J Pharmacol Sci **95**, 234 – 239 (2004)

Journal of Pharmacological Sciences

Full Paper

Development of a Halothane-Adrenaline Arrhythmia Model Using In Vivo Guinea Pigs

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Received October 20, 2003; Accepted April 8, 2004

Abstract. In vivo antiarrhythmic effects of diltiazem hydrochloride and nifekalant hydrochloride, a pure class III antiarrhythmic drug (Vaughan Williams' classification), on adrenaline induced ventricular arrhythmias were examined in halothane anesthetized guinea pigs. Continuous adrenaline infusion (12.5 μg/kg per min) induced ventricular arrhythmias. Arrhythmogenicity was significantly increased with vagotomy and higher concentration of halothane. After injection of diltiazem at 0.5 mg/kg, the arrhythmic ratio (the number of ventricular ectopic beats divided by the total heart beats) was significantly reduced compared with the predrug control value (0.69 *vs* 0.04, $P<0.05$). No significant change of arrhythmic ratio was observed after injection of nifekalant (0.57 *vs* 0.61, ns). After administration of nifekalant, the mean minimum adrenaline infusion rate that induced ventricular arrhythmia decreased from 9.29 to 6.43 μg/kg per min. On the other hand, before administration of diltiazem, the mean arrhythmogenic rate of adrenaline was 8.50 μg/kg per min, but ventricular arrhythmias were no longer induced during continuous infusion of diltiazem at 0.5 mg/kg per min. These results were qualitatively consistent with previous experiments using the canine halothane-adrenaline model. In conclusion, the halothane-adrenaline arrhythmia model using the in vivo guinea pig is useful for screening drugs with potential anti- or pro-arrhythmic properties.

Keywords: in vivo guinea pig, halothane-adrenaline arrhythmia model, ventricular arrhythmia, diltiazem, nifekalant

Introduction

Various kinds of experimental animal models have been introduced to evaluate antiarrhythmic and pro-arrhythmic effects of drugs. We have been using dog arrhythmia models, because clinical atrial and ventricular arrhythmias could be simulated and thus have been widely used for studying the mechanism of generation of arrhythmias and also evaluating drug effects (1). Recently, dogs have become expensive and thus using smaller animals have become popular. The use of smaller animals such as mice, rats, or guinea pigs is economical and can also be used for screening possible antiarrhythmic drugs. Among smaller animals, rats are frequently used for producing ischemia related arrhythmias; however, their ECG are different from humans in that their ventricular repolarization occurs very quickly. Thus rats cannot be used to examine QT prolonging drugs. On the other hand, among small animals, the guinea pig in particular has the advantage that its ECG is similar in QRS morphology to that of humans (2). Though there have been in vivo digitalis arrhythmia model studies using guinea pigs, halothane-adrenaline arrhythmias have been reported only in a few papers (3, 4). Numerous ionic channel studies have been done using guinea pig cardiomyocytes, and the guinea pig is known to have similar ventricular action potentials to that of humans.

In this study, we evaluated the usefulness and feasibility of examining QT prolonging drugs and also the halothane-adrenaline arrhythmia model of in vivo guinea pigs for screening anti- or pro-arrhythmic effects of drugs, especially the QT prolonging effect.

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Materials and Methods

Experimental preparation

These animal experiments were approved by the Yamanashi University Animal Experimentation Committee and animals were obtained through the Animal Laboratory for Research of Yamanashi University. Male guinea pigs (Std. Hartley) weighing 289 – 1200 g (444 ± 153 g, mean ± S.D.) were anesthetized initially with inhalation of dimethyl ether. After tracheal intubation, 2.0 – 4.0% halothane, vaporized with 100% oxygen, was administered with a volume-limited ventilator (15 ml/kg, 55 strokes/min, Model SN-480-7; Shinano, Tokyo). Both vagi were cut at the mid-cervical region. The leads I and II ECG were continuously monitored. A cervical artery catheter was inserted for blood pressure monitoring. The ECG and arterial pressure were recorded with a polygraph system (Sanei, Tokyo). ECG parameters including PQ interval, QRS duration, and QT interval were measured on the ECG chart recorded at a paper speed of 100 mm/s. The QTc interval was calculated using Bazett's formula, $QTc = QT / \sqrt{RR}$. Bilateral cervical veins were also cannulated for administering adrenaline and other drugs.

Production of adrenaline-induced arrhythmia

After surgical preparation, 30 – 45 min was allowed for stabilization, and then adrenaline diluted in 5 ml saline was intravenously infused. The rate of adrenaline infusion was varied from 2.5 to 15 μg/kg per min according to the protocol.

Protocol

Influence of halothane concentration and vagotomy: We observed the inducibility of ventricular arrhythmia in relation to the concentration of halothane for both vagotomized and non-vagotomized animals. The initial concentration of halothane was 2%. The rate of adrenaline infusion was 12.5 μg/kg per min. Five minutes after initiating adrenaline infusion, the hathothane concentration was increased to 3% and then to the maximal concentration of 4% after another 5 min. The same protocol was applied for the five vagotomized animals pretreated with a bolus injection of 1 mg/kg of *dl*-propranolol.

Arrhythmia suppressing effects of diltiazem and nifekalant: Ventricular arrhythmias were produced by continuous injection of adrenaline at an infusion rate of 12.5 μg/kg per min. The initial halothane concentration was 2%, and it was increased to 3% if no ventricular arrhythmias were induced 5 min after the start of adrenaline infusion. After induction of arrhythmia, a bolus injection of diltiazem at 0.5 mg/kg was made. Five minutes after the first injection of diltiazem, an additional bolus dose of 1.0 mg/kg was injected. The same protocol was applied for a bolus injection of 0.3 mg/kg and an additional 3.0 mg/kg of nifekalant (Fig. 1). The dose of diltiazem was chosen in accordance with a previous report on digitalis-induced in vivo guinea pig model (5). We also chose the first injection dose of nifekalant based on the preliminary experiments (n = 3) in which the QTc interval was prolonged by 25%. The blood pressure, heart rate, PQ interval, QRS duration, QT interval, and arrhythmic ratio were measured every minute between 5 min before and

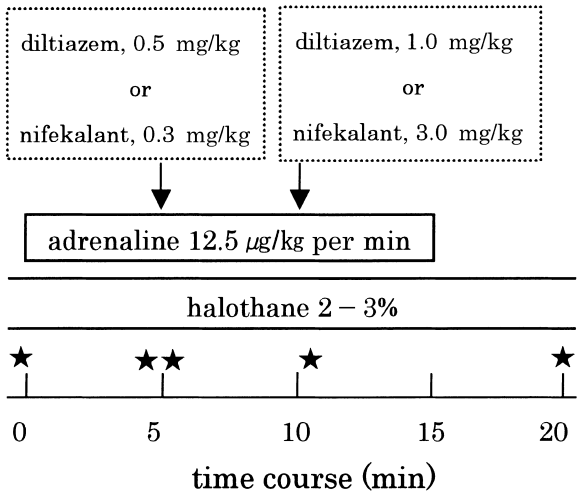

Fig. 1. Schema of experimental protocol to study the effect of diltiazem and nifekalant on adrenaline-induced arrhythmias in guinea pigs. The star symbols denote the time of measuring ECG parameters shown in Table 1.

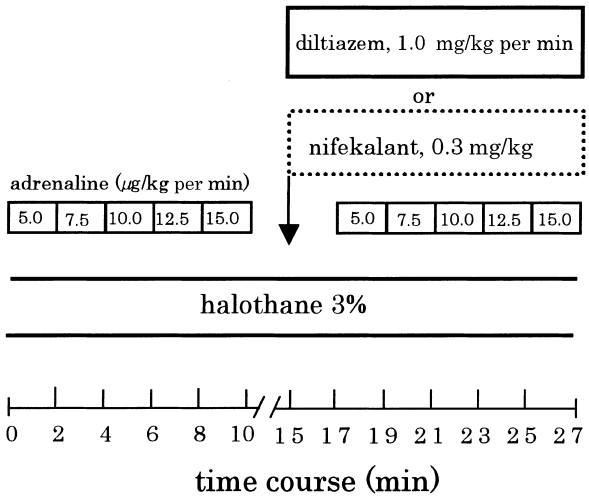

Fig. 2. Schema of experimental protocol to study the effect of diltiazem and nifekalant on arrhythmogenic dose of adrenaline in guinea pigs.

15 min after injection of drugs, and the mean value of these parameters during 2 min before and after the injection of drugs were statistically compared. Adrenaline infusion was discontinued 5 min after the second infusion of drugs. ECG parameters 5 min after the cessation of adrenaline infusion were also compared.

Effects of diltiazem and nifekalant on arrhythmogenic effects of adrenaline: Under anesthesia using 3% halothane, adrenaline was infused at an initial rate of 5.0 μg/kg per min and then increased by 2.5 μg/kg per min steps up to the maximum rate of 15 μg/kg per min every 2 min. These procedures were repeated before and after an infusion of diltiazem at 1.0 mg/kg per min to obtain the minimum adrenaline infusion rate at which ventricular arrhythmias were produced, namely the arrhythmogenic rate of adrenaline. The same protocol was applied for a bolus injection of 0.3 mg/kg of nifekalant (Fig. 2).

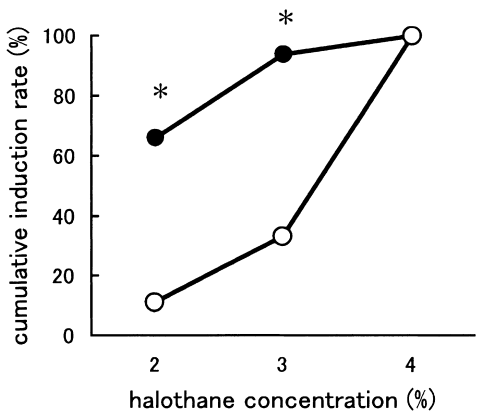

Fig. 3. Effects of halothane concentration on the cumulative induction rate of ventricular arrhythmias in vagotomized (solid circle, n = 65) and non-vagotomized (open circle, n = 9) animals. **P*<0.01, by Fisher's exact test to compare the cumulative induction rate of arrhythmia between vagotomized and non-vagotomized animals.

Drugs

The drugs used in the present study were diltiazem hydrochloride (Tanabe Seiyaku, Osaka), nifekalant hydrochloride (Mitsui Seiyaku Kogyou, Tokyo), *dl*-propranolol hydrochloride (Sigma Chemical Co., Tokyo), dimethyl ether (Wako Jyunyaku, Tokyo), halothane (Takeda Seiyaku, Tokyo), and adrenaline (Daiichi Seiyaku, Tokyo).

Data analysis and statistics

Severity of ventricular arrhythmia was expressed by the arrhythmic ratio: the number of ventricular ectopic beats divided by the total heart beats. Analysis of variance was performed to evaluate drug-induced changes in the blood pressure, heart rate, arrhythmic ratio, and ECG parameters. In evaluating the influence of vagotomy, Fisher's exact test was used to compare the arrhythmia induction rate in animals with and without vagotomy. Wilcoxon signed-rank test was used to compare before and after drug treatments. All data are presented as mean ± S.D. A *P* value less than 0.05 was accepted as statistically significant.

Results

Arrhythmia induction

A cumulative induction rate of ventricular arrhythmias in 2%, 3%, and 4% of halothane concentration was 66%, 94%, and 100%, respectively, in vagotomized animals (n = 65), whereas it was 11%, 33%, and 100%, respectively, in non-vagotomized animals (n = 9); and the differences between the two groups in 2% and 3% of halothane concentration were significant ($P<0.01$) (Fig. 3). When anesthetized with 4% halothane, ventricular fibrillation was induced in 78% and 44% of animals with and without vagotomy, respectively. However, in the five animals pretreated with *dl*-propranolol, no ventricular fibrillation was observed.

Arrhythmia suppressing effect of drugs

After the first injection of diltiazem at 0.5 mg/kg (n = 10), the arrhythmic ratio was significantly reduced compared with that just before the injection (0.69 *vs* 0.04, $P<0.05$). An additional second injection of diltiazem at 1.0 mg/kg completely suppressed ventricular arrhythmia (arrhythmic ratio = 0.0, $P<0.01$) (Fig. 4). No significant change of arrhythmic ratio was observed after injection of nifekalant (n = 10). The arrhythmic ratios before, after 0.3 and 3.0 mg/kg injection were 0.57, 0.61, 0.66, respectively (Fig. 4).

Both mean blood pressure and heart rate were significantly decreased after the administration of diltiazem. Two minutes before administration, the average mean blood pressure was 101 ± 14 mmHg, and after administration of 0.5 and 1.0 mg/kg diltiazem, it was 84 ± 12 and 75 ± 14 mmHg, respectively ($P<0.01$). Two minutes before administration, the heart rate was 269 ± 30 beats/min, and after administration of 0.5 and 1.0 mg/kg diltiazem, it was 250 ± 32 and 229 ± 38 beats/min, respectively ($P<0.01$). On the other hand, neither the blood pressure nor heart rate showed significant changes by administration of nifekalant. The mean blood pressure and heart rate before, after 0.3 mg/kg nifekalant, and after 3.0 mg/kg nifekalant were 110 ± 12, 102 ± 10, 103 ± 15 mmHg and 303 ± 23, 296 ± 36, 309 ± 36 beats/min, respectively.

As shown in the Table 1, none of the ECG parameters

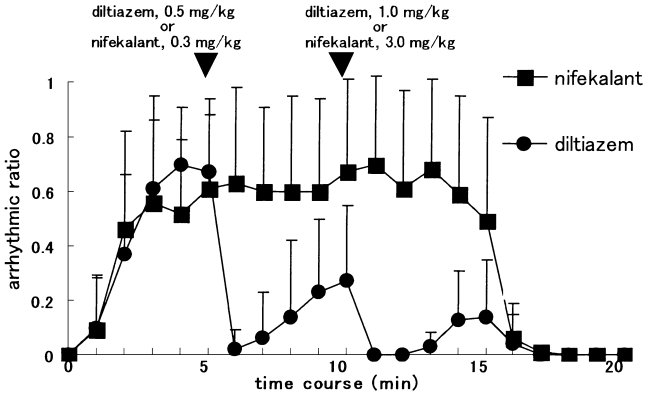

Fig. 4. Effects of diltiazem (n = 10) and nifekalant (n = 10) on the arrhythmic ratio. Each data point represents the mean, and vertical lines show S.D. **P*<0.05, ***P*<0.01, by paired Student's *t*-test between drug treatment and control.

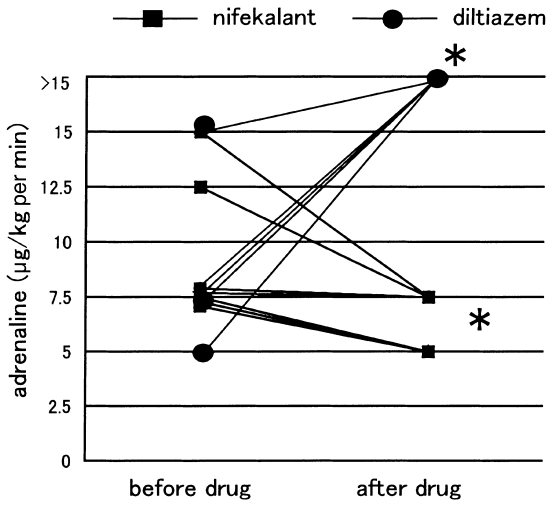

Fig. 5. Effects of diltiazem (n = 5) and nifekalant (n = 7) on the arrhythmogenic rate of adrenaline. **P*<0.05, by Wilcoxon signed-rank test.

showed significant changes with the administration of both diltiazem and nifekalant during continuous infusion of adrenaline. However, in the nifekalant group, compared with the baseline, 5 min after cessation of adrenaline infusion, the PQ interval, QRS duration, and QTc duration were significantly prolonged by 18% (*P*<0.05), 23% (*P*<0.05), and 11% (*P*<0.01), respectively. In the diltiazem group, only the change of PQ interval which was prolonged by 24% was significant (*P*<0.05).

Effect of drugs on arrhythmogenic effect of adrenaline

In this experiment investigating the arrhythmogenic effect of adrenaline, these two drugs showed opposite results. Before administration of nifekalant, the mean minimum adrenaline infusion rate that induced ventricular arrhythmia, namely, the arrhythmogenic rate of adrenaline, was 9 ± 3 μg/kg per min. After infusion of 3.0 mg/kg of nifekalant, the mean arrhythmogenic rate was significantly decreased to 6 ± 1 μg/kg per min (*P*<0.05) (n = 7) (Fig. 5). On the other hand, before administration of diltiazem, the mean arrhythmogenic rate of adrenaline was 8 ± 4 μg/kg per min, but no ventricular arrhythmia was induced during continuous infusion of diltiazem 0.5 mg/kg per min (*P*<0.05) (n = 5) (Fig. 5).

Discussion

Role of halothane on adrenaline arrhythmia

In the present study, it was shown that halothane enhanced arrhythmogenicity of adrenaline concentration-dependently. With 4% of halothane concentration, adrenaline infusion (12.5 μg/kg per min) produced ventricular arrhythmias in all animals irrespective of vagotomy.

Since Levy (6) demonstrated development of ventricular fibrillation in dogs after intravenous injection of adrenaline under moderately deep chloroform anesthesia, the use of sensitizing agents such as chloroform, cyclopropane, halothane, and so forth, in combination with

Table 1. Change in ECG parameters

	Diltiazem (n = 10)			Nifekalant (n = 10)		
	PQ	QRS	QT_C	PQ	QRS	QT_C
Baseline	65 ± 8	46 ± 8	383 ± 45	60 ± 7	39 ± 4	349 ± 5
Before drug	70 ± 12	41 ± 4	330 ± 35	60 ± 3	40 ± 5	327 ± 20
After 1st dose	72 ± 20	43 ± 4	305 ± 36	58 ± 6	41 ± 3	354 ± 31
After 2nd dose	82 ± 15	47 ± 7	320 ± 25	56 ± 9	43 ± 4	346 ± 14
5 min after the cessation of adrenaline	81 ± 16*	53 ± 15	343 ± 28	71 ± 13*	48 ± 7*	389 ± 17**

Values are shown as the mean (ms) ± S.D. **P*<0.05, ***P*<0.01 (compared with baseline).

exogenous catecholamine has been considered to be an important technique for the production of cardiac arrhythmias. Many experimental data suggested halothane sensitized the myocardium to the ventricular arrhythmogenic properties of catecholamines; however, the mechanisms for how halothane contributes to arrhythmia production has not been fully elucidated.

Previously, one of the authors (7) demonstrated the effect of different levels of supraventricular input by destroying the sinus node and atrial pacing in the canine adrenaline arrhythmia model. We concluded that the mechanism of sensitization to adrenaline by halothane to produce minor ventricular arrhythmia was mainly due to the slowing of the sinus rate by halothane and its direct effect of the ventricular myocardium was a subsidiary factor. Zukerman and Wheeler (8) reported that halothane inhibited sympathomimetic-induced arrhythmogenic activity in the single rat heart cell model. They speculated the probable mechanisms included altered impulse propagation, which might lead to phenomena such as reentry. As for investigators focused on adrenergic receptors, Maze and Smith (9) indicated that postsynaptic myocardial α_1 adrenergic receptors mediated most of the sensitization by halothane to the ventricular arrhythmogenic effects of catecholamines, while a lesser contribution was conferred by β_1 adrenoceptors. Hayashi et al. (10) reported the comparative roles of β_1 and β_2 adrenoceptors in myocardial sensitization by halothane in dogs. Their result suggested that myocardial β_1 adrenoceptors played an essential role in the genesis of arrhythmias during halothane anesthesia in dogs, whereas β_2 adrenoceptors did not. We have also indicated that β adrenoceptors played an important role in arrhythmogenicity by showing that ventricular fibrillation was completely inhibited by pretreatment with 1 mg/kg of propranolol administration. A recent study focusing on K^+ channels by Zhang et al. (11) showed I_{to} not $I_{K,ATP}$ might be involved in the mechanism producing halothane-adrenaline arrhythmias, using K^+ channel openers or blockers in rats. On the other hand, Rajani et al. (12) proposed that bradykinin, acting on the B_2 receptor via a mechanism involving the release of nitric oxide and prostaglandins, might attenuate the genesis of halothane-adrenaline arrhythmia. Thus the potential mechanism of sensitization is thought to be multifactorial and further investigation is required to determine the entire mechanism.

Arrhythmogenic dose of adrenaline

It is well known that arrhythmogenic doses of adrenaline vary among animal species. The mean arrhythmogenic dose of adrenaline, as shown in the present study of guinea pigs (Fig. 5), was 9.0 ± 3.3 μg/kg per min. It was quantitatively consistent with other reports using small animals such as rats and guinea pigs. Tripathi et al. (13) produced ventricular tachycardia by a bolus infusion of adrenaline at a dose 10 μg/kg intravenously in the rat and guinea pig anesthetized with intraperitoneal injection of urethane. Hoffman et al. (14) investigated the effects of ethanol treatment on adrenaline-induced arrhythmias in rats. They infused adrenaline at a rate of 10 μg/kg per min intravenously. Igic (15) showed intravenous administration of adrenaline (15 μg/kg per min) caused arrhythmias in rats. Using relatively large animals as the dog, we showed that adrenaline infusion at a rate between 0.25 and 1.5 μg/kg per 50 s caused ventricular arrhythmias with good reproducibility (7, 16). Therefore, it seems that dogs are almost tenfold more sensitive to adrenaline than smaller animals like rats and guinea pigs. As for other larger animal species, Gaynor et al. (17) investigated the effect of hypercapnia on the arrhythmogenic dose of adrenaline in horses anesthetized with halothane. They reported the arrhythmogenic dose of adrenaline at normocapnia was 1.35 μg/kg per min.

Vagotomy and arrhythmogenicity

It is now widely recognized that parasympathetic activity modulates some ventricular arrhythmias. As shown in the present study, the cumulative induction rate of ventricular arrhythmias during anesthesia using 2% and 3% halothane was 11% and 33% for the non-vagotomized group and 66% and 94% for the vagotomized group, respectively; and the difference of arrhythmia induction rate between the two groups was statistically significant ($P<0.01$). During anesthesia using 4% halothane, ventricular fibrillation was induced in 78% and 44% of vagotomized and non-vagotomized animals, respectively. In the present experiment, increment of the heart rate from the base line to the maximal sinus rate attained by adrenaline infusion was 25% in non-vagotomized animals and 37% in vagotomized animals ($P<0.05$). Also numerous other experimental reports suggest that vagal activities are cardioprotective, that is, antiarrhythmic in the ventricular arrhythmia models. Some of the investigators (18, 19) suggested that the antiarrhythmic property of the vagal nerve is related to its slowing effect on the heart rate. However, Zink et al. (20) concluded that bradycardia was not the sole mechanism of the vagal effect. They showed that the antiarrhythmic effect could be achieved with rapid stimulation of the vagus when the heart rate was maintained constant by atrial pacing in the halothane-adrenaline induced canine arrhythmia model. Taking inducibility of arrhythmia into consideration, it would

be advantageous to vagotomize in the experiments screening anti- or pro-arrhythmic effect of drugs. Actually, in the halothane-adrenaline arrhythmia model in dogs, vagotomy has been considered essential and is routinely performed.

Evaluation of antiarrhythmic drugs

The major object of the present study was to verify whether the in vivo guinea pig model could be substituted for the canine model for the evaluation of antiarrhythmic drugs. In the present study using guinea pig models, we demonstrated that diltiazem reduced halothane-adrenaline arrhythmia whereas nifekalant developed a tendency to aggravate ventricular arrhythmia. In the same way, diltiazem increased whereas nifekalant decreased the threshold for the induction of arrhythmias associated with adrenaline and halothane. These results are consistent with previous reports of the canine arrhythmia model. Iwatsuki et al. (21) indicated diltiazem significantly increased the threshold for the induction of ventricular arrhythmias in the canine halothane-adrenaline arrhythmia model. Komori et al. (22) also indicated that diltiazem was effective in suppressing halothane-adrenaline arrhythmias but ineffective in suppressing arrhythmia induced by digitalis. As for nifekalant, Xue et al. (23) investigated the proarrhythmic effects of nifekalant in canine models. They demonstrated administration of nifekalant significantly increased the arrhythmic ratio and also significantly shortened the interval between the injection and the occurrence of halothane-adrenaline arrhythmias.

Conclusions

The halothane-adrenaline arrhythmia model using the guinea pig is comparable to the canine model and is useful for screening drugs with potential anti- or pro-arrhythmic properties.

References

1 Hashimoto K, Xue YX, Chen JG, et al. Effects of class III antiarrhythmic drugs on ventricular arrhythmias in dogs. Exp Clin Cardiol. 1997;2:25–29.

2 Luisada AA, Sakai A, Feigen L. Comparative Electrocardiography and phonocardiography in six species of animals. Am J Vet Res. 1970;31:1695–1702.

3 Peterssen EN. Experimental anti-arrhythmic properties of melperone, a neuroleptic butyrophenone. Acta Pharmacol Toxicol. 1978;42:388–394.

4 Scott NC, French AM. The effect of a benzotriazinium salt on in vitro and in vivo arrhythmias in guinea-pigs and mice. Arch Int Pharmacodyn Ther. 1980;248:154–165.

5 Yamada K, Shimamura T, Nakajima H. Studies on a new 1,5-benzothiazepine derivative (CRD-401). V. Antiarrhythmic actions. Jpn J Pharmacol. 1973;23:321–328.

6 Levy G. The genesis of ventricular extrasystoles under chloroform with special references to consecutive ventricular fibrillation. Heart. 1914;5:299–334.

7 Hashimoto K, Hashimoto K. The mechanism of sensitization of the ventricle to epinephrine by halothane. Am Heart J. 1972;83:652–658.

8 Zuckerman RL, Wheeler DM. Effect of halothane on arrhythmogenic responses induced by sympathomimetic agents in single rat heart cells. Anesth Analg. 1991;72:596–603.

9 Maze M, Smith CM. Identification of receptor mechanism mediating epinephrine induced arrhythmias during halothane anesthesia in the dog. Anesthesiology. 1983;59:322–326.

10 Hayashi Y, Sumikawa K, Kuro M, et al. Roles of beta-1 and beta-2 adrenoceptors in the mechanisms of halothane myocardial sensitization in dogs. Anesth Analg. 1991;72:435–439.

11 Zhang S, Todoroki S, Urechino H, et al. Role of potassium channels in halothane-epinephrine arrhythmias. Res Commun Mol Pathol Pharmacol. 1998;100:339–350.

12 Rajani V, Hussain Y, Bolla BS, et al. Attenuation of epinephrine-induced dysrhythmias by bradykinin: role of nitric oxide and prostaglandins. Am J Cardiol. 1997;80:153A–157A.

13 Tripathi RM, Thomas GP. A simple method for the production of ventricular tachycardia in the rat and guinea pig. J Pharmacol Methods. 1986;15:279–282.

14 Hoffman P, Muller S, Zbinden G. Decrease of epinephrine-induced arrhythmia threshold in ethanol exposed rats. Arch Toxicol. 1992;66:430–434.

15 Igic R. Mechanism of epinephrine-induced dysrhythmias in rat involves local cholinergic activation. Can J Physiol Pharmacol. 1996;74:85–88.

16 Matsubara I, Hashimoto K, Katano Y, et al. Experimental anti-arrhythmic effects of *dl*-1-(tert.butylamono)-3-[(2-propinyloxy)phenoxy]2-propanol hydrochloride(*dl* Ko 1400-Cl), a new beta-adrenergic receptor blocking agent. Folia Pharmacol Jpn (Nippon Yakurigaku Zasshi). 1976;72:557–571. (text in Japanese with English abstract)

17 Gaynor JS, Bednarski RM. Muir WW 3rd. Effect of hypercapnia on the arrhythmogenic dose of epinephrine in horses anesthetized with guaifenesin, thiamylal sodium, and halothane. Am J Vet Res. 1993;54:315–321.

18 James RG, Arnold JM, Allen JD, et al. The effects of heart rate, myocardial ischemia and vagal stimulation on the threshold for ventricular fibrillation. Circulation. 1977;55:311–317.

19 Zuanetti G, De Ferrari GM, Priori SG, et al. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ Res. 1987;61:429–435.

20 Zink J, Sasyniuk BI, Dresel PE. Halothane-epinephrine-induced cardiac arrhythmias and the role of heart rate. Anesthesiology. 1975;43:548–555.

21 Iwatsuki N, Katoh M, Ono K, et al. Antiarrhythmic effect of diltiazem during halothane anesthesia in dogs and humans. Anesth Analg. 1985;64:964–970.

22 Komori S, Ishii M, Hashimoto K. Antiarrhythmic effects of coronary vasodilators on canine ventricular arrhythmia models. Jpn J Pharmacol. 1985;38:73–82.

23 Xue YX, Yamada C, Aye NN, Hashimoto K. MS-551 and KCB-328, two class III drugs aggravated adrenaline-induced arrhythmias. Br J Pharmacol. 1998;124:1712–1718.