

# Electrophysiological and Cardiohemodynamic Effects of AH-1058, a New Type Calcium Channel Blocker, Assessed by the In Vivo Canine Model

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**ABSTRACT**—AH-1058 (4-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride) is a novel calcium channel blocker whose chemical structure is quite different from those of typical calcium channel blockers. In this study, electrophysiological and hemodynamic effects of AH-1058 were assessed in the halothane-anesthetized, closed-chest canine model. Intravenous administration of a canine antiarrhythmic dose of 100 µg/kg of AH-1058 (*n* = 6) did not affect the cardiovascular variables, except that the cardiac output was decreased at 30 min after the drug administration. Additional administration of 200 µg/kg of AH-1058 (*n* = 6) suppressed the sinus nodal automaticity, AV nodal conduction and ventricular contraction and decreased the mean blood pressure, cardiac output and double product. The effects gradually appeared, while no change was detected in the intraventricular conduction, ventricular repolarization period, ventricular effective refractory period, preload to the left ventricle and total peripheral vascular resistance during the observation period of 30 min. The cardiosuppressive effects of AH-1058 can be explained by its calcium channel blocking action demonstrated in a previous in vitro experiment, while the lack of the effect on the vascular resistance would suggest that AH-1058 may become a slow-acting cardioselective calcium channel blocker.

**Keywords:** AH-1058, Calcium channel blocker, Electrophysiologic effect, Hemodynamic action, Monophasic action potential

AH-1058 is a novel cyproheptadine-derived calcium channel blocker and its chemical structure is quite different from each of the well-established calcium channel blockers, as shown in Fig. 1. In an electrophysiological in vitro study using guinea pig cardiomyocytes, AH-1058 blocked L-type calcium channels along with a weak inhibition of sodium channel currents (1). On the transmembrane action potential, AH-1058 shortened the action potential duration without affecting its maximum upstroke velocity (2). Moreover, in our previous studies (1, 3) using the animal arrhythmia models, AH-1058 suppressed various types of experimental ventricular arrhythmias of dogs, rats and guinea pigs. However, precise analysis of the cardiovascular effects of AH-1058 has not been reported.

The present study was designed to simultaneously analyze the electrophysiological and cardiohemodynamic effects of AH-1058 in both antiarrhythmic and intentionally high doses, using the halothane-anesthetized, closed-chest canine model (4–8). In this study, we recorded the

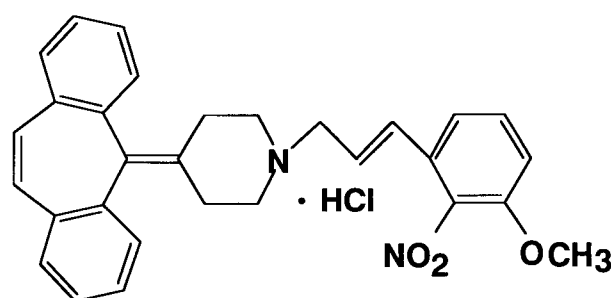


Fig. 1. Chemical structure of AH-1058.

His bundle electrogram and monophasic action potentials (MAPs) in addition to the surface lead II ECG to precisely analyze effects of the drug on the depolarization and repolarization processes of the heart (6–8). Moreover, the atrial pacing as well as the introduction of premature stimuli was applied to detect the latent inhibitory effects of the drug on the sinus nodal as well as AV nodal function (7, 9).

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## MATERIALS AND METHODS

All experiments were performed according to Guidelines for Animal Experiments, Yamanashi Medical University.

### *Surgical preparation*

Six beagle dogs were initially anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1.0% halothane was inhaled with a volume-limited ventilator (SN-408-3; Shinano, Tokyo). Heparinized catheters were placed in the aorta and the left ventricle via the right femoral artery for continuous monitoring of the systemic and left ventricular pressure, respectively. Maximum upstroke velocity of the left ventricular pressure ( $LVdP/dt_{max}$ ) and left ventricular end-diastolic pressure (LVEDP) were recorded to estimate the contractility and preload of the left ventricle, respectively. A thermodilution catheter (TC-704; Nihon-Kohden, Tokyo) was positioned at the right side of the heart via the left jugular vein. The cardiac output was measured by a standard thermodilution method using a cardiac output computer (MFC-1100, Nihon-Kohden). The double product was obtained using the following equation: double product = systolic blood pressure  $\times$  heart rate, which reflects the cardiac oxygen consumption rate (10). The total peripheral vascular resistance (TPR) was calculated using the basic equation:  $TPR = \text{blood pressure} / \text{cardiac output}$ . The surface lead II electrocardiogram (ECG) was obtained from the limb electrodes. A quad-polar electrodes catheter was positioned at the non-coronary cusp of the aortic valves via the left femoral artery to record the His bundle electrogram. Another quad-polar electrodes catheter was positioned at the right atrium via the left femoral vein for electrical pacing. A bi-directional steerable MAP recording/pacing combination catheter (model 1675P; EP Technologies, Inc., Sunnyvale, CA, USA) was positioned at the right ventricle via the right femoral vein.

### *Examinations by the programmed electrical stimulation of the heart*

As previously reported (7), the right atrium or right ventricle was electrically driven using a cardiac stimulator (SEC-3102, Nihon-Kohden). The pulses were rectangular in shape, 1–2 V (about twice the threshold voltage) and 1-ms duration.

**Sinus node recovery time (SNRT):** After the measurement of spontaneous sinus cycle length (SCL), the right atrium was driven at a cycle length of 300 ms for 30 s. The SNRT was obtained as a pause (ms) from the last paced atrial depolarization to the first sinus return cycle.

**Wenckebach blocking pacing cycle length (WBB-PCL):** The right atrium was driven at a cycle length just below SCL with progressive shortening of the cycle length in 10-

to 50-ms decrements. The WBB-PCL was obtained as the cycle length (ms) at which the Wenckebach phenomenon occurred.

**MAP signals:** The MAP signals obtained from the right ventricle were amplified with a DC preamplifier (model 300; EP Technologies, Inc.). The amplitude of the MAP is measured as the distance from the diastolic baseline to the crest of the MAP plateau phase as reported previously (11, 12). The duration of the MAP signal is measured as an interval from the MAP upstroke to the desired repolarization level, along a line horizontal to the diastolic baseline. The interval (ms) at 90% repolarization was defined as  $MAP_{90}$ . In this study, the  $MAP_{90}$  was measured during the sinus rhythm ( $MAP_{90(sinus)}$ ) and at a pacing cycle length of 400 ms ( $MAP_{90(CL400)}$ ).

**Effective refractory period of the atrio-ventricular node ( $ERP_{AV}$ ):** The refractory period of the atrio-ventricular (AV) node was assessed by a programmed electrical stimulation for the right atrium. The pacing protocol consisted of 8 beats of basal stimuli in a cycle length of 400 ms followed by an extrastimulus of various coupling interval. Starting from 400 ms, the coupling interval was shortened in 5- to 20-ms decrements until AV conduction block occurred. The  $ERP_{AV}$  is the longest coupling interval between the last basic stimulus and the premature impulse that fails to propagate through the AV node.

**Effective refractory period of the right ventricle ( $ERP_{RV}$ ):** The refractory period of the right ventricle (RV) was assessed by a programmed electrical stimulation for the right ventricle. The pacing protocol consisted of 8 beats of basal stimuli in a cycle length of 400 ms followed by an extrastimulus of various coupling intervals. Starting in the late diastole, the coupling interval was shortened in 5- to 20-ms decrements until refractoriness occurred.  $ERP_{RV}$  (ms) was defined as the shortest coupling interval that could produce an action potential. The postrepolarization refractoriness, defined as  $PRR = ERP - MAP_{90(CL400)}$ , was calculated to estimate the extent of the electrical vulnerability of the ventricular muscle (11–13).

### *Experimental protocol*

The hemodynamic and electrophysiological parameters were continuously monitored using a polygraph system (RM-6000, Nihon-Kohden) and recorded on a thermal array recorder (WS-682G, Nihon-Kohden) at a paper speed of 100 mm/s. The cardiovascular variables were assessed in the following order at each measurement point: The cardiac output was measured twice. The ECG, His bundle electrogram, systemic and left ventricular pressure, and MAP signal were recorded under sinus rhythm. Then, the His bundle electrogram and MAP signals were recorded during the atrial pacing at a cycle length of 400 ms. The SNRT was assessed twice to ensure that sinus entrance

block has not obscured the true SNRT. Then, the WBB-PCL,  $ERP_{AV}$  and  $ERP_{RV}$  were measured. After the control measurement, 100  $\mu\text{g}/\text{kg}$  of AH-1058, which has been demonstrated to suppress the canine ventricular arrhythmias (3), was intravenously administered. At 10, 20 and 30 min after the drug administration, the effects of the drug on each cardiovascular parameter were assessed. Additionally 200  $\mu\text{g}/\text{kg}$  of AH-1058 was administered at 40 min after 100  $\mu\text{g}/\text{kg}$  injection, and the drug effects were assessed in the same manner. The current model is known to be stable at least for 150 min, when drugs are not administered (6, 8).

### Drugs

The following drugs were used: AH-1058 (4-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride) (Ajinomoto Co., Inc., Kawasaki), thiopental sodium (Tanabe Seiyaku Co., Ltd., Osaka), halothane (Takeda Chemical Industries, Osaka) and heparin calcium (Mitsui Pharmaceuticals Co., Ltd., Tokyo). AH-1058 was dissolved in polyethylene glycol 400 / saline (70:30, vol/vol) at the concentration of 0.5 and 1.0 mg/ml for the drug administration of 100 and 200  $\mu\text{g}/\text{kg}$ , respectively. In our previous unpublished experiments, the same solvent was intravenously administered in a volume of 0.2 ml/kg, which did not affect any of the cardiovascular variables.

### Statistics

All values are expressed as the mean  $\pm$  S.E.M. Analysis of variance for repeated measures was employed for overall statistical analysis by using SuperANOVA (Abacus Concepts, Inc., Berkeley, CA, USA), followed by Contrasts for statistical analysis between basal values (zero time) and others. Differences at a *P* value  $< 0.05$  were considered to be statistically significant.

## RESULTS

### Cardiohemodynamic effects of AH-1058

**Effects on heart rate, mean blood pressure and double product:** Time course of the effects of AH-1058 on the heart rate, mean blood pressure and double product are summarized in Fig. 2 (upper), and their control values were  $116 \pm 4$  beats/min,  $112 \pm 6$  mmHg and  $15,162 \pm 1,019$  mmHg·beats/min, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g}/\text{kg}$  did not affect these parameters, but an additional 200  $\mu\text{g}/\text{kg}$  of AH-1058 significantly decreased the heart rate, mean blood pressure and double product. These bradycardic, hypotensive and oxygen saving effects developed slowly.

**Effects on  $LVdP/dt_{\text{max}}$  and LVEDP:** Time course of the effects of AH-1058 on the  $LVdP/dt_{\text{max}}$  and LVEDP are

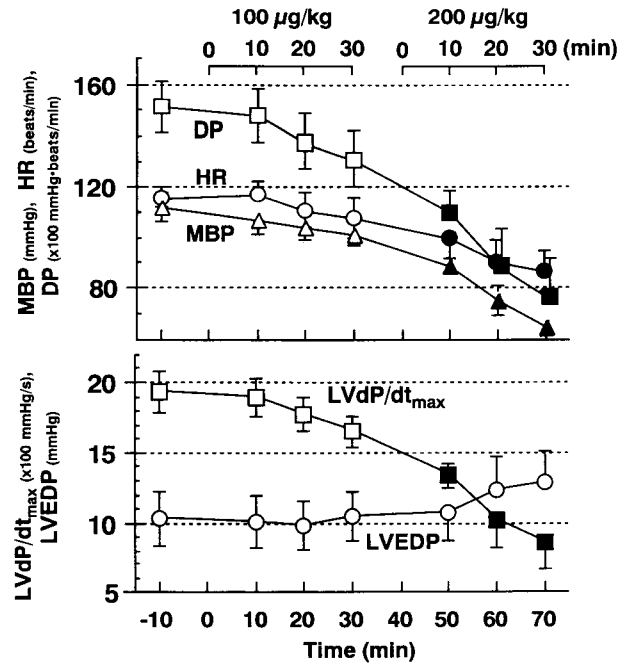


Fig. 2. Time course for the effects of intravenous administration of AH-1058 on heart rate (HR), mean blood pressure (MBP), double product (DP), the maximum upstroke velocity of left ventricular pressure ( $LVdP/dt_{\text{max}}$ ) and left ventricular end-diastolic pressure (LVEDP) in halothane-anesthetized dogs. Forty minutes after the administration of 100  $\mu\text{g}/\text{kg}$  of AH-1058, 200  $\mu\text{g}/\text{kg}$  of AH-1058 was additionally administered. Data are expressed as the mean  $\pm$  S.E.M. ( $n = 6$ ). Closed symbols represent significant change from the control values ( $P < 0.05$ ).

summarized in Fig. 2 (lower), and their control values were  $1,935 \pm 148$  mmHg/s and  $10 \pm 2$  mmHg, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g}/\text{kg}$  did not affect these parameters. Additional 200  $\mu\text{g}/\text{kg}$  of AH-1058 significantly decreased the  $LVdP/dt_{\text{max}}$ , but hardly affected the LVEDP. This negative inotropic effect developed slowly.

**Effects on cardiac output and TPR:** Time course of the effects of AH-1058 on the cardiac output and TPR are summarized in Fig. 3, and their control values were  $1.16 \pm 0.07$  l/min, and  $98.6 \pm 8.6$  mmHg·min/l, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g}/\text{kg}$  decreased the cardiac output at 30 min after the administration, while no significant change was detected in TPR. An additional 200  $\mu\text{g}/\text{kg}$  of AH-1058 further decreased the cardiac output, but no significant change was detected in TPR during the observation period.

### Electrophysiological effects of AH-1058

**Effects on ECG:** Time course of the effects of AH-1058 on ECG are summarized in Fig. 4 (upper). Control values of the PR interval, QRS width and QT interval were  $98 \pm 2$ ,  $71 \pm 2$  and  $280 \pm 18$  ms, respectively. Administration

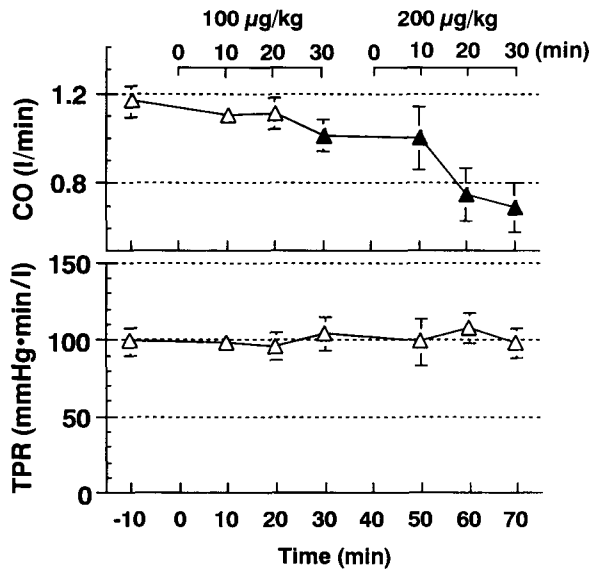


Fig. 3. Time course for the effects of intravenous administration of AH-1058 on cardiac output (CO) and total peripheral resistance (TPR) in halothane-anesthetized dogs. Forty minutes after the administration of 100  $\mu\text{g/kg}$  of AH-1058, 200  $\mu\text{g/kg}$  of AH-1058 was additionally administered. Data are expressed as the mean  $\pm$  S.E.M. ( $n=6$ ). Closed symbols represent significant change from the control values ( $P<0.05$ ).

of AH-1058 in a dose of 100  $\mu\text{g/kg}$  did not affect these parameters. An additional 200  $\mu\text{g/kg}$  of AH-1058 prolonged the PR interval at 20 and 30 min after the administration, while no significant changes were detected in the QRS width and QT interval during the observation period.

**Effects on sinus nodal function:** Time course of the effects of AH-1058 on the sinus nodal function are summarized in Fig. 4 (lower). Control values of SNRT and SCL were  $554 \pm 33$  and  $521 \pm 17$  ms, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g/kg}$  did not affect these parameters. An additional 200  $\mu\text{g/kg}$  of AH-1058 significantly prolonged the SNRT and SCL. This negative chronotropic action developed slowly. The corrected sinus node recovery time (CSNRT = SNRT – SCL) was calculated to estimate the effect of the drug on the intrinsic sinus nodal automaticity. The CSNRT was also prolonged by 200  $\mu\text{g/kg}$  of AH-1058.

**Effects on AV nodal function:** Time course of the effects of AH-1058 on the AV nodal function are summarized in Fig. 5. Control values of the WBB-PCL and  $\text{ERP}_{\text{AV}}$  were  $284 \pm 7$  and  $208 \pm 11$  ms, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g/kg}$  did not affect these parameters, but an additional 200  $\mu\text{g/kg}$  of AH-1058 significantly prolonged the WBB-PCL and  $\text{ERP}_{\text{AV}}$ . This negative dromotropic action developed slowly.

**Effects on His bundle electrogram:** Time course of the effects of AH-1058 on the His bundle electrogram are sum-

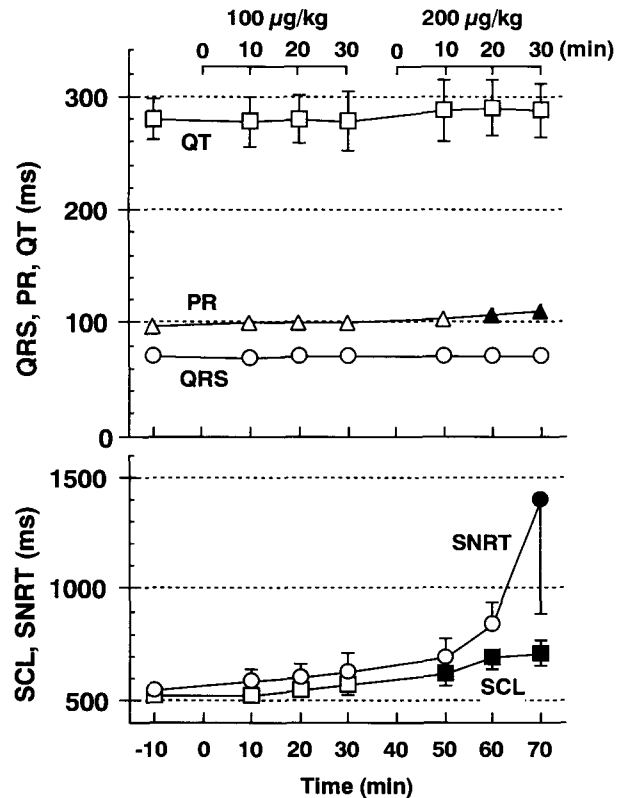


Fig. 4. Effects of intravenous administration of AH-1058 on the ECG and the sinus nodal function in halothane-anesthetized dogs. Forty minutes after the administration of 100  $\mu\text{g/kg}$  of AH-1058, 200  $\mu\text{g/kg}$  of AH-1058 was additionally administered. Data are expressed as the mean  $\pm$  S.E.M. ( $n=6$ ). Closed symbols represent a significant change from the control values ( $P<0.05$ ). PR, PR interval; QRS, QRS width; QT, QT interval; SNRT, sinus node recovery time; SCL, sinus cycle length.

marized in Fig. 5. Control values of the AH and HV intervals during sinus rhythm ( $\text{AH}_{(\text{sinus})}$  and  $\text{HV}_{(\text{sinus})}$ , respectively) were  $73 \pm 4$  and  $27 \pm 3$  ms, and those at a pacing cycle length of 400 ms ( $\text{AH}_{(\text{CL400})}$  and  $\text{HV}_{(\text{CL400})}$ , respectively) were  $76 \pm 6$  and  $25 \pm 2$  ms, respectively. Administration of AH-1058 in a dose of 100  $\mu\text{g/kg}$  did not affect these parameters, but an additional 200  $\mu\text{g/kg}$  of AH-1058 significantly prolonged the  $\text{AH}_{(\text{sinus})}$  and  $\text{AH}_{(\text{CL400})}$  at 30 min after the administration, while no significant change was detected in the  $\text{HV}_{(\text{sinus})}$  and  $\text{HV}_{(\text{CL400})}$  during the observation period.

**Effects on  $\text{ERP}_{\text{RV}}$  and  $\text{MAP}_{90}$  and PRR:** Control values of  $\text{ERP}_{\text{RV}}$ ,  $\text{MAP}_{90(\text{sinus})}$ ,  $\text{MAP}_{90(\text{CL400})}$  and PRR were  $244 \pm 12$ ,  $248 \pm 29$ ,  $238 \pm 8$  and  $3 \pm 8$  ms, respectively. Administration of AH-1058 in doses of 100  $\mu\text{g/kg}$  as well as 200  $\mu\text{g/kg}$  did not affect  $\text{ERP}_{\text{RV}}$ ,  $\text{MAP}_{90(\text{sinus})}$  and  $\text{MAP}_{90(\text{CL400})}$ . PRR tended to increase after AH-1058 administration, but this effect did not achieve statistical significance (data not shown).

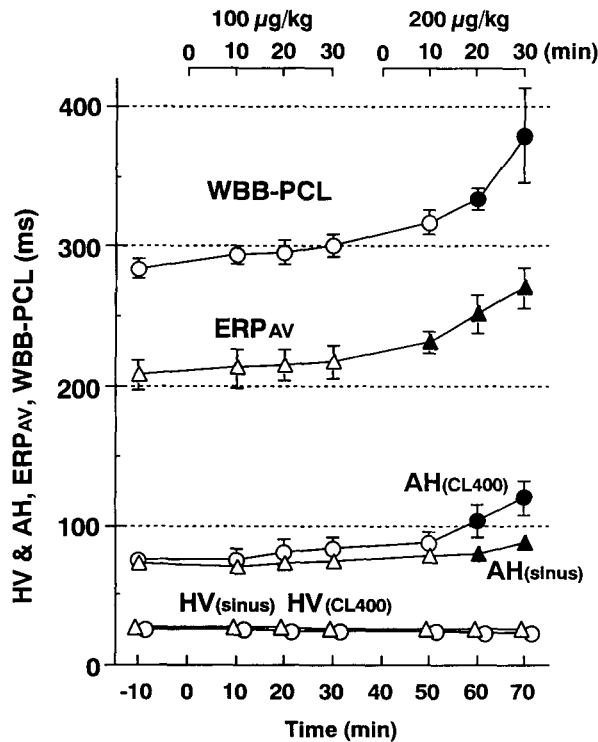


Fig. 5. Effects of intravenous administration of AH-1058 on the AV nodal function and the His bundle electrogram in halothane-anesthetized dogs. Forty minutes after the administration of 100 µg/kg of AH-1058, 200 µg/kg of AH-1058 was additionally administered. Data are expressed as the mean ± S.E.M. (n = 6). Closed symbols represent a significant change from the control values ( $P < 0.05$ ). AH<sub>(sinus)</sub>, AH interval during sinus rhythm; AH<sub>(CL400)</sub>, AH interval at a pacing cycle of 400 ms; HV<sub>(sinus)</sub>, HV interval during sinus rhythm; HV<sub>(CL400)</sub>, HV interval at a pacing cycle of 400 ms; WBB-PCL, Wenckebach block pacing cycle length of the AV node; ERP<sub>AV</sub>, effective refractory period of the AV node.

## DISCUSSION

The present study was designed to characterize the cardiovascular profile of a new type calcium channel blocker AH-1058 by simultaneously monitoring the hemodynamic and electrophysiological parameters (4–8). Intravenous administration of a canine antiarrhythmic dose of AH-1058 (3) did not significantly affect the cardiovascular variables except that the cardiac output was decreased. Additional administration of twice the antiarrhythmic dose suppressed the sinus nodal automaticity, AV nodal conduction and ventricular contraction and decreased the mean blood pressure, cardiac output and double product. These effects developed slowly, while no significant change was detected in the intraventricular conduction, ventricular repolarization period, preload to the left ventricle and total peripheral vascular resistance. The cardiosuppressive effects of AH-1058 can be explained by its calcium channel

blocking action observed in previous in vitro experiments (1, 2), while the lack of effect on the total peripheral vascular resistance is unique to this drug. In addition, AH-1058 failed to alter the intraventricular conduction as well as the refractoriness of the ventricle, suggesting that AH-1058 hardly affects sodium channels of the in vivo canine heart, unlike the observation in the isolated guinea pig cardiomyocytes (1).

The most important finding of this study is the lack of effect of AH-1058 on the total peripheral vascular resistance, since typical calcium channel blockers including verapamil, diltiazem and nifedipine are well known to exert a potent vasodilator action with variable extent of negative chronotropic, inotropic and dromotropic effects (14–16). Since the cardiac output is the product of the stroke volume and heart rate, the negative inotropic and chronotropic effects of AH-1058 must decrease the cardiac output leading to its hypotensive action. Thus, AH-1058 may become a cardioselective calcium channel blocker, and AH-1058 can be applied for the treatment of certain pathological processes, in which selective inhibition of the cardiac calcium channels would be essential for the drug therapy (3, 17–20).

The time course of the pharmacodynamic effects of AH-1058 also deserves a comment. The negative chronotropic, inotropic and dromotropic effects of AH-1058 developed slowly. Since any active metabolite modulating calcium channel functions was not found by extensive laboratory examinations and a similar slow kinetic property was demonstrated in a previous in vitro study (2), it might be explained by the high lipophilicity of AH-1058 (1, 3). However, precise mechanisms of this slow-acting property need to be further elucidated.

In conclusion, the present study showed that AH-1058 may become a slow-acting cardioselective calcium channel blocker and suggests that AH-1058 can be applied for the treatment of certain pathological processes including angina on effort (17), hypertrophic cardiomyopathy (18), vasovagal syncope (19), dissecting aortic aneurysm (20) and ventricular arrhythmias (3), in which selective inhibition of the cardiac calcium channels would be essential for drug therapy.

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