J Anesth (1994) 8:93–100

Journal of
Anesthesia

Electrophysiologic effects of volatile anesthetics, sevoflurane and halothane, in a canine myocardial infarction model

HISAKUNI HASHIMOTO, SATOSHI IMAMURA, KAZUYUKI IKEDA, and MITSUYOSHI NAKASHIMA

Departments of Pharmacology and Anesthesiology, Hamamatsu University School of Medicine, Hamamatsu, 431-31 Japan

Abstract: The effects of sevoflurane and halothane on the effective refractory period (ERP) and ventricular activation were examined in a canine myocardial infarction model. Sevoflurane (1 MAC) reduced the heart rate and prolonged ERP in both normal and infarcted zones. A prolongation of ERP with sevoflurane was observed also during atrial pacing at a fixed rate, but the effect was less than during sinus rhythm. Sevoflurane either further delayed or blocked the delayed activation entirely in the infarcted zones with only slight effects on the activation of the normal zones. Halothane (1 MAC) prolonged ERP during sinus rhythm and atrial pacing, but to a lesser extent during the latter. Halothane also depressed ventricular activation in the infarcted zone during atrial pacing. In conclusion, sevoflurane as well as halothane selectively depresed the delayed activation and the prolongation of ERP in myocardial infarction, which may inhibit ventricular arrhythmias in myocardial infarction.

Key words: Sevoflurane, Halothane, Canine myocardial infarction, Ventricular activation, Effective refractory period

Introduction

When a volatile anesthetic is administered to patients with ischemic heart diseases, it may affect not only hemodynamics, but also electrophysiologic properties in the ischemic myocardium. There are several papers dealing with effects of halothane on electrical activities of normal and ischemic myocardium [1–9]. According to Reynolds et al. [2], halothane inhibits automaticity, shortens refractoriness, and slows conduction in nonischemic ventricular tissues. Turner et al. [5] examined the effects of halothane on the electrical activities of Purkinje fibers derived from normal and infarcted canine hearts. They showed that halothane decreased the maximal rate of depolarization ($\dot{V}$max), slowed the conduction, and prolonged the effective refractory period (ERP) in the infarcted zones. According to Deutsch et al. [9], volatile anesthetics (halothane, enflurane, and isoflurane) suppress the induction of ventricular arrhythmias and prolong ERP in canine myocardial infarction, whereas they did not observe any significant effects on ventricular conduction.

Recently, sevoflurane has frequently been used as a volatile anesthetic. Hemodynamic effects and some electrophysiologic effects of sevoflurane have been studied by several investigators [10–12]. However, electrophysiologic effects of sevoflurane on the infarcted heart have not been clarified yet. In the present study, we examined the effects of sevoflurane on ERP and intraventricular conduction in a canine myocardial infarction model and compared them with those of halothane, a common volatile anesthetic.

Address correspondence to: H. Hashimoto

Received for publication on July 14, 1992; accepted on May 29, 1993

Materials and methods

Animal preparation

Mongrel dogs weighing between 8.0–13.0 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Each animal was intubated and ventilated with room air using a positive pressure ventilator. A left thoracotomy was performed in the fourth intercostal space and the heart was exposed. After opening the pericardium, the left anterior descending coronary artery (LAD) was occluded according to the method of Harris [13] and then several branches of LAD were also occluded. The chest was closed after the complete occlusion, and routine postoperative care was performed including prophylatic antibiotic therapy, i.e., intramuscular administration of ceftizoxime everyday, during postinfarction convalescence.

Measurement of the excitation threshold and the ERP

The effects of the drugs were examined in seven animals. Five to eight days after the LAD occlusion, the animals were reanesthetized with sodium pentobarbital 20 mg/kg i.v. Ventilation was performed at 12 times/min with 100% O_2 at a tidal volume of 15 ml/kg. The body temperature of the animal was maintained at 36–37°C. Left thoracotomy was performed and the pericardium was opened. After the heart was cradled on the pericardium, bipolar stimulating electrodes were sutured on the left atrial appendage for atrial pacing. Several bipolar electrodes were also sutured on the epicardial surface of the left and the right ventricle for measuring ERP. The measurement was performed during atrial pacing slightly above the sinus rate in the control state. The measurement was performed also during a sinus rhythm after administration of the drug. The excitation threshold was measured by applying premature stimuli with various strengths at a coupling interval of 260 msec to the infarcted or the normal zones. For measuring the ERP, premature stimuli with a strength of twice the threshold were introduced to the infarcted or the normal zones at progressively shorter coupling intervals. The ERP was defined as the shortest interval at which conduction was successful. The systolic blood pressure of the femoral artery and the heart rate were also measured. In each animal, the effects of both sevoflurane and halothane were examined at a time interval of 1 h when the effect of the first drug was considered negligible.

Measurement of the ventricular activation time

The effects of the drugs were examined in eight animals. Five to eight days after the LAD occlusion, the animals were prepared as mentioned above. After the heart was cradled on the pericardium, bipolar stimulating electrodes were sutured on the left atrial appendage and the right ventricle for atrial pacing and applying a ventricular premature stimulation, respectively. Several bipolar electrodes were also sutured on the epicardial surface of the left or the right ventricle for recording ventricular activation. Usually, one electrode was sutured on the normal area in the right ventricle, and other two were on the infarcted zone in the left ventricle (Fig. 1). By monitoring the electrocardiograms in the risk areas, an area was searched for where delayed activation was observed, and one of the electrodes was sutured to the surface of the area. Another electrode in the infarcted zone was located at any point within the infarcted area regardless of the activation delay. The atrial pacing was performed at a rate slightly above the sinus rate in a control state throughout the electrophysiological study. Premature stimulation of the right ventricle was performed by a 5-msec rectangular pulse with a stimulus strength triple the diastolic threshold. To study the effect of the drugs on ventricular activation, the conduction time of the premature stimulation-induced ventricular excitation was measured in both normal and infarcted zones of the ventricle. The time interval from the artifact of the premature stimulation to a sharp and reproducible deflection was measured on the epicardial bipolar electrocardiograms, and this value was estimated as the activation time. Premature stimulation was triggered by excitation of the normal zone (Fig. 1). The coupling interval of the stimulation (i.e., the time between the stimulation and the prior normal excitation, usually fell within the range 300–140 msec. The activation of the two drugs was compared in the same area. The bipolar electrocardiogram was amplified at a filter frequency of 5–1000 Hz. Lead II ECG, femoral arterial

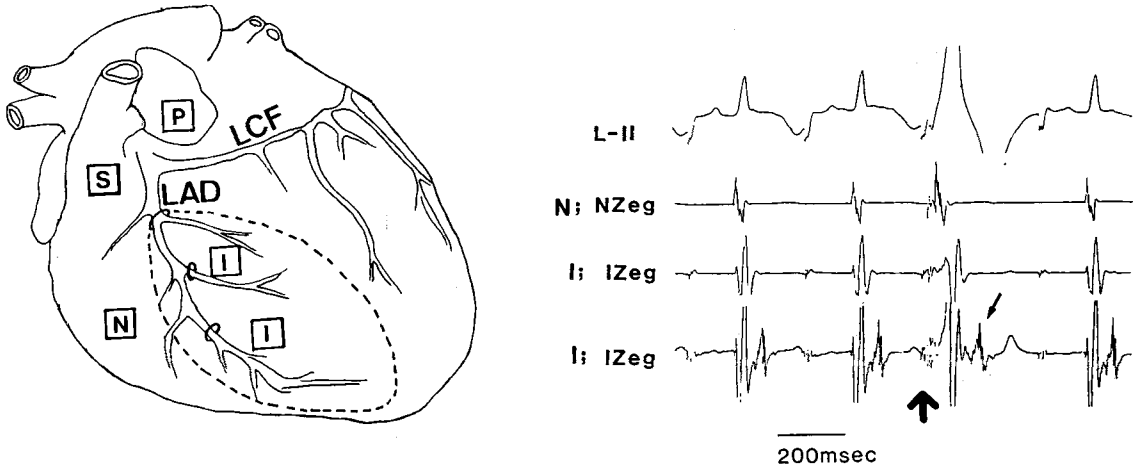

Fig. 1. Localization of the pacing electrode (*P*), stimulating electrode (*S*), and electrode for recording the ECGs of normal (*N*) and infarcted zone (*I*). *Right*, Typical ECGs of normal (*NZeg*) and infarcted zones (*IZeg*). *L-II*, standard limb lead II ECG. The *upward* and *downward arrows* indicate a premature stilumlation and delayed activation, respectively

pressure, and the epicardial bipolar electrocardiograms were recorded on an 8-channel polygraphic recorder (Nihon Koden, Tokyo, Japan) at a paper speed of 100 mm/sec. In each animal, the effects of the two drugs were examined at a time interval of 1 h when the effect of the first drug was considered negligible.

Drug administration

The concentrations of the volatile anesthetics were adjusted to maintain the end-tidal concentration at about 1 MAC (2.4% for sevoflurane, 0.9% for halothane). Similar concentrations were employed by other investigators [11,12]. An anesthetic gas analyzer (Engström EMMA, Engström, Stockholm, Sweden) was used to monitor both inspired and expired end-tidal anesthetic gas concentrations. The measurements after the volatile anesthetic were started after achieving a steady state for 60 min. In the study of the intraventricular activation time, effects of the volatile anesthetics were determined at a concentration of about 0.5 MAC.

Statistical analysis

All data were expressed as arithmetic means ± SD. Paired comparisons between pre- and post-administration values of the ERP or the ventricular activation time were performed by analysis of variance followed by a Dunnett test. Comparisons of pre- and post-administration values of the heart rate or the blood pressure were performed by a two-tailed, paired Student's *t*-test. Comparisons between the two treatment groups were performed by a two-tailed, unpaired Student's *t*-test. The criterion for statistical significance was $P < 0.05$.

Drugs

The following drugs were used: sevoflurane (Maruishi Pharmaceutical, Osaka, Japan) and halothane (Takeda Pharmaceutical, Osaka, Japan).

Results

Effects of sevoflurane and halothane on blood pressure and heart rate

Table 1 summarizes the results of seven animals. Sevoflurane 1 MAC reduced blood pressure by about 48 mmHg during sinus rhythm, and halothane 1 MAC exerted a similar effect. Both anesthetics also reduced blood pressure during atrial pacing to the same extent as during sinus rhythm (data not shown). Sevoflurane and halothane 1 MAC reduced the heart rate by about 36 and 38 beats/min, respectively.

Table 1. Effects of sevoflurane and halothane on the heart rate and the arterial blood pressure in dogs with myocardial infarction

	Sevoflurane		Halothane	
	Control	1 MAC	Control	1 MAC
Heart rate (beats/min)	174 ± 15	139 ± 7*	175 ± 19	114 ± 15*
Blood pressure (mmHg)	150 ± 10	103 ± 10*	153 ± 12	105 ± 15*

Values are the mean ± SD of seven animals.
* $P < 0.01$.

Effects of sevoflurane and halothane on ERP and excitation threshold

In the normal zone, sevoflurane 1 MAC significantly prolonged the ERP during sinus rhythm (Table 2). Sevoflurane prolonged the ERP during atrial pacing, but to a lesser extent than during sinus rhythm.

In the infarcted zone, the ERP in the control state was longer than that in the normal zone. During atrial pacing, sevoflurane 1 MAC significantly prolonged the ERP, but to a lesser extent than during sinus rhythm. Sevoflurane did not change the excitation threshold. Halothane 1 MAC also prolonged the ERP in both the normal and the infarcted zones during sinus rhythm. During atrial pacing, halothane prolonged the ERP, but to a lesser extent than during sinus rhythm.

Although sevoflurane and halothane both reduced blood pressure, there was no correlation between the reduction and prolongation of ERP (correlation coefficient = 0.09, Fig. 2).

Effects of sevoflurane and halothane on ventricular activation

Representative electrocardiograms recorded from normal and infarcted zones of the ventricle are shown in Fig. 3 (control). At the basic cycle length, the electrocardiogram recorded from the normal zone consisted of deflections with durations of less than 50 msec, whereas most of the electrocardiograms recorded from the infarcted zone were fractionated potentials, indicating that the activation in the infarcted zone was delayed. The delayed activation was further delayed in the premature excitation induced by premature stimulation.

The effect of sevoflurane 1 MAC on ventricular activation is shown in Fig. 3. Sevoflurane prolonged the activation time in the premature excitation in the infarcted zone. Sevoflurane did not change the configuration of the electrocardiogram in the infarcted zone except the prolongation of its duration. In the normal

Table 2. Effects of sevoflurane and halothane on the effective refractory period (ERP) in canine infarcted myocardium

	Sevoflurane 1 MAC			Halothane 1 MAC		
	Control	Sinus rhythm	Atrial pacing	Control	Sinus rhythm	Atrial pacing
Normal zone	148.9 ± 12.0	184.3 ± 12.5**	170.3 ± 8.5**#	151.4 ± 9.7	185.6 ± 9.5**	171.9 ± 8.1**#
Infarcted zone	193.1 ± 19.4	233.9 ± 18.3**	215.4 ± 16.4*#	186.9 ± 11.5	234.4 ± 11.7**	210.8 ± 12.4*#

Values are the means ± SD (msec) of seven animals.
* $P < 0.05$, ** $P < 0.01$ *vs* control; # $P < 0.05$ *vs* sinus rhythm.

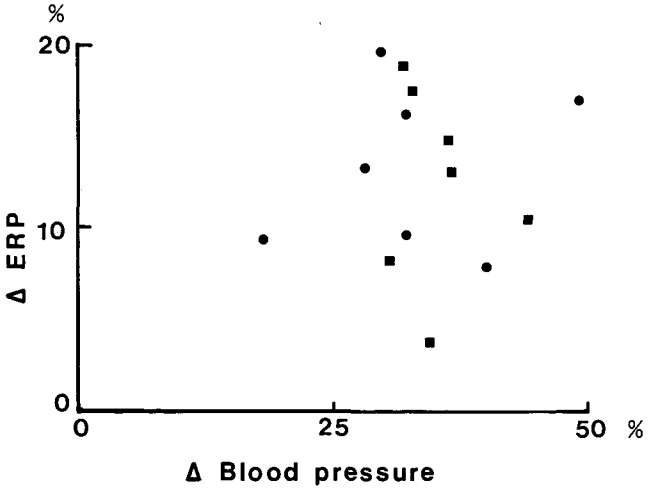

Fig. 2. Lack of a correlation between a reduction of systolic blood pressure (*SBP*) and a prolongation of effective refractory period (*ERP*) with sevoflurane (*squares*) and halothane (*circles*)

zone, sevoflurane did not show any obvious effect on the activation time of the premature excitation. The effect of sevoflurane disappeared rapidly after cessation of inhalation (Fig. 3). The blood pressure and activation delay recovered to the control levels 20 min after cessation. Figure 4 shows the effect of sevoflurane on seriously delayed activation in the infarcted zone. Sevoflurane at 1 MAC produced a block of delayed activation in three of seven animals examined. A similar block was observed also with halothane.

The effect of sevoflurane was coupling interval-related (Fig. 5): at a coupling interval of 280 msec, the activation time was prolonged from 135 to 165 msec, while at 180 msec the activation time was prolonged from 145 to 200 msec.

Table 3 summarizes the effects of sevoflurane and halothane at 1 MAC during atrial pacing in seven animals. The activation which was blocked by the volatile anesthetics was not included in these data. Sevoflurane markedly prolonged the activation time of infarcted zones at a coupling interval of 180 msec, while it was slightly but significantly prolonged at a coupling interval of 280 msec. In the normal zones, sevoflurane slightly prolonged the activation time to 180 msec. The effects of halothane were similar to those of sevoflurane. Sevoflurane and halothane at 0.5 MAC prolonged the activation time in the infarcted zone from 124 ± 7 to 133 ± 11 msec ($n = 5$, $P < 0.05$) and from 121 ± 8 to 135 ± 12 msec ($n = 5$, $P < 0.05$) at a coupling interval of 180 msec, respectively. The activation time in the normal zone was not affected.

In two of seven animals, the stimulation-induced premature beat was followed by ventricular ectopic beats (Fig. 6). These ventricular beats were not induced during anesthesia with sevoflurane or halothane.

Table 3. Effects of Sevoflurane and halothane on the activation time in canine infarcted myocardium

		Coupling interval (msec)	Activation time (msec)	
			Control	After drug
Sevoflurane (1 MAC)	Normal zone	180	43 ± 5	46 ± 7
		280	40 ± 5	42 ± 5
	Infarcted zone	180	125 ± 31	184 ± 27**
		280	113 ± 29	133 ± 36*
Halothane (1 MAC)	Normal zone	180	42 ± 7	42 ± 7
		280	42 ± 7	43 ± 7
	Infarcted zone	180	126 ± 22	172 ± 24**
		280	115 ± 24	129 ± 24*

Values are the mean ± SD of seven animals.
* $P < 0.05$, ** $P < 0.01$ *vs* contral.

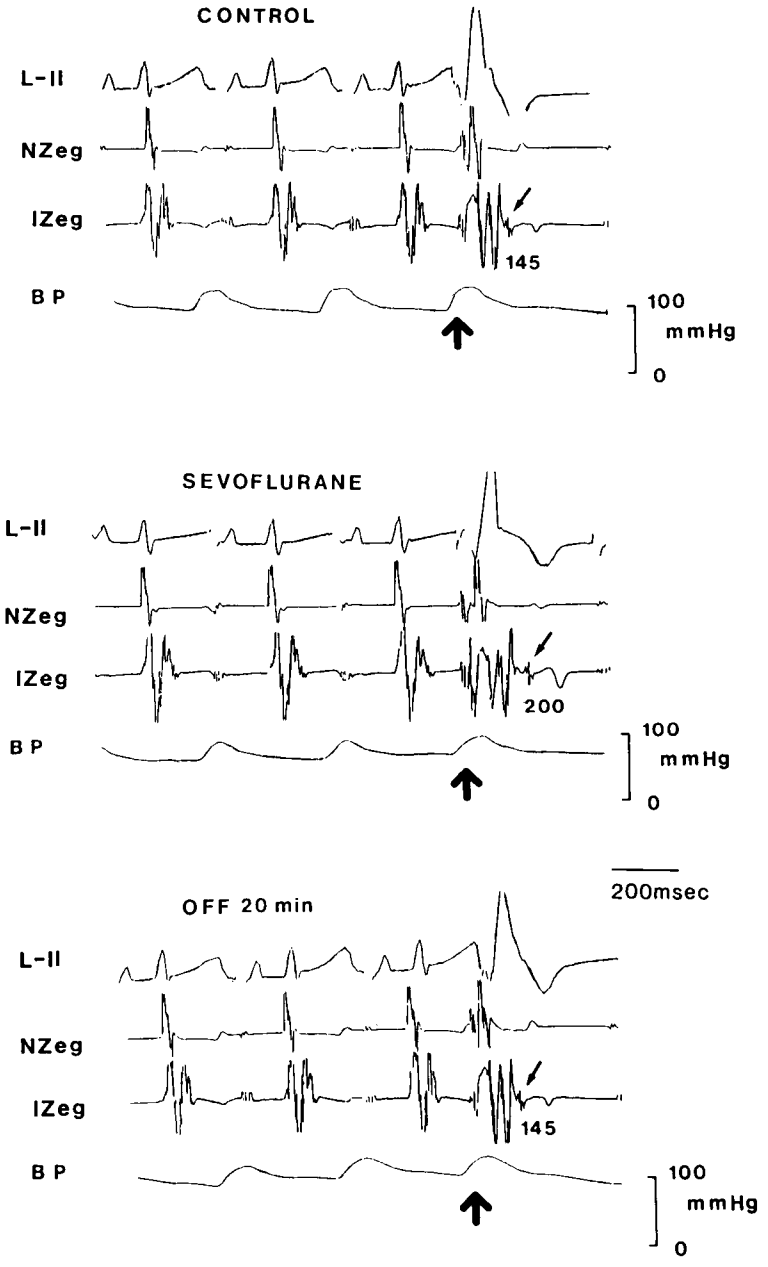

Fig. 3. Effects of sevoflurane on ventricular activation. *L-II*, standard limb lead II ECG; *NZeg, IZeg*, ECGs of the normal and the infarcted zones; *BP*, arterial blood pressure. The *upward arrows* indicate the premature stimulation with a coupling interval of 180 msec. The basic cycle length was 380 msec. The *downward arrows* are delayed activations. The numbers under IZeg are the activation times (msec)

Discussion

Electrophysiologic effects of the volatile anesthetics on infarcted hearts have not been fully examined yet. Many reports have dealt mainly with the effects of halothane [1–9,14]. In in vivo experiments, halothane reduced AV conduction and conduction in the His-bundle, Purkinje fibers and ventricular muscles [2]. Hauswirth reported that halothane at 2% lowered the maximal rate of depolarization ($\dot{V}$max) of Purkinje fibers in the sheep [1]. On the contrary, Lynch et al. reported that halothane did not depress $\dot{V}$max in the ventricular muscles of guinea pigs [15]. There are also several reports on the intraventricular conduction in ischemic hearts [7–9]. Turner et al. [8] showed that halothane depressed the $\dot{V}$max and slowed the conduction in isolated Purkinje fibers of canine infarcted hearts. However, Deutsch et al. [9] did not observe any significant effects of volatile anesthetics in a similar infarction model in vivo. Sevoflurane is now frequently used as a volatile anesthetic. However, an electrophysiologic effect of sevoflurane in a myocardial infarction model has not been examined.

The present study showed that sevoflurane depressed the delayed activation in infarcted zones of canine ventricles. The effect of sevoflurane was selective to the

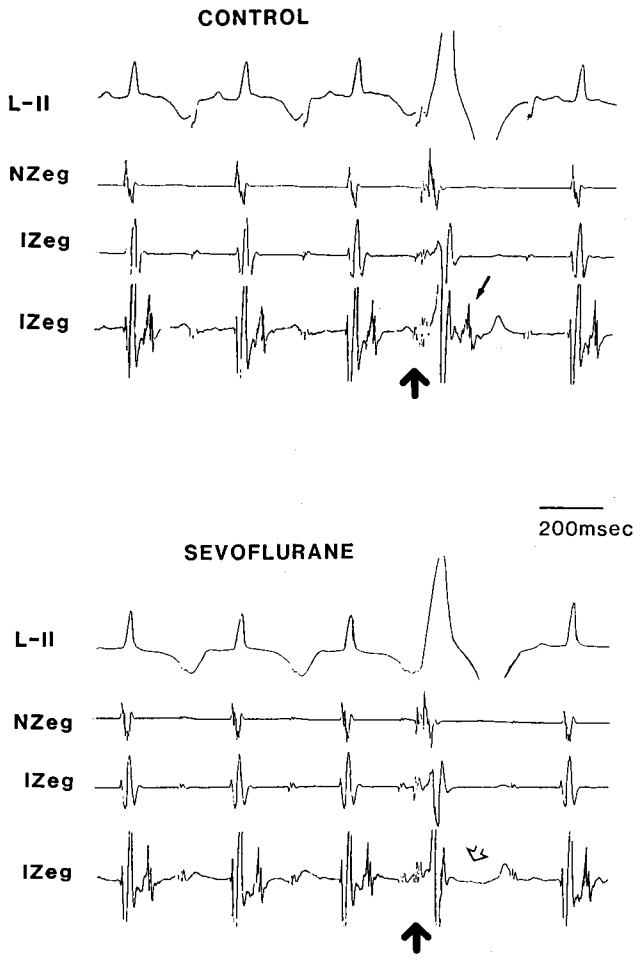

Fig. 4. Sevoflurane-induced block of delayed activation in the infarcted zone. *L-II*, standard limb lead II ECG; *NZeg, IZeg*, ECGs of the normal and the infarcted zones. The *upward* and *downward arrows* indicate the premature stimulation with a coupling interval of 220 msec and delayed activation, respectively. Basic cycle length was 350 msec

activation in the infarcted zone. The effect of sevoflurane on the activation of the normal zone was minimal. Halothane also showed a similar depression. A selective depression of the delayed activation was observed with class I antiarrhythmic drugs [16]. A previous study showed that halothane decreased the $\dot{V}m$ in the isolated Purkinje fibers of infarcted hearts [8]. Halothane showed only a slight effect on the activation of the normal zone, which was consistent with a previous report that halothane did not depress the $\dot{V}max$ of Purkinje fibers in non-infarcted zones [8]. According to Ikemoto et al. [17], halothane depresses the sodium currents of cardiac muscles, and shifts the steady state inactivation curve in a negative direction along the potential axis. Thus, the effect of halothane on delayed activation may be caused by an inhibition of sodium channels. On the other hand, Terrar and Victory [18] showed that halothane inhibits cell-to-cell electrical coupling. In addition, Ozaki et al. [19], reported that halothane and enflurane reduced the conduction velocity in guinea pig papillary muscles without any significant reduction of $\dot{V}max$. Spray and Burt [20] showed that a variety of lipophilic molecules, including halothane, and myoplasmic acidification reduce cell-to-cell electrical coupling. Therefore, a depression of cell-to-cell electrical coupling may also contribute to the depression of the delayed activation during the inhalation of the volatile anesthetic. Although electrophysiologic effects of sevoflurane have not been examined in vitro, similar mechanisms may be involved in the depressant effects of sevoflurane on the delayed activation.

A seriously depressed activation in the infarcted zones was blocked by sevoflurane and halothane in some cases. A markedly delayed activation may lead to reentrant arrhythmias, and the blockade of the activation with antiarrhythmic drugs prevents arrhythmias [16,21–23]. In the two animals in which ventricular arrhythmias were induced by the premature stimulation, which were suppressed during the inhalation of sevoflurane or halothane. The antiarrhythmic effects of halothane in canine myocardial infarction have been reported previously [24–26], which may be caused partly by a selective depression with halothane of delayed activation in the infarcted zone. Although antiarrhythmic effects of sevoflurane have not been examined previously, the results indicate that sevoflurane also may have similar antiarrhythmic effects.

Sevoflurane and halothane markedly prolonged ERP in both normal and infarcted zones, and a similar effect of halothane has also been reported by other investigators [9]. The prolongation of ERP with these anesthetics was significantly reduced during atrial pacing. Thus, these drugs prolonged ERP via both a direct action on myocardial cells and secondarily by reducing the heart rate. It is unlikely that a reduction of the blood pressure with sevoflurane and halothane resulted in a prolongation of ERP because there was no correlation between the two parameters. As in the case of antiarrhythmic drugs, a prolongation of ERP may contribute to the antiarrhythmic effects of halothane and sevoflurane.

The depressant effect of the volatile anesthetics on the delayed activation was related to the coupling interval. A similar effect was observed with class I antiarrhythmic drugs [16], which may be caused by a time-dependent inhibition of sodium channels [27]. However, it is not clear whether or not the mechanism of the coupling interval-related effects of the volatile anesthetics is similar to those of class I antiarrhythmic drugs. It is also probable that the prolongation of ERP with the anesthetics contributed to depression of the delayed activation at a short coupling interval.

In two animals, premature stimulation induced ven-

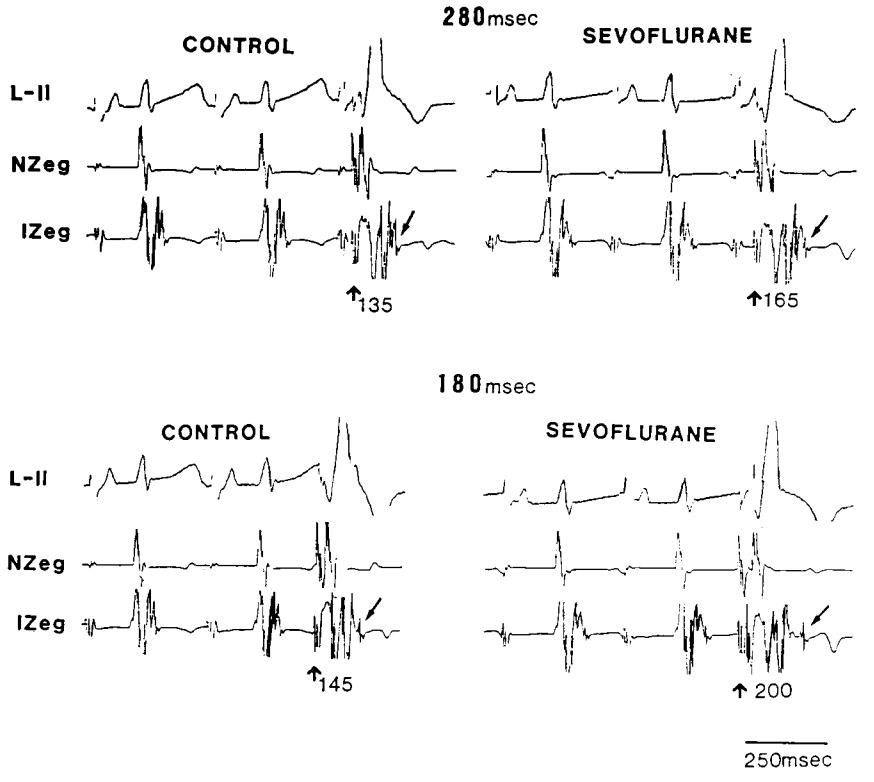

Fig. 5. Effects of sevoflurane on the activation time of the delayed activation at different coupling intervals. *L-II*, standard limb lead II ECG; *NZeg, IZeg*, ECGs of the normal and the infarcted zones. Coupling intervals were 280 msec (*upper*), 180 msec (*lower*). Basic cycle length was 380 msec. The *upward* and *downward arrows* are the premature stimulations and delayed activations, respectively. The numbers under IZeg are the activation times (msec)

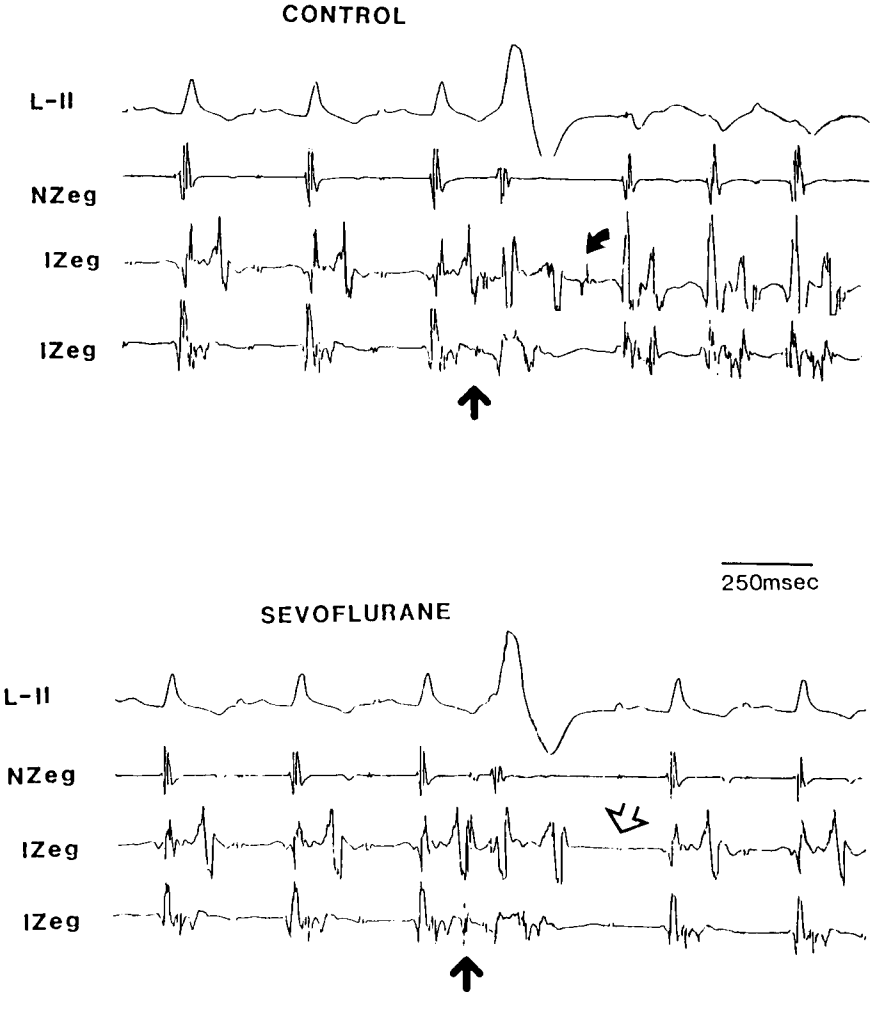

Fig. 6. Effect of sevoflurane on the premature stimulation-induced ventricular arrhythmias. *L-II*, standard limb lead II ECG; *NZeg, IZeg*, ECGs of the normal and the infarcted zones. Coupling interval was 140 msec. Basic cycle length was 350 msec. The *upward arrows* are the premature stimulations

tricular arrhythmias, which were suppressed by sevoflurane and halothane. Although it is not clear that the arrhythmias were caused by a reentry mechanism or abnormal automaticity, a prolongation of ERP and/or depression of delayed activation may be involved in the suppression of the arrhythmias by these anesthetics.

In conclusion, sevoflurane and halothane selectively depressed the delayed activation in the infarcted zones and prolonged ERP in both normal and infarcted zones, which may be caused by both direct and secondary effects of these drugs. These effects of the volatile anesthetics may inhibit the ventricular arrhythmias in myocardial infarction.

References

1. Hauswirth O (1969) Effects of halothane on single atrial, ventricular and Purkinje fibers. Circ Res 24:745–750
2. Reynolds AK, Chiz JZ, Pasquet AF (1970) Halothane and methoxyflurane—a comparison of their effects on cardiac pacemaker fibers. Anesthesiology 33:602–610
3. Atlee IJ, Rusy BF (1972) Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 36:112–118
4. Atlee JL, Alexander SC (1977) Halothane effects on conductivity of the AV node and His-Purkinje system in the dog. Anesth Analg 56:378–385
5. Turner LA, Zuperku EL, Purtock RV, et al. (1980) In vivo changes in canine ventricular cardiac conduction during halothane anesthesia. Anesth Analg 59:327–334
6. Pruett JK, Mote PS, Grover TE, et al. (1981) Enflurane and halothane effects on cardiac Purkinje fibers. Anesthesiology 55:A65
7. Goto Y, Tujinaga H, Yokota S, et al. (1984) Effect of halothane on the ischemic-induced conduction delay in canine myocardium (in Japanese, with English abstract). Masui (Jpn J Anesthesiol) 33:1317–1321
8. Turner LA, Bosnjak ZJ, Kampine JP. (1987) Actions of halothane on the electrical activity of Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 67:619–629
9. Deutsch N, Hantler CB, Tait AR, et al. (1990) Suppression of ventricular arrhythmias by volatile anesthetics in a canine model of chronic myocardial infarction. Anesthesiology 72:1012–1021
10. Brukner JB, Kielmann D, Gess W (1970) Sevoflurane: effects on the circulation and myocardial oxygen consumption with halothane. In: proceedings of the Central European Congress of Anesthesiology, Innsbruck, Austria
11. Imamura S, Ikeda K (1987) Comparison of the epinephrine-induced arrhythmogenic effect of sevoflurane with isoflurane and halothane. J Anesth 1:62–68
12. Kazama T, Ikeda K (1988) The cardiovascular effects of sevoflurane with halothane and isoflurane. J Anesth 2:63–68
13. Harris AS (1950) Delayed development of ventricular ectopic rhythm following experimental coronary occlusion. Circulation 1:1318–1324
14. Freeman LC, Muir WW (1991) Effects of halothane on propagation on Purkinje fibers and at Purkinje-muscle junctions: relationship of Vmax to conduction velocity. Anesth Analg 72:5–10
15. Lynch C, Vogel S, Sperelakis N (1981) Halothane depression of myocardial slow action potentials. Anesthesiology 55:360–368
16. Hashimoto H, Satoh N, Nakashima M (1991) Coupling interval-related effects of class I antiarrhythmic drugs, mexiletine, cibenzoline and disopyramide, on ventricular activation in canine myocardial infarction. Jpn J Pharmacol 57:463–472
17. Ikemoto Y, Yatani A, Imoto Y, et al. (1986) Reduction in the myocardial sodium current by halothane and thialmyl. Jpn J Physiol 36:107–121
18. Terrar DA, Victory JGG (1988) Influence of halothane on electrical coupling in cell pairs isolated from guinea-pig ventricle. Br J Pharmacol 94:509–514
19. Ozaki S, Nakaya H, Gotoh Y, et al. (1989) Effects of halothane and enflurane on conduction velocity and maximum rate of rise of action potential upstroke in giunea pig papillary muscles. Anesth Analg 68:219–225
20. Spray DC, Burt JN (1990) Structure-activity relations of the cardiac gap junction channel. Am J Physiol 258:C195–C205
21. El-Sherif N, Scherlag BJ, Lazzara R, et al. (1977) Re-entrant ventricular arrhythmias in the late myocardial infarction period. I: Conduction characteristics in the infarction zone. Circulation 55:686–702
22. El-Sherif N, Scherlag BJ, Lazzara R, et al. (1977) Re-entrant ventricular arrhythmias in the late myocardial infarction period. IV: Mechanism of action of lidocaine. Circulation 56:395–402
23. Hashimoto H, Satoh N, Nakashima M (1990) Effects of bepridil and lidocaine on the intraventricular conduction in acutely ischemic and infarcted canine myocardium. Naunyn Schmiedebergs Arch Pharmacol 342:683–690
24. Kroll D, Knight PR (1984) Antifibrillatory effects of three anesthetics in acute occlusion/reperfusion arrhythmias. Anesthesiology 61:657–666
25. Atlee JL (1987) Halothane: cause or cure for arrhythmias? Anesthesiology 67:617–618
26. Hunt GB, Ross DL (1988) Comparison of effects of three anesthetic agents on induction of ventricular tachycardia in a canine model of myocardial infarction. Circulation 78:221–226
27. Hondeghem LM, Katzung BG (1977) Time- and voltage-dependent interaction of antiarrhythmic drugs with cardiac sodium channels. Biochim Biophys Acta 472:373–398