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Blockade of ATP-Sensitive Potassium Channels by 5-Hydroxydecanoate Suppresses Monophasic Action Potential Shortening During Regional Myocardial Ischemia

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Summary. **We tested 5-hydroxydecanoate (5-HD), a specific blocker of ATP-sensitive potassium channels (IK.ATP), to determine if it mitigates electrophysiologic changes produced by regional myocardial ischemia *in vivo*. A sequence of 5-minute occlusion of the distal LAD and 30-minute reperfusion was repeated while recording the monophasic action potential (MAP) and bipolar electrogram (EG) from the epicardial center of the ischemic myocardium in anesthetized dogs. 5-HD (30 mg/kg, IV) or glibenclamide (0.15 or 0.3 mg/kg, IV) was administered before the third occlusion, and the data were compared to the second occlusion data. 5-HD did not affect baseline MAP duration at 90% and 50% repolarization (APD90, APD50) before LAD occlusion but suppressed occlusion-induced shortening of APD90 (16 ± 2% during the second occlusion vs. 5 ± 3% during the third occlusion, n = 8, $p < 0.01$) and APD50 (16 ± 3% vs. 10 ± 3%, n = 8, $p < 0.05$). Pretreatment with glibenclamide also suppressed occlusion-induced MAP shortening and eliminated an additional effect of 5-HD (n = 3). 5-HD did not affect the occlusion-induced increase in duration and activation time of EG. 5-HD, as well as glibenclamide, suppressed regional ischemia-induced MAP shortening, probably by blocking activation of IK.ATP, without affecting conduction delay. These differential effects of 5-HD on repolarization and conduction during the early phase of regional ischemia might have the potential to suppress reentrant ventricular arrhythmias.**

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Key Words. **regional myocardial ischemia, action potential shortening, ATP-sensitive potassium channels, 5-hydroxydecanoate, glibenclamide**

Previous studies using single cardiac cell and Langendorff-perfused heart have shown that activation of ATP-sensitive potassium channels (IK.ATP) under anoxic or globally ischemic conditions are at least in part responsible for an increase in outward potassium currents, shortening of action potential duration, and an increase in extracellular potassium concentration [1–3]. Involvement of IK.ATP activation in the electrophysiologic changes during regional ischemia *in vivo* remains to be determined; however, it may contribute to action potential change and conduction disturbance [4,5]. In the present study we determined whether intravenous administration of sodium 5-hydroxydecanoate (5-HD), a specific blocker of IK.ATP [6], mitigates the electrophysiologic changes produced by regional myocardial ischemia *in vivo*.

Materials and Methods

Surgical preparations

Studies were performed in 15 dogs weighing 9.5–19.2 kg. Dogs were anesthetized initially with pentobarbital (30 mg/kg IV), and additional doses were administered as needed to maintain anesthesia. Dogs were intubated and ventilated with room air by a constant volume-cycled respirator (Harvard Apparatus model 607). A fluid-filled cannula was placed in the right femoral artery and connected to a transducer (Nihon Kohden model TP-400T) to monitor arterial blood pressure. A femoral venous cannula was used to infuse normal saline at a rate of 100–200 ml/hr to replace spontaneous fluid losses and to inject the drugs. Following left thoracotomy, the left anterior descending coronary artery (LAD) was dissected free at a site distal to the first or second diagonal branch. An electromagnetic flow probe (Nihon Kohden model MF-27) was used to measure LAD blood flow. A silk suture was positioned around the LAD, passed through a

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plastic tube, and used as a noose to obtain complete occlusion and reperfusion of the LAD by tightening and releasing the suture. The distal occlusion was chosen to prevent the occurrence of ventricular fibrillation (VF), which precludes the measurements. A thermistor was used to monitor epicardial temperature, which was maintained 37–38°C by the use of an overhead heating lamp.

Placement of electrodes and electrographic recordings

The monophasic action potential (MAP) was recorded using a hand-held, pressure contact electrode probe with silver-silver chloride electrodes (EP Technologies model 200) [7]. The MAP recording probe was positioned in the anticipated epicardial center of the ischemic zone of the left ventricle, and signals were amplified with direct-current–coupled differential amplifiers at a frequency range of 0.04–500 Hz.

The bipolar electrogram (EG) was recorded with a pair of bipolar plunge electrodes, which were inserted into the subepicardium adjacent to the MAP recording site, and signals were amplified and then filtered between 30 and 1,000 Hz. MAP and EG were recorded simultaneously with the electrocardiogram (ECG), arterial blood pressure, and coronary blood flow on a recorder (Nihon Kohden polygraph system model RM-6000) at a paper speed of 100 mm/sec.

Heart rate was maintained constant by left atrial pacing at a cycle length slightly shorter than the individual sinus cycle length (300–500 msec, mean, 385 ± 15 msec) with a programmable stimulator (Fukuda Denshi model BC-02A).

MAPs were accepted if they fulfilled the following criteria [8,9]: (1) constant amplitude, configuration, and stable resting membrane potential at control recording; (2) stable amplitude of phase 2 >10 mV during a control recording. The MAP amplitude was measured as the potential difference between phase 2 and the maximal diastolic potential during phase 4. Then action potential durations at 90% repolarization and 50% repolarization were measured and expressed as APD90 and APD50, respectively. The activation time, defined as the interval from the onset of QRS to the intrinsicoid deflection of local EG, was measured. The duration of EG was also measured [10,11].

Experimental protocol

The control group consisted of 4 control dogs that received four sequences of 5-minute LAD occlusion and 30-minute reperfusion without any intervention. The study group consisted of 11 dogs that also received four sequences of 5-minute LAD occlusion and 30-minute reperfusion. In 8 dogs, 5-HD (30 mg/kg) [12] was administered intravenously 3 minutes before the third LAD occlusion. In the remaining 3 dogs, glibenclamide (0.15 or 0.3 mg/kg) [4,5] was administered intravenously 15 minutes before the third LAD occlusion, and 5-HD (30 mg/kg) was administered intravenously 3 minutes before the fourth LAD occlusion.

Data analysis

We compared the data obtained during the second to fourth occlusion-reperfusion sequences in both the control and study groups. Data obtained during the first occlusion were discarded because of possible differences from the following occlusions [10,13–16]. Data were expressed as mean ± SE. The paired or unpaired t-test was used when two measurements were compared. Statistical significance was set at a p value of <0.05.

Results

Changes in MAP duration and EG produced by 5-minute occlusion and reperfusion in the control group

In the control group (n = 4), APD90 and APD50 shortened during LAD occlusion as a function of time and returned to the baseline values within a few minutes after reperfusion. There was no significant difference in the baseline values immediately before the second, third, and fourth occlusions. The extent of APD shortening during the second, third, and fourth LAD occlusions was also similar (see Figs. 2 and 3). The duration and activation time of EG increased after LAD occlusion as a function of time and returned to the baseline values within a few minutes after reperfusion. The extent of change was similar among the three occlusions.

Effects of 5-HD on APD90 and APD50

Figure 1 shows a representative experiment from one animal of the study group. The MAP duration shortened as early as 1 minute after the second LAD occlusion. Intravenous 5-HD had little effect on baseline APD before the third LAD occlusion; however, it suppressed occlusion-induced APD shortening.

The APD data from the study group (n = 8) are shown in Figures 2 and 3. Changes in APD90 produced by LAD occlusion and reperfusion are depicted in the upper panel of Figure 2, and the mean percent changes in APD90 from each baseline value during 5-minute LAD occlusion (mean ΔAPD90) are depicted in the lower panel of Figure 2. Changes in APD50 and mean ΔAPD50 are shown in Figure 3 in the same manner. During the second LAD occlusion, shortening of APD90 and APD50 was evident as early as 1 minute after the onset of LAD occlusion and progressed thereafter. The APD90 and APD50 returned to the baseline values within several minutes after reperfusion. Pretreatment with 5-HD did not produce a significant change in baseline APD90 or APD50 before the third LAD occlusion; however, it significantly suppressed the occlusion-induced shortening of APD90 and APD50. Mean ΔAPD90 and mean ΔAPD50 during the third LAD occlusion shortly after

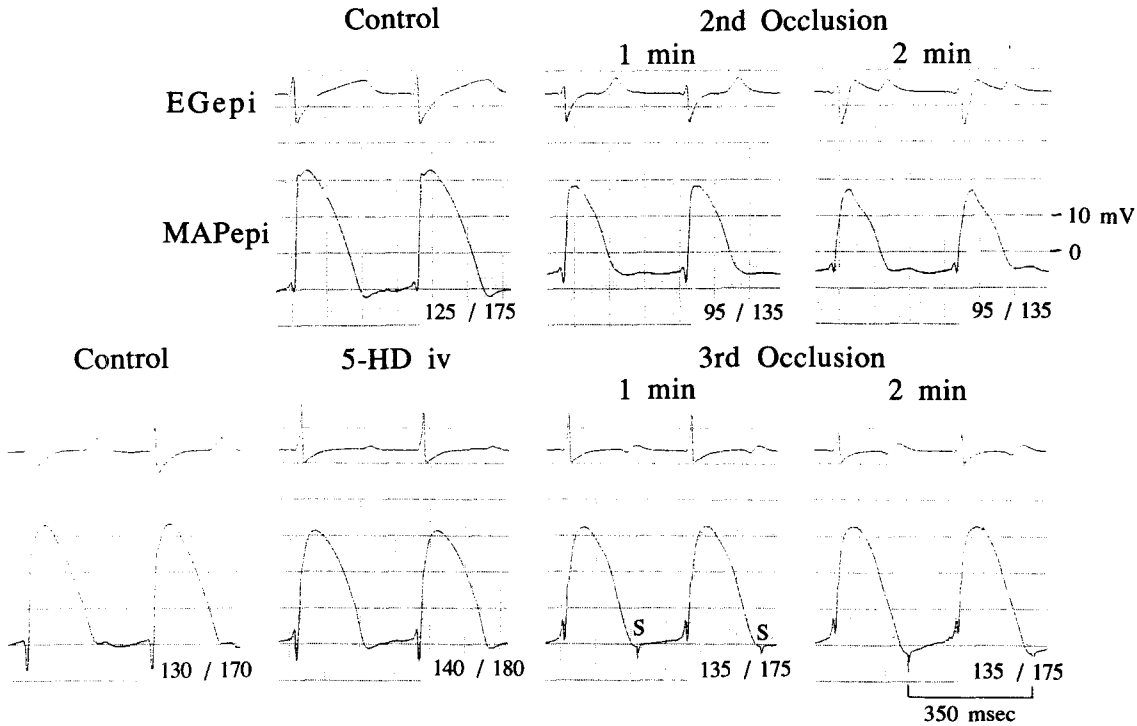

Fig. 1. Representative experiment from one animal in the study group. Simultaneous recordings of epicardial bipolar electrogram (EGepi) and monophasic action potential (MAPepi) during the second (upper panels) and third sequences (lower panels) are shown. Heart rate was maintained constant by left atrial pacing at a cycle length of 350 msec. Measured APD50/APD90 (msec) is indicated under each MAP. APD50 and APD90 shortened as early as 1 minute after the second LAD occlusion. Intravenous injection of 5-HD (30 mg/kg) had little effect on baseline APD before the third LAD occlusion; however, it attenuated occlusion-induced shortening of APD. Spike (S) denotes an artifact caused by left atrial pacing.

pretreatment with 5-HD were significantly less than those during the second LAD occlusion. However, mean ΔAPD90 and ΔAPD50 during the fourth LAD occlusion were similar to those during the second LAD occlusion, suggesting that the effect of 5-HD on occlusion-induced APD changes was transient.

Effects of 5-HD on EG

Changes in duration (upper panel) and activation time (lower panel) of EG produced by LAD occlusion and reperfusion are depicted in Figure 4. During the second LAD occlusion, the duration and activation time of EG were increased significantly as a function of time. Pretreatment with 5-HD had no effect on baseline duration and activation time of EG before the third LAD occlusion, or on the occlusion-induced increase in these variables.

Effect of 5-HD on coronary blood flow

5-HD had no effect on coronary blood flow immediately before the third LAD occlusion (17.2 ± 2 ml/min vs. 19.5 ± 1 ml/min, NS, n = 5).

Effect of 5-HD on arterial blood pressure

5-HD tended to increase systolic arterial blood pressure before the third LAD occlusion (133 ± 11 mmHg vs. 143 ± 9 mmHg, n = 8, NS). Also, systolic blood pressure at 5 minutes after the third LAD occlusion tended to be higher than that during the second LAD occlusion (138 ± 11 vs. 128 ± 12 mmHg, n = 8, NS).

Effect of 5-HD on ventricular arrhythmias

In the absence of 5-HD, no dog developed ventricular fibrillation (VF) during the second sequence of LAD occlusion and reperfusion. After pretreatment with 5-HD, one developed *de novo* VF upon reperfusion.

Effects of glibenclamide

The effects of glibenclamide on baseline APD90 and occlusion-induced shortening of APD90 (n = 3) are depicted in Figure 5. Intravenous glibenclamide did not produce a significant change in APD90 before the third LAD occlusion; however, it suppressed the occlusion-induced shortening of APD90. Administration of 5-HD before the fourth LAD occlusion had no additional effect on occlusion-induced changes in APD90. An example from one animal is shown in Figure 6.

Discussion

Major findings

Pretreatment with 5-HD (30 mg/kg, IV) suppressed regional ischemia-induced MAP shortening without

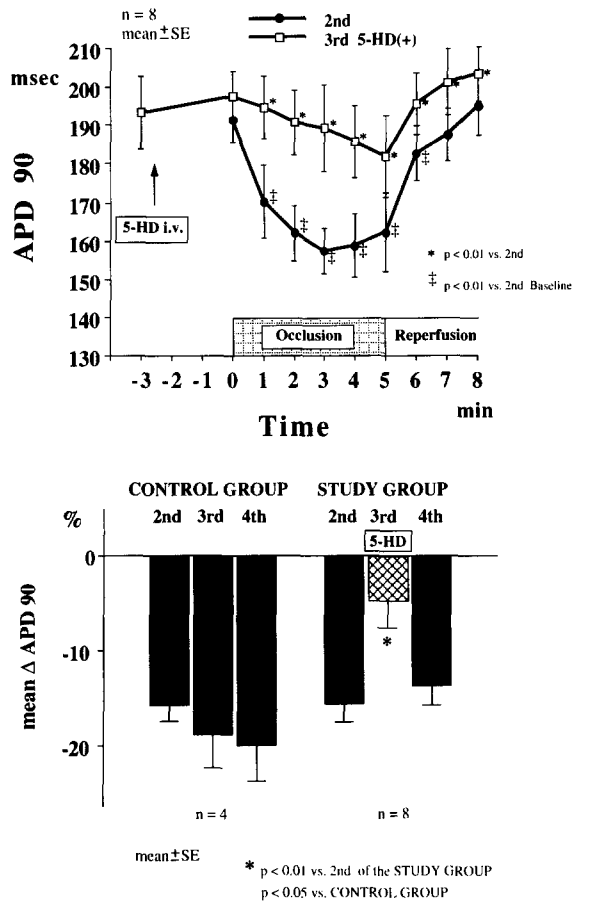

Fig. 2. The effect of 5-HD (30 mg/kg, IV) on APD90 before and during the LAD occlusion-reperfusion sequence in the study group (upper panel), and on the mean percent change in APD90 from each baseline value during a 5-minute LAD occlusion (mean ΔAPD90; lower panel). APD90 shortened significantly as a function of time during the second (control) LAD occlusion, and returned to the baseline value within several minutes after reperfusion. Intravenous administration of 5-HD did not affect baseline APD90 before the third LAD occlusion; however, it significantly attenuated the occlusion-induced shortening of APD90. Mean ΔAPD90 during the third LAD occlusion after pretreatment with 5-HD was significantly less than that during the second occlusion in the study group and than the control group values. Mean ΔAPD90 during the fourth LAD occlusion was similar to that during the second occlusion, suggesting that the effect of 5-HD was transient.

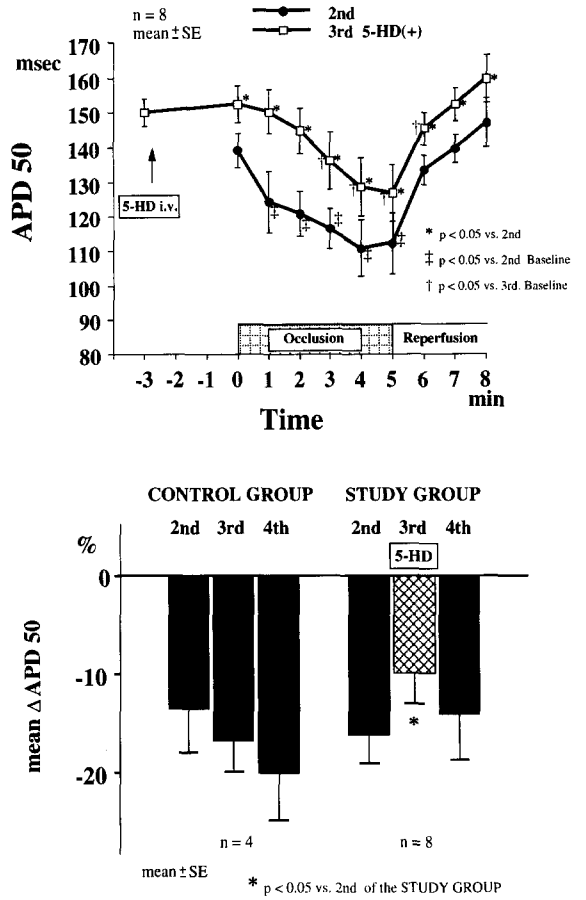

Fig. 3. The effect of 5-HD (30 mg/kg, IV) on APD50 before and during the LAD occlusion-reperfusion sequence in the study group (upper panel), and on the mean percent change in APD50 from each baseline value during a 5-minute LAD occlusion (mean ΔAPD50; lower panel). APD50 shortened significantly as a function of time during the second (control) LAD occlusion and returned to the baseline value within several minutes after reperfusion. Intravenous administration of 5-HD did not affect baseline APD50 before the third LAD occlusion; however, it significantly suppressed the occlusion-induced shortening of APD50. Mean ΔAPD50 during the third LAD occlusion after pretreatment with 5-HD was significantly less than that during the second occlusion in the study group.

affecting baseline MAP duration; however, it had little effect on the ischemia-induced conduction delay. Pretreatment with glibenclamide (0.15 or 0.3 mg/kg, IV) also suppressed the ischemia-induced MAP shortening and eliminated an additional effect of 5-HD.

Electrophysiologic effects of 5-HD and glibenclamide during regional ischemia

Hypoxia or metabolic inhibition causes shortening of action potential duration [17,18]; however, the ionic mechanisms involved in this change had not been proved until IK.ATP was described in cardiac cells that were activated by a decrease in intracellular ATP concentration [1]. Previous studies indicate that blockade of IK.ATP, in fact, prevents shortening of action potential duration during hypoxia or metabolic inhibition *in vitro* and during global ischemia [2,6,19–24]. However, involvement of IK.ATP activation in the electrophysiologic changes during regional ischemia *in vivo* remains to be studied.

In the present study we demonstrated that 5-HD (30 mg/kg, IV), a specific blocker of IK.ATP [6], tran-

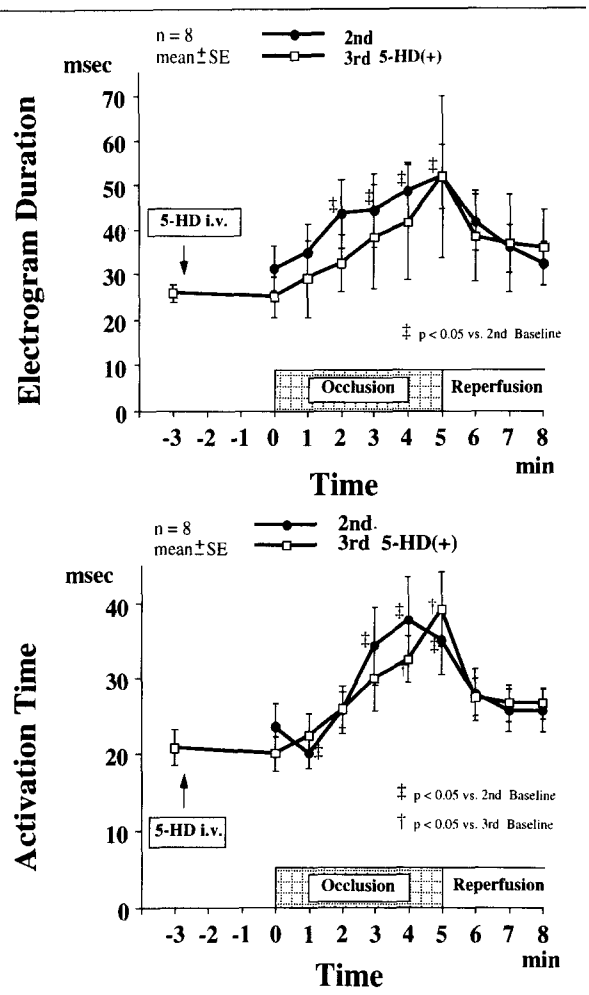

Fig. 4. *The effect of 5-HD (30 mg/kg, IV) on the duration (upper panel) and activation time (lower panel) of the bipolar electrogram before and during the LAD occlusion-reperfusion sequence in the study group. During the second LAD occlusion, the duration and activation time were increased significantly as a function of time. Pretreatment with 5-HD had no effect on the baseline duration and activation time before the third LAD occlusion, or on the occlusion-induced increase in these variables.*

siently attenuated regional ischemia-induced MAP shortening without affecting baseline MAP duration (see Figs. 1–3). The transient effect of 5-HD could be explained by its short biological half-life (7 minutes in dogs, data released from Mochida Pharmaceutical Co.).

The present results are concordant with recent reports [4,5]. Yao et al. [5] have shown that pretreatment with glibenclamide (0.3 mg/kg, IV) suppresses MAP shortening during a brief period of regional ischemia. Also, Bekheit et al. [4] have reported that pretreatment with glibenclamide (0.15 mg/kg, IV) reduces the regional ischemia-induced increase in extracellular potassium concentration. Our present data and these reports concordantly support the view that activation of IK.ATP is involved in the shortening of repolarization time and potassium efflux during the early phase of regional ischemia *in vivo*. Several lines of evidence from the present study support this view. First, 5-HD (30 mg/kg, IV) did not significantly prolong the baseline MAP duration before coronary occlusion (Figs. 1–3). This finding suggests that 5-HD at this dose did not inhibit major repolarization currents of the left ventricular myocardium, such as the delayed rectifying outward potassium current (IK), inward rectifying potassium current (IK1), transient outward current (Ito), etc. Therefore, it seems reasonable to consider that suppression by 5-HD of regional ischemia-induced MAP shortening could be attributed to inhibition of IK.ATP activated after the onset of ischemia. Second, plasma concentration shortly after intravenous injection of 5-HD (30 mg/kg) in dogs would be higher than a concentration of 10 μM of 5-HD (2.103 μg/ml), which is known to suppress potassium release from the ischemic myocardium in isolated rat heart [12]. The peak plasma concentration after single oral administration of 5-HD (100 mg/kg) in dogs reaches 100 μg/ml (data released from Mochida Pharmaceutical Co.). Finally, pretreatment with glibenclamide (0.15 or 0.3 mg/kg, IV), a better known blocker of IK.ATP, also suppressed regional ischemia-induced MAP shortening and eliminated an additional effect of 5-HD in the present model (Figs. 5 and 6).

If 5-HD and glibenclamide reduced the degree of ischemia during coronary occlusion in the present model, it might have also blunted ischemia-induced MAP shortening. However, it seems unlikely since 5-HD had no effect on LAD flow before its occlusion. Furthermore, it has been reported that blockade of IK.ATP by glibenclamide prevents hypoxic vasodilation of coronary arterioles [25]. Also, 5-HD tended to raise systolic arterial blood pressure during coronary occlusion. These effects of IK.ATP blockers may rather act to worsen the degree of ischemia during coronary occlusion.

The present results differ in some points from previous reports. Smallwood et al. [26] reported that glibenclamide (0.5 mg/kg, IV) prolonged endocardial MAP duration both before and during regional ischemia in dogs. In the present study, glibenclamide (0.15 or 0.3 mg/kg, IV) suppressed regional ischemia-induced MAP shortening recorded from the epicardium; however, it did not cause a significant prolongation of baseline MAP duration or MAP duration during ischemia (see Figs. 5 and 6). These different observations may indicate that the effects of glibenclamide are dose or site related in dogs. Bekheit et al. [4] have reported that pretreatment with glibenclamide (0.15 mg/kg, IV) reduces regional ischemia-induced increase in the duration of the local bipolar

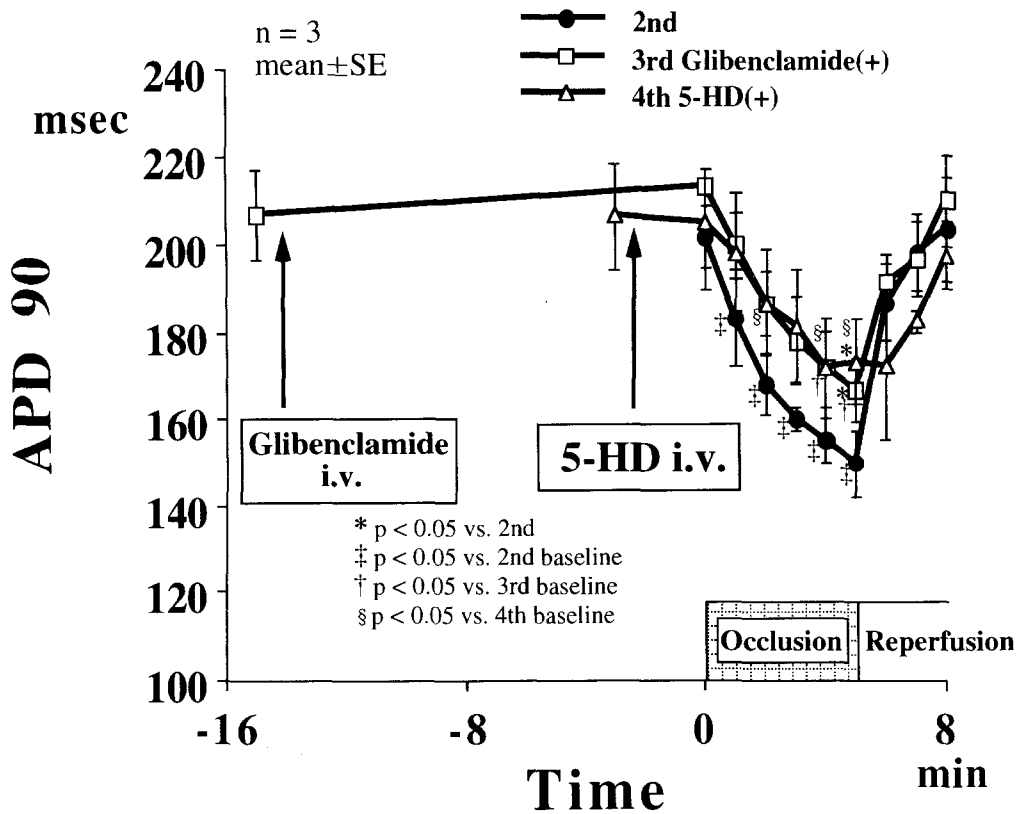

Fig. 5. The effect of glibenclamide (0.15 or 0.3 mg/kg, IV) on APD90 before and during the LAD occlusion-reperfusion sequence in the study group. Pretreatment with glibenclamide did not produce a significant change in APD90 before the third LAD occlusion; however, it suppressed the occlusion-induced shortening of APD90 compared with the changes during the second LAD occlusion. Administration of 5-HD (30 mg/kg, IV) before the fourth LAD occlusion had no additional effect on the occlusion-induced changes in APD90.

electrogram in dogs. In the present study, we could not demonstrate this effect following pretreatment with 5-HD. Since we used a constant dose of 5-HD (30 mg/kg, IV), it is not known whether its effect on conduction properties is a dose-related phenomenon.

Consideration of the experimental model and limitations of the study

In the present study, a sequence of 5-minute LAD occlusion and 30-minute reperfusion was repeated four times. In order to assess the effects of an intervention on the electrophysiologic changes within the same dog, we selected a 5-minute coronary occlusion. It is known that a 5-minute coronary occlusion causes reversible electrophysiologic changes [14], which was also confirmed in the present study. The first occlusion data were discarded because the first occlusion might cause more severe electrical disturbances than the following occlusions [10,13–16]. Therefore, we used the second occlusion-reperfusion sequence as a control in the present study. The MAPs were recorded from the epicardium because ischemia-induced shortening of the action potential duration is much greater in the epicardium than in the endocardium [27]. The distal LAD occlusion was chosen to prevent the occurrence of VF, which precludes the measurements. We cannot assess the antiarrhythmic effect of 5-HD on lethal ventricular arrhythmias because we did not observe the occurrence of VF during the control occlusion-reperfusion sequence. We observed the *de novo* occurrence of VF upon reperfusion in one case in the presence of 5-HD. Although the precise mechanism is unknown, the longer MAP duration upon reperfusion in the presence of 5-HD than that during the control reperfusion (see Figs. 2 and 3) may contribute to the occurrence of arrhythmia.

Clinical relevance

The present data indicate that blockade of IK.ATP by 5-HD suppresses regional ischemia-induced MAP shortening without affecting conduction delay. These differential effects of 5-HD on repolarization and conduction might have the potential to suppress reentrant ventricular arrhythmias immediately after coronary occlusion.

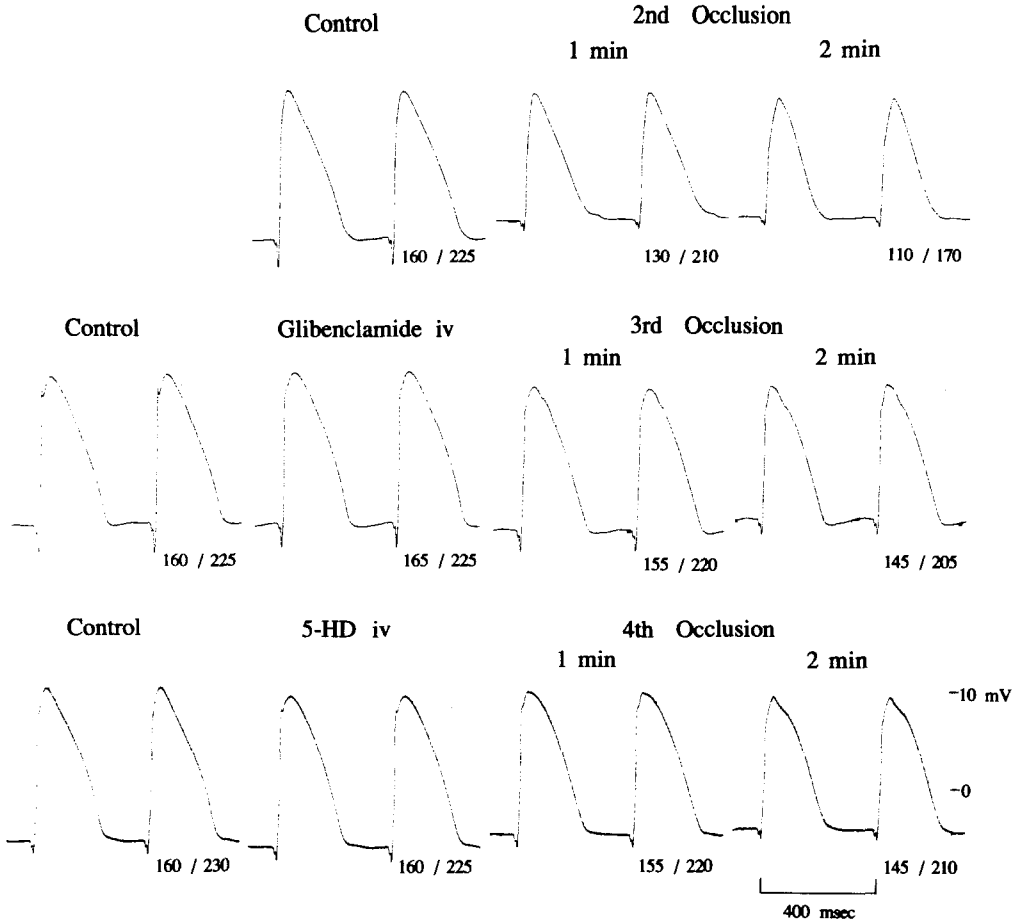

Fig. 6. *An example of the effect of glibenclamide on the duration of the epicardial monophasic action potential. Heart rate was maintained constant by left atrial pacing at a cycle length of 400 msec. Measured APD50/APD90 (msec) is indicated under each MAP. APD50 and APD90 shortened as early as 1 minute after the second LAD occlusion (upper panels). Intravenous injection of glibenclamide (0.15 mg/kg) had little effect on the baseline APD before the third LAD occlusion; however, it attenuated the occlusion-induced shortening of APD (middle panels). Administration of 5-HD (30 mg/kg, IV) before the fourth LAD occlusion had no additional effect on the occlusion-induced shortening of APD (lower panels).*

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