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Comparative Cardiovascular Effects of Verapamil, Nifedipine, and Diltiazem during Halothane Anesthesia in Swine

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The cardiovascular effects of the calcium channel blockers verapamil (V), nifedipine (N) and diltiazem (D) were compared in halothane-anesthetized swine. Equipotent hypotensive doses of the three calcium channel blocking drugs were administered randomly by continuous infusion to three groups of six animals each to produce a uniform 25–30% reduction in mean systemic arterial blood pressure (BP). An additional group of six animals received sodium nitroprusside (S) to demonstrate the effects of lowering blood pressure with a pure vasodilator on this experimental preparation. Hemodynamic indices monitored before and after drug administration included ECG, mean systemic and pulmonary artery blood pressure, mean central venous and pulmonary capillary wedge pressure, thermodilution cardiac output, left ventricular pressure, and left ventricular dP/dt. All four study drug infusions reduced BP an average of 28%. V and D reduced BP by decreasing cardiac output (41% and 42%, respectively) without affecting systemic vascular resistance. N and S produced hypotension by decreasing systemic vascular resistance (36% and 21%, respectively) without affecting cardiac output. D reduced heart rate (18%) and both D and V increased the PR interval (60% and 40%, respectively). Calcium chloride (20 $mg \cdot kg^{-1}$ intravenous bolus) improved indices of myocardial contractility but did not affect drug-induced changes in cardiac electrophysiology. These data demonstrate that in this halothane-anesthetized swine model the administration of equihypotensive doses of verapamil or diltiazem has a more pronounced affect on cardiac conduction and myocardial contractility than does nifedipine, which predominantly reduces systemic vascular resistance with minimal effects on cardiac function. (Key words: Anesthetics, volatile: halothane. Heart: cardiac conduction; myocardial function. Hemodynamics: systemic vascular resistance; pulmonary vascular resistance. Ions: calcium. Pharmacology: verapamil; nifedipine; diltiazem.)

VERAPAMIL, NIFEDIPINE, AND DILTIAZEM, three clinically available calcium channel-blocking drugs, possess distinct pharmacologic profiles.[1,2] Although isolated tissue preparations demonstrate dose-dependent vasodilatory, as well as negative chronotropic, dromotropic, and inotropic effects,[3–6] studies in awake, intact animals reveal net cardiovascular outcomes that are dramatically different from the direct drug effects.[7–9] Nifedipine, a potent vasodilator, reduces systemic arterial blood pressure.[8] The resultant reflex increase in sympathetic tone overrides the direct cardiac effects of nifedipine, resulting in increases in heart rate and cardiac output.[10] In contrast, doses of verapamil that reduce systemic arterial pressure may decrease cardiac conduction and myocardial contractility.[7,11] Hemodynamic effects of diltiazem are similar to verapamil, although diltiazem appears to produce greater negative chronotropic effects and less myocardial depression.[1,2,12,13]

Since verapamil, nifedipine, and diltiazem have distinct cardiovascular effects, it is important to differentiate their interactions with anesthetic agents. Although the verapamil–halothane[14] and nifedipine–halothane[15,16] interactions have been studied separately, no systematic study has investigated the hemodynamic differences among these clinically available calcium channel-blocking drugs during general anesthesia. Therefore, we have compared the cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia. For hemodynamic comparisons among this heterogeneous group of compounds, the drug doses were standardized to produce a uniform reduction in systemic arterial blood pressure. Sodium nitroprusside also was evaluated to demonstrate the effects of lowering blood pressure with a pure vasodilator on this experimental preparation.

Methods

Studies were performed on 28 swine weighing 20.2 ± 0.7 kg (mean ± SEM). Anesthesia was induced with 4% halothane in oxygen by spontaneous ventilation in an enclosed plastic animal hood. After endotracheal intubation, the animals were ventilated via constant volume positive-pressure ventilation to maintain end-tidal CO_2 at 35–40 mmHg (Perkin–Elmer® 1100 medical gas analyzer), which corresponded to an arterial *p*H of 7.4 ± 0.01. A heating blanket was used to maintain normothermia. One hundred per cent oxygen, delivered to a halothane vernitrol (Ohio Medical Products) supplied a semiclosed anesthesia circle containing a CO_2 absorber. End-tidal halothane levels of 0.92 ± 0.01% (0.91 = 1 MAC in swine[17]) as measured by mass spectrometry (Perkin-Elmer 1100) provided maintenance anesthesia.

Cannulation of the femoral vein was performed for intravenous fluid (sodium chloride 0.9%) and drug administration. Total fluid infusions were maintained at 3.0 $ml \cdot kg^{-1}h^{-1}$. Direct intraarterial blood pressure monitoring and blood sampling were provided by a femoral arterial cannula. A 7 French Swan–Ganz® flow-directed themodilution catheter (Edwards Laboratory) was advanced into the pulmonary artery via a femoral vein and

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furnished mean central venous (CVP), mean pulmonary arterial (PAP), mean pulmonary capillary wedge (PCWP) pressures, and cardiac outputs (CO) (Edwards 9520A computer). Stroke volume (SV), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated by standard formulas. A Millar catheter (Millar Instruments model PC350) was passed into the left ventricle via the right common carotid artery and used for measurements of intraventricular pressures. The first derivative, dP/dt, was electronically derived. Heart rate (HR), rhythm, and PR and QT intervals were determined from lead II of the electrocardiogram, recorded at 50 mm $\cdot$ s^{-1}. Pressures were transduced by P-23 Gould-Statham transducers and transcribed onto a Gould model 200 8-channel recorder. All cardiovascular measurements were made at end-expiration and CO was determined as the mean of triplicate measurements within a 2-min period. Arterial blood was sampled for the measurement of Pa_{O_2}, Pa_{CO_2}, *p*H, hematocrit, sodium, and potassium during each cardiovascular measurement period.

The study drug solutions verapamil (0.05%), diltiazem (0.15%), and sodium nitroprusside (0.02%) were prepared in 5% dextrose in water. Nifedipine (0.01%) was prepared in 15.0 g ethanol, 15.0 g polyethylene glycol, and water to a total of 100 ml. Due to its photosensitivity properties, nifedipine and nitroprusside were shielded from exposure to light during preparation and usage. Two animals received an infusion of the nifedipine vehicle (0.04 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, equal to the mean nifedipine infusion rate) to determine possible vehicle-induced cardiovascular effects. Two additional animals, serving as controls, did not receive a drug infusion to demonstrate the stability of this halothane-anesthetized swine model during a 2-h measurement period.

Study Protocol

The 24 animals were divided randomly into four equal groups. Following hemodynamic equilibration for 30 min, baseline cardiovascular variables were measured and repeated after 15 min. The study drugs then were administered. Group 1 received sodium nitroprusside, Group 2 received nifedipine, Group 3 received verapamil, and Group 4 received diltiazem. All study drugs were given by continuous intravenous infusion (IMED model 922) at rates that were titrated to reduce the mean systemic arterial blood pressure (BP) 25–30% from baseline values. After attaining the desired decrease in BP, drug infusion rates were not changed throughout the rest of the study. When BP and infusion rates were stable for 15 min, cardiovascular variables were measured and repeated after 15 min to determine hemodynamic stability. While stable drug infusion rates continued, calcium chloride 20 mg $\cdot$ kg^{-1} was administered over 1 min through the central venous injection port of the pulmonary artery catheter. Cardiovascular variables were measured 1 min after injection. Serum drug levels for nifedipine (gas chromatographic analysis) and verapamil and diltiazem (high pressure liquid chromatographic analysis) were obtained during each cardiovascular measurement period. Nifedipine, verapamil, and diltiazem levels were measured by R. G. McAllister, M.D.,[18] (Lexington, Kentucky), Bioscience Laboratories[19] (Belwood, Illinois), and Marion Laboratories[20] (Kansas City, Missouri), respectively. At the conclusion of the study, the animals were killed with intravenous potassium chloride infusion.

The data were evaluated by analysis of variance. Bonferroni *t* tests were used to assess intergroup comparisons. Significance was assumed at $P \leq 0.05$. All values in the text, tables, and figures are given as mean ± SEM.

Results

The hemodynamic data are displayed in table 1. Intergroup comparisons of baseline cardiovascular variables revealed no significant difference among the four groups. Study drug infusions successfully decreased the BP 22 ± 2 mmHg (28%) for all animals (NS among groups, fig. 1) in 65.6 ± 5.8 min (NS among groups). When the desired decrease in BP was achieved, drug infusion rates were not altered and the BP remained stable. Temporal stability within each group was demonstrated statistically by no significant change in any cardiovascular variable between the two baseline measurement periods and also between the two measurement periods during drug-induced hypotension. For analytic purposes, hemodynamic data from the two baseline measurements and also from the two measurement periods during drug-induced hypotension were pooled by averaging within each group. Temporal stability of this preparation was demonstrated by no change in cardiovascular variables over the 2-h measurement period in control animals. Arterial blood analysis revealed no significant difference among groups for Pa_{O_2} (430 ± 7 mmHg), Pa_{CO_2} (38 ± 1 mmHg), *p*H (7.44 ± 0.01), hematocrit (30.0 ± 0.05%), serum sodium 136 ± 1 mEq l^{-1}), and serum potassium (4.9 ± 0.1 mEq l^{-1}).

Sodium nitroprusside significantly decreased the BP (27%) and the SVR (21%, fig. 1). CVP and PCWP also decreased (39% and 31%, respectively, fig. 2). CO and SV were unchanged from baseline, while maximum ventricular dP/dt decreased (20%, fig. 2). HR, PR, and QT intervals remained unchanged (fig. 3).

Nifedipine, like sodium nitroprusside, significantly decreased the BP (26%) and SVR (36%, fig. 1). However, CVP and PCWP increased (29% and 39%, respectively, fig. 2). CO was maintained, while SV and dP/dt decreased (18% and 14%, respectively, fig. 2). HR increased (30%)

TABLE 1. Cardiovascular Indices before and after Study Drug Infusions and after Calcium Chloride

Cardiovascular Indices	Group	Baseline B			Drug Effect T1	Drug Effect T2	Calcium Chloride
HR (beats · min^{-1})	S	116 ± 7	118 ± 7		114 ± 9	116 ± 9	115 ± 8
	N	118 ± 7	117 ± 6	*·†	152 ± 6	154 ± 10	152 ± 3
	V	110 ± 8	110 ± 7		119 ± 7	119 ± 8	109 ± 6‡
	D	128 ± 8	128 ± 9	*·†	106 ± 8	103 ± 8	103 ± 7
PR interval (ms)	S	107 ± 6	107 ± 6		103 ± 6	107 ± 8	107 ± 6
	N	95 ± 7	97 ± 6		92 ± 6	92 ± 6	92 ± 6
	V	112 ± 8	112 ± 8	*	155 ± 10	158 ± 10	162 ± 9
	D	100 ± 8	100 ± 8	*	157 ± 12	163 ± 11	167 ± 12
Q-T interval (ms)	S	277 ± 16	280 ± 13		280 ± 17	277 ± 17	275 ± 16
	N	290 ± 21	290 ± 21	*	222 ± 11	222 ± 11	222 ± 11
	V	310 ± 11	303 ± 7	*	263 ± 9	267 ± 9	257 ± 6
	D	263 ± 11	260 ± 11		253 ± 14	253 ± 14	247 ± 12
Mean SBP (mmHg)	S	77 ± 2	77 ± 2	*	57 ± 2	55 ± 2	61 ± 2§
	N	76 ± 4	77 ± 4	*	56 ± 2	57 ± 2	66 ± 4‡
	V	80 ± 6	79 ± 5	*	57 ± 4	56 ± 3	68 ± 3†‡
	D	80 ± 1	81 ± 1	*	57 ± 1	57 ± 2	63 ± 2‡
Mean CVP (mmHg)	S	4.2 ± 0.3	4.2 ± 0.3	*·†	2.3 ± 0.6	2.8 ± 0.6	3.2 ± 0.8
	N	5.5 ± 0.8	5.1 ± 0.5	*	6.7 ± 0.9	7.0 ± 1.0	7.5 ± 1.0
	V	5.3 ± 0.6	4.9 ± 0.4	*	8.2 ± 0.6	8.2 ± 0.5	7.8 ± 0.8
	D	5.6 ± 0.6	4.8 ± 0.8	*	6.9 ± 0.7	7.0 ± 0.4	8.0 ± 0.8
Mean PAP (mmHg)	S	18.0 ± 1.5	18.0 ± 1.6	*	14.3 ± 2.0	14.6 ± 1.8	25.3 ± 3.3‡
	N	19.0 ± 0.9	18.1 ± 0.8	*	22.7 ± 1.7	22.8 ± 1.4	31.0 ± 2.6‡
	V	16.3 ± 1.1	16.6 ± 1.2		18.2 ± 0.9	18.0 ± 0.9	28.2 ± 2.5‡
	D	19.2 ± 1.3	18.8 ± 1.6		21.2 ± 1.7	21.4 ± 1.4	33.3 ± 2.8‡
PCWP (mmHg)	S	7.2 ± 1.0	7.8 ± 1.0	†·¶	5.2 ± 1.0	5.2 ± 1.0	5.1 ± 1.3
	N	8.3 ± 1.2	8.3 ± 0.9	*	11.5 ± 1.7	11.5 ± 1.6	10.7 ± 1.4
	V	7.7 ± 0.8	7.9 ± 0.6	*	12.2 ± 0.9	12.5 ± 0.9	10.0 ± 1.1
	D	8.9 ± 1.5	8.3 ± 1.6	*	12.1 ± 1.5	12.2 ± 1.2	11.8 ± 1.0
CO (l · min^{-1})	S	2.41 ± .26	2.42 ± .23		2.27 ± .18	2.18 ± .19	2.45 ± .18§
	N	2.10 ± .19	2.06 ± .19		2.24 ± .12	2.25 ± .14	2.99 ± .23†‡
	V	2.34 ± .23	2.27 ± .22	*	1.41 ± .17	1.34 ± .13	1.84 ± .15‡
	D	2.36 ± .18	2.39 ± .17	*	1.43 ± .09	1.33 ± .08	1.65 ± .10‡
SV (ml)	S	21.5 ± 3.0	21.2 ± 2.7		21.1 ± 2.8	19.9 ± 2.7	24.1 ± 3.1‡
	N	17.8 ± 1.3	17.7 ± 1.3	¶	14.8 ± 1.5	14.6 ± 0.7	19.6 ± 1.4‡
	V	21.9 ± 2.7	21.2 ± 2.7	*	12.2 ± 1.6	11.7 ± 1.5	17.2 ± 1.8‡
	D	18.5 ± 1.0	18.8 ± 1.0	*	13.6 ± 0.7	13.2 ± 0.7	16.3 ± 1.0‡
dP/dt (mmHg · s^{-1})	S	1,336 ± 187	1,306 ± 191	*·**	1,056 ± 164	1,070 ± 181	1,608 ± 225‡
	N	1,022 ± 90	993 ± 88	¶·**	872 ± 47	857 ± 48	1,724 ± 124‡
	V	1,206 ± 127	1,208 ± 121	*	704 ± 55	708 ± 43	1,514 ± 140‡
	D	1,249 ± 132	1,162 ± 126	*	621 ± 62	580 ± 43	1,302 ± 114‡
SVR (dyn · s · cm^{-5})	S	2,541 ± 195	2,532 ± 211	¶	2,043 ± 162	1,977 ± 158	1,927 ± 144
	N	2,763 ± 134	2,849 ± 127	*	1,803 ± 134	1,835 ± 161	1,632 ± 214‡
	V	2,724 ± 374	2,845 ± 422		3,012 ± 423	3,046 ± 366	2,719 ± 270‡
	D	2,593 ± 161	2,614 ± 180		2,898 ± 152	3,028 ± 108	2,689 ± 113‡
PVR (dyn · s · cm^{-5})	S	389 ± 60	368 ± 61		333 ± 51	362 ± 60	692 ± 93§
	N	420 ± 37	402 ± 36		404 ± 28	411 ± 40	584 ± 111
	V	331 ± 65	349 ± 76		399 ± 88	367 ± 64	849 ± 233‡
	D	363 ± 40	347 ± 29	*	562 ± 41	588 ± 75	1,079 ± 180‡

Values appear as mean ± SEM. For statistical analysis both baseline and both drug effect values were each pooled within each drug group for each measured function. Abbreviations: S = sodium nitroprusside; N = nifedipine; V = verapamil; D = diltiazem; HR = heart rate; SBP = systemic arterial blood pressure; CVP = central venous pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

* $P < 0.01$ between baseline and drug effect.
† $P < 0.05$ from other three drug groups.
‡ $P < 0.01$ between drug effect and calcium chloride.
§ $P < 0.05$ between drug effect and calcium chloride.
¶ $P < 0.05$ between baseline and drug effect.
** $P < 0.05$ from other two drug groups.

and there was no change in PR interval. The QT interval decreased concurrently with the increase in heart rate (fig. 3). An infusion of the nifedipine vehicle into two additional animals was not associated with any hemodynamic changes.

Verapamil significantly decreased the BP (30%) without changing SVR (fig. 1). The CVP and PCWP increased (61% and 58%, respectively) and CO, SV, and dP/dt decreased (41%, 45% and 42% from the baseline, respectively, fig. 2). HR was unchanged, while PR interval increased (40%) and QT interval decreased slightly (14%, fig. 3).

Diltiazem, like verapamil, significantly decreased the BP (30%) without altering SVR (fig. 1). Both the CVP and PCWP were increased (34%, 42%, respectively) and CO, SV, and dP/dt decreased (42%, 28%, and 50%, respectively, fig. 2). HR decreased (18%), PR interval increased (60%), and QT interval was unchanged (fig. 3). Occasional short periods of second-degree atrioventricular (AV) block developed in two animals in the diltiazem group but did not occur during the hemodynamic measurement periods.

All of the calcium channel-blocking drugs produced an equal increase in both the CVP and PCWP. While verapamil, nifedipine, and diltiazem all produced equal decreases in SV, verapamil and diltiazem both decreased the dP/dt more than did nifedipine. The decrease in both the CO and in the dP/dt was most profound with verapamil and diltiazem and for these indices there was no significant difference between these two drugs. HR

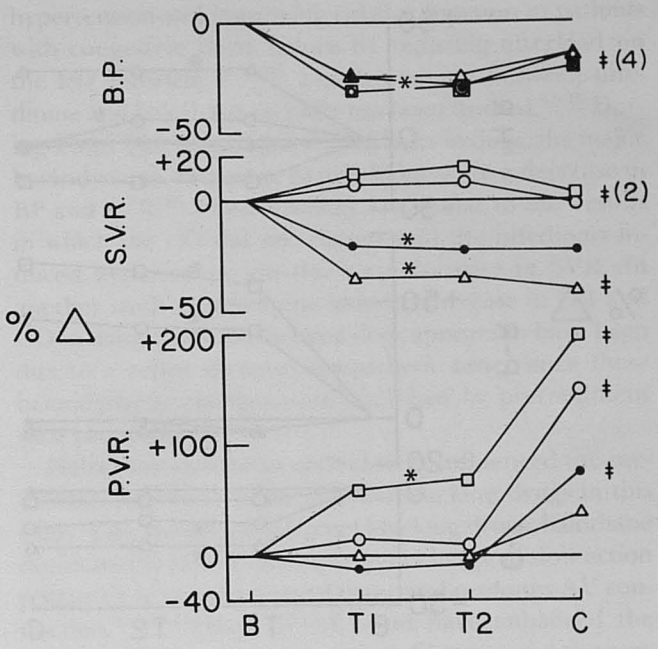

FIG. 1. Drug-induced changes in mean systemic arterial blood pressure (B.P.), systemic vascular resistance (S.V.R.), and pulmonary vascular resistance (P.V.R.) are shown. Values are plotted as per cent change (%Δ) from baseline (B) at 15 min (T_1) and 30 min (T_2) after drug-induced hypotension (25–30%) and after calcium chloride (C) administration for verapamil (○ —— ○), nifedipine (△ —— △), diltiazem (□ —— □), and sodium nitroprusside (● —— ●). *$P < 0.05$ significant change from B to the pooled data of T_1 and T_2. ‡$P < 0.05$ significant change from the pooled data of T_1 and T_2 to after C. ‡ (4) and (2) denotes ‡ applies to 4 and 2 groups, respectively. Symbols and method of statistical comparisons apply to all figures.

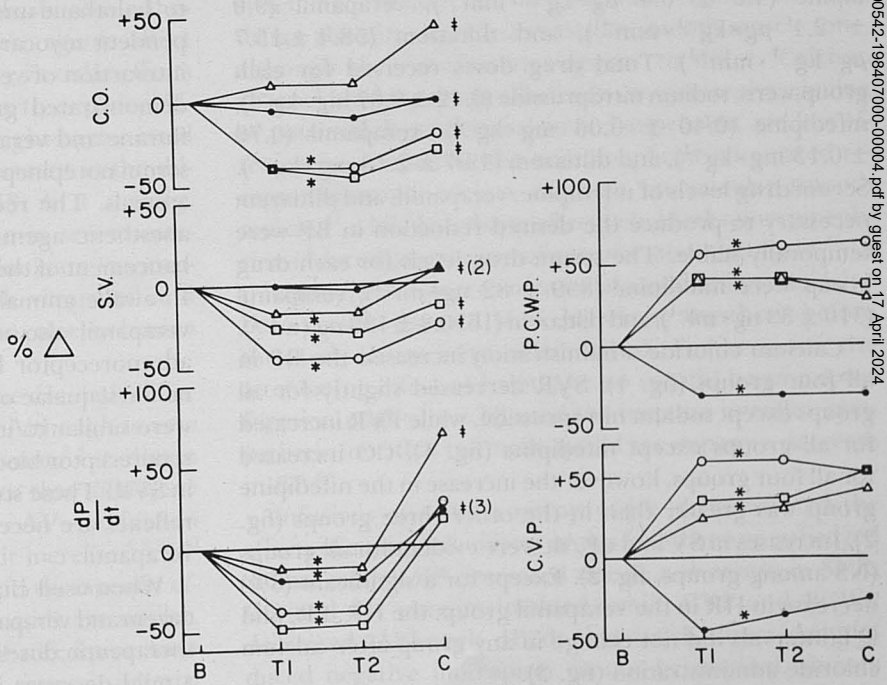

FIG. 2. Drug-induced changes in cardiac output (C.O.), stroke volume (S.V.), left ventricular (dP/dt), pulmonary capillary wedge pressure (P.C.W.P.), and central venous pressure (C.V.P.) are shown. See figure 1 for explanation of symbols.

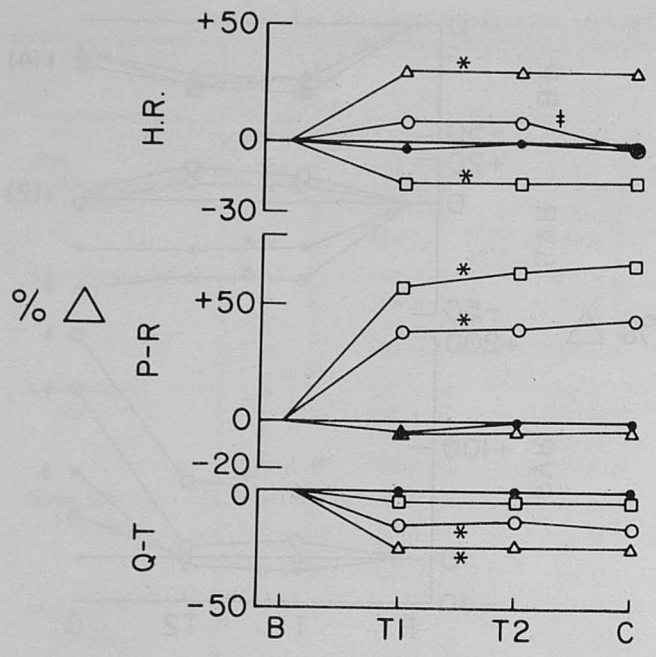

FIG. 3. Drug-induced changes in heart rate (H.R.), P-R interval, and Q-T interval are shown. See figure 1 for explanation of symbols.

was increased only with nifedipine and decreased only with diltiazem. The increase in PR interval was not significantly different between verapamil and diltiazem. PVR increased significantly only with diltiazem (62%, fig. 1).

The drug infusion rates for each drug group were sodium nitroprusside (5.6 ± 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), nifedipine ($4.0 \pm 0.4$ $\mu g \cdot kg^{-1} \cdot min^{-1}$), verapamil ($9.0 \pm 2.1$ $\mu g \cdot kg^{-1} \cdot min^{-1}$), and diltiazem ($58.4 \pm 15.7$ $\mu g \cdot kg^{-1} \cdot min^{-1}$). Total drug doses received for each group were: sodium nitroprusside (0.42 ± 0.07 $mg \cdot kg^{-1}$), nifedipine (0.40 ± 0.06 $mg \cdot kg^{-1}$), verapamil (0.70 ± 0.13 $mg \cdot kg^{-1}$), and diltiazem (4.97 ± 2.18 $mg \cdot kg^{-1}$). Serum drug levels of nifedipine, verapamil, and diltiazem necessary to produce the desired reduction in BP were temporally stable. The serum drug levels for each drug group were nifedipine (859 ± 82 $ng \cdot ml^{-1}$), verapamil (310 ± 33 $ng \cdot ml^{-1}$), and diltiazem (1650.8 ± 139 $ng \cdot ml^{-1}$).

Calcium chloride administration increased the BP in all four groups (fig. 1). SVR decreased slightly for all groups except sodium nitroprusside, while PVR increased for all groups except nifedipine (fig. 1). CO increased for all four groups, however the increase in the nifedipine group was greater than in the other three groups (fig. 2). Increases in SV and dP/dt were evident for all groups (NS among groups, fig. 2). Except for a significant (8%) decrease in HR in the verapamil group, the HR, PR, and QT intervals did not change in any group after calcium chloride administration (fig. 3).

Discussion

These results indicate that in this experimental preparation, constant infusion rates of the calcium channel blocking drugs, verapamil, nifedipine, and diltiazem as well as sodium nitroprusside produce a stable decrease in BP during halothane anesthesia. However, comparisons of drug-induced changes in cardiovascular variables reveal differing mechanisms of achieving this hypotensive effect. Verapamil and diltiazem decreased BP by decreasing CO. Nifedipine and sodium nitroprusside produced hypotension by decreasing SVR.

Although verapamil, nifedipine, and diltiazem possess direct dose-dependent vasodilatory as well as negative chronotropic, dromotropic, and inotropic effects,[3-6] the *in vivo* effects of these drugs are difficult to extrapolate from *in vitro* studies, since drug-induced changes in preload and afterload profoundly affect cardiac performance. Furthermore, a vasodilatory induced decrease in BP is associated with a reflex increase in sympathetic tone.[7-10] Studies in awake animals and humans demonstrate that clinically relevant doses of verapamil prolong AV nodal conduction and reduce SVR, while HR and CO remain unchanged or increase.[7,21] Volatile anesthetic agents, however, appear to augment the negative inotropic effects of verapamil. Verapamil administration to swine is associated with a decrease in CO during halothane anesthesia but not during nitrous oxide analgesia.[22] In a canine right heart bypass preparation, the direct myocardial depressant effects of verapamil were enhanced by isoflurane in a dose-dependent manner.[23] Verapamil administration to halothane-anesthetized dogs also produced dose-dependent myocardial depression.[14] A comparison of the interaction of verapamil with isoflurane *versus* enflurane demonstrated greater myocardial depression with enflurane and verapamil.[24] This was associated with lower serum norepinephrine levels in the enflurane-anesthetized animals. The reduction in sympathetic tone by volatile anesthetic agents may be one mechanism for the enhancement of the negative inotropic effects of verapamil. In awake animals, the myocardial depressant effects of verapamil also were found to be accentuated by beta adrenoreceptor blockade.[25] Furthermore, the hemodynamic sequelae of verapamil administration in our study were similar to its effects in patients after prior beta adrenoreceptor blockade,[26] a decrease in CO and no change in SVR. These studies suggest that adequate sympathetic reflexes are necessary for the maintenance of CO with verapamil.

When used clinically, the hemodynamic effects of diltiazem and verapamil are similar. Awake subjects receiving therapeutic doses of diltiazem usually demonstrate only a mild decrease in HR and BP, while CO increases or

remains unchanged.[27] A review by Mitchell *et al.*[28] of several clinical studies has revealed that diltiazem decreases HR more frequently than verapamil and although both drugs prolong AV nodal conduction, verapamil has a greater effect on increasing AV nodal refractoriness, which might explain the greater incidence of heart block associated clinically with verapamil compared with diltiazem.[28] In awake animals receiving high-dose diltiazem, CO is maintained or increases while BP and SVR decrease.[9,13] In pentobarbital-anesthetized dogs, diltiazem infusions that achieved clinically relevant serum levels produced a prolongation in AV nodal conduction without hemodynamic changes, while much greater serum levels were required to decrease BP and SVR; SV remained unchanged.[12] No previous studies have evaluated the hemodynamic interaction between diltiazem and volatile anesthetic agents. Our study demonstrated that high serum drug levels were necessary to produce a moderate hypotensive effect during halothane anesthesia. However, the intrinsic negative chronotropic, dromotropic, and inotropic properties of diltiazem were evident in our halothane-anesthetized swine model at serum levels that did not depress cardiac function in pentobarbital-anesthetized dogs.[12] Also, profound electrophysiologic effects, intermittent second-degree AV block, occurred in our study and in this previous animal study during high-dose diltiazem.[12] It must be emphasized, however, that serum drug levels in our study were much greater than those achieved from therapeutic doses in humans. Only in the diltiazem group did PVR increase during stable drug infusions. A study comparing the effects nifedipine, verapamil, and diltiazem on PVR in pentobarbital-anesthetized dogs has shown that none of these agents affect normal PVR.[29] The disparate pulmonary vascular effects between this study and ours is difficult to explain. Alterations in Pa_{O_2}, Pa_{CO_2}, and *p*H that might have caused pulmonary vasoconstriction were not present in the diltiazem group (411 ± 92 mmHg, 38 ± 4 mmHg, 7.43 ± 0.04, respectively). An increase in serum catecholamine levels that also can cause pulmonary vasoconstriction has been shown to occur with verapamil and enflurane or isoflurane,[24] however, serum catecholamine levels were not measured in this study.

The hemodynamic effects of nifedipine distinctly differ from those of verapamil and diltiazem. Although *in vitro* nifedipine is a potent myocardial depressant,[3,5] studies in awake animals and humans demonstrate that nifedipine profoundly decreases SVR, while HR, AV conduction velocity, CO, and left ventricular dP/dt increase.[4,8,28,30] In awake subjects, the hemodynamic and therapeutic effects of nifedipine and sodium nitroprusside are similar. The arterial vasodilating properties of nifedipine have been found to be effective in treating systemic arterial hypertension and improving cardiac function in patients with congestive heart failure by reducing afterload on the left ventricle.[10,31–33] The interaction between nifedipine and halothane recently has been studied.[15,16] During 1 and 2 MAC halothane anesthesia in dogs, the major hemodynamic responses to nifedipine were a decrease in BP and SVR.[15] These findings are similar to our results in which the CO did not change and the nifedipine-induced hypotension was due to a decrease in SVR. In another study, a nifedipine-induced increase in HR and CO in halothane-anesthetized dogs appears to have been due to a reflex increase sympathetic tone, since these hemodynamic changes were abolished by pretreatment with propranolol.[16]

Halothane anesthesia undoubtedly influenced the cardiovascular effects of the calcium-blocking drugs in this study. Like the calcium channel-blocking drugs, halothane decreases the rate of spontaneous discharge of slow action potentials in sinoatrial nodal tissue and prolongs AV conduction.[4,34,35] These effects could have enhanced the negative chronotropic property of diltiazem and the negative dromotropic property of verapamil and diltiazem in this study. Myocardial depression due to halothane may have contributed to the negative inotropic properties of the calcium channel-blocking drugs. The depressant effect of halothane on the myocardium partially may be due to the same mechanism of action as the calcium channel-blocking drugs, an inhibition of the slow calcium current across the sarcolemma.[36–39] However, halothane also has been shown to affect intracellular calcium flux at both the sarcoplasmic reticulum and the actinomyosin ATPase system.[40,41] Halothane, like calcium channel-blocking drugs, also directly relaxes vascular smooth muscle tone, although their mechanisms appear to differ. Calcium channel-blocking drugs effectively antagonize the opening of potential-dependent calcium channels but are less effective in attenuating the norepinephrine stimulated receptor-operated calcium channels on vascular smooth muscle,[42] while halothane effectively blocks norepinephrine-induced contraction of vascular smooth muscle.[43] In this study, some degree of arterial vasodilation may have been present due to 1 MAC halothane anesthesia before the study drugs were administered. Furthermore, the attenuating effect of halothane on carotid baroreceptor function might have blunted the increase in reflex sympathetic tone that normally would accompany a decrease in BP.[44]

Infusions of sodium nitroprusside demonstrated the effects of a pure vasodilator in this halothane-anesthetized animal model. BP decreased due to a decrease in SVR. CO and SV were maintained, while CVP and PCWP decreased. Although dP/dt decreased, direct drug-induced negative inotropism cannot be implied, since a

decrease in preload and afterload also decreases ventricular dP/dt.[45] When both preload and afterload change simultaneously, contractility may be described more accurately by dividing dP/dt/CPIP (common peak intraventricular pressure) by end-diastolic volume or pressure, however, this was not done in our study.[45] Our findings agree with previous studies of sodium nitroprusside administration to halothane-anesthetized animals.[46,47] However, in our experimental preparation the reflex increase in HR usually produced by sodium nitroprusside did not occur. This could be due to an attenuation of the baroreceptor-induced reflect sympathetic tone by halothane.[44] Other studies have shown that increasing halothane levels decreases or abolishes the tachycardia that usually accompanies sodium nitroprusside as well as nifedipine administration.[15,16,47,48] Why HR increased during the nifedipine but not the sodium nitroprusside infusion cannot be ascertained from this study.

Calcium chloride has been shown to increase the cardiac index and stroke index in halothane anesthetized patients.[49] It also has been shown to counteract the hemodynamic but not the electrophysiologic depression due to verapamil.[50] In the canine, right heart bypass preparation calcium chloride administration decreased the direct myocardial depression of verapamil during isoflurane anesthesia.[23] In agreement with these findings, our study demonstrated that calcium chloride administration counteracts the myocardial depression of verapamil, nifedipine, and diltiazem during halothane anesthesia but does not affect drug-induced electrophysiologic changes. However, the increase in PVR after calcium chloride administration in all drug groups except the nifedipine groups was unexpected, since previous studies did not reveal this pulmonary vasoconstrictor response from calcium chloride.[51]

Measurement of serum drug concentrations demonstrated that drug levels were stable during the hemodynamic measurement periods and that serum drug levels require to produce equipotent hypotensive effects were dramatically different for verapamil, nifedipine, and diltiazem. Previous pharmacologic studies indicated different potencies for these three drugs. In pentobarbital-anesthetized animals, verapamil produced hemodynamic effects at serum levels greater than 200 $ng \cdot ml^{-1}$,[11] the same range required to reduce BP in our study. In our study, serum verapamil levels were greater than standard therapeutic serum levels (50–150 $ng \cdot ml^{-1}$), however, they were within the range achieved by bolus administration of clinically relevant doses of verapamil (0.075 $mg \cdot kg^{-1}$) to anesthetized humans.[52] In animals, diltiazem infusions producing serum levels of 100–300 $ng \cdot ml^{-1}$ produce solely electrophysiologic effects, while serum levels greater than 1,500 $ng \cdot ml^{-1}$ are required to produce hemodynamic effects.[12] In our study, large serum diltiazem levels also were required to produce the desired hemodynamic effect. However, clinical antianginal doses of diltiazem in patients produce much smaller serum levels, in the range of 100–200 $ng \cdot ml^{-1}$.[4,53] Although nifedipine infusion rates in our study were only slightly greater than in a previous clinical study (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), which produced a decrease in BP and coronary vascular resistance,[54] serum nifedipine levels in our study were considerably greater than serum levels (50–100 $ng \cdot ml^{-1}$) after orally administered clinical doses of nifedipine. Undoubtedly, one of the reasons for the increased serum drug levels was the drug-induced hypotension required by this study, which is a recognized hemodynamic property of the calcium channel-blocking drugs but is not an approved clinical indication.

In summary, this comparative study demonstrates the disparate pharmacologic properties of verapamil, nifedipine, and diltiazem during halothane anesthesia. By standardizing one cardiovascular variable, drug-induced hypotension, the relative potencies of the other hemodynamic effects could be compared for each drug and among the three drugs. Clinical extrapolation from these data must be limited, since these drugs are not approved as continuous infusions for elective hypotension. Also, when used for approved clinical indications, serum drug levels may be considerably smaller and the hemodynamic effect would be expected to differ from this study. However, our results do demonstrate that during halothane anesthesia the administration of verapamil or diltiazem has a more pronounced effect on cardiac conduction and myocardial contractility than does nifedipine, which predominantly reduces SVR with minimal effects on cardiac function.

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