

# Antiarrhythmic Effects of Bisamil on Triggered Arrhythmias Produced by Intracoronary Injection of Digitalis and Adrenaline in the Dog

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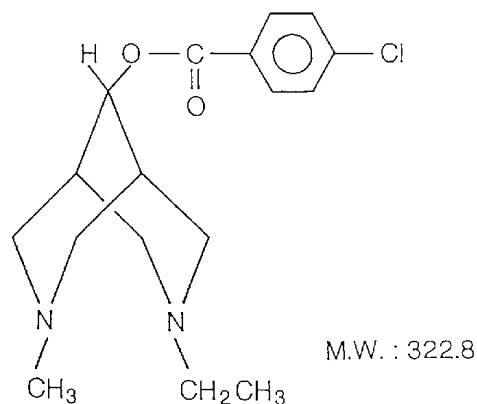
**ABSTRACT**—Antiarrhythmic effects of bisamil were examined by using new in vivo triggered arrhythmia models, and they were compared with those of other antiarrhythmic drugs. Bisamil (3–10  $\mu$ g, i.c.) suppressed triggered ventricular arrhythmias that were produced during pauses between trains of rapid ventricular stimulation (cycle length: 250 msec, train number: 15) in anesthetized open-chest dog hearts administered with subtoxic doses of digitalis or adrenaline to the anterior descending coronary artery. The potencies of bisamil, disopyramide, lidocaine and flecainide suppressing digitalis-induced triggered ventricular arrhythmias were similar to those suppressing adrenaline-induced ones. The potency of verapamil for suppressing digitalis-induced triggered ventricular arrhythmias were weaker than that for suppressing the adrenaline-induced ones. Bisamil was the most effective among the antiarrhythmic drugs used in the present experiment. Since bisamil has been reported to be effective in suppressing other canine automatic ventricular arrhythmias, and the triggered ventricular arrhythmias occur in clinical situations, bisamil may become a useful drug for the treatment of clinical arrhythmias.

**Keywords:** Bisamil, Antiarrhythmic effect, Triggered arrhythmia

Bisamil, syn-9-(4-chlorobenzoyloxy)-3-ethyl-7-methyl-3,7-diazabicyclo [3.3.1] nonane hydrochloride (Fig. 1), is a newly developed antiarrhythmic drug. Electrophysiologically, it has been reported to have class I actions (1) according to the Vaughan Williams classification (2), and we reported that it is effective in three canine automatic ventricular tachycardia (VT) models and has proved to be one of the strongest among the class I agents, as judged by its low antiarrhythmic plasma concentrations (3). The three canine models of VT (4) were produced by two-stage coronary ligation, digitalis intoxication and halothane-adrenaline combination. By comparing the efficacy of various antiarrhythmic drugs on the three VTs, we concluded that the adrenaline-induced arrhythmias are Ca channel-dependent (i.e., suppressed by Ca channel blockers or  $\beta$ -blockers), whereas the coronary ligation and digitalis-induced arrhythmias are Na channel-dependent (i.e., suppressed by Na channel blockers) (4).

Triggered activity due to early or delayed afterdepolarizations is one type of abnormal automaticity, and it has been suggested to be an important mechanism involved in some clinical arrhythmias such as those occurring in digitalis toxicity or in ischemic myocardium (5). The mechanism of occurrence of delayed afterdepolarizations

is related to Ca overload in the myocytes, and it then causes an oscillatory release of Ca from the sarcoplasmic reticulum and induces transient depolarization either due to activation of nonselective cation channels in the sarcolemma or due to activation of the Na-Ca exchange current. This phenomenon has been demonstrated to occur in isolated cardiac preparations (6–14), but there have been few demonstrations of triggered activity in vivo in



**Fig. 1.** The chemical structure of bisamil.

the intact heart of experimental animals (15). Recently, we reported a new *in vivo* canine triggered arrhythmia model, and we examined the antiarrhythmic effects of lidocaine, disopyramide, and verapamil (16–19). The properties of these ventricular ectopic beats induced after a train of stimuli were quite similar to those observed *in vitro* (5, 20–22). Namely, both could be triggered by rapid ventricular stimulation before the occurrence of the spontaneous ventricular arrhythmia, and the coupling interval of the first ectopic beat was shortened as the stimulation rate was increased (16, 17). In these studies, intravenous Na channel blockers, lidocaine and disopyramide, suppressed the triggered arrhythmias induced by intravenous digitalis, but a Ca channel blocker, verapamil, when given intravenously, did not suppress the occurrence (17). However, when the Ca channel blocker gallopamil was given locally into the anterior descending coronary artery in order to block selectively the cardiac Ca channels, it suppressed the triggered arrhythmias induced by selective infusion of adrenaline into the same coronary artery of the halothane anesthetized dogs (19). These results in the new *in vivo* canine triggered arrhythmia model were similar to those on the three automatic VTs in that the digitalis-induced one was more easily suppressed by Na channel blockers, but the adrenaline-induced one was suppressed easily by Ca channel blockers.

In the present study, we investigated antiarrhythmic effects of the potent class I drug bisaramil on this new triggered arrhythmia model produced by locally administering digitalis and adrenaline into the canine anterior descending coronary artery and compared them with those of other antiarrhythmic drugs.

## MATERIALS AND METHODS

### *Locally produced triggered arrhythmia in vivo*

Thirty-seven mongrel dogs of either sex, weighing 9.5–23 kg, were anesthetized initially with thiopental sodium (30 mg/kg, *i.v.*). Both vagi were cut at the midcervical level to suppress the occurrence of digitalis, or reflex, induced A-V block. After intubation, 1.0% halothane vaporized with 100% oxygen was introduced using a volume-limited ventilator to maintain anesthesia and to keep the heart rate at relatively low levels. Two catheters were placed into the right femoral artery and vein for recording the blood pressure and for administering drugs, respectively. After left thoracotomy at the fifth intercostal space, the pericardium was incised to expose the left anterior descending coronary artery (LAD), and the heart was placed in a pericardial cradle. LAD was carefully dissected from the surrounding tissue for about 1 cm between the base of LAD and the first diagonal branch. Bipolar stimulating electrodes were sutured on the

epicardium of the left ventricle. Other bipolar electrodes were sutured on the left atrial appendage for recording the atrial electrograms. After injection of heparin calcium (initially 500 units/kg and additionally 200 units/kg every hour), the left carotid artery was cannulated in order to drain arterial blood, a polyethylene cannula was inserted into the LAD, and the perfusion of the LAD area was immediately started. The rate of blood flow through the LAD was measured with an electromagnetic flowmeter (MVF-1100; Nihon Kohden, Tokyo) attached to the perfusion circuit. The lead II ECG, atrial electrograms and blood pressure were continuously recorded. Repeated trains of ventricular stimulation with pulses of 3-msec duration and twice the threshold voltage were provided by a programmed stimulator (DSP-910; Dia Medical, Tokyo). The standard pattern of stimulation was 15 pulses, enough to capture the ventricular excitable period, of 250 msec cycle length followed by a 5 sec pause; and with the use of ouabain or adrenaline, this pattern of stimulation produced 1–4 ectopic beats as described later. Sustained VT was rarely induced even after changing the cycle length or introducing early premature stimulation. As reported earlier (16), for induction of digitalis-induced triggered arrhythmias, a bolus intracoronary dose of 20  $\mu$ g ouabain followed by an additional dose of 10  $\mu$ g every 30–40 min was given through the rubber tube connecting the cannula. For induction of adrenaline-induced triggered arrhythmias, adrenaline was initially infused into the perfusion system at a speed of 0.1  $\mu$ g/ml/min; and if there was no induction of triggered arrhythmias, then the perfusion rate was increased by a 0.1  $\mu$ g/ml/min increment until ventricular ectopic beats were continuously induced soon after the end of a train of the ventricular stimulation. Then a peristaltic pump (Cole-Parmer Instrument, Chicago, IL, USA) was connected to the perfusion system to maintain a constant blood flow under various pharmacological interventions at the control level while administering drugs intraarterially. Bisaramil and other reference drugs were injected into the rubber tube connecting the cannula. The number of ventricular ectopic beats were counted during the consecutive three 5-sec pauses between electrical stimulation applied immediately before (0 min) and 1, 3, 5 and 10 min after drug injections. After confirming the recovery of the number of ventricular ectopic beats following rapid ventricular stimulation, a higher dose or the next drug was tested.

All these animal experiments were approved by our medical university animal experimentation committee, and animals were obtained through the Institute for Experimental Animals of Yamanashi Medical University.

### *Drugs and statistics*

Bisaramil was supplied by Taiho Pharmaceutical Co.

(Tokushima). The reference drugs used were disopyramide phosphate (an intermediate kinetic class I drug; Nippon Roussel K.K. through Chugai Pharmaceutical Co., Tokyo), lidocaine hydrochloride (a fast kinetic class I drug; Fujisawa Pharmaceutical Co., Osaka), flecainide acetate (a slow kinetic class I drug; Eisai Co., Tokyo) and verapamil hydrochloride (a class IV drug; Sigma Chemical Co., St. Louis, MO, USA). These drugs were dissolved in physiological saline. Each data were calculated as the mean  $\pm$  S.E. of 3 determinations, and statistical analyses were performed by a paired *t*-test, as compared to the 0 time values.

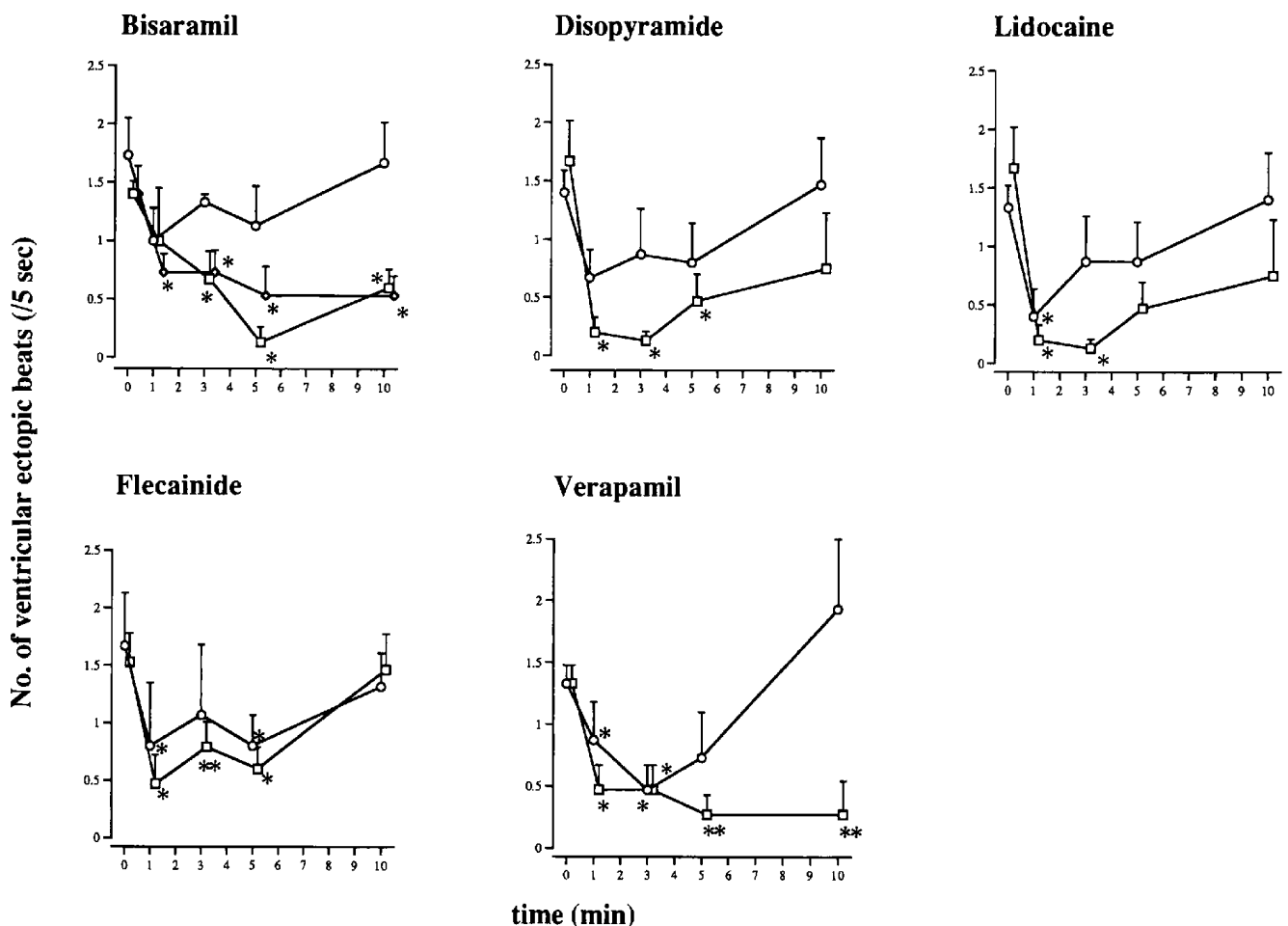
## RESULTS

### *Effects of bisamil and other antiarrhythmic drugs on*

### *locally produced digitalis-induced triggered arrhythmias in vivo*

No ventricular ectopic beats were induced by rapid ventricular stimulation before the administration of ouabain. However, after treatment with ouabain 20–130  $\mu$ g, directly injected into the LAD, there was a period when no spontaneously occurring ventricular ectopic beats were observed, but several coupled ventricular ectopic beats could be induced immediately following the last driven beat within about 20 min after ouabain injection in 25 out of 30 dogs. The number of induced ventricular ectopic beats were from 1 to 4 (mean: 1.4,  $n=25$ ), and the morphology of the ventricular ectopic beats usually changed in a beat-to-beat fashion. During the period when the triggered arrhythmia was induced, the mean blood pressure, the heart rate and the coronary blood flow changed little

### Digitalis-induced



**Fig. 2.** Effects of bisamil and the other antiarrhythmic drugs on digitalis-induced triggered activity ( $n=5$ ). Vertical bar: mean  $\pm$  S.E. of the numbers of ventricular ectopic beats during a pause between trains of rapid ventricular stimulation. Horizontal bar: time course after drug administration. \* $P < 0.05$ , \*\* $P < 0.01$ . Bisamil:  $\circ$  1  $\mu$ g,  $\square$  3  $\mu$ g,  $\diamond$  10  $\mu$ g; Disopyramide:  $\circ$  300  $\mu$ g,  $\square$  1000  $\mu$ g; Lidocaine:  $\circ$  300  $\mu$ g,  $\square$  1000  $\mu$ g; Flecainide:  $\circ$  10  $\mu$ g,  $\square$  30  $\mu$ g; Verapamil:  $\circ$  10  $\mu$ g,  $\square$  30  $\mu$ g.

after ouabain injection. After observing repeated induction of stable ventricular ectopic beats during the 5-sec pause, effects of drugs injected into the perfusion system were examined for 10 min.

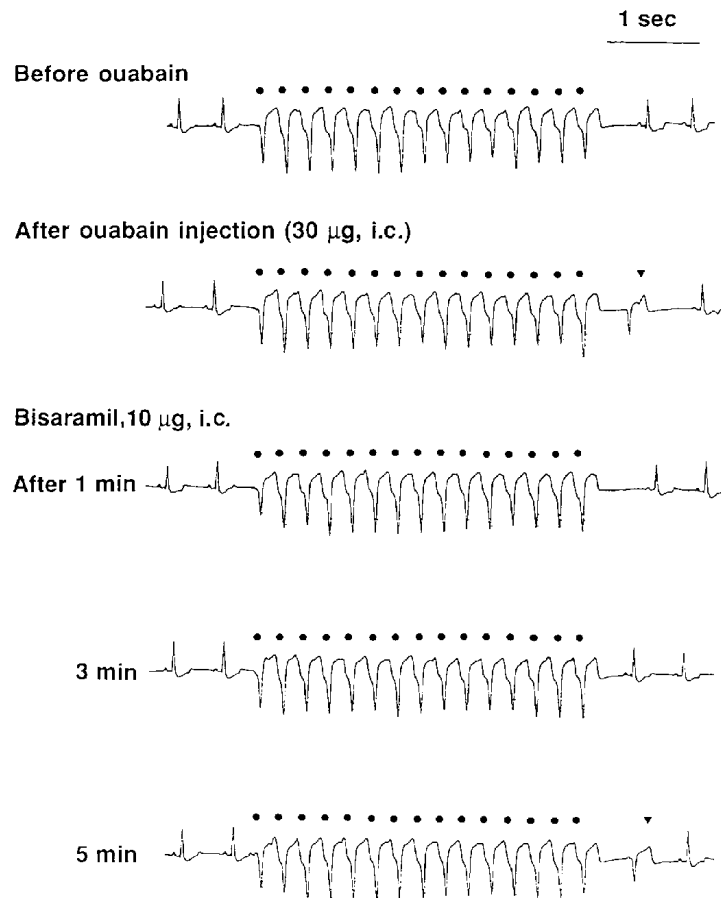
Bisaramil at a dose of 1  $\mu\text{g}$ , i.c. had no effect on the occurrence of triggered ventricular ectopic beats, but at doses of 3  $\mu\text{g}$ , i.c. and above, it suppressed them 1 or 3 min after injection (Fig. 2). Figure 3 represents typical data of 10  $\mu\text{g}$  bisaramil, showing that bisaramil suppressed the occurrence of triggered ventricular ectopic beats from 1 to 3 min after injection (Fig. 2). Disopyramide at a dose of 300  $\mu\text{g}$ , i.c. had little effect on the number of triggered ventricular ectopic beats, but 1000  $\mu\text{g}$ , i.c. suppressed them significantly from 1 to 5 min after injection (Fig. 2). Lidocaine at doses of 300  $\mu\text{g}$ , i.c. and above suppressed the triggered ventricular ectopic beats from 1 to 3 min after injection (Fig. 2). Flecainide at doses of 10  $\mu\text{g}$ , i.c. and above suppressed the occurrence of triggered ventricular ectopic beats from 1 to 5 min after injection (Fig. 2). Verapamil at doses of 10  $\mu\text{g}$ , i.c. and above suppressed

the triggered ventricular ectopic beats 1 min after injection, and the effect of 30  $\mu\text{g}$ , i.c. lasted more than 10 min (Fig. 2).

*Effects of bisaramil and other antiarrhythmic drugs on locally produced adrenaline-induced triggered arrhythmias in vivo*

The rapid ventricular stimulation under adrenaline infusion into the perfusion system at a speed of 0.1–0.5  $\mu\text{g}/\text{ml}/\text{min}$  induced several ventricular ectopic beats during the 5-sec pauses in 14 out of 15 dogs. The number of ventricular ectopic beats were from 1 to 4 (mean: 1.4,  $n=14$ ), and their morphology and their mode of occurrence were similar to those of the digitalis-induced ones. The mean blood pressure, the heart rate and the coronary blood flow changed little after adrenaline infusion. After confirming repeated induction of stable ventricular ectopic beats during the 5-sec pause, the effects of drugs were examined.

At a dose of 1  $\mu\text{g}$ , i.c., bisaramil barely suppressed the



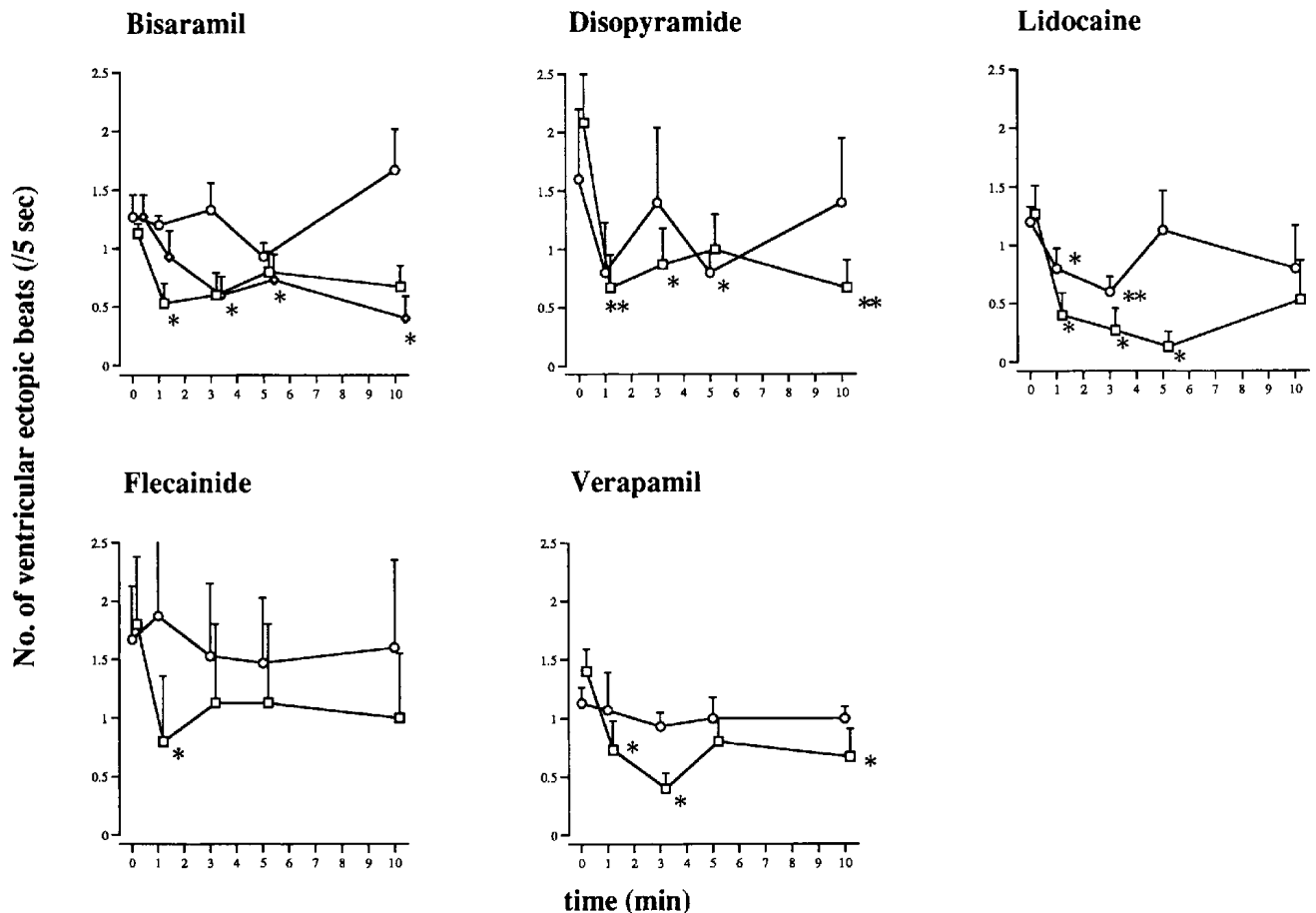
**Fig. 3.** Effects of bisaramil on digitalis-induced triggered activity. Each trace represents the limb lead II. ●: ventricular stimulation, ▼: ventricular ectopic beat. After ouabain administration (30  $\mu\text{g}$ , i.c.), the ventricular ectopic beats were induced during a pause between trains of rapid ventricular stimulation. Bisaramil, at the dose of 10  $\mu\text{g}$ , i.c., suppressed the ventricular ectopic beats.

triggered ventricular ectopic beats. However, at doses of 3  $\mu\text{g}$ , i.c. and above, it suppressed the occurrence of ectopic beats 1 and 3 min after injection (Fig. 4). As shown in Fig. 5, 10  $\mu\text{g}$ , i.c. of bisaramil decreased the average number of the triggered ventricular ectopic beats 1 to 3 min after injection. Both disopyramide and lidocaine at doses of 300  $\mu\text{g}$ , i.c. and above suppressed the ventricular ectopic beats. Flecainide at a dose of 10  $\mu\text{g}$ , i.c. had no effect on the occurrence of triggered ventricular ectopic beats, but the dose of 30  $\mu\text{g}$ , i.c. suppressed them. Verapamil at a dose of 3  $\mu\text{g}$ , i.c., which was lower than that necessary for suppressing the digitalis-induced triggered arrhythmia, suppressed the ventricular ectopic beats 1 min after injection (Fig. 4).

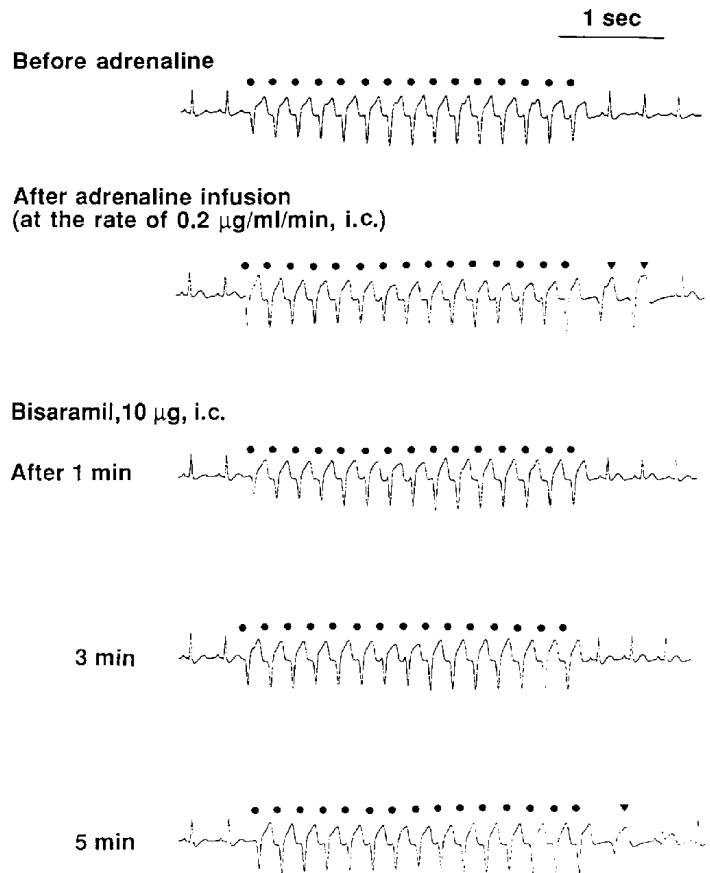
## DISCUSSION

Bisaramil is a newly synthesized potent class I antiarrhythmic drug. We recently reported that bisaramil (0.3–1.5 mg/kg, i.v.) is effective in suppressing canine models of digitalis-, adrenaline- and two-stage coronary ligation-induced arrhythmias; and it is also quite a potent agent, judging from its low antiarrhythmic plasma concentrations (plasma concentration that decreased the arrhythmic ratio, the number of ectopic beats divided by the total heart rate to 50% of the control value ( $\text{IC}_{50}$ ) for digitalis, adrenaline and two stage coronary ligation-induced arrhythmias: 0.1, 0.8 and 0.8  $\mu\text{g}/\text{ml}$ ) (3). An in vitro cardiac electrophysiological study indicates that at concentrations of 0.3  $\mu\text{M}$  (0.1  $\mu\text{g}/\text{ml}$ ) and above, bisaramil suppresses Na channels; and its potency is higher than those of flecainide, lidocaine and disopyramide, and

### Adrenaline-induced



**Fig. 4.** Effects of bisaramil and the other antiarrhythmic drugs on adrenaline-induced triggered activity ( $n=5$ ). Vertical bar: mean  $\pm$  S.E. of the numbers of ventricular ectopic beats during a pause between trains of rapid ventricular stimulation. Horizontal bar: time course after drug administration. \* $P < 0.05$ , \*\* $P < 0.01$ . Bisaramil:  $\bigcirc$  1  $\mu\text{g}$ ,  $\square$  3  $\mu\text{g}$ ,  $\diamond$  10  $\mu\text{g}$ ; Disopyramide:  $\bigcirc$  300  $\mu\text{g}$ ,  $\square$  1000  $\mu\text{g}$ ; Lidocaine:  $\bigcirc$  300  $\mu\text{g}$ ,  $\square$  1000  $\mu\text{g}$ ; Flecainide:  $\bigcirc$  10  $\mu\text{g}$ ,  $\square$  30  $\mu\text{g}$ ; Verapamil:  $\bigcirc$  1  $\mu\text{g}$ ,  $\square$  3  $\mu\text{g}$ .



**Fig. 5.** Effects of bisamil on adrenaline-induced triggered activity. Each trace represents the limb lead II. ●: ventricular stimulation. ▼: ventricular ectopic beat. After adrenaline infusion at the rate of  $0.2 \mu\text{g}/\text{min}$ , the ventricular ectopic beats were induced during a pause between trains of rapid ventricular stimulation. Bisamil suppressed the ventricular ectopic beats at the dose of  $10 \mu\text{g}$ , i.c.

it also suppresses cardiac Ca channels at  $1\text{--}3 \mu\text{M}$  ( $0.3\text{--}1 \mu\text{g}/\text{ml}$ ) (1).

The triggered ventricular arrhythmias are new model arrhythmias probably occurring from triggered activity induced by the delayed afterdepolarizations (DAD) (17, 19). The delayed afterdepolarizations have been proved to be due to a Ca overload of the myocardium, so in previous papers, we used intravenous digitalis or intravenous and intracoronary adrenaline to increase Ca intracellularly via Na,K ATPase inhibition or opening Ca channels (23, 24). The doses of digitalis and adrenaline were chosen so that they would not induce spontaneous automaticity, but induce triggered activity when rapid stimulation followed by a pause was applied to the heart. Our in vivo triggered arrhythmia models produced by digitalis or adrenaline were probably produced by the DAD, because they were induced only after rapid driving and the coupling interval between the last driven beat and the first ectopic beats shortened as the driving rates were increased. In the present study, we tried to produce triggered arrhythmias by intracoronary injection of adrena-

line and ouabain so that we could examine the effects of drugs without their systemic vascular effects. We could induce runs of ectopic beats, which were stable enough to examine drug effects on the induction of these arrhythmias. For those locally induced triggered ventricular arrhythmias by digitalis and adrenaline, both Na and Ca channel blockers were effective. The inhibitory effects of bisamil or flecainide on locally produced digitalis-induced triggered arrhythmia were stronger than those of lidocaine or disopyramide. This order of potency of Na channel blockers is similar to that on the canine spontaneous occurring digitalis-induced arrhythmia model where the  $\text{IC}_{50}$  was  $0.1$ ,  $1.4$ ,  $5.7$  and  $6.9 \mu\text{g}/\text{ml}$  for bisamil, flecainide, lidocaine and disopyramide, respectively (3). Thus our results of the effectiveness of Na channel blockers on this triggered digitalis arrhythmia can be explained by either the suppression of the Na channel of the surrounding normal cardiac cells responding to the action potential conducted from the arrhythmogenic foci or by direct suppression of the occurrence of the Na channel-dependent action potential of the arrhythmogenic foci.

As for the Ca channel blocker, intracoronary verapamil suppressed the locally produced digitalis-induced triggered arrhythmias. Previously, we reported that verapamil, when given intravenously to digitalis induced triggered arrhythmias, was not effective (17). It may be that in the case of intravenous administration, verapamil did not reach sufficient concentration to suppress cardiac Ca channels due to its systemic vasodilating action, whereas in the present case of intracoronary administration, verapamil reached sufficient concentration to suppress cardiac Ca channels and to suppress the amplitude of DAD. Verapamil was also effective in suppressing locally produced adrenaline-induced triggered arrhythmias at doses that were lower than those suppressing the digitalis-induced locally produced triggered arrhythmias, and these results are consistent with our previous reports on the intravenously produced adrenaline triggered arrhythmias (16, 17). Since adrenaline opens Ca channels, the direct Ca channel blocking effect of verapamil might have antagonized adrenaline to increase intracellular Ca and to induce DAD. Na channel blockers were also effective in suppressing adrenaline-induced triggered arrhythmias, probably indicating that Na currents may be indirectly involved in the generation of DAD.

In conclusion, the locally produced triggered arrhythmias were suppressed by both Na and Ca channel blockers regardless of the use of ouabain or adrenaline to induce arrhythmias, and there seems to be no specific drug that suppresses these triggered arrhythmias. However, as bisaramil is one of the strongest class I antiarrhythmic drugs, and is also effective on the triggered arrhythmias, it may become a useful drug for the treatment of various types of clinical arrhythmias.

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