapamil reduced the ischemia-induced conduction delay whereas lidocaine prolonged the delay.

The findings that lidocaine increased the conduction delay in the ischemic myocardium without any effect on conduction time in the non-ischemic zone are consistent with the observations reported by Kupersmith et al. (9). Earlier studies, based largely on data from the normal cardiac tissue in vitro, demonstrated that lidocaine, in a therapeutic concentration, had little effect on conduction velocity, membrane responsiveness and refractoriness (15, 16). However, in in vitro studies, lidocaine depressed the membrane responsiveness and conductivity in the partially depolarized cardiac cells isolated from the ischemic myocardium (17, 18) or perfused with increased extracellular potassium (19). This selective action of lidocaine on partially depolarized cardiac cells provides an adequate explanation for our observations, in consideration of the high extracellular level of potassium in the ischemic myocardium (20).

The extent of conduction delay in the ischemic myocardium was reduced by verapamil. This finding is in accord with the observations reported by Elharrar et al. (10). However, contrary to this, Kupersmith et al. (12) have found that verapamil further prolonged the ischemia-induced conduction delay. The discrepancy between these studies may stem from the different mode of drug administration. We and Elharrar et al. administered verapamil prior to the coronary occlusion, whereas Kupersmith et al. administered it immediately after the coronary ligation.

Diltiazem which is clinically prescribed for the treatment of angina pectoris as it has a coronary vasodilating action also reportedly has calcium antagonistic effects on the cardiac muscle cells (13, 14). Diltiazem has various effects seen with other calcium antagonists
We found that pretreatment with diltiazem as well as verapamil reduced the extent of the ischemia-induced conduction delay, thereby suggesting the possibility that this reducing effect on the conduction delay may be a pharmacological feature common to all calcium antagonists.

However, it is difficult to attribute the reducing effect on the ischemia-induced conduction delay to the slow channel blocking effect. Extracellular potassium in the ischemic region is known to be elevated in minutes after coronary occlusion, such an alteration results in a decrease in the membrane potentials (20). These electrophysiological changes, associated with catecholamine release (22, 23), may be sufficient to depress the fast responses and induce the slow responses, with a resultant slowing conduction velocity. In this situation, slow channel blockers would be expected to deteriorate further rather than to improve the ischemia-induced conduction delay.

There are alternate explanations for the salutary effect of these calcium antagonists on the conduction. Firstly, these drugs may diminish the degree of ischemic injury by increasing the collateral flow to the ischemic myocardium. It is well known that collateral vessels develop to various degrees in the dog heart. Yamaguchi et al. reported that conduction delay in the ischemic zone did not occur until the coronary flow was reduced by more than 75 per cent (24). Increase in the blood supply to the ischemic myocardium through the collateral vessels, albeit slight, may improve the slowed down conduction.

Another possibility is that the calcium antagonists may reduce the ischemic injury through a reduction in the afterload induced by the dilatation of peripheral vessels. Such effects may decrease the oxygen requirement of the ischemic myocardium and minimize the ischemic injury. Smith et al. demonstrated that verapamil reduced epicardial ST segment elevation and selectively depressed the contractile function in the ischemic myocardium following experimental coronary occlusion (25, 26).

Lastly, the calcium antagonists could improve the ischemia-induced conduction delay by a direct effect on cellular function. An increased level of intracellular free calcium ions in the ischemic myocardial cells induces cellular damage (27) and increases the resistance of cell-to-cell electrical junctions (28–30). It has been reported that catecholamine-induced myocardial necrosis caused by excessive intracellular calcium accumulation was prevented by pretreatment with verapamil (31). Calcium antagonists may protect cardiac cells from ischemic injury by inhibiting cytoplasmic calcium accumulation.

Further studies are underway to elucidate the underlying mechanism of the favorable effect of calcium antagonists on the ischemia-induced conduction delay and, of the relation of this effect to the antiarrhythmic action during ischemia.

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