

Epinephrine-induced Arrhythmias and Cardiovascular Function after Verapamil during Halothane Anesthesia in the Dog

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The antiarrhythmic and cardiovascular effects of the slow channel inhibitor, verapamil, were studied during 1.1 MAC halothane anesthesia in the dog. The control epinephrine arrhythmogenic dose to induce ventricular arrhythmias was $2.58 \pm 0.77 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (mean \pm SEM). Three consecutive doses of 0.2 mg/kg verapamil each elevated the dose of epinephrine required to produce a ventricular arrhythmia to 5.17 ± 1.27 , 8.07 ± 1.85 , and $12.03 \pm 2.76 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, all of which were significantly elevated above the control value and the preceding values. A second group of dogs, unperturbed by epinephrine, received the same sequence of verapamil doses at similar time intervals for evaluation of effects on cardiovascular function and atrioventricular conduction. Heart rate remained unchanged. Mean arterial pressure decreased maximally by 37 per cent of control, left ventricular dP/dt by 24 per cent, and systemic vascular resistance by 51 per cent. These effects were transient with recovery times of up to one hour. Central venous pressure increased by 44 per cent and left ventricular end diastolic pressure by 27 per cent, while PR interval was prolonged by 40 per cent. Thus, verapamil raised the dose of epinephrine required to elicit a ventricular arrhythmia during halothane anesthesia promptly and cumulatively. At the same time verapamil produced transient peripheral vasodilation, direct depression of myocardial contractility, and prolongation of atrioventricular conduction time that was not cumulative at the intervals studied. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmia; antiarrhythmics; myocardial function. Ions: calcium. Pharmacology: verapamil. Sympathetic nervous system: catecholamines, epinephrine.)

VERAPAMIL SELECTIVELY INHIBITS slow calcium currents across excitable membranes. It thereby relaxes vascular smooth muscle, inhibits myocardial contractility, and has depressant effects on the sinus node and atrioventricular conduction.¹ Because of its effects on electrophysiological properties, verapamil has been successfully used in the treatment of re-entrant type cardiac arrhythmias¹ which may be the type of arrhythmia induced by epinephrine during halothane anesthesia.² Catecholamines are known to increase the incidence of arrhythmias during anesthesia with a number of inhalational anesthetics.³ The amount of adrenergic agent that will elicit such

arrhythmias is demonstrably less during halothane anesthesia than with other presently used inhalational anesthetics⁴⁻⁶ and considerably less than in the awake state.⁴

There is some evidence from animal studies that verapamil can suppress hydrocarbon-epinephrine ventricular arrhythmias⁷ as well as chloroform-epinephrine arrhythmias.^{8,9} Successful treatment with verapamil of a number of arrhythmias occurring spontaneously or under various conditions in patients under "light" halothane anesthesia has been reported, though blood pressure decreases and PR interval prolongation were noted.¹⁰ Recent evidence indicates that halothane itself depresses the slow channel conductance.¹¹ Halothane is known to cause vasodilatation,^{12,13} have negative inotropic effects,¹²⁻¹⁴ prolong atrioventricular conduction,^{15,16} and to depress baroreflex control of heart rate.^{17,18} The interference by halothane with slow inward calcium currents might account in part for the observed halothane-induced decrease in smooth muscle and myocardial contractility and suggest an interaction, additive or potentiating, of the hemodynamic effects of verapamil by halothane.

Therefore, we decided to systematically evaluate the effect of verapamil on epinephrine-induced arrhythmias during halothane anesthesia and to study the cardiovascular changes resulting from verapamil in combination with halothane.

Methods

Eleven mongrel dogs of either sex, weighing 22.3 ± 0.44 kg (mean \pm SEM), range 20.0-24.5 kg,

ABBREVIATIONS

AV	atrioventricular
bpm	beats per minute
CVP	central venous pressure
CO	cardiac output
EAD	epinephrine arrhythmogenic dose
HR	heart rate
LVEDP	left ventricular end-diastolic pressure
LV dP/dt	first derivative of left ventricular pressure with time
MAP	mean arterial pressure
PR	time interval between the P and R waves of the ECG
SA	sinoatrial
SEM	standard error of the mean
SVR	systemic vascular resistance

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were studied. Anesthesia was induced with thiopental, 17.6 ± 0.5 mg/kg, iv. The animals were intubated orally with a cuffed endotracheal tube and mechanically ventilated (Harvard® Apparatus Company Model 607) to maintain a pH of 7.37 ± 0.01 and a P_{aCO_2} of 39.5 ± 0.7 torr (Corning® Blood Gas Analyzer model 165). A circulating water blanket was used to maintain esophageal temperature between $37-39^\circ\text{C}$ (Yellow Springs Corp. thermistor probe). One hundred per cent oxygen was delivered to a halothane vaporizer (Draeger) in the inspiratory limb of the non-rebreathing circuit, which was adjusted to maintain serum halothane levels measured by gas chromatography¹⁹ equivalent to an alveolar concentration of 0.93 ± 0.03 per cent (MAC in the dog = 0.87 per cent²⁰).

Cannulas were placed in a femoral artery for intra-arterial pressure monitoring and arterial blood sampling and in a femoral vein for intravenous fluid and drug administration. Fluids consisted of a crystalloid solution iso-osmolar to physiologic saline containing the following milliequivalents per liter: sodium 155, chloride 66, and bicarbonate 89, which was chosen to avoid base deficit in the face of the metabolic products from repeated epinephrine infusions. Group I dogs received approximately $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ while group II dogs received approximately $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ to maintain urine flow. A balloon-tipped flow-directed catheter was placed in a pulmonary artery via an external jugular vein for the measurement of central venous pressures and thermodilution cardiac outputs (Santa Barbara Technology Cardiac Output Computer 1700). Lead II of the electrocardiogram, heart rate, and end-tidal CO_2 concentration (Beckman® LB-3 infrared CO_2 analyzer) were also continuously measured. Data were recorded on a direct writing oscillograph (Hewlett Packard® Model 7758). To measure PR interval the ECG was also recorded separately (Grass Model 79) at a paper speed of 100 mm/s.

GROUP I

In six dogs, after 95 ± 7 min of stabilization on halothane, the arrhythmogenic dose of epinephrine was determined by the method of Pace *et al.*²¹ Epinephrine was freshly diluted in 0.9 per cent saline to concentrations of 50 $\mu\text{g}/\text{ml}$ for lower doses and 100 $\mu\text{g}/\text{ml}$ for higher doses. Epinephrine in standardized logarithmically spaced increasing doses (0.67, 0.82, 1.00, 1.22, etc. $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was infused (Sage Instruments syringe pump model 355) for three min each with a 10-min recovery period up to the rate that produced four or more premature ventricular contractions within 15 s on duplicate trials.

The determination of the control epinephrine arrhythmogenic dose (EAD) took approximately 160 min. Following this, verapamil‡, 0.2 mg/kg, in a concentration of $0.01 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{ml}^{-1}$ diluted in 0.9 per cent saline, was infused over 10 min by a constant infusion pump (Princeton Medical Instruments model 520) while electrocardiographic and hemodynamic parameters were recorded. Then the EAD was again determined. The initial epinephrine test dose was the next higher above the control EAD. Three doses of verapamil were given in this way with approximately 100 min between the first and second dose and 75 min between the second and third dose.

On eight occasions in five dogs, before the termination of the experiment, ventricular tachycardia was deliberately elicited by infusion of epinephrine, 100 $\mu\text{g}/\text{ml}$. Verapamil was then administered by rapid infusion until sinus rhythm was restored. The epinephrine infusion was continued at the same rate for five min under continuous ECG monitoring to ascertain that the arrhythmias did not recur.

GROUP II

To assess the hemodynamic consequences of rapid verapamil administration during halothane anesthesia unperturbed by repeated epinephrine infusions, five dogs were anesthetized and monitored as described. In addition a micromanometer tipped catheter (Millar Instruments, Inc.) was advanced into the left ventricle via the left carotid artery. Verapamil was prepared as described for Group I. After 137 ± 3.6 min of stabilization on halothane, the first of three doses of verapamil, 0.2 mg/kg each, was infused over 30 s during continuous electrocardiographic and hemodynamic monitoring. The time intervals between the first and second, and second and third doses of verapamil were chosen to approximate those in Group I and were 93 ± 1.4 min and 85 ± 1.7 min, respectively. In four dogs a fourth dose of verapamil, 0.4 mg/kg in a concentration of 5 mg/ml, was given over 30 s (61 ± 0.4 min after the third dose), and a fifth dose of 0.8 mg/kg was given over 30 s, 55 ± 6.0 min later.

All values in the text, tables, and figures are given as means \pm SEM. No effort was made to express CO and SVR in terms of body weight or surface area because the differences in weight were small. A two-tailed paired *t* test was used to analyze progressive changes in values resulting from verapamil administration within each group of dogs, while a two-tailed non-paired *t* test was used to compare changes between Groups I and II. Analysis of variance was used

‡ Isoptin®, Knoll Pharmaceuticals, Whippany, New Jersey.

TABLE 1. Epinephrine Arrhythmia Threshold (n = 6)

Verapamil (0.2 mg/kg)	Time Between Doses (min)	Cumulative Dose (mg/kg)	Arrhythmogenic Dose of Epinephrine* ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	Comparison†		
				vs. Control	vs. Dose 1	vs. Dose 2
Control	—	—	2.58 ± 0.77	—	—	—
Dose 1	0	0.2	5.17 ± 1.27	$P < 0.02$	—	—
Dose 2	100	0.4	8.07 ± 1.85	$P < 0.005$	$P < 0.01$	—
Dose 3	75	0.6	12.03 ± 2.76	$P < 0.001$	$P < 0.01$	$P < 0.01$

* Values given as means ± SEM.

† Paired *t* test.

to determine if there were significant differences among the three doses of verapamil in the control values or magnitude of verapamil-induced changes at comparable times over the course of the experiment. Significant difference between values was assumed when $P < 0.05$. A variable was considered to have returned to control level when the P value compared to control was greater than 0.05.

Results

The preparation was stable over the course of the experiments for both groups. In Group I, analysis of variance revealed no significant difference in HR or MAP when the values before the first epinephrine dose were compared to the control values before the three injections of verapamil. Similarly, there was no difference in Group II among the control values of hemodynamic variables and PR interval before the three doses of verapamil.

EFFECT OF VERAPAMIL ON EPINEPHRINE ARRHYTHMIAS

In the Group I dogs, the control EAD during 1.1 MAC halothane in oxygen anesthesia was $2.58 \pm 0.77 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (table 1). The initial dose of 0.2 mg/kg verapamil raised the EAD to $5.17 \pm 1.27 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Approximately 100 min later, the second dose raised the EAD to $8.07 \pm 1.85 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and approximately 75 min following the second dose, the third dose raised the EAD to $12.03 \pm 2.76 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (table 1). Thus, the effects of verapamil on the EAD were cumulative even when the drug was given at these intervals.

At the end of the experiments, verapamil was used to terminate ongoing epinephrine-induced ventricular tachycardia on all eight attempts in five dogs. Verapamil, 0.1–0.2 mg/kg, was injected over 23–85 s, and converted the arrhythmia to sinus rhythm, which was maintained in spite of continued epinephrine challenge for five min. On five of those eight occasions the new EAD was sought. It was always found to be further elevated, with the new mean

EAD of $12.91 \pm 1.71 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for that subset of five, significantly greater than their mean EAD of $9.88 \pm 1.42 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($P < 0.01$), prior to the ventricular tachycardia challenge.

HEMODYNAMIC EFFECTS

In Group II, an analysis of variance of each variable not only at control, but at maximum change, and at subsequent 10-min intervals revealed no significant difference among the three doses. Therefore, the data for the three injections were pooled (fig. 1). Heart rate remained unchanged post-verapamil in these halothane-anesthetized dogs. All other measured functions changed post-verapamil with the following maximum changes in the mean values significant at the $P < 0.001$ level. MAP decreased 37 per cent within one min and returned to control values by 70 min postinjection. The LV dp/dt decreased 24 per cent by two min and returned to control by 30 min postinjection. SVR dropped precipitously by 51 per cent within one min postinjection but returned to control by 10 min. LVEDP rose 27 per cent by six min and remained elevated above control for 40 min, while CVP rose 44 per cent by four min and remained elevated for 80 min. CO rose immediately by 16 per cent within one min post-verapamil and then dropped below control by 10 min; CO mean values were not significantly different from control at subsequent time intervals.

To evaluate the differences in effects between giving the drug over a 10-min infusion (Group I) or over 30 s (Group II), the values for HR and MAP for the three doses of 0.2 mg/kg verapamil were compared between the two groups. There was no significant difference between the control values of the two groups nor was there a significant change in HR post-verapamil in either group. The maximum drop in MAP from control in Group II was 36.3 ± 2.1 torr, significantly greater ($P < 0.001$) than the maximum decrease in MAP of 14.6 ± 1.6 torr if the drug was given more slowly (Group I). However, within 10 min after the rapid administration of 0.2 mg/kg verapamil

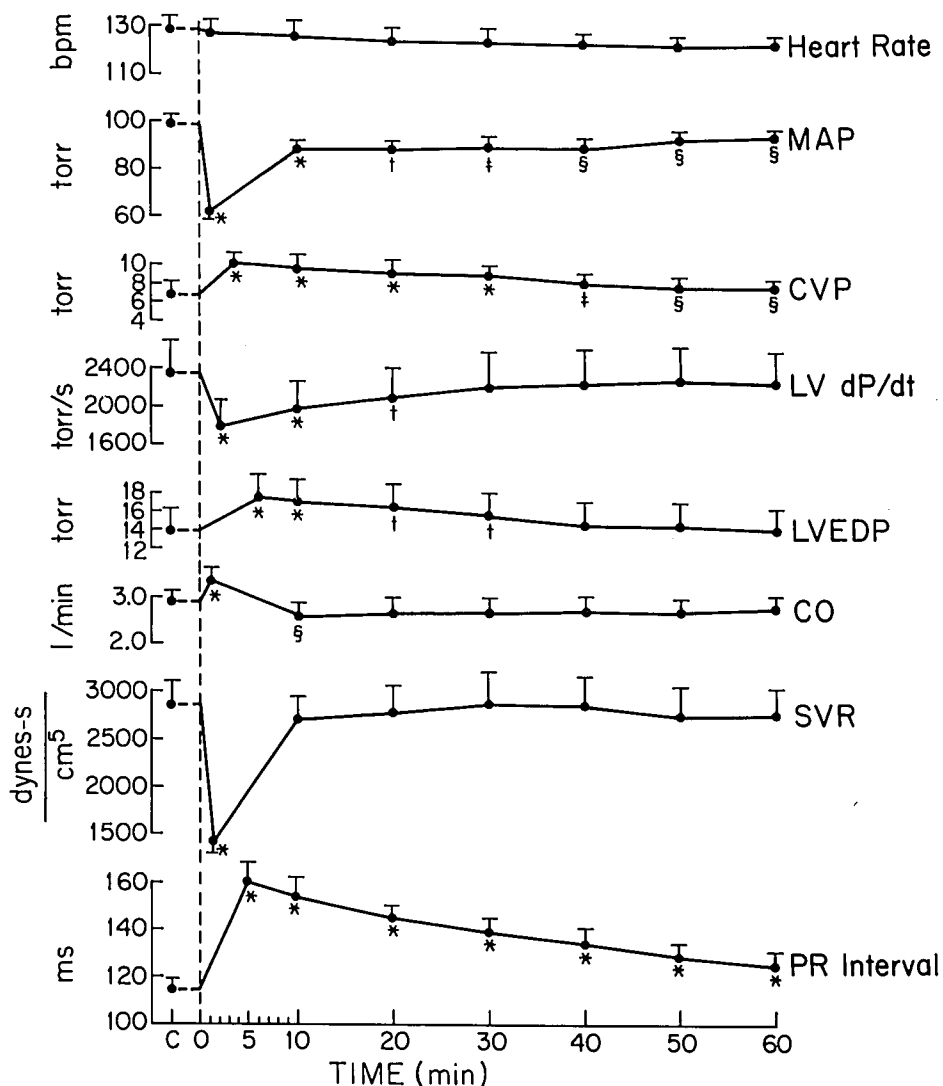


FIG. 1. Cardiovascular and PR interval changes following infusions at time zero of verapamil, 0.2 mg/kg, over 30 s (Group II). Pooled data from five dogs. C = control. First values plotted after zero were the maximum changes. Note the differences in time to peak response. * $P < 0.001$, † $P < 0.005$, ‡ $P < 0.1$, § $P < 0.05$.

(Group II) the decrease in MAP from control (11.8 ± 3.0 torr) was not significantly different from the change in MAP from control (14.6 ± 1.6 torr) at the completion of the 10-min infusion of 0.2 mg/kg (Group I).

An example of changes in ventricular function after verapamil administration is shown in figure 2 for an animal that responded by maintaining a high CO following each of the three injections of 0.2 mg/kg verapamil. At this dose CO increased, though with an increase in LVEDP. Larger doses of verapamil, however, caused a decrease in CO with increase in LVEDP. The maximal depressant effect occurred six min after injection while recovery proceeded more slowly. In all cases, as the effect of the drug dissipated, the relationship between CO and filling pressure moved back upward and to the left towards the control. However, the filling pressure rise which reached a maximum four to six min after injection was later than the CO

peak which occurred by one min and the LV dP/dt nadir which occurred by one to two min after injection.

CHANGES IN AV CONDUCTION

The PR interval was significantly prolonged following verapamil administration. Analysis of variance revealed no difference comparing control values as well as comparing subsequent values of PR interval before and following each of the three doses of 0.2 mg/kg in Group II; therefore, the data for the three injections were pooled (fig. 1). The PR interval increased maximally (40 per cent) by five min and remained significantly above control until 90 min post-injection.

There was no significant difference between the Group I and Group II PR intervals pre-verapamil, nor was there a significant difference between the maximal increase in PR interval, which was noted at

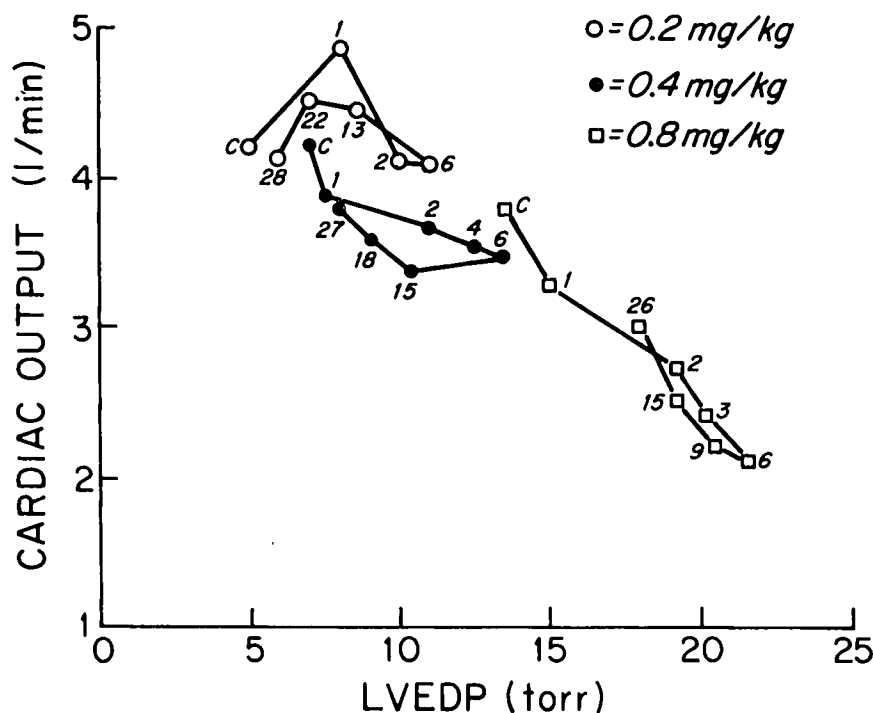


FIG. 2. Changes in ventricular function following successive infusions of verapamil, 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg, over 30 s. C = control. Numbers indicate min after verapamil administration. \circ = the second rapidly injected dose of 0.2 mg/kg verapamil in this dog. Response to the other injections of the same dose was similar; for clarity only one is depicted. \bullet = 0.4 mg/kg verapamil over 30 s given 147 min after \circ and 61 min after an intervening third dose of 0.2 mg/kg. \square = 0.8 mg/kg verapamil given 62 min after \bullet .

the end of the 10-min infusion in Group I and 5 min after the 30-s infusion in Group II.

On five occasions in four Group II dogs, second or third degree heart block resulted from verapamil doses two to eight times the standard 0.2 mg/kg dose, with the cumulative total dose of verapamil given between 1.0 and 3.4 mg/kg. The block lasted between 10 and 76 min postinjection. Episodes of 2° heart block were Mobitz type I (Wenckebach phenomenon). One Group I dog experienced sinus arrest for approximately 20 min each after sixth and seventh verapamil infusions of 0.2 mg/kg.

In another dog from Group I, an episode of supra-ventricular tachycardia at a rate of 240 bpm followed EAD determination. Verapamil infusion was begun and sinus rhythm was restored after the administration of only 0.05 mg/kg.

Discussion

We have shown in this study that verapamil produced a sustained rise in the epinephrine arrhythmogenic threshold and aborted ongoing epinephrine-induced ventricular arrhythmias in the intact dog during halothane anesthesia. However administration of 0.2 mg/kg verapamil resulted in prolongation of atrioventricular conduction time, as well as a reduction in systemic vascular resistance and myocardial contractility with a net decrease in blood pressure. Slower administration of verapamil de-

creased the magnitude of the peak blood pressure drop.

Verapamil is a member of a relatively new class of drugs, the slow channel inhibitors, that interfere with the inward flux of calcium across excitable membranes. Whereas the initial upstroke of the action potential of atrial and ventricular myocardium is rapid and is carried by the inward movement of sodium ions, it is now recognized that a second, slower, inward current occurs at plateau level potentials, carried largely by calcium ions. The slow calcium current can even depolarize a cell independently when the fast sodium current is inactivated by ischemia, hyperkalemia, or tetrodotoxin, or by inhibition of the $\text{Na}^+\text{-K}^+$ pump by digitalis.²² Under these conditions the predominance of the slow calcium current results in slowed conduction velocity, which along with unidirectional block, favors the development of re-entrant arrhythmias.²³

Verapamil is a specific antagonist of the slow calcium current with no observable effect on the fast sodium current. In contrast, lidocaine acts on the fast sodium current without significantly affecting calcium conductivity.²⁴ Kohlhardt *et al.* proposed that the decreased contractility observed with verapamil is a result of net diminished intracellular calcium stores consequent to diminished calcium inflow.²⁴ Alternatively, in the mammalian heart, calcium transported by the slow inward current may only be a trigger for a proportional release of calcium from sarcoplasmic

reticulum, with the trigger amount presumably decreased by verapamil.²⁵

Unlike atrial and ventricular fibers with a normal sodium dependent fast action potential upstroke, the SA node and AV node depend on a slow inward calcium current for their action potentials,²⁶ and have been shown to be sensitive to direct depressant effects of verapamil experimentally²⁷⁻³⁰ and clinically.^{26,31-33} In both dogs and human, PR interval prolongation has been correlated with verapamil concentration.^{34,35} Concentrations of verapamil too low to slow AV conduction at normal rates will slow conduction of premature impulses and interfere with transmission at high atrial rates. Ultimately, high concentrations of verapamil result in AV block, sinus bradycardia, or sinus arrest.^{27,29}

Because of its effects on electrophysiological properties, verapamil has been successfully used in the treatment of supraventricular tachyarrhythmias,¹ ischemic arrhythmias,²⁷ and may be useful in the treatment of arrhythmias associated with mitral valve prolapse.³⁶ By decreasing contractility in vascular smooth muscle, verapamil is effective in the treatment of classical angina pectoris¹ and Prinzmetal's variant angina.³⁷ By decreasing myocardial contractility it is effective in the treatment of hypertrophic cardiomyopathy.³⁸

In the intact animal and in humans, the direct negative chronotropic effects of verapamil are modified by homeostatic reflex responses to verapamil-induced systemic arterial hypotension^{32,39} and thus positive, negative, or no changes in heart rate have been reported following verapamil administration.^{30,32,39} Similarly, the effects on myocardial contractility in the intact organism may also be interpreted as the net balance between the direct negative inotropic effects of the drug and reflex cardiac stimulation. Reflex sympathetic stimulation predominates at lower doses with direct myocardial depression evident at higher doses.²⁸

Halothane itself has recently been shown to inhibit the slow channel.¹¹ It depresses the SA node⁴⁰ and slows AV conduction in a concentration dependent manner.^{15,16} Halothane also slows intraventricular conduction.^{15,16} In combination with catecholamines which enhance the spontaneous firing of Purkinje fibers and may cause a difference in the rate of recovery of excitability in various areas of ventricular myocardium, halothane may thus favor the development of re-entrant circuits, as a premature impulse could enter a recovered pathway prior to the arrival of a normal impulse.⁴¹

Animal investigations support reentry as a likely etiology of epinephrine-induced arrhythmias during

halothane anesthesia.² Pharmacologic agents used to reduce the incidence of such arrhythmias include beta-adrenergic antagonists, lidocaine, and other amide local anesthetics.^{3,41-43} However, the pharmacokinetics of lidocaine are such that the effects of a single injection are quite transient and the drug must be used by continuous infusion.⁴⁴ Beta-adrenergic blockade does not reduce left ventricular afterload, leaves alpha-adrenergic actions including coronary vasoconstriction intact, and impairs the response to cardiac sympathetic activation, while nonspecific beta blockers may be contraindicated in some patients, for example those with bronchospastic disorders.^{41,45}

The results of our study show that another type of drug, the slow channel inhibitor, verapamil, is a potent agent which caused a long-lasting rise in the threshold for epinephrine-induced arrhythmias during halothane anesthesia and aborted such arrhythmias when they occurred. The dose we chose, 0.2 mg/kg, is approximately midway among the dose ranges investigated previously in studies of the effects of verapamil.^{26-28,31-33,39} In the present study, however, we did not attempt to define a threshold antiarrhythmic dose. Recent evidence indicates that thiopental induction may potentiate epinephrine-induced ventricular arrhythmias during halothane anesthesia;⁴⁶ however, we waited a minimum of 75 min after induction to begin control EAD determination by which time thiopental plasma concentrations are in the slow elimination phase and changes with time are small.⁴⁷ Thus, acute increases in EAD from control can reasonably be attributed to verapamil administration.

Halothane results in dose-dependent depression of ventricular function when compared to the conscious state in both dogs^{12,14} and humans,¹³ an effect which may be explained in part by its recently demonstrated ability to inhibit slow channel calcium fluxes.¹¹ Clinical studies have reported decreases in blood pressure after administration of verapamil in humans.^{1,33} Dose-dependent negative inotropic effects of verapamil have been observed,^{34,39} as well as reductions in systemic vascular resistance.^{28,33} In our study combining these two slow channel inhibitors, 0.2 mg/kg verapamil administered during 1.1 MAC halothane anesthesia resulted in depression of MAP and cardiac function to values below those already existing under the influence of halothane.

During neuroleptanesthesia verapamil has been recently proposed as a useful agent for afterload reduction with decreased MAP and SVR accompanied by increased left ventricular stroke volume.⁴⁸ In the present study with halothane, the mean values of the data obscured the fact that there appeared to be a

variability in CO response to verapamil. When the results of all 13 injections of 0.2 mg/kg verapamil in Group II for which complete 60-min follow-up of CO was available were examined individually, it was apparent that immediately after acute (30-s) injection of 0.2 mg/kg verapamil, during the period of acute hypotension, the cardiac output always rose. After four injections in two dogs, the CO remained high and returned to control by 30 min postinjection. After nine injections in four dogs, the CO fell after the initial rise to below control within 20 min and did not return to control value until 50 min postinjection. Within the limitation of the present study we are unable to delineate with certainty the basis for the apparent distinction between these responses. It is known that in nonanesthetized patients, the sum of two cardiovascular effects of verapamil, beneficial afterload reduction *vs.* deleterious direct myocardial depression, varies with the level of ventricular function.⁴⁵ It is reasonable to expect the same variability of response to verapamil during anesthesia, especially when the contractility of myocardium and vascular smooth muscle is also compromised by another slow current inhibitor, halothane.

Cardiac output was depressed with higher doses of verapamil in all dogs, reflecting the predominant effect of myocardial depression over afterload reduction at high doses. The dose dependent negative inotropic effects of verapamil had a relatively rapid onset but slower recovery during halothane anesthesia and were best shown by following the relationship between CO and filling pressure over time (fig. 2).

The PR interval prolongation and higher degree conduction abnormalities we observed are consistent with the known effects of verapamil on AV conduction. In conscious dogs 0.2 mg/kg verapamil prolonged the PR interval by approximately 30 per cent and PR intervals persisted greater than control at 60 min after administration of 0.1 mg/kg.²⁸ In the presence of halothane we observed the same long-lasting prolongation of AV conduction. Heart rate was stable and therefore was not a factor in PR interval prolongation. The maximum PR prolongation measured was equivalent regardless of the rate of verapamil administration. The Wenkebach type of second degree heart block we observed with high doses of verapamil is consistent with the observations of others.^{26,30,33-35}

The time course of the pharmacodynamic effects of verapamil showed interesting differences. Following rapid administration (30 s) the first effect was vasodilation (fig. 1). Cardiac effects developed more slowly. The maximum effects on contractility, as shown in the ventricular function relationship between filling pressure and CO (fig. 2), as well as on PR interval (fig. 1), occurred at five to six min. However the

values for all these were indistinguishable from control at a time when the antiarrhythmic effect was still very much in evidence. The reported pharmacokinetics of the drug (an initial distribution phase half-life of 6-35 min and an elimination half-life of from 2.6-7.7 h^{35,49}) do not explain these differences in time course and the presence of antiarrhythmic effects when hemodynamic functions had returned to baseline and when plasma levels could be expected to be low. These differences in time course of effects are significant if the desired therapeutic goal is arrhythmia suppression. While this question was not specifically addressed in the present study, it is possible that antiarrhythmic effects may be achieved at doses or infusion rates that cause only minor hemodynamic, especially myocardial depressant, effects.

Verapamil, a slow inward calcium current inhibitor, was effective in preventing and suppressing epinephrine-induced ventricular arrhythmias during halothane anesthesia beyond the duration of its other cardiovascular effects. The hemodynamic depressant effects of antiarrhythmic doses of verapamil under the conditions of our experiments were tolerated and were reduced with slower rates of administration. However, in clinical situations in the presence of halothane, dose-dependent effects, such as first and higher degrees of heart block, sinus node depression, and negative inotropic effects must be anticipated in patients with underlying poor baseline cardiovascular status or abnormalities of impulse formation or conduction. It is possible that smaller doses of verapamil, resulting in smaller hemodynamic changes will still demonstrate antiarrhythmic effects.

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