Anesthesiology
61:657-661, 1984

Antifibrillatory Effects of Volatile Anesthetics in Acute Occlusion/Reperfusion Arrhythmias

Donald A. Kroll, M.D., Ph.D., and Paul R. Knight, M.D., Ph.D.*

Halothane, enflurane, and isoflurane were evaluated for antifibrillatory efficacy and compared with lidocaine, propranolol, procainamide, and verapamil in a canine acute left anterior descending (LAD) coronary artery occlusion/reperfusion model with basal pentobarbital anesthesia. Of the antiarrhythmic drugs, only verapamil prevented ventricular fibrillation during occlusion and reperfusion. Halothane 1% inspired after 15 min showed similar protection. Enflurane 2.5% inspired after 15 min resulted in significant protection but caused hypotension after occlusion in 4 of 17 dogs. Isoflurane 1.7% inspired after 15 min showed intermediate results. At inspired concentrations of 0.5% and 1.25%, respectively, halothane and enflurane protected against ventricular fibrillation without hypotension. It is concluded that the volatile anesthetics have antifibrillatory effects in this canine model but differ in their ability to cause hypotension in the presence of proximal LAD coronary artery occlusion. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: arrhythmias; fibrillation; ischemia.)

THE ABRUPT OCCLUSION and reperfusion of a coronary artery is well known to be arrhythmogenic and may result in ventricular fibrillation.[1] Occlusion/reperfusion arrhythmias may occur clinically in a variety of settings such as revascularization of the heart by saphenous vein aortocoronary grafts, thrombolytic procedures, or coronary artery spasm. Calcium ion flux and the intracellular accumulation of calcium ions are thought to be important in mediating the development of arrhythmias during acute coronary occlusion.[2] Further support for the role of calcium ions in the genesis of ischemic arrhythmias is provided by studies that have shown that verapamil[3,4] and other slow calcium channel-blocking drugs[5-7] exert a protective effect against ventricular fibrillation during acute coronary occlusin and reperfusion. A similar protective effect is not afforded reliably by other antiarrhythmic drugs.[1]

The volatile anesthetics interfere with calcium uptake and utilization in myocardial cells. This interference is a possible mechanism by which these anesthetics cause myocardial depression. The exact sites of interference have not been elucidated fully, but it is known that halothane depresses myocardial cell slow action potentials[8] and increases sarcoplasmic reticular calcium efflux at low pH and ATP concentrations.[9] Enflurane also affects slow calcium action potentials, but these effects are less marked than the effects of halothane.[10] Enflurane and isoflurane have effects on calcium transport and uptake by cardiac sarcoplasmic reticulum similar to halothane, but with quantitative differences.[11]

Recent investigations have demonstrated interactions between the calcium channel-blocking drugs and volatile anesthetics on myocardial contractility and hemodynamics.[12-14] In some of these reports additive effects were shown.

Because of the similar hemodynamic effects of volatile anesthetics and calcium channel-blocking drugs and the known efficacy of the calcium blockers against occlusion–reperfusion fibrillation, this study was designed to evaluate the potential protective effects of volatile anesthetics against ventricular fibrillation associated with acute occlusion/reperfusion arrhythmias.

Materials and Methods

Mongrel dogs 11–18 kg were anesthetized with pentobarbital sodium 30 mg/kg. Mechanical ventilation via an endotracheal tube was established with room air at a tidal volume of 15 ml/kg and a rate of 12–15/min, known from prior studies to result in a Pa_{CO_2} of approximately 30 mmHg. The use of room air rather than oxygen and hyperventilation increase the likelihood of reperfusion ventricular fibrillation.[1] Blood pressure was measured directly by cannulation of the femoral artery. Lead II of the electrocardiogram was monitored. A thoracotomy was performed in the left fourth or fifth intercostal space, and the heart was exposed via a pericardiotomy. The left atrial appendage was reflected, and a ligature was passed under the left anterior descending coronary artery distal to the first septal perforator near its origin. The free ends of the ligature were passed through a short section of polyethylene tubing. The artery then could be occluded by pressing the tubing onto the vessel while pulling up on the free ends of the ligature. The occlusion was maintained for 20 min by clamping the ligature with Kelly forceps. It the animal survived, the occlusion was released and blood flow restored by releasing the clamp and pulling the tubing away from the vessel.

* Assistant Professor. Awardee of a Burroughs Wellcome Fellowship in Anesthesiology, which supported this research.

** Associate Professor. Awardee of a Research Career Development Award, United States Department of Health, Education and Welfare, Public Health Service, GMA100 00477 01.

Received from the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan 48109. Accepted for publication May 11, 1984. Presented in part for Resident Essay Competition American Society of Anesthesiologists, New Orleans, 1982.

Address reprint requests to Dr. Kroll.

TABLE 1. Occurrence of Ventricular Fibrillation

	Total (N)	Ventricular Fibrillation		Hypotension	Survival		P* Control	P* Halothane
		During	Release		n	%		
Control	30	9	20	0	1	3.3	(a) (b) (c)	
Halothane 1%	17	0	5	0	12	70.6	0.0001 0.0001 0.0001	—
Enflurane 2.5%	17	0	7	4	6	35.3	0.0001 0.0001 0.0001	0.0421 0.0191 0.042
Isoflurane 1.7%	10	0	2	1	7	70.0	0.0001 0.0001 0.0001	NS NS NS
Halothane 0.5%	5	0	2	0	3	60.0	0.0009 0.0045 0.009	NS NS NS
Enflurane 1.25%	6	0	3	0	3	50.0	0.0027 0.0063 0.008	NS NS NS
Verapamil	5	0	1	0	4	80.0	0.0001 0.0004 0.0001	NS NS NS
Propranolol	7	2	3	0	2	28.6	NS NS NS	0.0364 0.0316 0.054
Procainamide	8	2	4	0	2	25.0	NS NS NS	0.0316 0.0236 0.034
Lidocaine	5	1	3	0	1	20.0	NS NS NS	0.0481 0.0511 0.060
Halothane 1% no pentobarbital	5	0	2	0	3	60.0	0.0009 0.0045 0.009	NS NS NS
Enflurane 2.5% no pentobarbital	5	0	3	1	1	20.0	0.0222 0.0435 0.050	0.0481 NS NS

* Values shown are for χ^2 (a), maximum likelihood (b), and Fishers Exact (c) Tests.

Intravenous drugs and anesthetic agents were administered following an initial 15-min equilibration period, and recordings were made at 5-min intervals for 15 min before occlusion. The intravenous drugs administered were lidocaine 2 mg/kg + 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$, propranolol 1 mg/kg, procainamide 10 mg/kg, and verapamil 0.4 mg/kg. Halothane 1% inspired was chosen as a reference concentration, and the inspired concentrations of enflurane (2.5%) and isoflurane (1.7%) were adjusted to be approximately equivalent to 1% halothane. Because of the initial results obtained, enflurane also was given at 1.25% inspired concentration and the results compared with halothane at 0.5% inspired.

In a second series of experiments, inhalation inductions were performed with halothane or enflurane in room air. No pentobarbital was given, and the animals were maintained at either 1% halothane or 2.5% enflurane inspired concentrations for at least 30 min before occlusion and for the remainder of the experiment.

Statistical analysis of nonparametric data was performed by computing chi-squaqre statistics, maximum

TABLE 2. Blood Pressure Responses

	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
	Predrug	Preocclusion	Postocclusion	Predrug	Preocclusion	Postocclusion
Control	139 ± 33	119 ± 40	100 ± 43	90 ± 27	75 ± 31	62 ± 33
Halothane 1%	147 ± 20	104 ± 25*	83 ± 20*	110 ± 17	75 ± 20*	60 ± 15
Enflurane 2.5%	142 ± 14	92 ± 17*	64 ± 30*	102 ± 16	65 ± 15*	47 ± 19*
Isoflurane 1.7%	142 ± 17	103 ± 16*	77 ± 32	103 ± 19	72 ± 12*	53 ± 19*
Halothane 0.5%	171 ± 22	147 ± 17*	141 ± 17*	123 ± 18	108 ± 13*	105 ± 16
Enflurane 1.25%	171 ± 15	137 ± 10*	116 ± 16*	120 ± 13	92 ± 10*	86 ± 13*

Values are mean ± SD.

* $P < 0.05$ paired to predrug value.

likelihood ratios, and Fisher's Exact probabilities using the Freeman-Halton modification. Parametric data were analyzed using paired Student's t tests and analysis of variance. $P < 0.05$ was required for statistical significance.

Results

The results are shown in Table 1. A total of 30 dogs received no drug treatment and served as a control group. All but one animal fibrillated. Nine animals fibrillated during the occlusion, and 20 fibrillated following reestablishment of coronary blood flow by removing the occlusive ligature. The onset of ventricular fibrillation following reperfusion typically occurs within a few seconds. Thus, in the absence of effective drug treatment, it is expected that a third of the animals would fibrillate during the occlusion and two thirds would fibrillate on release with very few survivors. Lidocaine, procainamide, and propranolol did not significantly change these expectations. Ventricular fibrillation occurred with the same frequencies as in the untreated group. Verapamil exerted a marked protective effect. No dogs fibrillated during the occlusion, and four out of five survived reperfusion. Halothane caused highly significant protection, with 12 out of 17 dogs surviving and five fibrillating on release of the occlusion and restoration of coronary blood flow.

The results with enflurane 2.5% inspired, which is approximately equivalent in potency to 1% halothane inspired in the dog, differed from both halothane and control groups. Four of 17 dogs exhibited electromechanical dissociation immediately with profound hypotension progressing to global ischemia and an agonal rhythm. This response never was observed in the control group. When separate analysis was performed excluding the hypotensive group, enflurane was significantly different from the control group, but not from the halothane group.

Isoflurane at a concentration of 1.7% inspired causes results significantly different from the control group and showing features of the responses seen with halothane and enflurane at approximately equivalent potencies. One dog became profoundly hypotensive with electromechanical dissociation, two dogs fibrillated on release, and the remaining seven dogs were protected. The blood pressure was decreased by all three anesthetics prior to occlusion, but the degree of decrease was no different among the groups and cannot explain the results following occlusion.

Repeating the experiments at 1.25% enflurane inspired demonstrated protection against fibrillation. At this lower concentration no dog fibrillated during the occlusion and three of six dogs survived the reestablishment of coronary blood flow. Electromechanical dissociation did not occur. These results were significantly different from the control group, but no different from the group pretreated with an approximately equipotent inspired halothane concentration of 0.5%.

As expected, systolic and diastolic blood pressures were decreased in the groups receiving inhalational anesthetics (table 2). Heart rates were similarly decreased by the inhalational anesthetics (table 3). Analysis of variance among the groups receiving inhalational anesthetics showed no statistical difference among the groups for approximately equivalent doses. Halothane and enflurane at the lower concentrations decreased blood

TABLE 3. Heart Rate (beats/min)

	Predrug	Preocclusion	Postocclusion
Control	136 ± 16	129 ± 24	136 ± 24
Halothane 1%	135 ± 22	111 ± 24*	109 ± 18*
Enflurane 2.5%	149 ± 33	113 ± 10*	113 ± 14*
Isoflurane 1.7%	131 ± 36	110 ± 19*	112 ± 15*
Halothane 0.5%	146 ± 25	131 ± 22*	140 ± 20
Enflurane 1.25%	151 ± 28	127 ± 25	128 ± 22*

Values are mean ± SD.
* $P < 0.05$ paired to predrug value.

pressure compared with the untreated control group and to their pretreatment levels but to a lesser extent than at the higher concentrations. Although the decrease in blood pressure prior to occlusion did not differ among the volatile anesthetics at the higher concentrations, the preocclusive diastolic blood pressure with 1.25% enflurane was statistically lower than with 0.5% halothane.

In the series of experiments omitting pentobarbital, five animals received halothane. None of the dogs fibrillated during the occlusion, two fibrillated with reperfusion, and three survived. This behavior was significantly different from the untreated control group. Of the five dogs receiving enflurane, only one survived. Although no dog fibrillated during occlusion, one exhibited electromechanical dissociation and three fibrillated with reperfusion. This pattern was also significantly different from the control group.

Discussion

The results of this study demonstrate an unequivocal antifibrillatory effect of volatile anesthetics. The animal model used is quite stringent in that the antiarrhythmic drugs lidocaine, propranolol, and procainamide did not prevent ventricular fibrillation. The ability of verapamil to prevent fibrillation in this animal model was confirmed and is in agreement with the results of others[3,5] Since a number of other calcium channel-blocking drugs are also effective against these arrhythmias,[5,7] it would appear that the ability to prevent ventricular fibrillation in this model is closely correlated with calcium channel blockade. The failure of lidocaine to protect against fibrillation indicates that this effect is not dependent on fast sodium blockade, and the failure of propranolol to protect indicates that beta-adrenergic blockade is not sufficient for protection, although the role of alpha-adrenergic receptors in mediating ischemic reperfusion fibrillation cannot be distinguished by these data.

The incidences of fibrillation in the two groups without pentobarbital were both significantly different from the pentobarbital control group, with the primary effect apparently due to the lack of fibrillation during occlusion, although the halothane group also had a low incidence of reperfusion fibrillation. Comparison of the 1% halothane group and the 2.5% enflurane group with and without pentobarbital showed no difference by either chi-square or maximum likelihood tests dependent on pentobarbital. Thus, it would seem that the antifibrillatory effects of halothane and enflurane are not dependent on any pentobarbital interaction.

The observation that enflurane differed from halothane in causing electromechanical dissociation in approximately one-fourth of the dogs after LAD occlusion may be explained by the observations of others[15] that enflurane may be more potent than halothane in interfering with contractile function.

It is conceivable that acute myocardial ischemia with the resultant depletion of ATP stores and intracellular acidosis might predispose to the negative inotropic effects of enflurane and halothane and that there is insufficient reserve contractile functions of the myocardium to maintain cardiac output with the slightly greater negative inotropic effect of enflurane. There were no differences in preocclusion heart rates or blood pressures, which can explain the development of electromechanical dissociation in the enflurane-treated group and the lower postocclusion blood pressures in the enflurane group reflect those animals demonstrating electromechanical dissociation. When only animals without electromechanical dissociation were compared, there were no differences among the groups. Dose dependency is suggested by the fact tht low-dose enflurane did not cause electromechanical dissociation, and although an interaction with pentobarbital cannot be completely ruled out, this interaction is not necessary since electromechanical dissociations was observed in one of five dogs who did not receive pentobarbital, approximately the same incidence as in the pentobarbital pretreated high-dose enflurane group. Thus, it appears that electromechanical dissociation in the presence of proximal LAD occlusion is related more specifically to enflurane and is dose dependent. Since isoflurane also caused electromechanical dissociation, but with a lower incidence, it might be more accurate to relate the phenomenon to ether structures. Further evaluation with methoxyflurane might lend credence to this theory.

The observation that inhalational anesthetics exhibit antifibillatory properties in myocardial ischemic models also has been made by others,[16,17] using a rat ischemic model. Although the data of Jang *et al.*[17] are difficult to compare directly with our results because the methods are substantially different, these authors were able to demonstrate a decreased incidence of death due to ventricular fibrillation in rats with proximal LAD occlusions treated with halothane, enflurane, and chloroform. They did not examine reperfusion fibrillation and extended the observation period beyond the acute phase of ischemic injury. It is interesting that they showed no effect on ventricular ectopy during the observation period. This may reflect the variable time course of ischemic arrhythmogenesis that occurs after acute occlusion of a coronary artery but also may illustrate the lack of association between ventricular ectopy and the tendency to fibrillate. When considered together, their results and ours would mandate a reconsideration of the commonly held idea that halothane is arrhythmogenic. Catecholamine-induced arrhythmias and ischemic arrhythmias respond quite differently to halothane.

We conclude that the volatile anesthetics have significant antifibrillatory activity in acute myocardial ischemia and reperfusion. Although these data do not directly indicate the mechanism of this protective effect, they support the inference that the most likely explanation is related to calcium channel blockade. Reduction of infarct size, improved collateral blood flow, and autonomic effects also may be important approaches for further study.

The authors gratefully acknowledge the statistical advice and assistance in calculations of Drs. Richard G. Cornell and J. Richard Landis of the Department of Biostatistics, University of Michigan School of Public Health.

References

1. Dreifus LS, Naito M, Michelson EL: What animal models should be used to define antiarrhythmic efficacy? Acute dog models, The Evaluation of New Antiarrhythmic Drugs. Edited by Morganroth J. Boston, Martinus Nijhoff, 1981, pp 17–28
2. Clusin WT, Bristow MR, Karagueuzian HS, Katzung BG, Schroeder JS: Do calcium-dependent ionic current mediate ischemic ventricular fibrillation? Am J Cardiol 49:606–612, 1982
3. Kaumann AJ, Aramendia P: Prevention of ventricular fibrillation induced by coronary ligation. J Pharmacol Exp Ther 164:326–332, 1968
4. Brooks WW, Verrier RL, Lown B: Protective effect of verapamil on vulnerability to ventricular fibrillation during myocardial ischaemia and reperfusion. Cardiovasc Res 14:295–302, 1980
5. Ribeiro LGT, Brandon TA, Debauche TL, Maroko PR, Miller RR: Antiarrhythmic and hemodynamic effects of calcium channel blocking agents during coronary artery reperfusion. Comparative effects of verapamil and nifedipine. Am J Cardiol 48:69–74, 1981
6. Fagbemi O, Parratt JR: Calcium antagonists prevent early post-infarction ventricular fibrillation. Eur J Pharmacol 75:179–185, 1981
7. Fagbemi O, Parratt JR: Suppression by orally-administered nifedipine, nisoldipine and niludipine of early life-threatening ventricular arrhythmias resulting from acute myocardial ischaemia. Br J Pharmacol 74:12–14, 1981
8. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
9. Blanck TJJ, Thompson M: Calcium transport by cardiac sarcoplasmic reticulum: Modulation of halothane action by substrate concentration and pH. Anesth Analg 60:390–394, 1981
10. Lynch C, Vogel S, Pratila MG, Sperelakis N: Enflurane depression of myocardial slow action potentials. J Pharm Exp Ther 222:405–409, 1982
11. Blanck TJJ, Thompson M: Enflurane and isoflurane stimulate calcium transport by cardiac sarcoplasmic reticulum. Anesth Analg 61:142–145, 1982
12. Kapur PA, Flacke WE: Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. ANESTHESIOLOGY 55:218–225, 1981
13. Kapur PA, Flacke WE, Olewine SK: Comparison of effects of isoflurane versus enflurane on cardiovascular and catecholamine responses to verapamil in dogs. Anesth Analg 61:193–194, 1982
14. Kates RA, Kaplan JA, Guyton RA, Dorsey LM, Hug CC: Hemodynamic interactions of verapamil and isoflurane. ANESTHESIOLOGY 59:132–138, 1983
15. Christian CM, Fagraeus L, Van Trigt P, Spray TL, Pasque MK: ID_{20}: Defining myocardial depression in dogs. Anesth Analg 61:174–175, 1982
16. 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
17. Jang TL, MacLeod BA, Walker MJA: Effects of halogenated hydrocarbon anesthetics on responses to ligation of a coronary artery in chronically prepared rats. ANESTHESIOLOGY 59:309–315, 1983