Anesthesiology
59:309–315, 1983

Effects of Halogenated Hydrocarbon Anesthetics on Responses to Ligation of a Coronary Artery in Chronically Prepared Rats

T. L. Jang, B.Sc., B. A. MacLeod, M.D.,† and M. J. A. Walker, Ph.D.‡*

Responses to ligation of the left anterior descending coronary artery (blood pressure, heart rate, ECG, arrhythmias, myocardial tissue loss, and mortality) were investigated in chronically prepared rats anesthetized with one of various halogenated hydrocarbon anesthetics. Halothane (inhaled concentrations of 0, 0.25, 0.5, 1.0, and 2.0%) reduced arrhythmias, mortality, and "S-T" segment changes in the ECG in a dose-related manner. The most effective antiarrhythmic concentrations were 0.5 and 1.0%. Other halogenated hydrocarbon anesthetics (chloroform, enflurane, isoflurane, methoxyflurane, and trichlorethylene) were investigated at minimal anesthetic concentrations. Of these, only chloroform and enflurane reduced arrhythmias. However, both increased mortality as a result of nonarrhythmic causes. At one-half anesthetic concentrations, chloroform (0.25%) and enflurane (0.75%) were not antiarrhythmic and mortality resulting from nonarrhythmic causes was not increased.

In the chronically prepared rat, halothane at anesthetic and subanesthetic concentrations has antiarrhythmic actions against ligation-induced arrhythmias, reducing mortality. Of the other halogenated hydrocarbons tested, only enflurane and chloroform had antiarrhythmic actions, however, mortality was high with both agents because of accompanying cardiovascular depression. (Key words: Anesthetics, volatile: chloroform; enflurane; halothane; isoflurane; methoxyflurane; trichlorethylene. Heart: arrhythmia; coronary occlusion.)

THE EFFECTS OF ANESTHETICS on the outcome of myocardial ischemia and infarction continues to be a topic of both experimental and clinical interest. We have described the effects of halothane and fetanyl anesthesia on responses to ligation of a coronary artery in the rat.[1] When compared with conscious control animals, halothane-anesthetized animals had less severe responses to ligation. Ventricular arrhythmias were fewer and of lesser severity in the halothane treated animals and, as a direct consequence, more animals survived ligation. ECG signs of ischemia were less during halothane, although myocardial tissue loss was not different from control. Fentanyl, administered intravenously to produce an equal level of anesthesia, had no beneficial effects and did not change responses to ligation when compared with conscious controls. Similar findings for halothane administered to the dog have been reported.[2,3]

In view of these findings, we investigated a series of halogenated hydrocarbon anesthetics to determine whether they shared halothane's protective actions against the effects of ligation of a coronary artery. Each agent was administered at an inspired concentration just sufficient to produce surgical anesthesia. Enflurane and chloroform, those agents that showed antiarrhythmic activity, then were administered at concentrations one-half the average concentration required to produce surgical anesthesia. Halothane, the agent with the most pronounced antiarrhythmic activity, was given over a dose range from subanesthetic to two times minimal anesthetic concentration. These experiments were designed to investigate the possibility of antiarrhythmic actions of halogenated hydrocarbon anesthetics, and to determine if halothane's antiarrhythmic actions were dependent on the state of general anesthesia.

The anesthetics investigated were halothane, enflurane, isoflurane, methoxyflurane, chloroform, and trichlorethylene. This list includes compounds of differing chemical groups and various pharmacologic properties.

The responses to ligation in chronically prepared rats exposed to the various anesthetics were recorded as arrhythmias, blood pressure changes, heart rate changes, ECG changes, myocardial tissue loss, and mortality.

Methods

Our procedure for preparing rats§ has been described in detail.[1,4] In brief, under halothane anesthesia, a snare was placed around the left anterior descending artery and permanent aortic cannula and ECG leads were implanted. Animals were left to recover for seven days prior to ligation. On the day of ligation, blood pressure and ECG were recorded from 30 min before ligation to 4 h after ligation.

Anesthetic or control treatment was initiated 30 min before, and continued for 4 h after, ligation. To ligate, the snare was pulled so as to occlude the left anterior

* Research Assistant.
† Assistant Professor, Department of Anaesthesiology.
‡ Associate Professor, Department of Pharmacology.
Received from the Departments of Pharmacology and Anaesthesiology, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, B. C., V6T 1W5, Canada. Accepted for publication April 4, 1983. Supported by the Medical Research Council of Canada and the British Columbia Heart Foundation.
Address reprint requests to Dr. MacLeod.

§ Male Sprague-Dawley rats (wt. 250–300 g) were used except for one enflurane and one control group of Wistar rats, which had to be used because of an outbreak of respiratory infections in other rats. The only difference in responses between the two strains was that the Wistar rats had slightly smaller occluded zones with an accompanying minor reduction in arrythmias.

0003-3022/83/1000/0309 $01.15

descending coronary artery. Twenty-four hours after ligation, blood pressure and ECG were recorded for 30 min, the animal was killed, and its heart removed. The heart was perfused by the Langendorf technique with a green dye to reveal the occluded zone. This was cut out and its weight expressed as a percentage of the ventricular weight. Incubation in tetrazolium then was used to reveal the mass of infarcted myocardium.[1,4] The incidence, type, and duration of ventricular arrhythmias, heart rate, "S-T" segment changes, R wave size, Q wave appearance, blood pressure, and mortality were recorded. The total number of ventricular premature contractions was expressed as $\log_{10}$, because this transform gave a Gaussian distribution, permitting the use of parametric statistics. Our previously defined scale,[1,4] the arrhythmia score, was used as comprehensive score for arrhythmias. This scale assigns integers from 0–9 based upon the presence, duration, and reversibility of ventricular arrhythmias. Ventricular tachycardia (VT) and ventricular fibrillation (VF) were recorded as the number of episodes, their duration, and whether these episodes were spontaneously reversible, could be reversed by chest tapping, or were irreversible. As previously shown,[4] chest taps are associated with reversion to sinus rhythm in over 80% of cases. The "S-T" segment was recorded as the height above the isoelectric line 20 ms after the start of the R wave. The change in the "S-T" height at time "t" was multiplied by the ratio of "R" during control to "R" at time "t" to correct for changes in signal size. This standardization reduces the variance of the estimate of "S-T" changes.

The nature and precision of the above variables have been analyzed and their variability, type of frequency distribution, and intravariable correlations determined.

One experiment investigated how responses of rats to coronary artery ligation were affected by halogenated hydrocarbon anesthetics given at minimal anesthetic concentrations. The minimal anesthetic concentration was defined as the lowest inspired concentration that abolished gross movement when a standard squeeze was applied to the rat's tail. The average inspired anesthetic concentrations were methoxyflurane 0.3% (by Pentec® vaporizer), enflurane 1.5% (Enfluratec® vaporizer), isoflurane 1.4% (Fortec® vaporizer), chloroform 0.5% (Vernitrol®), and trichlorethylene 1% (Vernitrol® vaporizer).* Halothane was given as previously reported.[1] Rats were assigned randomly to either anesthetic or oxygen control groups.

The anesthetics were delivered in humidified oxygen to spontaneously breathing animals. Controlled ventilation (10 ml/kg × 60/min) was required occasionally for respiratory failure, which presumably resulted from decreased cerebral perfusion because of falls in blood pressure. Respiratory failure preceded death from cardiac output failure in cases of death resulting from nonarrhythmic causes. Three of 10 rats receiving the anesthetic dose of chloroform, 1 of 12 receiving the anesthetic dose of enflurane, and 1 of 10 receiving either methoxyflurane or trichlorethylene required ventilation. These animals all eventually died of *nonarrhythmic* causes. Animals anesthetized with enflurane, methoxyflurane, and trichlorethylene required occasional endotracheal suction, whereas those anesthetized with halothane, isoflurane, and chloroform did not.

Blood gases were determined on a Radiometer® PHM-71. Usually one blood sample was taken 60–90 min after induction. This sampling time was chosen as being after the major period of arrhythmogenesis. Where a second sample was taken, it did not differ significantly from the first. After analysis, the blood (0.4 ml) was returned to the animals, along with 0.2 ml of normal saline wash. This determination was performed on at least six rats chosen randomly from each anesthetic group.

The second experiment in the series tested, at less than anesthetic concentrations, those agents that were shown to have antiarrhythmic activity at anesthetic concentrations. Chloroform and enflurane were tested at one-half of their average minimal inspired anesthetic concentration (0.25 and 0.75%, respectively). A dose–response study for halothane tested concentrations of 0, 0.25, 0.5, 1, and 2% halothane in oxygen. Rats were placed in a glass container previously equilibrated with the desired subanesthetic concentration. Rats remained in the container from 30 min before ligation to 4 h after ligation. Periodically, their ability to respond to a light touch or a tail squeeze was assessed. Control groups of animals were kept in 100% oxygen for 30 min before, and 4 h after, ligation.

In view of the possibility that respiratory depression may have occurred with some of the anesthetics, a trial experiment was performed to observe the effects of hypoxia, combined with hypercapnia, on arrhythmic responses to ligation. This involved placing rats in an atmosphere of low oxygen and 13% CO_2 in nitrogen. after 15 min, ligation was performed and the animals were left in the atmosphere as with the other treatments.

Animals that died during the 4 h treatment period, or earlier, had their hearts removed for estimation of occluded zone size. Animals that survived 24 h were killed, and their hearts were removed for estimation of occluded and infarcted zones.

Data were collected on computer file for final analysis by analysis of variance and standard tests for differences between means (Duncan's, Tukeys).[1]

* The vaporizers were calibrated before the experiment. Each animal's anesthetic was titrated continuously to give the same level of anesthesia for all anesthetics throughout the experimental periods.

TABLE 1. Antiarrhythmic Effects of the Halogenated Hydrocarbon Anesthetics by 4 Hours after Ligation

Anesthetic Agent	n	Arrhythmias		No. of Group Having Major Arrhythmias of:				Mortality		
		Log_{10}PVC	AS	VT	VF	VTVF	IrrVF	Arrh. Deaths by 4 h	Nonarrh. Deaths by 4 h	All Deaths by 24 h
Control (three groups accumulated)	27	2.0 ± 0.2	5.5 ± 0.4	24	24	27	12	12	0	12
Methoxyflurane	10	1.6 ± 0.3	4.8 ± 0.4	9	8	10	2	2	1	5
Isoflurane	12	1.5 ± 0.1	4.9 ± 0.6	10	8	10	5	5	0	9
Trichlorethylene	10	0.8 ± 0.3*	6.4 ± 0.8	7	10	10	5	5	2	9
½ chloroform	9	1.6 ± 0.4	5.3 ± 0.6	8	7	9	2	2	0	6
Chloroform	10	1.3 ± 0.3	2.6 ± 0.4*	8	1*	8	0*	0*	4*	8
½ enflurane	9	1.9 ± 0.4	5.3 ± 0.6	8	7	9	3	3	2	6
Enflurane	12	1.3 ± 0.3	2.9 ± 0.6*	9	3*	9	1*	1*	6*	9
Control for enflurane	8	2.2 ± 0.5	5.2 ± 0.7	7	8	8	3	2	1	6
0% halothane	11	1.9 ± 0.4	5.9 ± 0.5	8	10	10	5	5	0	7
0.25% halothane	11	2.0 ± 0.3	4.8 ± 0.6	9	8	10	3	3	1	6
0.5% halothane	11	1.3 ± 0.4	2.5 ± 0.8*	6	4*	7	1*	1*	2	4
1.0% halothane	11	1.3 ± 0.2	2.5 ± 0.7*	7	3*	6	1*	1*	2	4
2.0% halothane	11	0.6 ± 0.2*	3.7 ± 1.0	7	4*	7	3	3	7*	11*

Log_{10}PVC and arrhythmia score (AS) are given as $\bar{x}$ ± SEM. Arrhythmia score is a normalized scoring system encompassing the whole arrhythmia history for 4 h after ligation (see "Methods"). The major arrhythmias of ventricular flutter (VT), ventricular fibrillation (VF), ventricular flutter and/or ventricular fibrillation (VTVF), or irreversible ventricular fibrillation (IrrVF) leading to death, are given as the number of animals in each group have one or more such events. The second-to-last column gives the number of animals dying nonarrhythmic deaths by 4 h after ligation, while the number of animals dead by 24 h after ligation is shown in the last column. Halothane was given at one of four (0.25, 0.5, 1.0, and 2.0% in oxygen) concentrations. All other anesthetics were given at concentrations producing anesthesia except for chloroform and enflurane, which also were given at half-anesthetic concentrations (½C = 0.25% chloroform, ½E = 0.75% enflurane).

* Indicates $P < 0.05$ from controls by analysis of variance.

Results

The responses of animals to stimuli decreased as inspired anesthetic concentration was increased. Rats receiving 0.25% halothane moved less than control animals but were spontaneously active, moving, chewing, eating, *etc.* At 0.5% halothane (one-half minimal inspired anesthetic concentration), rats moved in response to touch, tail squeeze, and noise, but showed little spontaneous activity. Rats receiving the one-half anesthetic concentrations of chloroform and enflurane reacted similarly. Rats receiving the minimal anesthetic concentration of all agents (including 1% halothane) did not *move* in response to a standard tail squeeze, however, the heart rate increased slightly. Rats receiving 2% halothane were unresponsive to all stimuli.

Blood gases ranges, obtained under the various anesthetics, were 80–130 mmHg Pa_{O_2} and 38–55 mmHg Pa_{CO_2} for methoxyflurane; 125–255 mmHg Pa_{O_2} and 45–52 mmHg Pa_{CO_2} for isoflurane; 140–280 mmHg Pa_{O_2} and 37–48 mmHg Pa_{CO_2} with trichlorethylene; 80–105 mmHg Pa_{O_2} and 45–60 mmHg Pa_{CO_2} with chloroform; and 70–245 mmHg Pa_{O_2} and 40–50 mmHg Pa_{CO_2} with enflurane. With halothane, values ranged from 200–250 mmHg Pa_{O_2} and 25–35 mmHg Pa_{CO_2}, with 0.25% halothane to 100–200 mmHg and 35–50 mmHg Pa_{CO_2} with 2% halothane. When breathing 100% oxygen, values were 140–350 mmHg Pa_{O_2} and 35–45 mmHg p_{CO_2}.

In the trial experiment, where (n = 6) rats breathing low O_2 and 13% CO_2 (100 mmHg) in N_2 were subjected to ligation, no marked effect on arrhythmia production was seen (mean arrhythmia score ± SEM = 4.3 ± 1.3 and mean $\log_{10}$ PVC = 1.3 ± 0.4), despite Pa_{O_2}values of 50–60 mmHg and Pa_{CO_2} values of 90–110 mmHg.

Ligation in all groups produced arrhythmias, mortality, blood pressure, and heart rate changes; an occluded mass of myocardium; infarcted myocardium; and changes in the ECG complex.

The arrhythmias that occurred during the 4 h of treatment are summarized in table 1. Three of the anesthetics produced statistically significant reductions in arrhythmias, halothane at 0.5 and 1%, chloroform at 0.5%, and enflurane at 1.5%. Their antiarrhythmic actions were shown by significant decreases in the incidence of ventricular fibrillation (reversible and irreversible) and in arrhythmia score. The statistically significant decrease in $\log_{10}$ PVC incidence seen for trichlorethylene and 2% halothane was an artifact resulting from the high mortality that occurred soon after ligation with these anesthetics.

Mortality was divided into that resulting from arrhythmias or that resulting from nonarrhythmic cardiac failure. The reality of this division was very evident during the experiment. Animals dying nonarrhythmic cardiac output failure deaths had a prolonged period of decreased blood pressure, occasionally resulting in respiratory arrest and then asystole. Deaths resulting

TABLE 2. Cardiac Tissue Loss and ECG Changes in the Various Groups Treated with Halogenated Hydrocarbon Anesthetics

Anesthetic Agent	Occluded (OZ) and Infarcted Zones (IZ) as Percentage of Total Ventricular Weight			ECG Changes (at 1 hr after-Ligation)	
	n	OZ	IZ	R wave	dSTR
Control	27	38 ± 2	26 ± 3	0.77 ± 0.08	0.49 ± 0.07
Methoxyflurane	10	35 ± 2	27 ± 4	1.05 ± 0.17	0.28 ± 0.06*
Isoflurane	12	34 ± 2	27 ± 5	0.88 ± 0.06	0.17 ± 0.04*
Trichlorethylene	10	34 ± 2	—	1.10 —	0.30 —
½ chloroform	9	38 ± 3	—	0.79 ± 0.11	0.43 ± 0.05
Chloroform	10	35 ± 4	—	0.75 ± 0.08	0.23 ± 0.04*
½ enflurane	9	42 ± 3	—	0.50 ± 0.10*	0.15 ± 0.03*
Enflurane	12	35 ± 3	22 ± 6	0.98 ± 0.22*	0.15 ± 0.05
Control for enflurane	8	28 ± 2	17 ± 4	0.45 ± 0.11	0.20 ± 0.05
0% halothane	11	36 ± 3	27 ± 7	0.80 ± 0.10	
0.25% halothane†	11	32 ± 3	21 ± 3	0.60 ± 0.10*	
0.5% halothane	11	36 ± 3	24 ± 3	0.50 ± 0.10*	
1.0% halothane	11	34 ± 3	25 ± 3	0.40 ± 0.10*	
2.0% halothane	11	34 ± 3	—	—	

The amount of cardiac tissue nonperfused (occluded zone—OZ) and lost as infarcted tissue (IZ) following ligation is given as $\bar{x} \pm$ SEM, with values expressed as percentage by weight of total ventricular weight. ECG changes (as $\bar{x} \pm$ SEM) at 1 h after-ligation are summarized as R-wave size (mV) and the change in "S-T" segment (mV) corrected for changes in R wave size (see "Methods"). Values are omitted (indicated by —) when number in group (n) was too small to give a meaningful estimate of $\bar{x}$ or SEM.

* Indicates $P < 0.05$ by analysis of variance.

† See figure 1 for halothane data.

from nonarrhythmic cardiac failure were significantly increased by chloroform 0.5%, enflurane 1.5%, and halothane 2%. However, because there was a decreased mortality due to arrhythmic causes with chloroform and enflurane, the combined mortality at anesthetic concentrations was not increased. As the antiarrhythmic actions of chloroform and enflurane were reduced when their concentrations was halved, deaths due to nonarrhythmic cardiac failure decreased.

Neither the percentage of myocardium occluded or infarcted were influenced by the anesthetic (table 2). In those groups (trichlorethylene, chloroform 0.25 and 0.5%, enflurane 0.75%, and halothane 2%), with increased mortality occurring soon after occlusion, the infarct zone could not be determined by tetrazolium staining.

As indicated in table 3 and figure 1, both anesthesia and ligation reduce blood pressure. The decrease in blood pressure increased with increased concentration of agent. The degree of blood pressure decrease resulting from the anesthetic (*e.g.*, −1 min) was worse after coronary artery ligation (*e.g.*, +10 min).

While most of the agents decreased heart rate, the changes were more erratic than those seen in blood pressure. The low heart rate seen during one-half anesthetic concentrations of chloroform was due to atrial arrhythmias with slow ventricular response. These disappeared after ligation.

ECG changes are recorded in table 2 and figure 1. Halothane decreased R wave size in a dose-related manner as the concentration increased from 0–1%; at 2%, there was an insufficient number of animals surviving

TABLE 3. Cardiovascular Changes in the Various Groups Treated with Halogenated Hydrocarbon Anesthetics

	Mean Blood Pressure (mmHg)			Heart rate (beats/min)		
	−1 min	+10 min	+4 h	−1 min	+10 min	+4 h
Control	117 ± 3	103 ± 4	102 ± 5	390 ± 10	420 ± 20	380 ± 20
Methoxyflurane	111 ± 4	70 ± 9*	110 ± 5	350 ± 10*	300 ± 20*	310 ± 20*
Isoflurane	106 ± 3	82 ± 6*	101 ± 7	370 ± 10	370 ± 10*	330 ± 20*
Trichlorethylene	98 ± 3	70 ± 11*	90 —	370 ± 10	350 ± 20*	380 —
1/2 chloroform	119 ± 6	95 ± 7	97 ± 8	280 ± 20*	380 ± 40	310 ± 40*
Chloroform	95 ± 4*	69 ± 8*	68 ± 11*	350 ± 10*	360 ± 10*	310 ± 50*
1/2 enflurane	120 ± 7	85 ± 12*	91 ± 6*	440 ± 20	380 ± 40	400 ± 90
Enflurane	106 ± 5*	43 ± 11*	87 ± 14	360 ± 10*	340 ± 30	290 ± 60*
Control Halothane†	117 ± 4	81 ± 13	88 ± 12	440 ± 10	320 ± 50	360 ± 50

All values are $\bar{x} \pm$ SEM, with n = 4–12 for groups other than first control, (—) indicates SEM not given for n < 4. Mean blood pressure calculated from systolic and diastolic pressures.

* Indicates $P < 0.05$ (by analysis of variance) from appropriate controls. Heart rates are given to two significant places.

† Data for halothane given in figure 1.

to estimate R wave. R wave size was decreased by one-half anesthetic concentrations of enflurane but increased at anesthetic concentrations. The "S-T" segment elevated dramatically after ligation. This elevation was reduced as the concentration of halothane increased from 0–0.25 to 0.50–1%. For 2% halothane, the "S-T" segment elevation was greater than control. Methoxyflurane, isoflurane, chloroform (0.5%), and half-enflurane (0.75%) also significantly decreased the "S-T" segment elevation.

Relationship between dose and effect are shown best by classic dose-response curves, as for halothane in figure 2. The effect of varying halothane concentration upon arrhythmia score, arrhythmic mortality, nonarrhythmic mortality, "S-T" segment elevation, and blood pressure changes are shown. The close correlation between the effects of increasing halothane on blood pressure decrease and nonarrhythmic mortality is apparent. Similarly, the correlation between arrhythmia score, arrhythmic mortality, and "S-T" segment changes also are evident.

Discussion

Our study confirms and extends the observation that halothane decreases the incidence of ventricular arrhythmias that occur after ligation of a coronary artery in the rat.[1] This antiarrhythmic action of halothane was dose related and occurred at subanesthetic as well as anesthetic concentrations. We have shown previously that, halothane at a concentration producing surgical anesthesia is antiarrhythmic when compared with fentanyl anesthesia and conscious controls.[1]

Of the other halogenated hydrocarbon anesthetics tested (chloroform, enflurane, isoflurane, methoxyflurane, and trichlorethylene) only chloroform and enflurane had antiarrhythmic effects at anesthetic concentrations. However, the antiarrhythmic action of both chloroform and enflurane was lost at half-anesthetic concentrations.

The mechanism of the above antiarrhythmic actions is unclear, but if we assume that only one mechanism is responsible for the action of all three agents, then a number of conclusions can be drawn from our experiments, and some possible explanations for the antiarrhythmic actions of the agents can be dismissed.

It is apparent that the state of anesthesia did not account for the observed antiarrhythmic actions of halothane, chloroform, and enflurane. Subanesthetic concentrations of halothane were as antiarrhythmic as anesthetic concentrations, while equally anesthetic agents (isoflurane, methoxyflurane, and trichlorethylene) were not antiarrhythmic. It is possible that nonanesthetic hydrocarbons also may have antiarrhythmic actions; this possibility will be investigated in the future.

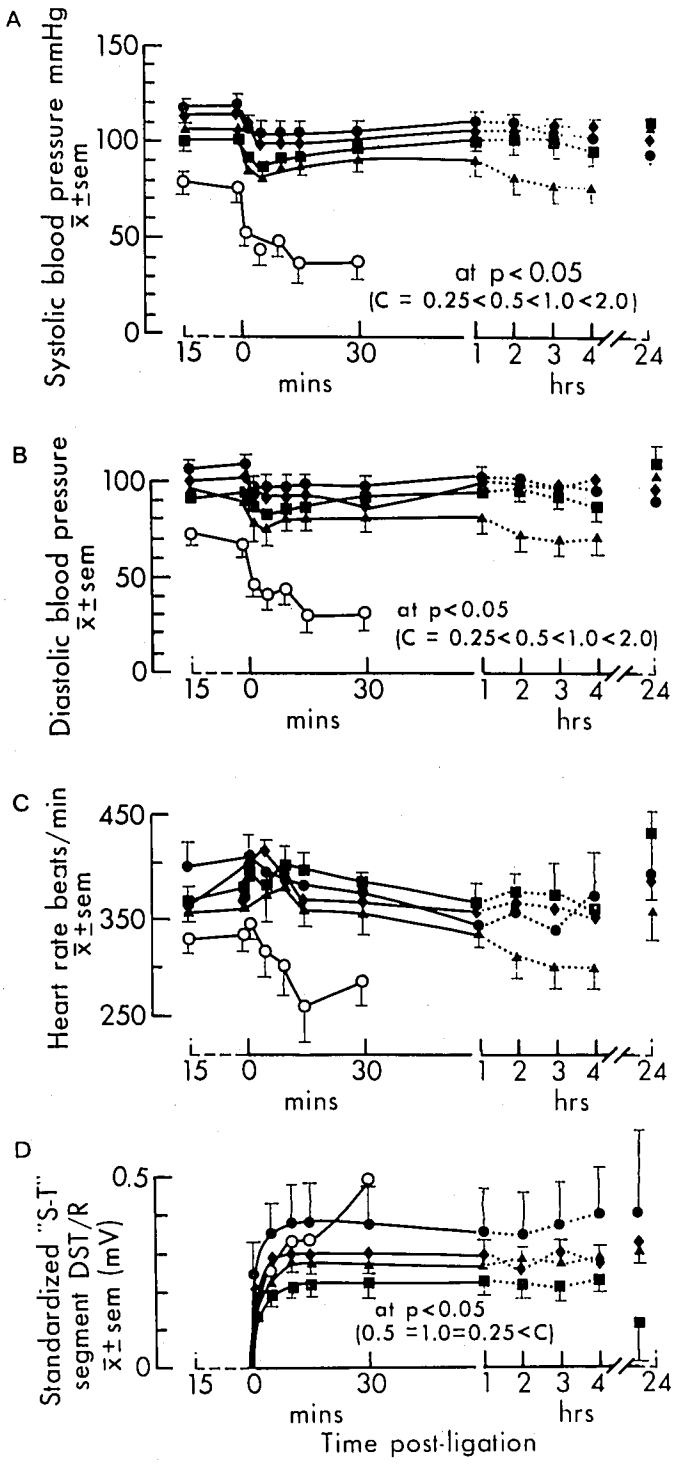

FIG. 1. Effect of varying concentrations of halothane on the blood pressure (*A* and *B*), heart rate (*C*), and ECG (*D*), responses to ligation of the LAD coronary artery. Values are the mean ± SEM for group size of 4–11. In each figure, the symbol ● is control (0% halothane) values, ♦ for 0.25%, ■ for 0.5%, ▲ for 1.0%, and O for 2.0% halothane. In the corner of each figure is the summary of a statistical significant differences at $P < 0.05$. Systolic pressure is shown in (*A*), diastolic pressure in (*B*), heart rate in (*C*), and the change in "S-T" segment standardized for changes in R-wave size in (*D*).

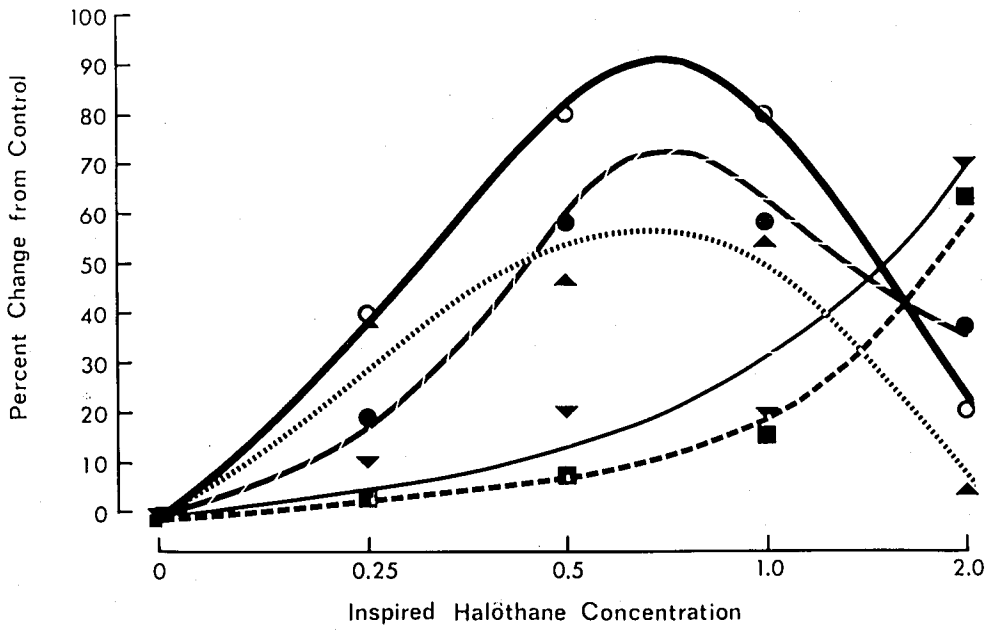

FIG. 2. Halothane dose (concentration)–response relationships for arrhythmia score, blood pressure, ECG, and mortality. Responses, expressed as percentage changes from control, were calculated from data contained in tables and figure 1. The symbol ● is for arrythmia score data, ■ for systolic blood pressure, ▲ for standardized "S-T" segment changes, ▼ for *increased* mortality due to *nonarrhythmic* causes, and O for *decrease* in mortality due to arrhythmias (expressed as a change in percentage).

Changes in occluded and infarcted zone sizes did not explain the antiarrhythmic actions of the agents.

We did not find a correlation between effects on blood pressure or heart rate and effects on arrhythmias. Although the three most vasodepressor agents were antiarrhythmic, the overall order of vasodepressive effectiveness of the agents was different from that for antiarrhythmic action. The correlation between blood-pressure-lowering effects and antiarrhythmic actions was poor at both low and high concentrations of halothane.

Heart rate responses did not parallel antiarrhythmic effects. Most of the halogenated hydrocarbons lowered heart rate; methoxyflurane, isoflurane, and trichlorethylene were as effective in this regard as enflurane, chloroform, and halothane. No obvious relationships were apparent between R-wave size and antiarrhythmic action. Thus, a comparison of the orders of effectiveness of the anesthetics on blood pressure, heart rate, nonarrhythmic mortality, and on ECG, with their antiarrhythmic effectiveness, reveals no correlation that would explain the antiarrhythmic actions of halothane, chloroform, and enflurane.

It does not appear that the anesthetics produced their effects via depression of respiration and resultant hypercapnia and hypoxia. Levels of blood gases were not statistically different between anesthetic doses of the various agents. At the same level of respiratory depression, as judged by blood gases, some agents were antiarrhythmic whereas others were not. For example, 2% halothane was antiarrhythmic and 1.4% isoflurane was not. The arrhythmogenic stimulus in ischemia may be so great that any added arrythmogenic stimulus of combined hypoxia and hypercapnia is relatively minor.

Weak correlations were found between antiarrhythmic actions and effects on nonarrhythmic mortality as well as changes in "S-T" segment of the ECG. With regard to the correlation between nonarrhythmic mortality and antiarrhythmogenic action, it was apparent that although 2% halothane, enflurane, and chloroform all increased nonarrhythmic mortality they were much less antiarrhythmic than 0.5% halothane, which did not significantly raise nonarrhythmic mortality. Figure 2 shows a close relationship between "S-T" segment changes and the antiarrhythmic effects of halothane. However, such a relationship did not hold for other agents. Agents that were not antiarrhythmic (isoflurane, methoxyflurane, and half-enflurane) all caused a fall in "S-T" segment when compared with controls.

From the above discussion, cardiovascular responses to anesthesia and ligation do not explain the antiarrhythmic actions of halothane, enflurane, and chloroform. Few workers have investigated the actions of halogenated anesthetics on the arrhythmias induced by ischemia and infarction. Two abstracts[2,3] report that halothane is antiarrhythmic during coronary ligation in the dog. Kroll and Knight (1982)[3] also showed that enflurane (at inspired concentrations of 1.25 and 2.5%) and isoflurane (1.7%) were antiarrhythmic against ligation-induced arrhythmias. They postulated that the antiarrhythmic effect of halothane, enflurane, and isoflurane resulted from suppression of slow calcium currents. Slow calcium currents are believed to be arrhythmogenic, particularly during ischemia.[5,6] They did not rule out other mechanisms.

The electrophysiologic actions of the halogenated anesthetics are not well known. Halothane (1%)[7] has been reported to depress slow calcium potentials and

reduce action potential duration, as does enflurane[8] at higher concentrations (3%). Both halothane and enflurane depress sinus node potentials.[9] Halothane (1%) was more effective than enflurane (4.5%). Sinus node potentials are also calcium dependent.[10] It appears that enflurane was not as potent as halothane in depressing calcium dependent cardiac electrogenesis.

Other halogenated anesthetics have not been as well studied. Some potentiate the arrhythmogenic actions of epinephrine, as with halothane,[11] chloroform,[12] and trichlorethylene,[13] while others, such as the ethers (enflurane,[11] isoflurane[11]) do so, but to a lesser degree.

In addition to electrophysiologic actions, the halogenated anesthetics cause myocardial depression. As slow calcium currents are essential to cardiac excitation–contraction processes, it is possible that all halogenated hydrocarbons anesthetics depress calcium potentials when given at sufficient concentrations. To investigate this possibility, we intend to test methoxyflurane and isoflurane for antiarrhythmic activity at maximally tolerated concentrations. A relative selectivity of halothane, and to a lesser extent, enflurane and chloroform, for depression of slow calcium potentials in the heart, compared with the production of anesthesia in the brain, would explain why their antiarrhythmic action was revealed in this study. Wolfson *et al.* (1978)[14] found that halothane was not apparently more selective in cardiovascular depressant actions than enflurane, although they did not differentiate between cardiac depression and vascular depression.

While depression of arrhythmogenic slow calcium potentials in the ischemic region may be antiarrhythmic, other mechanisms may dominate. For example, ischemic tissue has action potentials whose duration is reduced drastically.[15] This change is arrhythmogenic because of the resultant disparity in refractoriness between ischemic and nonischemic tissue. A preferential reduction of duration in nonischemic tissue would be antiarrhythmic by reducing such disparity.[16] Both halothane and enflurane reduce action potential duration in normal tissue,[7,8] and this may be the most important mechanism of their antiarrhythmic action. Changes in action potential duration in normal tissue also may explain some of our observed effects on "S-T" segment changes; we intend to investigate such possible electrophysiologic mechanisms in the future.

Regardless of mechanisms involved, it has been established that halothane has an antiarrhythmic action against ischemia-induced arrhythmias in the rat at subanesthetic as well as anesthetic concentrations. Enflurane and chloroform also have such actions, but only at anesthetic concentrations. Other anesthetics may have such actions, but only at concentrations greater than those required to produce surgical anesthesia.

In the future we intend to determine whether the antiarrhythmic actions that we have observed in the rat occur also in the pig. The importance of our observations to the administration of an anesthetic to humans in a setting of myocardial ischemia is unclear but deserves further study.

The authors thank Elaine L. Jan and Tracy L. Slocombe for their help in preparing this document. They also thank Glen Collins and Kathleen Johnston for technical help.

References

1. MacLeod BA, Augereau P, Walker MJA: Effects of halothane anesthesia compared with fentanyl anesthesia and no anesthesia during coronary ligation in rats. ANESTHESIOLOGY 58:44–52, 1983
2. Fukuyama T. Marmor A, Roberts R: The disparate effects of anesthetics on infarct size and mortality during experimental infarction. Clin Res 29:193A, 1981
3. Kroll DA, Knight PR: Antifibrillatory effects of volatile anesthetics in acute occlusion/reperfusion arrhythmias. ANESTHESIOLOGY 57:A503, 1982
4. Johnston KM, MacLeod BA, Walker MJA: ECG and other responses to ligation of a coronary artery in the conscious rat, Rat Electrocardiogram in Pharmacology and Toxicology. Edited by Budden R, Detweiler DK, Zbinden G. Oxford, Pergamon Press, 1981, pp 243–252
5. Wit AL, Bigger JT: Possible electrophysiological alterations during myocardial ischemia and infarction. Circulation 51(suppl 3):96, 1975
6. Clusin WT, Bristow MR, Karagueuzian HS, Katzung BG, Schroeder JS: Do calcium-dependent ionic currents mediate ischemic ventricular fibrillation. Am J Cardiol 49:606–612, 1982
7. Lynch C III, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
8. Lynch C III, Vogel S, Pratila MG, Sperelakis N: Enflurane depression of myocardial slow action potentials. J Pharm Exp Ther 222:405–409, 1982
9. Merlos JR, Bosnjak ZJ, Purtock RV, Turner LA, Kampine JP: Halothane and enflurane effects on SA node cells. ANESTHESIOLOGY 53:S143, 1980
10. Kohlhardt M, Figulla H–R, Tripathi O: The slow membrane channel as the predominant mediator of the excitation process of the sinoatrial pacemaker cell. Basic Res Cardiol 71:17–26, 1976
11. Johnston RR, Eger EI II, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 55:709–712, 1976
12. Morris LE: Chloroform, Halogenated Anesthetics. Edited by Artusio JF Jr. Philadelphia, FA Davis, 1963, pp 23–41
13. Waters RM, Orth OS, Gillespie NA: Trichloroethylene anesthesia and cardiac rhythm. ANESTHESIOLOGY 4:1–5, 1943
14. Wolfson B, Hetrick WD, Lake CL, Siker ES: Anesthetic indices—Further data. ANESTHESIOLOGY 48:187–190, 1978
15. Elharrer V, Zipes DP: Cardiac electrophysiologic alterations during myocardial ischemia. Am J Physiol 233:H329–345, 1977
16. Zipes DP, Heger JJ, Prystowsky EN: Sudden cardiac death. Am J Med 70:1151–1154, 1981