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Cardiovascular Effects of and Interaction between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. II. Verapamil, Enflurane, and Isoflurane

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The effects of enflurane and isoflurane on the cardiovascular system and cellular calcium kinetics are somewhat different. Consequently, the interaction with the calcium channel blocking drug, verapamil, may also differ. In order to compare the anesthetics, the authors studied the effects of two infusion doses of verapamil (which produced plasma levels of 90 and 180 ng · ml^{-1}) on cardiovascular dynamics and regional blood flow in awake dogs. On two other days, in the same dogs, the effects of approximately 1.1 and 2 MAC enflurane and isoflurane were first studied and then the same verapamil dose regimens while the same anesthetic concentrations were maintained. Verapamil produced only increases in heart rate and the P–R interval in the awake animal. The high dose of both anesthetics markedly decreased mean aortic pressure and left ventricular rate of tension development (dP/dt), and increased heart rate. However, only enflurane also decreased myocardial segment length shortening and increased left atrial pressure. Neither anesthetic alone affected coronary or renal blood flow, while both increased carotid blood flow at the low dose. Verapamil infusion during 1.2 MAC enflurane was more depressant than during 1.2 MAC isoflurane, but the combination of verapamil with 2 MAC concentration of both anesthetics was equally depressant. Both doses of both anesthetics increased plasma verapamil levels compared with the same verapamil dosing regimen awake. When these results are compared with those previously reported for halothane, the effects of verapamil during all three anesthetics are more similar than different. All anesthetics increased plasma verapamil levels at both doses of verapamil, and verapamil was profoundly depressant to the cardiovascular system during high concentrations of all three anesthetics. However, because of a tendency for increased incidence of sinus arrest and bradycardia and more hemodynamic depression during enflurane, the authors conclude that intravenous verapamil is better tolerated during low-dose isoflurane and halothane anesthesia than during comparable concentrations of enflurane anesthesia in healthy dogs. (Key words: Anesthetics, volatile: enflurane; isoflurane. Heart: blood flow; rhythm; ventricular function. Ions: calcium blocker, verapamil. Kidney: blood flow. Pharmacology: drug interaction.)

ALTHOUGH ENFLURANE and isoflurane have essentially replaced halothane as the most widely used inhalation anesthetics in the United States, there is minimal information available about the interaction of another widely used class of cardioactive drugs, the calcium channel blocking drugs, with these anesthetics. Evidence is accumulating to suggest that the inhalation anesthetics may produce different effects on calcium kinetics in cardiac muscle.[1,2] Three laboratories have reported varying degrees of cardiovascular depression when verapamil was administered to dogs anesthetized with enflurane[3,4] or isoflurane.[4,5] However, only one anesthetic dose and, in two studies, subanesthetic concentrations, were studied without awake control observations. In order to document the drug interaction more completely, we have examined the effects of verapamil, enflurane, and isoflurane on the cardiovascular system of conscious, chronically instrumented dogs separately and with verapamil and the anesthetics in combination.

Materials and Methods

The instrumentation, measurement techniques, experimental protocol, and statistical analysis were described in detail in the previous study of halothane and verapamil.[6] In brief, healthy, conditioned, mongrel dogs were surgically instrumented with: 1) pulsed Doppler blood-flow probes on the common carotid, left circumflex coronary, and left renal arteries; 2) left ventricular myocardial ultrasound crystals for myocardial segment length measurements; 3) a miniature high-fidelity transducer in the left ventricle; and 4) Tygon® catheters in the thoracic aorta and left atrium. The animals were carefully trained to lie quietly for awake control recordings and during infusion of verapamil *via* calibrated pump through a peripheral venous catheter inserted on the day of the experiment. Two infusion regimens for verapamil were

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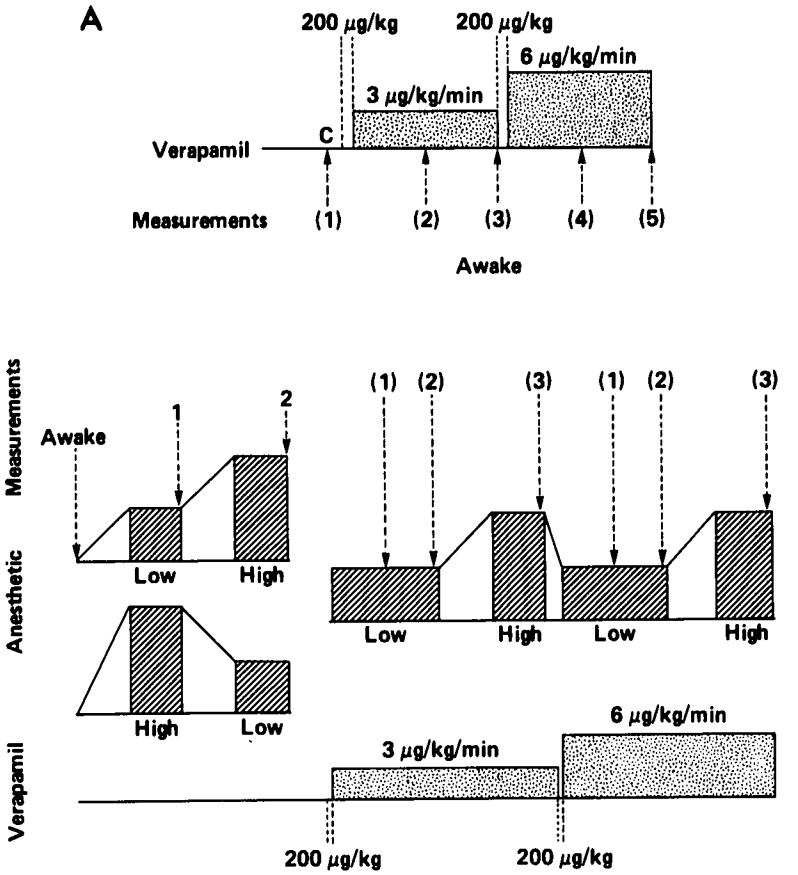

FIG. 1. The experimental protocol. Numbers in parentheses indicate the times of measurement and blood sampling. *A.* The verapamil protocol conducted on one day. *B.* The enflurane and isoflurane and the combination of enflurane, isoflurane, and verapamil protocol conducted on another day at least 48 h before or after *A.* The effect of enflurane and isoflurane was first tested after 15 min of a constant end-tidal enflurane and isoflurane 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 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.

studied. A rapid (3 min) infusion of 0.2 $mg \cdot kg^{-1}$ was followed by 27 min of a 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil infusion; after another rapid infusion of 0.2 $mg \cdot kg^{-1}$, 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was infused for 27 min. Verapamil plasma levels in the conscious animals using this regimen averaged 80–95 $\mu g \cdot ml^{-1}$ and 165–180 $\mu g \cdot mg^{-1}$, respectively. The effects of enflurane and isoflurane and their interaction with verapamil were studied on a separate day in each dog. Experiments were separated by at least 48 h, and the order of the anesthetic administration was randomized, both for the anesthetic and for the dose. End-tidal (ET) anesthetic concentrations on 2.5% and 4% for enflurane and 1.6% and 3.5% for isoflurane were planned to equal 1.2 MAC and the highest concentration that would allow a mean aortic pressure of greater than 50 mmHg. In pilot studies, if the high concentration of the anesthetic produced a mean aortic pressure of less than 50 mmHg, the addition of verapamil was usually fatal. Therefore, in a few animals the high dose was less than the planned amount (see table 2). Anesthetic induction and tracheal intubation were accomplished with the appropriate anesthetics and nitrous oxide by mask. Nitrous oxide was discontinued as soon as controlled ventilation was initiated. Ventilation, fractional inspired O_2 concentration (FI_{O_2}), and external temperature were adjusted to maintain values similar to the awake state for each dog (ET and Pa_{CO_2}, Pa_{O_2}, and rectal temperature). At least 30 min elapsed between tracheal intubation and the study (15 min of steady ET anesthetic concentration). The order of the protocol was identical to the previous study (fig. 1).[6] A two-way analysis of variance with repeated measures design was used with the Bonferroni modification of the paired *t* test to compare individual means. In addition, a linear regression was also employed to estimate the influence of verapamil plasma level on various measurements. Data are expressed as mean ± SEM.

Results

Nine animals were studied, although not all values were reported for each animal (see "n" in the tables). The awake control values for heart rate and mean aortic pressure were consistent with those previously reported for trained, unstressed animals.[7-9] Verapamil had minimal

TABLE 1. Effects of Verapamil in the Conscious Dog

	(n)	Verapamil Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) 0	3	6
HR (min^{-1})	(9)	77 ± 5	94 ± 6*	98 ± 7*
MAP (mmHg)	(9)	101 ± 6	100 ± 3	98 ± 5
LAP (mmHg)	(6)	1.0 ± 0.4	2.7 ± 0.8	3.7 ± 6
LVdP/dt ($mmHg \cdot s^{-1}$)	(7)	3090 ± 290	2970 ± 230	2675 ± 180*
SL (mm)	(5)	1.8 ± 0.3	1.7 ± 0.2	1.7 ± 0.3
PR (ms)	(9)	120 ± 6 (8)	140 ± 7* (7)	150 ± 8*
CarBF ($ml \cdot min^{-1}$)	(7)	148 ± 13	178 ± 15*	166 ± 17
CorBF ($ml \cdot min^{-1}$)	(7)	40 ± 8	45 ± 10	51 ± 13
RenBF ($ml \cdot min^{-1}$)	(7)	99 ± 16	104 ± 17	101 ± 14

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; CarBF = carotid blood flow; CorBF = coronary blood flow; RenBF = renal blood flow:
* $P < 0.05$ *vs.* 0.

effects in the awake animals (table 1). Both infusion rates increased heart rate and P–R intervals, and the high dose decreased left ventricular rate of tension development (dP/dt). Enflurane alone was more depressant to the cardiovascular system than isoflurane because the low concentration (2.4% ET) depressed mean aortic pressure and left ventricular dP/dt and the high concentration also increased left atrial pressure and decreased segment length shortening, while isoflurane only decreased aortic pressure at the low concentration and aortic pressure and left ventricular dP/dt at the high concentration. Both anesthetics produced a nondose-related tachycardia (table 2). Neither coronary blood flow nor renal blood flow was changed by either anesthetic, while both enflurane and isoflurane reduced carotid blood flow at the high concentration compared with the low concentration. In addition, carotid blood flow was increased at the low concentration by both anesthetics, but only with isoflurane was there statistical significance.

As might be expected, the effects of the combination

TABLE 2. Effects of Enflurane and Isoflurane in the Conscious Dog

	(n)	Anesthetic Dose 0	Low	High
%ET			2.44 ± .05	3.97 ± .09
			1.6 ± 0.0	3.04 ± 0.5
HR (min^{-1})				
E	(9)	77 ± 5	107 ± 6*	119 ± 4*
I			113 ± 6*	111 ± 4*
MAP (mmHg)				
E	(9)	101 ± 6	71 ± 3*	50 ± 2*†
I			79 ± 5*	53 ± 3*†
LAP (mmHg)				
E	(6)	1.3 ± 0.4	5.3 ± 1.7	9.0 ± 1.6*†
I			3.3 ± 1.5	6.2 ± 2
LVdP/dt ($mmHg \cdot s^{-1}$)				
E	(7)	3090 ± 290	1570 ± 80*	890 ± 70*†
I			2360 ± 240	1310 ± 200*†
SL (mm)				
E	(5)	1.8 ± 0.3 (6)	1.5 ± 0.2 (6)	0.95 ± 0.1*
I		(4)	1.95 ± 0.1 (5)	1.5 ± 0.2
PR (ms)				
E	(9)	120 ± 6	131 ± 6	128 ± 4
I			117 ± 5	120 ± 5
CarBF ($ml \cdot min^{-1}$)				
E	(7)	148 ± 13	185 ± 15	135 ± 15†
I			197 ± 13*	132 ± 14†
CorBF ($ml \cdot min^{-1}$)				
E	(7)	40 ± 8	39 ± 8	33 ± 6
I			51 ± 12	43 ± 8
RenBF ($ml \cdot min^{-1}$)				
E	(7)	99 ± 16	88 ± 11	83 ± 9
I			106 ± 16	102 ± 13

* $P < 0.05$ *vs.* 0.

† $P < 0.05$ *vs.* 2.44% enflurane or 1.6% isoflurane.

TABLE 3. Effects of the Combination of Enflurane and Verapamil

	(n)	Enflurane % End-tidal			
		2.43 ± .06		3.96 ± .09	
		3V	6V	3V	6V
HR (min^{-1})	(9)	111 ± 3	88 ± 10	110 ± 4	98 ± 10
MAP (mmHg)	(9)	71 ± 3‡	58 ± 3*·§	39 ± 2‡·¶	37 ± 3†·§·**
LAP (mmHg)	(6)	7.7 ± 2.0‡	10 ± 1.7§	9.2 ± 2.1‡	8.2 ± 2.1§
LVdP/dt ($mmHg \cdot s^{-1}$)	(7)	1110 ± 90* (6)	900 ± 70*·§·‡	600 ± 50†·‡·¶ (4)	650 ± 90†·§·**
SL (mm)	(6)	1.2 ± 0.2†	1.2 ± 0.2§	0.9 ± 0.1‡·¶ (5)	1.2 ± 0.2
PR (ms)	(9)	149 ± 7* (6)	158 ± 8* (9)	148 ± 5† (4)	158 ± 12**
CarBF ($ml \cdot min^{-1}$)	(7)	152 ± 10	110 ± 20*	98 ± 15†·‡·¶ (5)	57 ± 56†·§·**
CorBF ($ml \cdot min^{-1}$)	(7)	27 ± 7	28 ± 7	23 ± 4 (6)	22 ± 6
RenBF ($ml \cdot min^{-1}$)	(7)	85 ± 12	68 ± 13§	53 ± 9†·‡·¶ (5)	53 ± 4†·§·**

3V = verapamil 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 6V = verapamil 6 $\mu g \cdot kg^{-1} \cdot mm^{-1}$. Also see table 1 for abbreviations.

Compared to enflurane (E) without verapamil (V): * = $P < 0.05$ *vs.* 2.4% E; † = $P < 0.05$ versus 3.9% E.

Compared to verapamil without enflurane: ‡ = $P < 0.05$ *vs.* 3V; § = $P < 0.05$ versus 6V.

Compared to combination of verapamil and enflurane: ¶ = $P < 0.05$ *vs.* 2.4% E, 3V; ** = $P < 0.05$ *vs.* 2.4% E, 6V; ‡ = $P < 0.05$, 6V *vs.* 3V, 2.4% or 3.9% E.

of verapamil with enflurane and isoflurane were more complex and different between the low and high anesthetic concentrations.

LOW ANESTHETIC CONCENTRATION

The infusion of verapamil produced some cardiovascular depression with both anesthetics (tables 3 and 4). The effect was somewhat more pronounced with enflurane because aortic pressure and segment length shortening were decreased compared with verapamil alone (table 3). Both anesthetics decreased dP/dt and increased left atrial pressure during both doses of verapamil. However, heart rate was increased only with isoflurane. Verapamil increased left atrial pressure during isoflurane anesthesia, predominantly because the atrial pressures were lower during 1.2 MAC isoflurane without verapamil (table 2). The only significant verapamil dose effect was on dP/dt with enflurane.

HIGH ANESTHETIC CONCENTRATION

Verapamil produced even more left ventricular depression during high doses of enflurane and isoflurane, and the differences between the two anesthetics were less pronounced. In addition, there was no dose effect of verapamil at the high concentrations. Of some interest is the fact that both carotid and renal blood flows were markedly decreased by the combination of high anesthetic concentrations and verapamil while coronary blood flow was not affected (tables 3 and 4).

Plasma verapamil concentrations were increased significantly and markedly by both enflurane and isoflurane, although not in a dose-dependent manner (table 5).

Discussion

As in our previous study, the effect of verapamil infusion in the awake dog was minimal.[6] The effects of the

TABLE 4. Effects of the Combination of Verapamil and Isoflurane

	(n)	Isoflurane % End-tidal			
		1.6 ± 0		3.05 ± .53	
		3V	6V	3V	6V
HR (min^{-1})	(9)	119 ± 5‡ (8)	113 ± 9§ (9)	113 ± 5‡ (9)	94 ± 12
MAP (mmHg)	(9)	80 ± 3‡ (8)	76 ± 2§ (9)	49 ± 4‡·¶ (9)	41 ± 3§·**
LAP (mmHg)	(6)	7.7 ± 2*·‡ (5)	9.2 ± 2*·§ (6)	9.3 ± 2‡ (6)	9.4 ± 2
LVdP/dt ($mmHg \cdot s^{-1}$)	(8)	1875 ± 180** (7)	1765 ± 210*·§ (8)	990 ± 85†·‡·¶ (4)	990 ± 120†·§·**
SL (mm)	(5)	1.5 ± 0.2 (5)	1.5 ± 0.2 (5)	1.2 ± 0.2†·‡·¶ (7)	1.2 ± 0.1†·**
PR (ms)	(9)	141 ± 6* (7)	159 ± 6* (9)	142 ± 8† (7)	153 ± 8†
CarBF ($ml \cdot min^{-1}$)	(8)	168 ± 13 (7)	149 ± 9* (8)	111 ± 14‡·¶	87 ± 9†·§·**
CorBF ($ml \cdot min^{-1}$)	(6)	51 ± 12 (5)	40 ± 11 (6)	39 ± 12 (6)	30 ± 7
RenBF ($ml \cdot min^{-1}$)	(7)	92 ± 13 (6)	95 ± 15 (7)	66 ± 5‡ (7)	57 ± 7

3V = verapamil 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 6V = verapamil 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Also see table 1 for abbreviations.

Compared to isoflurane (I) without verapamil (V): * = $P < 0.05$ *vs.* 1.6% I; † = $P < 0.05$ *vs.* 3% I.

Compared to verapamil without isoflurane: ‡ = $P < 0.05$ *vs.* 3V; § = $P < 0.05$ *vs.* 6V.

Compared to combination of verapamil and isoflurane: ¶ = $P < 0.05$ *vs.* 1.6% I, 3V; ** = $P < 0.05$ *vs.* 1.6% I, 6V; ‡ = $P < 0.05$, 6V *vs.* 3V, 1.6% or 3.0% I.

TABLE 5. Plasma Verapamil (V) Concentration ($ng \cdot ml^{-1}$)

Verapamil Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	(n)	Anesthetic Dose		
		0	Low	High
3				
E	(9)	95 ± 10	139 ± 13*	164 ± 17*
I			117 ± 11*	130 ± 18*
6				
E	(9)	180 ± 14	326 ± 34†‡	339 ± 38†‡
I			220 ± 21†‡	269 ± 31†‡

E = enflurane; I = isoflurane.
* $P < 0.05$ *vs.* 3V-0.
† $P < 0.05$ *vs.* 6V-0.
‡ $P < 0.05$ 6V *vs.* 3V.

two inhalation anesthetics, enflurane and isoflurane, alone were similar to previously reported publications,[10-13] although this is the first study where the two anesthetics were compared in the same experimental preparation and in many of the same animals. Enflurane produced more cardiovascular depression, especially at the low dose. In previous studies, the predominant effect of isoflurane was peripheral vasodilation.[11-14] Because we did not measure cardiac output in most of our animals, we could not document this effect. However, the rather marked decrease in mean aortic pressure coupled with lesser decreases in left ventricular dP/dt and segment length shortening suggests a similar conclusion. Neither anesthetic produced much change in the regional blood flows that we measured. As previously observed with halothane anesthesia,[6] carotid blood flow was increased during low concentrations of enflurane and isoflurane and returned to control levels at the high concentrations. Although we did not measure cerebral blood flow in our animals, we suspect that this observation is related to cerebral vasodilation previously observed with enflurane and isoflurane.[15-17] Because carotid blood flow did not correlate with measured pulmonary artery blood flow in our animals, the increase observed with low concentrations of all three anesthetics is likely to reflect increased cerebral perfusion.[6] Although not statistically significant, coronary blood flow tended to be higher during both low- and high-dose isoflurane than during enflurane, which is also in agreement with previous observations.[15] The maintenance of coronary blood flow in the face of decreased mean arterial pressure also suggests coronary vasodilation with both anesthetics. Apparently renal blood flow autoregulation was well preserved even at high anesthetic concentrations because renal blood flow did not change significantly in spite of a 40–50% decrease in mean arterial pressure.

The effect of verapamil infusion during enflurane anesthesia was more pronounced than during isoflurane anesthesia, especially at low concentrations. At high concentrations of isoflurane and enflurane, the effects of verapamil were similar, with more depression of mean aortic pressure, left ventricular dP/dt, segment length shortening, and carotid blood flow during both the 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions than seen without verapamil.

One of the reasons for the greater cardiovascular depression produced by verapamil during low-dose enflurane anesthesia could have been the high plasma levels of verapamil during the low concentrations of enflurane (table 5). Although not as well studied as halothane and isoflurane, it would appear that enflurane depressed liver blood flow in a dose-dependent manner.[18,19] Thus, decreased liver blood flow could decrease the clearance of verapamil. However, isoflurane does not change liver blood flow even at high concentrations.[15] Hamman *et al.* showed that increasing concentrations of verapamil produced dose-related depression of hepatic blood flow and suggested that the hemodynamic effects of verapamil interfere with the clearance of the drug.[20] It is possible that the combined effect of verapamil and isoflurane on hepatic blood flow resulted in the increased plasma levels of verapamil during anesthesia with isoflurane.

Interaction between isoflurane and verapamil was first reported by Kates *et al.*[5] In an acute right heart bypass preparation, they reported significant depression of left ventricular function by isoflurane at 1 MAC concentrations (and less) in contrast to our experience and previous reports.[11,13] Although they used exactly the same dosing technique for verapamil, their plasma levels were 50% of those in our awake animals and less than 30% of those in our animals anesthetized with similar isoflurane concentrations. In spite of these very low plasma verapamil levels (subtherapeutic for the low dose[21]), they reported profound depression in left ventricular function. The contrast between their results and ours highlights the importance of defining experimental conditions. Their bypass preparation must have accentuated the negative inotropic effects of both isoflurane and verapamil. In addition, the effects of compensatory reflexes, which certainly come into play with verapamil awake,[22,23] would not be apparent. Holland *et al.*, in an open-chest, acutely instrumented dog, could see minimal depression of mean aortic pressure and cardiac output with a bolus injection of up to 0.3 $mg \cdot kg^{-1}$ verapamil during 1.8% ET enflurane.[3] However, ventricular function, as measured by left ventricular dP/dt, segment length shortening, and aortic blood flow acceleration, was markedly decreased by verapamil during enflurane. Again, the difference in the model as well as the bolus *versus* infusion dosing was probably responsible for the observed differences. Kapur *et al.* studied only low anesthetic doses of enflurane and isoflurane with increasing infusion doses of verapamil.[4] Their findings with enflurane are very similar to ours at the same plasma verapamil levels. However, our animals were more depressed with 1.6% ET isoflurane (*vs.* 1.34% in their preparation) at comparable plasma verapamil levels. In particular, in their model the heart rates were 20% faster (140 min^{-1}

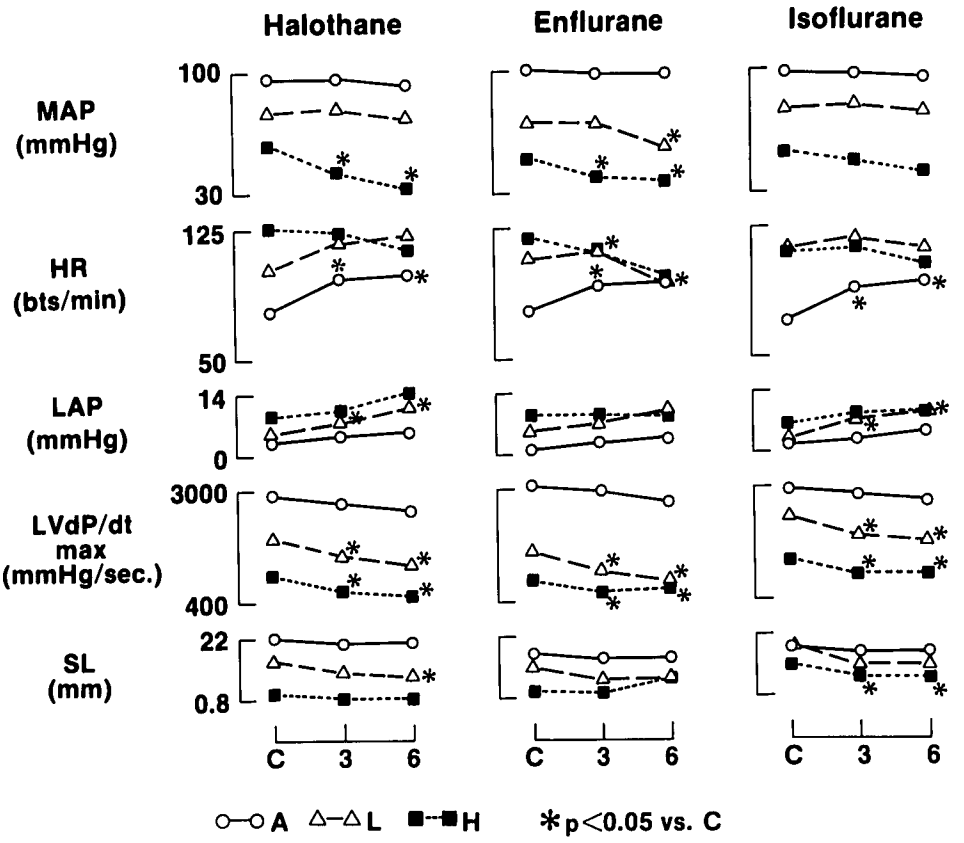

FIG. 2. Comparison of the effects of infusion of verapamil in the chronically instrumented dog during the awake state (A), low dose (L), and high dose (H) of halothane,[6] enflurane, and isoflurane. MAP = mean aortic pressure; HR = heart rate; LAP = left atrial pressure; LVdP/dt max = maximum rate of rise of left ventricular pressure; SL = myocardial segment length shortening; C = control without verapamil; 3 = 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil infusion; 6 = 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil infusion. Only statistics comparing the effect of verapamil are presented for the sake of clarity.

vs. 110 min^{-1}), which most likely accounted for the higher left ventricular dP/dt and mean aortic pressure.

Because we have also studied halothane in a similar experiment,[6] a graphic comparison of the effects of the 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil awake and during high and low concentrations of the three anesthetics is presented in figures 2 and 3. The effects of verapamil during halothane, enflurane, and isoflurane were qualitatively similar. In general, verapamil produced much more cardiovascular depression during high-dose anesthesia with all three anesthetics than awake or during low concentrations, with minimal differences between anesthetics. We could not confirm the findings of Kapur *et al.* that cardiac performance is at least affected by increasing doses of verapamil during low-dose halothane anesthesia.[4] In our study, the effects of halothane and isoflurane were

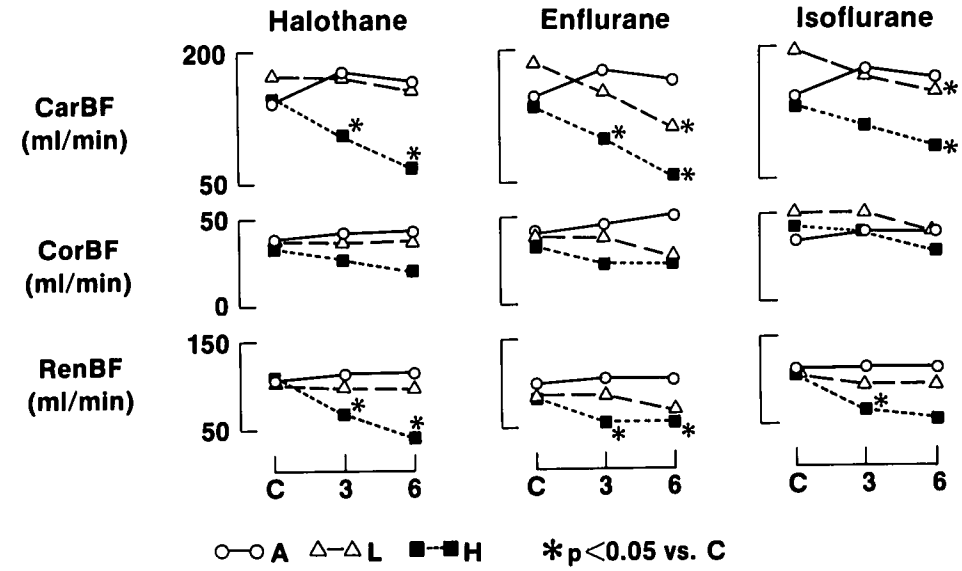

FIG. 3. Comparison of the effects of verapamil on regional blood flows during halothane,[6] enflurane, and isoflurane anesthesia. A = awake; L = low concentrations of the anesthetic; H = high concentrations of the anesthetic; C = control without verapamil; 3 = 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil infusion; 6 = 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil infusion; CarBF = carotid blood flow; CorBF = coronary blood flow; RenBF = renal blood flow. Only statistics comparing the effect of verapamil are presented for the sake of clarity.

TABLE 6. Effects of Verapamil on Cardiac Rhythm

	(n)	AVB	SA
Awake	(12)	2*	—
Halothane	(11)	2†	2
Enflurane	(9)	1†	5
Isoflurane	(9)	1	2

AVB = Wenckeback or intermittent A–V block; SA = sinus arrest with slow junctional rhythm ($<50 \cdot min^{-1}$).

* Both dogs developed either AVB or SA during anesthesia, one with all three anesthetics and one only with enflurane.

† AVB proceeded to SA at higher verapamil dose.

similar. However, our low doses of all three anesthetics were higher than theirs. We intentionally chose the low dose of greater-than-MAC to simulate light surgical anesthesia. Of course, we could compare the effect of verapamil without the anesthetic because we had awake control animals. Calcium channel blockers[23] and inhalation anesthetics[24] both depress sinus node automatism and atrioventricular (A-V) conduction. In our awake dogs, verapamil occasionally produced measurable delays in A-V conduction (table 6). During anesthesia, these and several other dogs developed a sinus arrest and slow junctional rhythm, which led to some hypotension and cardiovascular collapse (table 6). Although not statistically significant, this syndrome was more frequently observed with enflurane (5 of 9 dogs) than with halothane (2 of 11 dogs) or isoflurane (2 of 9 dogs). Kapur *et al.*[4] also observed a similar distribution, although they grouped A-V block and sinus arrest.

TABLE 7. Correlation between Plasma Verapamil Concentrations and Cardiovascular Measurements

	R	R^2	P
Awake	—	—	—
Halothane			
MAP	0.48	0.23	≤0.05
LAP	0.51	0.26	≤0.05
CarBF	0.58	0.33	≤0.01
CorBF	0.40	0.16	≤0.05
LVdP/dt	0.48	0.23	≤0.05
RenF	0.41	0.16	≤0.05
PR	0.71	0.50	≤0.001
Enflurane			
HR	0.69	0.48	≤0.001
CarBF	0.59	0.35	≤0.01
Isoflurane			
HR	0.52	0.27	≤0.01
LAP	0.56	0.32	≤0.01
All*			
HR	0.19	0.04	≤0.05
MAP	0.38	0.15	≤0.001
LAP	0.51	0.26	≤0.001
CarBF	0.36	0.135	≤0.001
CorBF	0.25	0.06	≤0.01
LVdP/dt	0.37	0.13	≤0.001
PR	0.55	0.30	≤0.001
RenBF	0.31	0.09	≤0.01

R = correlation coefficient. See table 1 for other abbreviations.

* Awake, and all anesthetics.

Kapur *et al.* presented their data according to plasma verapamil concentrations rather than administered dose and suggested that hemodynamic changes could be correlated with plasma levels, although no statistics documenting this contention were presented.[4] When we examined the relationship between plasma verapamil levels and the cardiovascular changes produced by increasing doses of verapamil, we did find some statistically significant correlations (table 7). Of particular note are the lack of any correlations in the awake animal, the relatively large number of correlations during halothane anesthesia as compared with enflurane and isoflurane, and the large number of statistically significant correlations when all the experimental conditions were grouped together. However, it must be remembered that statistical significance and practical significance are not necessarily the same thing.[25] If the usually recorded correlation coefficient is squared, this figure gives the predictive ability of the correlative term. For instance, with a correlation coefficient of 0.50, the squared correlation coefficient would be 0.25. The meaning of this correlation is that 25% of the change in the dependent observation could be accounted for by the correlated observation. Thus, it can be seen that even with the relatively high correlation coefficient between plasma verapamil level and the P–R interval during halothane anesthesia, only 50% of this change could be predicted by the changing plasma verapamil levels. Even more striking are the R-squared values in the total group. The only reason that there are so many significant correlates in this group is because of the large number evaluated. However, the highest R value awake is the P–R interval and, even here, only 30% of the change in P–R interval could be explained by changes in plasma verapamil levels. Consequently, we believe that our decision to divide the verapamil dosing groups according to dose rather than to plasma level is as reasonable as the decision of Kapur *et al.* to group their animals according to plasma verapamil concentrations. In addition, of course, in the clinical situation, only the dose, not the plasma concentration, will be known.

Although there may be subcellular differences between the effects of the three inhalation anesthetics currently used in the United States on calcium kinetics, our results suggest that the effect of the calcium channel blocking drug verapamil on the hemodynamics during both low and high concentrations of halothane, enflurane, and isoflurane are more similar than different. Relatively high doses of verapamil given by an infusion technique are well tolerated by the canine cardiovascular system during low concentrations of all three anesthetics. In contrast, even low plasma concentrations of verapamil produced

marked cardiovascular depression during high concentrations of the three anesthetics. However, there must be several notes of caution. First, we noted with all three anesthetics that rapid injection of verapamil (0.2 mg · kg^{-1}) often resulted in considerably more cardiac depression than was apparent at the steady-state plasma levels 15 and 30 min later. Second, our results and those of Kapur *et al.*[4] suggest that the combination of verapamil and enflurane may be more likely to result in prolonged A-V conduction and, in particular, sinus arrest. In our experience, the latter is associated with profound cardiovascular depression that often is difficult to reverse. Third, most experiments thus far have used healthy animals. The bypass preparation of Kates *et al.*[5] more closely simulates the failing heart, and the profound cardiac depression resulting from low-dose isoflurane and low plasma levels of verapamil suggests that the combination should be used very cautiously in patients with compromised ventricular function. Finally, the results from canine experiments must be used only as indicators of clinical drug interaction. However, even in healthy patients we would suggest that intravenous verapamil should be given with great caution during enflurane anesthesia, considering both the effect of the interaction on the cardiac conduction system and the high plasma levels of verapamil produced during even low-dose enflurane anesthesia.

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