Cardiovascular Effects of and Interaction between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. I. Verapamil and Halothane

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In order to assess the interaction between halothane and verapamil on the cardiovascular system, mongrel dogs were instrumented so that the following measurements could be made awake and under the influence of the drugs: aortic, left ventricular, and left atrial blood pressures; myocardial segment length shortening; heart rate and rhythm; and coronary, carotid, and renal blood flows. The effect of two infusion doses of verapamil (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after 200 $\mu g \cdot kg^{-1}$ bolus) were examined awake. On a different day in the same dogs, two concentrations of halothane (1.2-low and 2.4-high % end-tidal) and the effect of the two infusion doses of verapamil during low and high halothane were studied. Thirty minutes of either infusion dose of verapamil produced only heart rate and electrocardiographic P–R interval increases in conscious dogs. Halothane produced dose-related decreases in mean aortic pressure, left ventricular maximum rate of tension development (dP/dt), and segment length shortening and increases in heart rate and left atrial pressure. Carotid blood flow was increased by low halothane concentrations and returned to control with high halothane concentrations. There were no significant changes in coronary or renal blood flow produced by halothane. Verapamil infusion during low halothane concentration produced minimal effects. However, both the 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil doses further depressed hearts already depressed by the high concentrations of halothane and decreased renal and carotid blood flows. Verapamil plasma levels were significantly higher during both low and high halothane concentrations than when the same dose was given to the same dogs awake. The authors conclude that: 1) the predominant effect of the combination of halothane and verapamil was from halothane; 2) halothane alters the pharmacokinetics of intravenous verapamil, resulting in marked increases in plasma verapamil levels when compared with the same dose awake; 3) verapamil infusion is well tolerated during low concentrations of halothane, but the combination of high halothane concentrations and verapamil produces profound cardiovascular depression. (Key words: Anesthetics, volatile: halothane. Heart: blood flow; rhythm; ventricular function. Ions: calcium blocker, verapamil. Kidney: blood flow. Pharmacology: drug interactions.)

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THE MOST POPULAR new group of cardiovascular drugs in the decade of the 1980s has been, and continues to be, the calcium channel (entry) blocking drugs.[1–3] The most widely used of these drugs has been verapamil (Calan®, Isoptin®), both experimentally and clinically. In the United States, verapamil remains the only intravenous formulation available to the clinician. In conscious animals (dogs[4,5] and humans[6,7]), verapamil produced hypotension, a negative inotropic effect on the heart, and reflex tachycardia. Similar effects have been produced by the volatile anesthetic, halothane, in dogs[8] and humans.[9] In addition, recent experimental evidence suggests that interference in intracellular calcium kinetics is a major mechanism of the cardiovascular effects of halothane.[10,11] In view of the usefulness of verapamil in the perioperative period for treatment of myocardial ischemia and supraventricular tachycardias[2,3] and the likelihood that many patients coming to operation will be treated with the drug, the interaction between verapamil and the prototype inhaled anesthetic, halothane, needs to be known. Although there have been prior published investigations of this interaction, none has used the awake animal as a control,[12–14] nor has more than one anesthetic dose been studied. Consequently, the true extent of the drug interaction has not been previously elucidated.[15–17] In order to allow accurate interpretation of the interaction between anesthetics and calcium channel blocking drugs, a new model of a conscious, chronically instrumented dog will be described. Our original plan was to examine the interaction between verapamil and the three clinically used inhaled anesthetics, halothane, enflurane, and isoflurane, in the same animals, so that each dog would serve as his own control. However, at the completion of the study of the first group of animals, we discovered that the numbers of valid experiments for the enflurane and isoflurane dogs were insufficient for

statistical analysis because of loss of either dog or instrumentation. Consequently, we studied the interaction of halothane and verapamil separately from that of enflurane, isoflurane, and verapamil.

Methods and Materials

INSTRUMENTATION

Heartworm-free, mongrel dogs weighing between 14.7 and 27.1 kg (mean 21.6 kg) were preconditioned nutritionally with high protein, vitamin, and iron-supplemented diets as directed by a veterinarian. Using endotracheal halothane anesthesia, the animals were instrumented as follows: after a left thoracotomy, Tygon® (Norton, Akron, OH) catheters were placed in the left atrium and in the thoracic aorta through the left subclavian artery. Two 20-MHz ultrasound crystals were implanted through transmural stab incisions 1–1.5 cm apart in the left ventricular myocardium parallel to the short axis of the heart at a depth of 5–10 mm in order to measure myocardial segment length shortening. A miniature high-fidelity pressure transducer (Konigsberg Co., Pasadena, CA) was inserted through the left ventricular apex into the cavity and positioned adjacent to the endocardial surface. A 20-MHz pulsed Doppler flow probe was positioned around the left circumflex coronary artery in the atrioventricular groove at the lateral border of the heart. Through a separate flank incision, the left renal artery was identified, and another 20 MHz pulsed Doppler flow probe was positioned on that artery. Finally, through a midline incision in the neck, the left common carotid artery was instrumented with a third pulsed Doppler flow probe. The catheters, transducer and flow probe leads, and ultrasound crystal wires were tunneled subcutaneously to a common exit point just caudad to the skull on the dorsum of the animal's neck. All instrumentation was carefully checked for function before and after wound closure. Bupivacaine, 0.5%, was infiltrated around the adjacent intercostal nerves before chest closure for postoperative analgesia. A specially designed jacket protected the catheters and the instruments for the remainder of the experiment. The catheters were flushed daily with a dilute heparin solution and kept filled with a concentrated heparin solution. Ampicillin and streptomycin were administered before surgery and for 5 days following surgery. No animal was studied less than 10 days following surgery and only when body temperature, white blood count, and general appearance were normal. The animals were trained to lie quietly in the laboratory both before and after the completion of the surgical implantation.

MEASUREMENT TECHNIQUES

Aortic and left atrial pressures were transduced with Statham db23 strain gauges, which were zeroed and cal-

ibrated against a mercury manometer before each experiment. The Konigsberg® micromanometer was calibrated in vitro with a mercury manometer and, in the animal, was zeroed against the left atrial pressure before and during experiments.[17] In addition, calibration was checked against peak aortic pressure. Konigsberg® transducers are renowned for the stability of their calibration.[8,15–17] The output of the ultrasound crystals was amplified and directly displayed on a polygraph, and maximal length change from diastolic length was recorded as myocardial segment shortening.[18] The KHz output of the pulsed Doppler flow meters has been shown to be related linearly to volume flow for a variety of flow probe sizes.[19,20] Arterial blood gas determinations were made at intervals during the various phases of the experiments as indicated subsequently using a Radiometer ABL® electrode system. During anesthesia, airway anesthetic (Beckman LB-2®) and carbon dioxide (Lifespan 100®) concentrations were continually monitored using infrared absorption techniques. Rectal temperature was measured with a thermocouple probe (Yellow Springs Instruments, Yellow Springs, OH). Complete blood counts were measured preoperatively and postoperatively and at frequent intervals during the experiment using standard laboratory techniques. Plasma verapamil levels were analyzed using high-performance liquid chromatography.[21]

EXPERIMENTAL PROTOCOL

The experiments were conducted on two separate days. On one day, the effects of an intravenous verapamil infusion in the conscious animal were assessed. On another day, the effects of halothane at two dose levels were measured and, subsequently, the same protocol that had been used in the dog awake with verapamil was repeated at high and low anesthetic concentrations. In some animals, the awake study was carried out following the anesthetized study (fig. 1).

On the day of the experiment, an intravenous catheter was placed in a foreleg or hindleg vein, and an infusion of lactated Ringer's solution was initiated. The infusion was continued at $3–5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for the duration of the experiment. Continuous low-speed polygraph recordings were made of left ventricular, mean left atrial, and aortic pressures and mean renal, coronary, and carotid blood flows. At the indicated measurement intervals, high-speed polygraph recordings were made of the electrocardiogram (via surface electrodes), left ventricular pressure and its first derivative, left ventricular maximum rate of tension development (dP/dt max) (by electronic differentiation), mean and phasic left atrial and aortic pressures, myocardial segment length shortening, and mean and phasic renal, coronary, and carotid blood flows (fig. 2). During anesthesia, all measurements were made
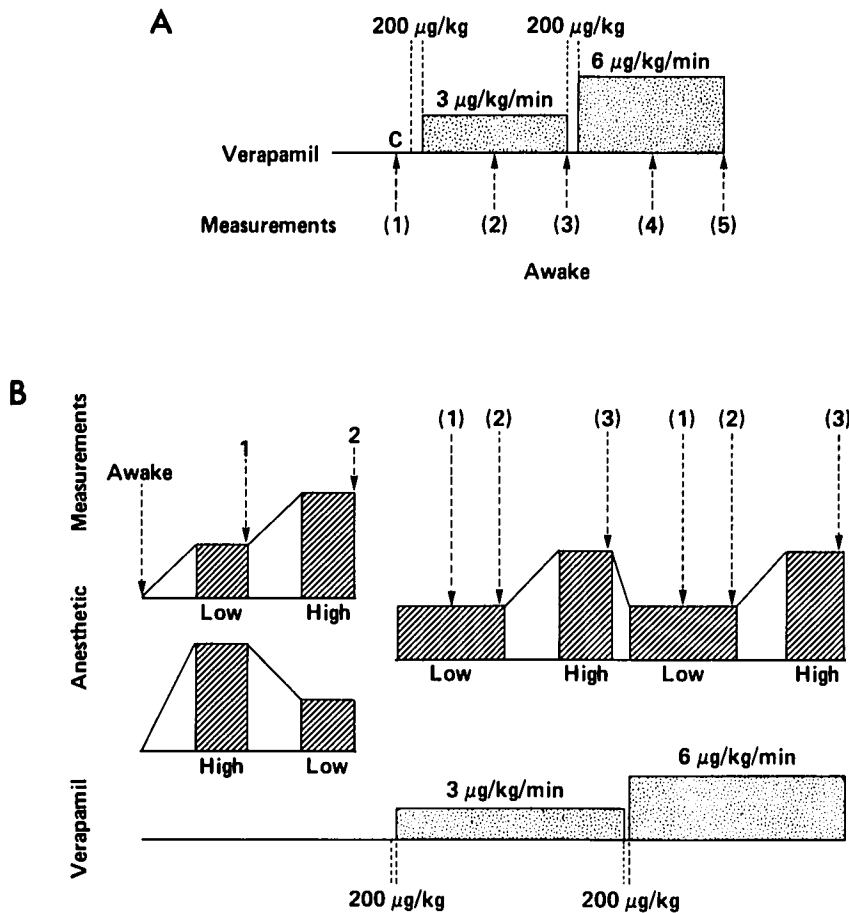
FIG. 1. Experimental protocol. Numbers in parentheses indicate the times of measurement and blood sampling. *A*. The verapamil protocol conducted on one day. *B*. The halothane and the combination of halothane and verapamil protocol conducted on another day at least 48 h before or after *A*. The effect of halothane was first tested after 15 min of a constant end-tidal halothane concentration either at the low or high dose. Notice that the order of the low and high dose was randomized to decrease the influence of time. As soon as the anesthetic measurements were completed, the exact same protocol for verapamil administration as noted in *A*. was initiated at the low anesthetic concentration (if the high concentration had been administered last in the first part of the experiment, again 15 min of constant end-tidal concentration of the low dose was administered before initiating the verapamil infusion). The only difference between the verapamil infusion protocols was that because the slow infusion had already been given for 30 min during the low concentration of the anesthetic, it was only necessary to wait until 15 min of constant end-tidal high anesthetic concentration to establish a new steady state for the anesthetic. Then the low concentration was again established for 15 min of constant end-tidal concentration and now the high dose verapamil was given as in *A*., but again, only 15 min of constant end-tidal high concentration was necessary because there had already been more than 30 min of a constant, slow verapamil infusion. The open bars represent the time necessary to reach the desired end-tidal halothane concentration. The striped bars indicate at least 15 min of a constant end-tidal anesthetic concentration.

at end-expiration. At the end of each measurement period, arterial blood was drawn for verapamil measurement and blood gas analysis. After control cardiovascular measurements were made, a dose of $0.2 \text{ mg} \cdot \text{kg}^{-1}$ of verapamil was administered over a 3-min period intravenously. Immediately following the rapid infusion, $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of verapamil was infused for another 27 min; measurements were made, and blood was withdrawn at 15 and 30 min after the beginning of the verapamil infusion. Then, another $0.2 \text{ mg} \cdot \text{kg}^{-1}$ was administered over 3 min, and the infusion was continued at $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for another 27 min. Again, blood sampling and measurements were made at 15 and 30 min after the beginning of the second infusion (fig. 1*A*).

On the day of the anesthetic experiments, the animals were prepared in the same fashion as for the verapamil experiments. Anesthesia was induced by mask with nitrous oxide–oxygen–halothane. When the animals were sufficiently anesthetized, the trachea was intubated, and ventilation was controlled using a Harvard ventilator at tidal

volumes of $10\text{–}15 \text{ ml} \cdot \text{kg}^{-1}$ with the rate adjusted to maintain end-tidal carbon dioxide concentrations equal to those in the awake animal. Immediately after tracheal intubation, nitrous oxide was discontinued, and nitrogen was substituted in a concentration that maintained arterial oxygen tension at approximately the same level as in the awake animal. Rectal temperature was maintained throughout the experiment by external heating if necessary. The effects of two concentrations of halothane were studied: a low concentration of 1.2% end-tidal and a high concentration of 2.4% end-tidal. In two animals, the high concentration had to be decreased to maintain a mean aortic pressure greater than 50 mmHg. (In our pilot studies, the combination of verapamil with a halothane concentration that produced a mean aortic pressure of less than 50 mmHg without verapamil was fatal, and our animal preparation was dear in terms of effort and cost.) Measurements during the anesthesia study were never made before 15 min of constant end-tidal anesthetic concentration. The order of the low and high concentra-

tions of halothane was randomized (fig. 1B). As soon as the last measurement of the anesthetic effect was completed, halothane was continued at the low concentration if the low concentration had been administered last. If the high concentration had been administered last, another 15 min of constant, low end-tidal halothane concentration was maintained prior to the initiation of the verapamil infusion. As in the awake study, 0.2 mg $\cdot$ kg^{-1} was given intravenously over 3 min, and 3 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} was infused for 27 min with measurements and blood sampling at 15 and 30 min after the initiation of the infusion. With the infusion continuing at 3 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}, the anesthetic concentration was increased to the high dose, 15 min were allowed for equilibration at a constant end-tidal concentration; and the measurements were repeated. Next, the halothane concentration was decreased to the low dose again and 0.2 mg $\cdot$ kg^{-1} of verapamil was administered intravenously over 3 min and 6 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} infused over 27 min. Again, measurements were made at 15 and 30 min. Finally, the anesthetic was changed to the high concentration again and, after 15 min of constant end-tidal halothane concentration, the protocol was repeated a third time (fig. 1B). Preliminary experiments indicated that by 48 h after previous experiments, no verapamil could be measured in the plasma of the animals. Consequently, no experiments were repeated within 2 days of each other.

STATISTICAL ANALYSIS

We used the SPSS software package for a two-way analysis of variance with a repeated measures design. If the analysis of variance indicated significance, the Bonferroni modification of the paired t test compared data sets.[22] $P < 0.05$ was considered significant. Results are expressed as mean $\pm$ SEM.

Results

Eleven animals were studied. However, not all functions could be assessed in each animal (see "n" in the tables). Pa_{CO_2} was maintained within 10 mmHg of the awake values (mean 32.5 $\pm$ 3.1 mmHg); Pa_{O_2} was maintained within 40 mmHg of the awake values (mean 92 $\pm$ 3.1 mmHg); and pH was maintained within 0.07 of the awake values (mean 7.43 $\pm$ 0.2). Body temperature was controlled within 1° C of awake value (mean 38.3 $\pm$ 4° C).

During the control state, the animals were generally relaxed and appeared content (heart rate < 80 $\cdot$ min^{-1}, mean arterial pressure < 100 mmHg).[17] Verapamil plasma levels and hemodynamic measurements were similar at 15 and 30 min after the start of the infusion, so the 30-min data were tabulated and analyzed. Verapamil infusion produced minimal effects in the awake dogs (table 1). The
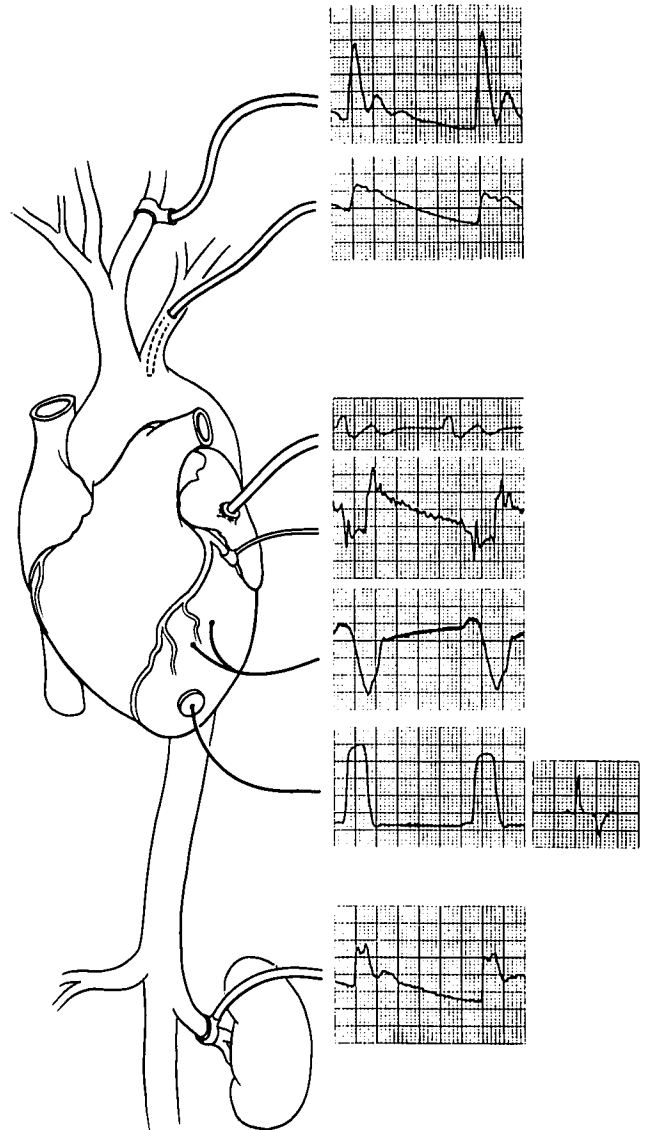

FIG. 2. Representative recordings in the chronically instrumented dog. *From above, downward:* carotid artery blood flow; aortic blood pressure; left atrial blood pressure; circumflex coronary artery blood flow; myocardial segment length; left ventricular blood pressure and first derivative (dP/dt); and renal artery blood flow.

only significant changes were increases in heart rate (3 μg: 24%; 6 μg: 28%) and in P-R interval (3 μg: 18%; 6 μg: 28%) at both doses. In two dogs, there were incomplete atrioventricular (AV) blocks at both the low and high doses of verapamil.

The administration of halothane produced a dose-related increase in heart rate and left atrial pressure and a dose-related decrease in mean aortic pressure, left ventricular dP/dt, and myocardial segment shortening (table 2). Carotid blood flow increased at the low dose, but neither coronary nor renal blood flow was significantly changed by halothane.

TABLE 1. Effect of Verapamil on Hemodynamics and Regional Blood Flow in the Conscious Dog

	(n)	Verapamil Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)		
		0	3	6
HR (min^{-1})	(11)	78 ± 4	96 ± 5*	99 ± 6*
MAP (mmHg)	(11)	96 ± 4	97 ± 2	94 ± 3
LAP (mmHg)	(9)	3.2 ± 0.9	4.4 ± 0.9	5.3 ± 1.0
LVdP/dt (mmHg·s⁻¹)	(10)	2890 ± 160	2695 ± 108	2545 ± 125
SL (mm)	(6)	2.2 ± 0.3	2.05 ± 0.3	2.1 ± 0.3
PR (ms)	(11)	114 ± 4.5 (9)	135 ± 6.5* (9)	146 ± 6.5*
CaF (ml·min⁻¹)	(10)	140 ± 10	176 ± 13	165 ± 14
CoF (ml·min⁻¹)	(6)	38 ± 7	42 ± 8	43 ± 7
ReF (ml·min⁻¹)	(10)	108 ± 16	111 ± 16	112 ± 15

HR = heart rate; MAP = mean aortic blood pressure; LAP = mean left atrial blood pressure; LVdP/dt = maximum rate of rise of left ventricular pressure; SL = myocardial segment length shortening; PR = P–R interval; CaF = carotid blood flow; CoF = coronary blood flow; ReF = renal blood flow.
* $P < 0.05$ vs. 0.

During low-dose halothane anesthesia, neither dose of verapamil produced striking effects (table 3). Heart rate was increased by both 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while left ventricular dP/dt was decreased. P–R intervals were increased in a dose-related manner just as was seen with verapamil awake. One of the dogs with an AV block during verapamil infusion awake also blocked during low halothane and both verapamil doses. Another dog who died after high-dose-halothane–high-dose-verapamil (not included in the data) had a sinus arrest with a slow junctional rhythm (15 · min⁻¹). However, during the high-dose halothane anesthesia, both doses of verapamil produced significant and dramatic changes. In fact, two animals died during high-dose-halothane–high-dose-verapamil, but all measurements were completed before their deaths. Subsequently, the protocol was abandoned in another dog to prevent his death. There were dose-dependent decreases in mean arterial pressure and carotid artery flow and increased P–R intervals. Left ventricular dP/dt and renal blood flow were decreased by both doses of verapamil, but not in a dose-dependent manner.

The infusion of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of verapamil in the conscious animals produced mean plasma levels of 81.2

ng·ml⁻¹ (table 4). A doubling of the dose to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ also doubled the plasma level. The same doses given to the same dogs during halothane anesthesia produced significantly greater plasma levels. In addition, the high dose of verapamil resulted in a significantly greater plasma level during high-dose halothane than during low-dose halothane.

According to the two-way analysis of variance, the only true interactions between halothane and verapamil occurred in mean aortic pressure, carotid blood flow, and plasma verapamil levels.

Discussion

The previous studies of verapamil in awake dogs and humans have used bolus doses instead of the rapid–slow infusion technique we employed.[4-7] During the rapid infusion of 0.2 mg · kg⁻¹ of verapamil, we observed, but did not quantify, much greater depressions of mean aortic pressure, left ventricular dP/dt, and segment length shortening similar to effects noted in previous studies with bolus injections in awake dogs.[4,5] In both of these investigations, the importance of systemic reflex responses was

TABLE 2. Effect of Halothane on Hemodynamics and Regional Blood Flow in the Conscious Dog

	(n)	Halothane % (ET)		
		0	1.2 ± 0.0	2.43 ± 0.04
HR (min⁻¹)	(11)	78 ± 4	102 ± 6*	126 ± 5*·†
MAP (mmHg)	(11)	96 ± 4	77 ± 3*	57 ± 3*·†
LAP (mmHg)	(9)	3.2 ± 0.9	5.2 ± 1.1*	9.0 ± 1.05*·†
LVdP/dt (mmHg·s⁻¹)	(10)	2890 ± 160	1900 ± 170*	1020 ± 90*·†
SL (mm)	(6)	2.2 ± 0.3	1.7 ± 0.2*	0.9 ± 0.03*
PR (ms)	(11)	114 ± 4.5	123 ± 4.9	118 ± 4
CaF (ml·min⁻¹)	(10)	140 ± 10	172 ± 10*	145 ± 5†
CoF (ml·min⁻¹)	(6)	38 ± 7	37 ± 9	33 ± 7
ReF (ml·min⁻¹)	(10)	108 ± 16	102 ± 14	106 ± 12

ET = end-tidal. Also see table 1 for abbreviations.
* $P < 0.05$ vs. 0.
† $P < 0.05$ vs. 1.2% halothane.

TABLE 3. Effect of the Combination of Halothane and Verapamil on Hemodynamics and Regional Blood Flow in the Dog

	(n)	Halothane % End-tidal			
		1.2		2.22	
		3V	6V	3V	6V
HR (min⁻¹)	(11)	117 ± 6‡	122 ± 6§	124 ± 6‡	114 ± 11
MAP (mmHg)	(11)	79 ± 2‡	75 ± 2§	43 ± 3†‡¶ (10)	34 ± 4*†·§
LAP (mmHg)	(9)	7.7 ± 1.6*	11.4 ± 2*·§	10.4 ± 1.5‡¶ (7)	12.6 ± 2.6§‡
LVdP/dt (mmHg·s⁻¹)	(10)	1440 ± 110*·‡	1230 ± 100*·§	665 ± 65†·‡¶ (9)	560 ± 70†·§·**
SL (mm)	(6)	1.4 ± 0.2	1.3 ± 0.2*·§	0.8 ± 0.1‡¶ (5)	0.8 ± 0.1§
PR (ms)	(10)	136 ± 4.5*	158 ± 4.7*·‡ (11)	138 ± 5.4† (9)	178 ± 15.1†·§
CaF (ml·min⁻¹)	(10)	170 ± 13	155 ± 13	104 ± 90† (9)	66 ± 8*·†·§·‡
CoF (ml·min⁻¹)	(6)	36 ± 7	36 ± 7	26 ± 7 (4)	20 ± 8
ReF (ml·min⁻¹)	(10)	96 ± 12	95 ± 12	66 ± 9§·†	50 ± 9†·§·**

3V = verapamil 3 μg·kg⁻¹·min⁻¹; 6V = verapamil 6 μg·kg⁻¹·min⁻¹. Also see table 1 for abbreviations.

Compared to halothane (H) without verapamil (V): * = $P < 0.05$ vs. 1.2% H; † = $P < 0.05$ vs. 2.2% H. Compared to V without H: ‡

= $P < 0.05$ vs. 3V; § = $P < 0.05$ vs. 6V.

Compared to combination of V and H: ¶ = $P < 0.05$ vs. 1.2% H − 3V; ** = $P < 0.05$ vs. 1.2% H − 6V; ‡ = $P < 0.05$, 6V vs. 3V, 1.2% or 2.2% H.

observed by comparing intracoronary and intravenous injections[4] and by comparing effects with and without beta-adrenergic blockade.[5] In our awake animals, such reflex responses, as shown by the significant increase in heart rate, were able to return blood pressure and the measures of cardiac function back to normal by 15 min after the start of the infusion (table 1). Indeed, except for the increase in P–R interval and the increased plasma verapamil levels, we might have wondered if, in fact, we were giving any drug. However, the measured plasma levels corresponded well with therapeutic levels measured in patients.[23]

The decreased left ventricular dP/dt and myocardial segment shortening accompanied by increasing left atrial pressures produced by increasing concentrations of halothane documented the negative inotropic effect of this anesthetic.[8,24] The effect of halothane on regional blood flow has been less well documented. The studies using awake animals as a control have demonstrated no change in coronary blood flow at low halothane concentrations.[8,25] However, Vatner and Smith reported that 1% end-tidal halothane decreased coronary blood flow by 25% with no further decrease at 2% halothane.[24] Merin et al.[8] and Gelman et al.[25] observed significant decreases in coronary blood flow at 1.7 and 1.8% end-tidal halothane in contrast to no change at 0.8% and 0.9%. The present study showed no statistical change in coronary blood flow at either 1.2% or 2.4% end-tidal halothane concentration, thus differing from all the previous studies. However, the method of coronary blood flow measurement and determinants of myocardial O_2 consumption were different in all studies. The maintenance of renal blood flow even during high-dose halothane anesthesia in this study is in agreement with the previous studies that have used the awake dog as a control.[25,26] The only blood flow to change significantly in our study during halothane

anesthesia was the carotid, which increased during low-dose halothane (table 2). It is tempting to ascribe this to the cerebral vasodilation observed at similar halothane doses in previous experiments,[25] but the common carotid artery also supplies a significant amount of extracranial tissue. Consequently, we thought that perhaps common carotid blood flow might reflect aortic (or pulmonary artery) blood flow. However, in nine other dogs where we obtained simultaneous carotid and pulmonary artery flows, the correlation coefficients were less than 0.05 (unpublished observations). Consequently, carotid blood flow cannot be used to estimate cardiac output (pulmonary blood flow) in our model.

Although Kapur et al.[14] and Kates et al.[13] demonstrated that the administration of verapamil during halothane anesthesia produced hemodynamic depression, they could not truly study the interaction because they did not document the effects of halothane or verapamil alone. Vatner's group has demonstrated that anesthesia markedly modifies the effect of cardioactive drugs.[17,27] Consequently, the use of an awake control is essential for a true evaluation of drug interaction. In addition, although Kapur et al. quantified the effect of verapamil dose,[14] no one

TABLE 4. Plasma Verapamil Concentrations (ng·ml⁻¹)

Verapamil Dose (μg·kg⁻¹·min⁻¹)	Halothane % End-tidal		
	0	1.20	2.22 ± 0.2
3	81 ± 7	132 ± 2*	155 ± 15*·§
6	166 ± 15‡	229 ± 23†·‡	324 ± 34†·‡·¶

Effect of verapamil (V) alone: * = $P < 0.05$ vs. 3V; † = $P < 0.05$ vs. 6V; ‡ = $P < 0.05$ 6V vs. 3V. Effect of combination of verapamil (V) and halothane (H): § = $P < 0.05$ vs. 3V–1.2% H; ¶ = $P < 0.05$ vs. 6V–1.2% H.

heretofore had studied the effect of halothane dose. Our results with the combination of 2.4% end-tidal halothane and 323 ng·ml^{-1} verapamil demonstrated much more cardiac depression than Kapur *et al.* showed with 0.93% halothane and verapamil concentrations ranging from 500 to 1100 ng·ml^{-1}.[14] In general, in our study, the effects of halothane predominated during the administration of both halothane and verapamil. In addition, the interaction tended to be synergistic. The only nonadditive interactions occurred for aortic blood pressure, carotid blood flow, and plasma verapamil concentration. The latter is discussed subsequently. Verapamil did not change aortic pressure or carotid blood flow awake, whereas halothane decreased aortic pressure and increased carotid blood flow. The combination of the two drugs resulted in decreased aortic pressure and carotid blood flow by both doses of verapamil at high halothane concentrations.

As in the awake state, the rapid infusion of 200 µg·kg^{-1} of verapamil resulted in considerably more depression during 1.2% halothane than that observed after 15 min of slow infusion (3 or 6 µg·kg^{-1}·min^{-1}). In fact, our original protocol design, in which the order of the high and low halothane doses was randomized after the verapamil infusion as well as before, had to be changed because of the profound cardiovascular depression produced by the rapid infusion of 200 µg·kg^{-1} during high-dose halothane. There must have been some depression of ventricular function, however, during low-dose halothane and verapamil infusion, for left ventricular dP/dt was lower during both 3 and 6 µg·kg^{-1} verapamil infusions in spite of no difference in mean aortic pressure and increases in heart rate and left atrial pressure.[28] Interestingly, the regional blood flows during 1.2% halothane were unchanged by either verapamil dose. However, during high-dose halothane anesthesia, verapamil produced rather striking effects. Only heart rate, myocardial segment length shortening, and coronary blood flow were unaffected, and the latter two were both very low to begin with. There were marked decreases in left ventricular dP/dt, renal and carotid blood flows, and mean aortic pressure. The latter two changes were dose-dependent. These observations are consistent with previous observations made in humans where verapamil produced a decrease in ventricular function predominantly in patients with already compromised ventricular function.[6,29] Because halothane produces severe depression in ventricular function in high doses (table 2),[8,9] it is logical that a similar effect of verapamil should be seen during high-dose halothane. Alternatively, because reflex responses to the direct effects of verapamil tend to reverse these effects (see previous discussion),[4,5] the interaction could also be related to the decrease in baroreflex mechanisms produced by increasing halothane doses.[30] There is also evidence to suggest that verapamil adds to the effect of CNS de-

pressants. Maze *et al.* reported that verapamil decreased the MAC of halothane in dogs.[31] Another calcium channel blocker, nimodipine, has been reported to prolong barbiturate anesthesia in mice.[32] If the cardiovascular depressant effects of halothane are related to the CNS depression, then perhaps verapamil is merely decreasing the anesthetic dose requirement, thus intensifying the effects seen at a fixed end-tidal concentration.

There may be yet a fourth explanation. Exactly the same dose of verapamil given in the same time interval by the same route in the same dogs resulted in a much higher plasma verapamil concentration in the animals when they were anesthetized with halothane. Kapur *et al.* demonstrated that the hemodynamic effects of verapamil during low-dose halothane were related to the plasma levels.[14] However, the plasma levels during 6 µg·kg^{-1}·min^{-1} verapamil during the awake state and at 3 µg·kg^{-1}·min^{-1} verapamil during high-dose halothane were similar in our study (table 4), yet the hemodynamic effect was much greater during halothane (table 3). Consequently, the hemodynamic interactions observed can result only partly from the increased plasma levels. The mechanism of this increase could be either a decreased volume of distribution or decreased plasma clearance. Verapamil is highly extracted by the liver and, presumably, decreased hepatic blood flow or extraction could account for increased plasma levels.[33] Halothane does decrease hepatic blood flow,[25] and Reilly *et al.* have recently shown that halothane decreases hepatic clearance of another drug, propranolol, that is highly dependent on the liver for its metabolism.[34] In order to answer this question, we are currently examining the pharmacokinetics of verapamil awake and during halothane anesthesia in the same dogs.

We conclude that steady-state plasma levels of verapamil, which are in the therapeutic dose range for humans,[23] produced minimal hemodynamic effects during low concentrations of halothane compared with the same dose awake in the healthy dog. However, the combination of similar plasma levels during high-dose halothane anesthesia resulted in a marked depression of both ventricular function and regional blood flows. The mechanism is undetermined but is probably a combination of the direct negative inotropic effect of verapamil and halothane as well as the increased plasma levels seen during halothane anesthesia compared with the awake state. Whether the steady-state plasma verapamil levels produced by chronic oral dosing rather than slow intravenous dosing would result in the same drug interaction is not clear. We are currently conducting studies in our chronically instrumented animals designed to answer this question.

References

1. Dargie H, Rowland E, Krikler D: Role of calcium antagonists in cardiovascular therapy. Br Heart J 46:8–16, 1981
2. Awan NA, De Maria AN, Mason DT: Therapeutic importance of calcium antagonists in coronary artery disease and congestive heart failure: An overview. Drugs 23:235–241, 1982
3. Singh BN: An overview of slow channel blocking drugs: Pharmacological basis for therapeutic application. Cardiology 69(Suppl 1):2–25, 1982
4. Walsh RA, Badke FR, O'Rourke RA: Differential effects of systemic and intracoronary calcium channel blocking agents on global and regional left ventricular function in conscious dogs. Am Heart J 102:341–350, 1981
5. Nakay AH, Schwartz A, Millard RW: Reflex chronotropic and inotropic effects of calcium channel-blocking drugs in conscious dogs: Diltiazem, verapamil and nifedipine compared. Circ Res 52:302–311, 1983
6. Klein HO, Nino R, Oren V, Lang R, Sareli P, Disegnie DD, Guerrero J, Kaplinsky E: The acute hemodynamic effects of intravenous verapamil in coronary artery disease. Circulation 67:101–110, 1983
7. Vlietstra RE, Farias MAC, Frye RL, Smith HC, Ritman EL: Effect of verapamil on left ventricular function: A randomized placebo controlled study. Am J Cardiol 51:1213–1217, 1983
8. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. ANESTHESIOLOGY 44:401–413, 1976
9. Sonntag H, Donath U, Hillebrend W, Merin RG, Radke J: Left ventricular function in conscious man and during halothane anesthesia. ANESTHESIOLOGY 48:320–324, 1978
10. Merin RG: Subcellular mechanisms for the negative inotropic effect of inhalation anesthetics, Molecular Mechanism of Anesthesia, Vol. 1, Progress in Anesthesiology. Edited by Fink BR. New York, Raven Press, 1975, pp 603–615
11. Lynch C, Vogel M, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
12. Kapur PA, Flacke WE: Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. ANESTHESIOLOGY 55:219–225, 1981
13. Kates RA, Zaggy AP, Norfleet EA, Heath KR: Comparative cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia in swine. ANESTHESIOLOGY 61:10–18, 1984
14. Kapur PA, Bloor BC, Flacke WE, Olewine SK: Comparison of cardiovascular responses to verapamil during enflurane, isoflurane, or halothane anesthesia in the dog. ANESTHESIOLOGY 61:156–160, 1984
15. Vatner SF, Higgins CB, Ratouck P, Franklin D, Braunwald E: Effects of cardiac depression and of anesthesia on the myocardial action of a cardiac glycoside. J Clin Invest 50:2585–2595, 1971
16. Theroux P, Ross J, Franklin D, Kemper WS, Sasayama S: Regional

myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerine, and lidocaine. Circulation 53:302–314, 1976
17. Vatner SF, Baig H, Manders WT, Murray PA: Effects of a cardiac glycoside in combination with propranolol on the ischemic heart of conscious dogs. Circulation 57:568–575, 1978
18. Hartley CJ, Lewis RM, Ishida T, Chelly JE, Entman ML: High frequency pulsed Doppler measurements of blood flow and myocardial dimensions in conscious animals, Cardiovascular Instrumentation, Applicability of New Technology to Behavioral Research. Edited by Herd JA, Grotto AM, Kauffman PG, Weiss SM. Washington, DC, NIH Publications #84-165, US Dept HHS, 1984, pp 95–106
19. Hartley CJ, Cole JS: An ultrasonic pulsed Doppler system for measuring blood flow in small vessels. J Appl Physiol 37:626–635, 1974
20. Ishida T, Lewis RM, Hartley CJ, Entman ML, Field JB: Comparison of hepatic extraction of insulin and glucagon in conscious and anesthetized dogs. Endocrinology 112:1098–1109, 1983
21. Harapat SR, Kates RE: High performance liquid chromatographic analysis of verapamil. II. Simultaneous quantitation of verapamil and its active metabolite, norverapamil. J Chromatogr 181:484–489, 1980
22. Keppel G: Correction for multiple comparisons, Design and Analysis. Englewood Cliffs, Prentice-Hall, 1982, pp 144–146
23. Frishman W, Kirsten E, Klein M, Pina M, Johnson SM, Hillis LD, Packer M, Kates R: Clinical relevance of verapamil plasma levels in stable angina pectoris. Am J Cardiol 50:1180–1184, 1982
24. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and in primates. Circ Res 34:155–167, 1974
25. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557–565, 1984
26. Leighton KM, MacLeod BA, Bruce C: Renal blood flow: Differences in autoregulation during anesthesia with halothane, methoxyflurane and alphaprodine in the dog. Anesth Analg 57:389–394, 1978
27. Vatner SF: Effects of anesthesia on cardiovascular control mechanisms. Environ Health Perspect 26:193–206, 1978
28. Mason DT: Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) on the evaluation of myocardial contractility in man. Am J Cardiol 23:516–527, 1969
29. Chew CYC, Hecht HS, McAllister RG, Singh BH: Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Am J Cardiol 47:917–922, 1981
30. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP: Halothane and the carotid sinus reflex: Evidence for multiple sites of action. ANESTHESIOLOGY 57:191–201, 1982
31. Maze M, Mason DM, Kates RE: Verapamil decreases MAC for halothane in dogs. ANESTHESIOLOGY 59:327–329, 1983
32. Hoffmeister F, Benz Y, Heise A, Krause HP, Neuser V: Behavioral effects of nimodipine in animals. Arnzeimittelforsch 32:347–360, 1982
33. Kates RE: Calcium antagonists: Pharmacokinetic properties. Drugs 25:113–124, 1983
34. Reilly CS, Wood AJ, Koshakji R, Wood M: Effects of halothane on drug disposition: Contributions of intrinsic drug metabolizing capacity and hepatic blood flow. ANESTHESIOLOGY 63:70–76, 1985