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Alterations of Alpha$_1$ and Alpha$_2$ Adrenoceptor-mediated Pressor Responses by Halothane and Isoflurane Anesthesia

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The mechanism by which halothane and isoflurane interfere with catecholamine-mediated vasoconstriction was investigated, utilizing selective agonists of postjunctional alpha$_1$ and alpha$_2$ adrenoceptors in chronically instrumented dogs. After ganglionic, cholinergic, and beta adrenergic blockade, dose responses to phenylephrine (0.3–1.2 μg/kg, iv), a selective alpha$_1$ adrenoceptor agonist, and azepexole [B-HT 933] (5–20 μg/kg, iv), a selective alpha$_2$ adrenoceptor agonist, were obtained in conscious dogs. Each dog was subsequently anesthetized with either halothane (1.7%) or isoflurane (2%) in oxygen in equihypotensive concentrations. After a 1 h equilibration period, the dose response curves were repeated. Twenty experiments in ten chronically instrumented dogs were completed. Halothane and isoflurane produced significant ($P < 0.05$) attenuation of both the increase in systolic and diastolic arterial pressure after bolus administration of all doses of phenylephrine and azepexole. No specific selectivity of either volatile anesthetic for alpha$_1$ or alpha$_2$ mediated pressor responses was found. Therefore, in chronically instrumented dogs, alpha$_1$- and alpha$_2$-mediated pressor responses were similarly influenced by halothane and isoflurane. The present results suggest that both halothane and isoflurane act as functional antagonists to alpha adrenergic mediated vasoconstriction. (Key words: Anesthetics, volatile: halothane; isoflurane. Sympathetic nervous system, alpha adrenergic agonists: azepexole; phenylephrine. Receptors, adrenergic: alpha$_1$; alpha$_2$.)

VASOCONSTRICTION IN both the systemic and coronary circulation can be produced by endogenous circulating and neuronally released catecholamines which act at postjunctional alpha$_1$ and alpha$_2$ adrenergic receptors located on vascular smooth muscle membranes.[1] In addition to causing an abrupt vasoconstriction when stimulated, alpha adrenergic receptors are involved in the maintenance of vascular tone.[2] Certain vasodilator agents not classified as alpha adrenergic antagonists have been previously shown to interact with alpha$_1$ and/or alpha$_2$ adrenoceptors attenuating pressor responses mediated by selective alpha$_1$ or alpha$_2$ agonists.[3] The mechanism whereby various vasodilators decrease the pressor response to stimulation of either alpha$_1$ or alpha$_2$ receptors by highly selective agonists has not been well elucidated.

The influence of the volatile anesthetics on alpha adrenergic pressor responses has only recently been investigated. Both halothane and isoflurane have been shown to produce a reduction in arterial pressure by decreasing vascular resistance and cardiac output; however, isoflurane has been demonstrated to cause a more pronounced vasodilation than halothane.[4,5] Whether the greater effect of isoflurane on the peripheral vasculature was mediated through a differential attenuation of the response to alpha receptor stimulation is unknown. It has been suggested that halothane may selectively attenuate alpha$_2$ adrenoceptor-mediated vasoconstriction;[6] however, whether a portion of the vasodilator action of isoflurane is due to an interaction at either postjunctional vascular alpha$_1$ or alpha$_2$ adrenoceptors has not been studied.

Previous work demonstrating a depression of the vascular response to selective alpha agonists by halothane was performed in pithed rats and isolated vascular rings.[6] In addition, results from another study in pithed rats[7] in which pressor responses elicited by a selective alpha$_2$ agonist were described to be reduced by calcium channel blocking agents have been demonstrated to be at variance with investigations performed in conscious dogs and primates.[8]

The objective of the present investigation was to delineate the effects of halothane and isoflurane on selected hemodynamic responses following selective stimulation of alpha$_1$ and alpha$_2$ adrenergic receptors by phenylephrine and azepexole, respectively.[9] This work was performed in chronically instrumented dogs to eliminate any potential interaction with basal anesthesia[10] and to afford a direct comparison between the conscious and anesthetized state. Furthermore, all experiments were completed in the presence of cholinergic, beta adrenergic, and ganglionic blockade to eliminate any indirect reflex-induced actions of alpha$_1$ and alpha$_2$ agonists.[11] Thus, the direct effect of alpha agonists with alpha adrenoceptors in the absence and presence of volatile anesthetics was examined.

Methods

ANIMAL INSTRUMENTATION

The dogs used in this study were maintained in accordance with the guidelines of the Animal Care Committee

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of the Medical College of Wisconsin. Conditioned mongrel dogs of either sex, weighing 22–33 kg were anesthetized with sodium thiamylal (10 mg/kg, iv). After tracheal intubation, anesthesia was maintained with enflurane (2.0–2.5%) in 100% oxygen *via* a respirator (Monaghan 300 D/M). Ventilation was adjusted to maintain normal arterial blood gases. A positive end expiratory pressure of 5 cm of water was used to prevent atelectasis. A thoracotomy was performed in the left fifth intercostal space under sterile conditions. Heparin-filled catheters were inserted into the thoracic aorta and right atrial appendage for measurement of arterial pressure and drug administration, respectively. The heart was supported in a pericardial cradle. A precalibrated Doppler ultrasonic flow transducer (20 MHz) was placed on the proximal left anterior descending coronary artery for measurement of phasic and mean coronary blood flow velocity. Pairs of miniature ultrasonic segment length transducers (5 MHz) were implanted in a circumferential plane within the subendocardium (10–15 mm apart and 10 mm deep) in the region of the left ventricular free wall supplied by the left anterior descending artery for measurement of myocardial segment shortening. A miniature solid-state pressure guage (P7 Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricle through an incision in the apex. The rate of rise of left ventricular pressure (dP/dt_{50}) at 50 mmHg, an index of global left ventricular contractility, was obtained by electronic differentiation of the left ventricular pressure waveform. A catheter was positioned in the left atrial appendage. The left ventricular micromanometer was cross-calibrated *in vivo* against pressure measured *via* the arterial and left atrial fluid-filled catheters (Gould P50 pressure transducer, Oxnard, CA). All catheters and leads were secured, tunneled between the scapulae, and exteriorized *via* a small incision. The chest wall was closed in layers and pneumothorax evacuated by a chest tube.

After surgery, each dog was treated with chloramphenicol (1.5 g b.i.d., p.o.) and allowed to recover for a minimum of 7 days. During the postoperative period, the dogs were trained to stand quietly in a sling during monitoring of hemodynamics. Segment length and coronary blood flow velocity signals were driven and monitored *via* ultrasonic amplifiers (Hartley, Houston, TX). End systolic segment length (ESL) was determined at maximum negative left ventricular dP/dt, and end diastolic segment length (EDL) was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method of Theroux *et al.*[12] Percent segment shortening (%SS) was calculated by use of the equation: $\%SS = [(EDL-ESL)/EDL] \times 100$. Relative mean coronary vascular resistance was calculated as the quotient of mean aortic pressure (mmHg) and mean coronary blood flow velocity ($Hz \times 10^2$). All hemodynamic data were recorded continuously on a Beckman polygraph (Sensormedics, Anaheim, CA) and digitized *via* a computer interfaced with an analog-to-digital converter.

Experimental Protocol

Baseline recordings of hemodynamics were completed in the awake, unsedated dog. Hemodynamics were again recorded following ganglionic [hexamethonium (20 mg/kg, iv)], cholinergic [atropine methylnitrate (3 mg/kg, iv)], and beta adrenergic blockade [propranolol (2 mg/kg, iv)]. Systemic and coronary hemodynamic dose-response relationships were obtained to the $alpha_1$ adrenoceptor agonist, phenylephrine (0.3, 0.6, and 1.2 μg/kg, iv), or the $alpha_2$ adrenoceptor agonist, azepexole (5, 10, and 20 μg/kg, iv) in the conscious dogs. Adequacy of pharmacologic blockade of the autonomic nervous system was demonstrated by lack of reflex change in heart rate following abrupt increases in arterial pressure. Previous studies have demonstrated that the doses of hexamethonium, atropine methylnitrate, and propranolol are adequate to block hemodynamic responses to intravenous acetylcholine and isoproterenol.[13] Hemodynamic responses were recorded at the time of peak effect of each agonist on systemic arterial pressure. Hemodynamics were allowed to return to baseline values before subsequent doses of agonists were given. Agonist doses were administered in a Latin square design. An ordered, numerical sequence of the various agonists and doses was utilized to avoid bias of any given specific drug sequence.

To determine the effects of halothane and isoflurane anesthesia on the pressor responses mediated by $alpha_1$ and $alpha_2$ adrenoceptor stimulation, each dog was anesthetized following characterization of dose-response relationships in the conscious state with concomitant ganglionic, cholinergic, and beta adrenergic blockade. Inhalation induction was accomplished with halothane or isoflurane in oxygen (30%) and nitrous oxide (70%) utilizing high flow rates. Following tracheal intubation, nitrous oxide was discontinued, positive pressure ventilation initiated, and anesthesia maintained with equihypotensive concentrations (approximately 2 MAC) of either halothane (1.7%) or isoflurane (2%) (corresponding to settings of a vaporizer previously calibrated with a mass spectrometer) in 100% oxygen (2 l/min) in separate groups. During each experiment, arterial blood samples were obtained at various intervals for measurement of blood gas tensions. Ventilation was adjusted to maintain arterial *p*H and P_{CO_2} within conscious levels. Hemodynamics were again recorded 1 h after anesthesia. The same doses of phenylephrine and azepexole as used in the conscious state were again administered in randomized fashion to the same dog and the hemodynamic responses recorded as above. Anesthesia was discontinued and emergence al-

TABLE 1. Summarized Hemodynamic Data Following Autonomic Nervous System Blockade and Halothane Anesthesia (Group 1)

	Control	ANS Blockade	Halothane
HR (bpm)	85 ± 6	118 ± 5*	100 ± 4*†
SBP (mmHg)	120 ± 6	92 ± 6*	86 ± 7*
DBP (mmHg)	84 ± 5	71 ± 6*	65 ± 7*
MBP (mmHg)	96 ± 5	78 ± 6*	72 ± 7*
LVSP (mmHg)	123 ± 5	95 ± 5*	90 ± 6*
LVEDP (mmHg)	8 ± 1	3 ± 1*	9 ± 2†
dP/dt_{50} (mmHg/s)	2087 ± 97	1625 ± 112*	1101 ± 100*†
MCBFV (Hz × 10^2)	29 ± 5	26 ± 4	23 ± 3
MCVR (ru)	3.99 ± 0.68	3.48 ± 0.50	3.63 ± 0.58
SS (%)	19.2 ± 2.0	16.7 ± 2.5	14.0 ± 2.4*†

Values are mean ± SEM data (N = 10). HR = heart rate; LVSP and LVEDP = left ventricular systolic and end diastolic pressures; SBP, DBP, and MBP = systolic, diastolic, and mean blood pressures; MCBFV = mean coronary blood flow velocity; MCVR = mean coronary vascular resistance; SS = segment shortening.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from autonomic nervous system (ANS) blockade.

lowed to occur. Each dog was housed for at least 3 days prior to subsequent experimentation with the alternate volatile anesthetic. A total of 20 experiments in two separate groups (group 1: halothane [N = 10]; group 2: isoflurane [N = 10]) were completed using ten chronically instrumented dogs.

DRUGS

Fresh solutions of all drugs were prepared on the day of each experiment. Hexamethonium bromide, atropine methylnitrate, propranolol hydrochloride, azepexole hydrochloride (Boehringer Ingelheim, Ridgefield, CT), and phenylephrine hydrochloride were dissolved in 0.9% sodium chloride.

STATISTICAL ANALYSIS

Data are presented as mean ± SEM. Hemodynamic responses were compared to control by use of analysis of variance with repeated measures followed by Dunnett's modification of the *t* test or Least Significant Difference (LSD) test. Changes between the conscious state, pharmacological blockade of the autonomic nervous system, and anesthesia, or following administration of $alpha_1$ and $alpha_2$ adrenoceptor agonists, were considered significant when the probability (*P*) value was less than 0.05.

TABLE 2. Summarized Hemodynamic Data Following Autonomic Nervous System Blockade and Isoflurane Anesthesia (Group 2)

	Control	ANS Blockade	Isoflurane
HR (bpm)	90 ± 8	118 ± 8*	103 ± 5*†
SBP (mmHg)	118 ± 5	90 ± 6*	80 ± 2*†
DBP (mmHg)	83 ± 4	67 ± 5*	55 ± 2*†
MBP (mmHg)	95 ± 4	75 ± 5*	63 ± 2*†
LVSP (mmHg)	120 ± 4	94 ± 6*	80 ± 2*†
LVEDP (mmHg)	7 ± 1	4 ± 1*	6 ± 1†
dP/dt_{50} (mmHg/s)	1953 ± 64	1654 ± 72*	1250 ± 99*†
MCBFV (Hz × 10^2)	28 ± 3	28 ± 5	26 ± 4
MCVR (ru)	3.86 ± 0.55	3.38 ± 0.65	2.91 ± 0.42
SS(%)	19.9 ± 2.3	19.4 ± 1.7	15.4 ± 1.9*†

Values are mean ± SEM data (N = 10). See table 1 for abbreviations.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from autonomic nervous system (ANS) blockade.

Results

HEMODYNAMIC EFFECTS OF AUTONOMIC NERVOUS SYSTEM BLOCKADE

Hemodynamic alterations during autonomic nervous system blockade produced by administration of hexamethonium, atropine methylnitrate, and propranolol in groups 1 and 2 are shown in tables 1 and 2, respectively. Ganglionic, cholinergic, and beta adrenergic blockade produced significant ($P < 0.05$) reductions in left ventricular systolic and end diastolic pressures, mean arterial pressure, and left ventricular dP/dt_{50} and increases in heart rate in both groups. Mean coronary blood flow velocity and coronary vascular resistance were unchanged.

HEMODYNAMIC EFFECTS OF VOLATILE ANESTHETICS

Hemodynamic effects of halothane anesthesia following autonomic nervous system blockade (group 1) are summarized in table 1. Halothane anesthesia produced a significant reduction in heart rate, left ventricular dP/dt_{50}, and %SS. Left ventricular systolic pressure and mean arterial pressure were only slightly reduced by halothane. In contrast, left ventricular end diastolic pressure was significantly increased. Mean coronary blood flow velocity and coronary vascular resistance were unchanged.

The hemodynamic changes during isoflurane anesthesia following autonomic nervous system blockade (group 2) are summarized in table 2. Similar to halothane, isoflurane produced reductions in heart rate, left ventricular dP/dt_{50}, %SS, and an increase in left ventricular end diastolic pressure. Mean coronary blood flow velocity and coronary vascular resistance were also unchanged following isoflurane. In contrast to halothane, isoflurane produced a significant decrease in both left ventricular systolic and arterial pressures. There was no significant difference in arterial pressure between the two groups after anesthesia.

ALPHA RECEPTOR STIMULATION IN CONSCIOUS DOGS

Summarized changes in systemic and coronary hemodynamics following intravenous bolus administration of phenylephrine (0.3, 0.6, and 1.2 μg/kg), and azepexole

TABLE 3. Changes in Systemic and Coronary Hemodynamics by Azepexole before and after Halothane Anesthesia

	Before Halothane Azepexole Dose (μg/kg)			After Halothane Azepexole Dose (μg/kg)		
	5	10	20	5	10	20
ΔHR (bpm)	−1 ± 1	−1 ± 1	−1 ± 1	1 ± 1	−1 ± 1	1 ± 1
ΔMBP (mmHg)	20 ± 2*	27 ± 1*	35 ± 3*	11 ± 1†*	17 ± 2†*	22 ± 2†*
ΔLVSP (mmHg)	17 ± 1*	24 ± 3*	29 ± 3*	9 ± 2†*	13 ± 2†*	17 ± 2†*
ΔLVEDP (mmHg)	2 ± 1	2 ± 1	3 ± 1	1 ± 1	2 ± 1	3 ± 1
$\Delta dP/dt_{50}$ (mmHg/s)	−56 ± 17	−80 ± 30*	−75 ± 15*	−33 ± 13	−19 ± 15	−35 ± 15
ΔMCBFV (Hz × 10^2)	1 ± 1	3 ± 1*	1 ± 2	1 ± 1	0 ± 1	0 ± 1
ΔMCVR (ru)	0.58 ± 0.09	0.77 ± 0.21*	1.39 ± 0.41*	0.60 ± 0.34*	0.95 ± 0.25*	1.21 ± 0.38*
ΔSS (%)	−0.2 ± 0.8	−2.5 ± 1*	−2.1 ± 1.4*	−0.2 ± 0.9	−1.8 ± 0.5	−1.7 ± 0.8

Values are mean ± SEM changes (Δ) from baseline (N = 10). See table 1 for abbreviations.
* Significantly ($P < 0.05$) different from baseline.
† Significantly ($P < 0.05$) different: Before *vs.* after halothane at comparable doses.

(5, 10, and 20 μg/kg) in ganglionic, cholinergic, and beta adrenergic blocked conscious dogs are shown in tables 3–6. Dose-related increases in arterial pressure were mediated by both $alpha_1$ and $alpha_2$ agonists. Systolic and diastolic aortic pressure and left ventricular systolic pressure were increased by all doses of both agonists. Left ventricular end diastolic pressure remained unchanged. Heart rate remained unchanged over the course of all experiments during abrupt pressor responses demonstrating continued and effective autonomic nervous system blockade. Both agonists caused an increase in coronary vascular resistance. There was a reduction in %SS concomitant with the abrupt increases in left ventricular afterload produced by both phenylephrine and azepexole.

EFFECTS OF HALOTHANE AND ISOFLURANE ON ALPHA RECEPTOR MEDIATED RESPONSES

Systemic and coronary hemodynamic changes produced by phenylephrine and azepexole before and after 1 h of halothane anesthesia (group 1) are summarized in tables 3 and 4, respectively. Halothane attenuated the agonist-induced increases in systolic and diastolic arterial pressure (figs. 1 and 2) at each dose ($P < 0.05$). Changes in mean coronary blood flow velocity and vascular resistance produced by $alpha_1$ and $alpha_2$ agonists were unchanged by halothane.

Summarized systemic and coronary hemodynamic alterations produced by phenylephrine and azepexole before and after 1 h of isoflurane anesthesia (group 2) are shown in tables 5 and 6, respectively. Similar to halothane, isoflurane caused a significant attenuation of agonist-induced increases in systolic and diastolic arterial pressure (figs. 3 and 4). The responses of mean coronary blood flow velocity and vascular resistance were unchanged by isoflurane.

Discussion

Results of this investigation indicate that the $alpha_1$ agonist, phenylephrine, and the $alpha_2$ agonist, azepexole, produce qualitatively similar changes in the systemic and coronary hemodynamics measured. The results confirm the presence of two subpopulations of alpha adrenoceptors mediating pressor responses in the peripheral arterial bed of the dog. Both halothane and isoflurane nonselectively attenuated pressor responses to phenylephrine and azepexole in chronically instrumented dogs. Although both

TABLE 4. Changes in Systemic and Coronary Hemodynamics by Phenylephrine before and after Halothane Anesthesia

	Before Halothane Phenylephrine Dose (μg/kg)			After Halothane Phenylephrine Dose (μg/kg)		
	0.3	0.6	1.2	0.3	0.6	1.2
ΔHR (bpm)	−1 ± 1	1 ± 1	2 ± 1	−1 ± 1	0 ± 1	1 ± 1
ΔMBP (mmHg)	23 ± 2*	35 ± 3*	49 ± 5*	13 ± 1†*	20 ± 2†*	27 ± 2†*
ΔLVSP (mmHg)	21 ± 2*	29 ± 3*	42 ± 5*	11 ± 1†*	19 ± 2†*	27 ± 3†*
ΔLVEDP (mmHg)	3 ± 1	3 ± 1	6 ± 1	2 ± 1	5 ± 1	6 ± 1
$\Delta dP/dt_{50}$ (mmHg/s)	−23 ± 17	−21 ± 23	−63 ± 41*	−6 ± 14	−27 ± 27	−26 ± 27
ΔMCBFV (Hz × 10^2)	2 ± 1	3 ± 1	6 ± 3*	1 ± 1	1 ± 1	0 ± 1
ΔMCVR (ru)	0.66 ± .20*	1.09 ± .29*	1.26 ± 0.32*	0.41 ± 0.12	0.80 ± 0.20*	1.21 ± 0.23*
ΔSS (%)	−1.5 ± 0.9*	−2.6 ± 1.1*	−2.8 ± 1.3*	−1.2 ± 0.5*	−1.6 ± 0.7*	−2.3 ± 1.1*

Values are mean ± SEM changes (Δ) from baseline (N = 10). See table 1 for abbreviations.
* Significantly ($P < 0.05$) different from baseline.
† Significantly ($P < 0.05$) different: Before *vs.* after halothane at comparable doses.

TABLE 5. Changes in Systemic and Coronary Hemodynamics by Azepexole Following Autonomic Nervous System Blockade and Isoflurane Anesthesia

	Before Isoflurane Azepexole Dose (μg/kg)			After Isoflurane Azepexole Dose (μg/kg)		
	5	10	20	5	10	20
ΔHR (bpm)	1 ± 1	−1 ± 1	−1 ± 1	−1 ± 1	−2 ± 1	−1 ± 1
ΔMBP (mmHg)	24 ± 3*	26 ± 2*	37 ± 4*	15 ± 3†*	18† ± 1†*	27 ± 2†*
ΔLVSP (mmHg)	20 ± 3*	25 ± 2*	34 ± 5*	13 ± 3*	14 ± 2†*	21 ± 2†*
ΔLVEDP (mmHg)	2 ± 1	2 ± 1	3 ± 1	2 ± 1	2 ± 1	3 ± 1
$\Delta dP/dt_{50}$ (mmHg/s)	−33 ± 20	−59 ± 25*	−99 ± 20*	−51 ± 23	−31 ± 21	−55 ± 25
ΔMCBFV (Hz × 10^2)	1.4 ± 0.6	2.8 ± 0.6	2.9 ± 1.1	1.9 ± 1.0	1.5 ± 0.8	1.1 ± 1.5
ΔMCVR (ru)	0.45 ± 0.23	0.53 ± 0.18*	0.91 ± 0.12*	0.36 ± 0.13	0.50 ± 0.11*	0.76 ± 0.11*
ΔSS (%)	−3.7 ± 2.9*	−3.4 ± 1.7*	−3.9 ± 0.9*	−1.6 ± 0.5	−2.9 ± 1.7*	−2.9 ± 1.3*

Values are mean ± SEM changes (Δ) from base line (N = 10). See table 1 for abbreviations.

* Significantly ($P < 0.05$) different from base line.

† Significantly ($P < 0.05$) different: Before *vs.* after isoflurane at comparable doses.

anesthetics decreased the pressor response to phenylephrine and azepexole in the peripheral vasculature, no significant changes were observed in the coronary circulation. Halothane and isoflurane, as well as autonomic nervous system blockade, had minimal effects on coronary hemodynamics in the present study. The lack of effect of autonomic blockade may be explained in that metabolic autoregulation and alpha-adrenergic constrictor tone remained intact.[14] Reasons for the lack of action of halothane and isoflurane are unknown and surprising in that coronary blood flow autoregulation has been described to be mildly disrupted by these agents in chronically instrumented dogs.[15]

Chronically instrumented dogs were used in this study to eliminate the influence of surgical trauma and basal anesthesia on pharmacologically mediated pressor responses. Autonomic nervous system blockade was produced by administration of hexamethonium, atropine methylnitrate, and propranolol to eliminate reflex changes mediated by cholinergic or beta-adrenergic nervous system stimulation. In addition, the effects of the volatile anesthetics on the beta adrenergic or parasympathatic nervous system were eliminated. Anesthetic concentrations were not measured in gas or blood phases, and this represents a possible limitation of the study, although the anesthetics were delivered from a vaporizer calibrated with a mass spectrometer, and the animals were allowed to stabilize for 1 h. Blockade of resting ganglionic, beta adrenergic, and parasympathetic tone resulted in a significant increase in heart rate and decrease in aortic blood pressure and dP/dt_{50} without change in coronary hemodynamics.

Halothane and isoflurane produce vasodilation by direct relaxation of vascular smooth muscle *in vitro*.[16] Whether a portion of this response is mediated *in vivo* through inhibition of sympathetic vasoconstriction at the level of the postjunctional alpha receptor or by mechanisms involved in alpha-adrenergic vasoconstriction which lie distal to the receptor is unknown. In this investigation, halothane and isoflurane reduced the pressor response to selective $alpha_1$ and $alpha_2$ agonists. The selectivity of phenylephrine and azepexole for $alpha_1$ and $alpha_2$ vascular receptors, respectively, has been well established.[9] Wynsen *et al.*[3] have shown that in conscious dogs, a re-

TABLE 6. Changes in Systemic and Coronary Hemodynamics by Phenylephrine before and after and Isoflurane Anesthesia

	Before Isoflurane Phenylephrine Dose (μg/kg)			After Isoflurane Phenylephrine Dose (μg/kg)		
	0.3	0.6	1.2	0.3	0.6	1.2
ΔHR (bpm)	−1 ± 1	1 ± 1	2 ± 1	−1 ± 1	−1 ± 1	1 ± 1
ΔMBP (mmHg)	24 ± 5*	40 ± 4*	55 ± 6	16 ± 2†*	27 ± 3†*	38 ± 3†*
ΔLVSP (mmHg)	20 ± 4*	36 ± 3*	48 ± 8*	14 ± 2†*	23 ± 2†*	35 ± 4†*
ΔLVEDP (mmHg)	4 ± 2	5 ± 2	7 ± 2*	2 ± 1	3 ± 1	5 ± 1
$\Delta dP/dt_{50}$ (mmHg/s)	−35 ± 45	−61 ± 33	−17 ± 67*	−21 ± 25	−33 ± 29	−8 ± 39
ΔMCBFV (Hz × 10^2)	3.7 ± 1.8	3.4 ± 1	3.9 ± 1.4	1.4 ± 0.8	3.4 ± 1.5	2.2 ± 1.7
ΔMCVR (ru)	0.13 ± 0.28	0.94 ± 0.13*	1.19 ± 0.20*	0.39 ± 0.09	0.53 ± 0.13	1.19 ± 0.25*
ΔSS (%)	−3.5 ± 1.3*	−3.9 ± 1.0*	−5.3 ± 1.0*	−3.1 ± 0.7*	−3.5 ± 1.5*	−3.2 ± 1.3*

Values are mean ± SEM changes (Δ) from baseline (N = 10). See table 1 for abbreviations.

* Significantly ($P < 0.05$) different from baseline.

† Significantly ($P < 0.05$) different: Before *vs.* after isoflurane at comparable doses.

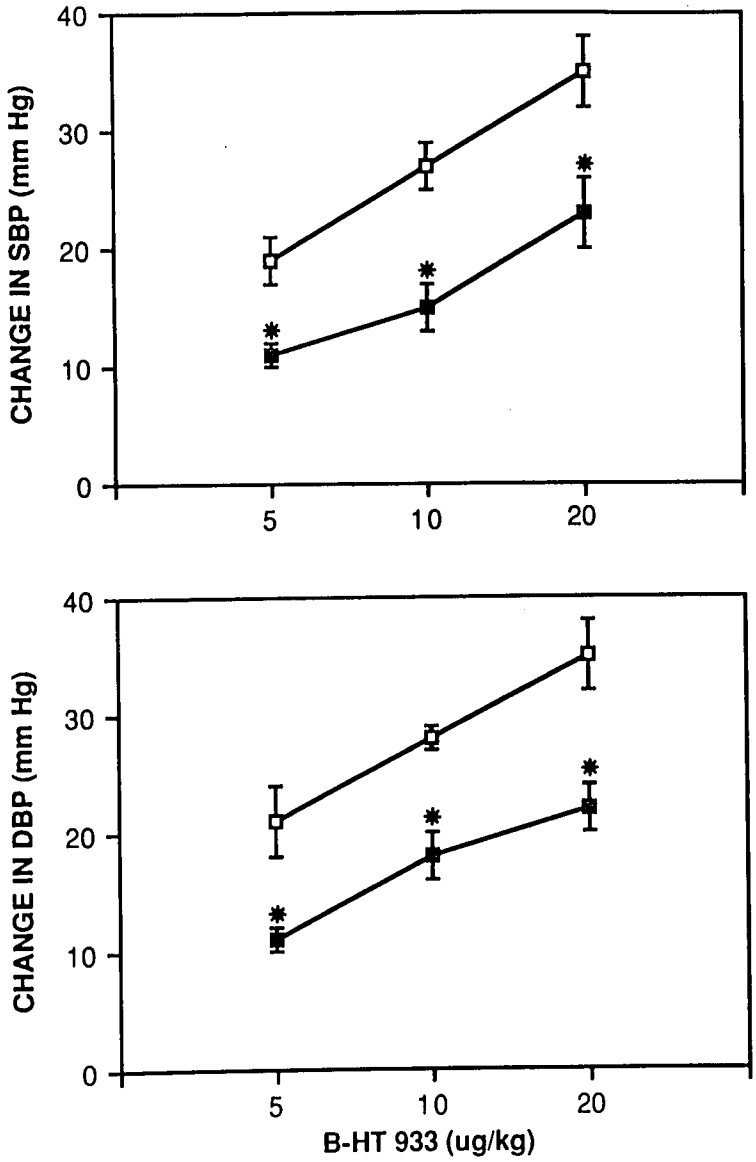

FIG. 1. Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) produced by azepexole (5, 10, and 20 μg/kg) (mean ± SEM; N = 10) before (open squares) and after (closed squares) 1 h of halothane anesthesia. *Significantly ($P < 0.05$) different: before *vs.* after halothane.

duction of arterial pressure does not cause a preferential attenuation of the alpha$_2$ pressor responses.[3] Vasodilator agents with different mechanisms of action may differentially alter the pressor response to alpha$_1$ and alpha$_2$ agonists.

The mechanism by which halothane and isoflurane reduced the pressor response mediated by alpha adrenergic receptors is unclear. Larach *et al.*[6] recently demonstrated that halothane selectively attenuated alpha$_2$ adrenoceptor-mediated vasoconstriction in pithed rats and in canine saphenous vein rings. However, other work *in vitro* utilizing isolated vascular strips has suggested that both halothane and isoflurane may also interfere with alpha$_1$-mediated vasoconstriction.[16]

Larach *et al.*[6] and others[17] have suggested that alpha$_1$-mediated vasoconstriction (*e.g.*, phenylephrine-induced) results from the entry of extracellular calcium and/or the release of stored intracellular calcium. In contrast, alpha$_2$-mediated vasoconstriction, *e.g.*, by the selective agonist, azepexole has been shown to be primarily dependent on an influx of extracellular calcium[18] and is sensitive to calcium-entry blockade with calcium antagonists.[19] Larach *et al.*[6] have suggested that halothane may interfere with alpha$_2$ excitation-contraction coupling by limiting the influx of extracellular calcium *via* calcium channels in vascular smooth muscle cells. Such an action may explain the results obtained in the canine saphenous vein preparation and in the pithed rat model.[6] The observation of Larach *et al.*[6] that halothane did not antagonize alpha$_1$ constriction of the canine saphenous vein *in vitro* may also be partially explained by the presence of a large alpha$_1$ adrenoceptor reserve. Receptor reserve may conceal an un-

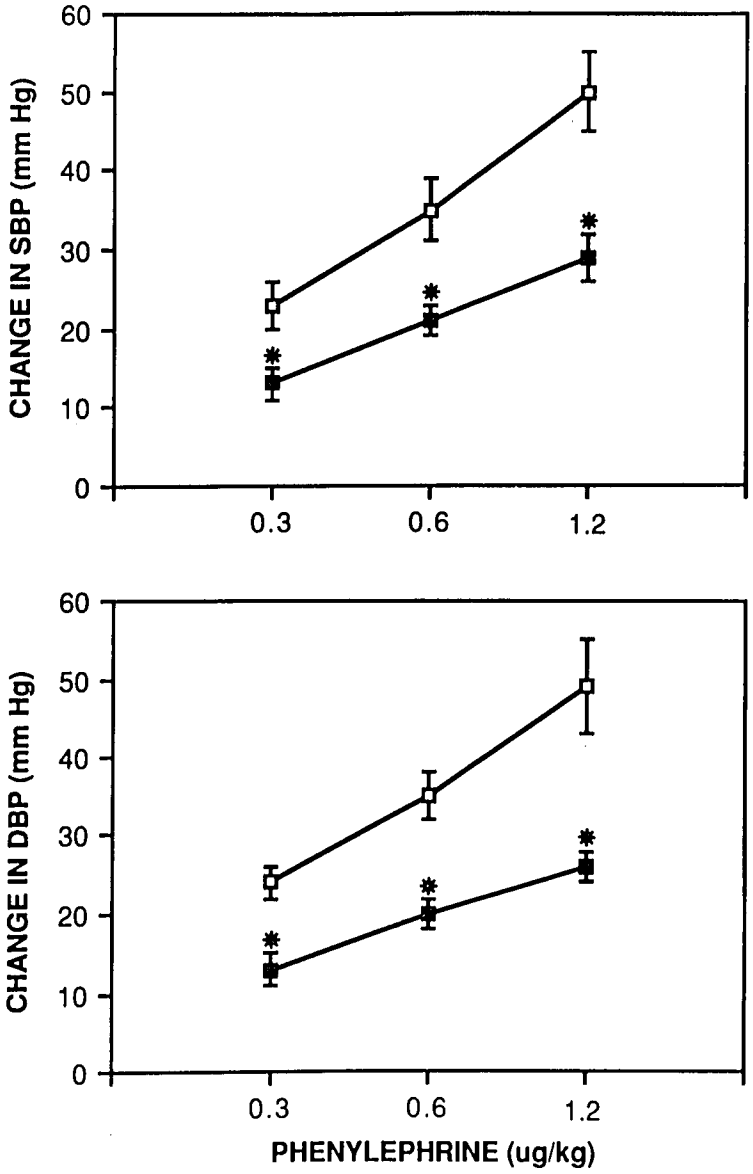

FIG. 2. Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) produced by phenylephrine (0.3, 0.6, and 1.2 μg/kg) (mean ± SEM; N = 10) before (open squares) and after (closed squares) 1 h of halothane anesthesia. *Significantly ($P < 0.05$) different: before *vs.* after halothane.

derlying antagonism to alpha$_1$ adrenoceptor-mediated responses in canine saphenous vein[20] and in pithed rats.[21] Similarly, Lew and Angus[22] have shown that hypotension induced by hemorrhage, nitroprusside, or nifedipine preferentially inhibited the pressor effect of a selective alpha$_2$ agonist in the pithed rat. Recent evidence has also suggested that the relative susceptibility of alpha$_2$ mediated vasoconstriction to calcium antagonists may simply be due to a reserve population of alpha$_1$ adrenoceptors.[23] Spare alpha$_1$ receptors may also serve to conceal an underlying functional antagonism to calcium entry blockade. Thus, the selective inhibition of alpha$_2$-mediated vasoconstriction may not be due to interference with the calcium excitation-contraction coupling mechanism, but instead to a large alpha$_1$ adrenoceptor reserve.

Not all experimental evidence has supported the hypothesis of a receptor reserve[24,25] to account for the inhibition of alpha$_1$ receptor-induced vasoconstriction by calcium antagonists. It has been suggested that α_1-adrenoceptor agonists can be subdivided into those eliciting calcium entry dependent and independent vasoconstriction *in vivo,* and that this would explain the variable susceptibility of α_1-adrenoceptor-mediated pressor responses to inhibition calcium channel blocking agents.[26] In the conscious dog, the postsynaptic vascular alpha$_1$ and alpha$_2$ receptor pressor response is associated with an influx of extracellular calcium.[27] While alpha$_1$- and alpha$_2$-mediated pressor responses are highly susceptible to calcium entry blockade in both anesthetized[28] and conscious dogs,[8] and humans,[29] these studies are in sharp contrast to other investigations in pithed rats, cats, and rabbits.[30] Thus, it is possible that these results are species dependent, and

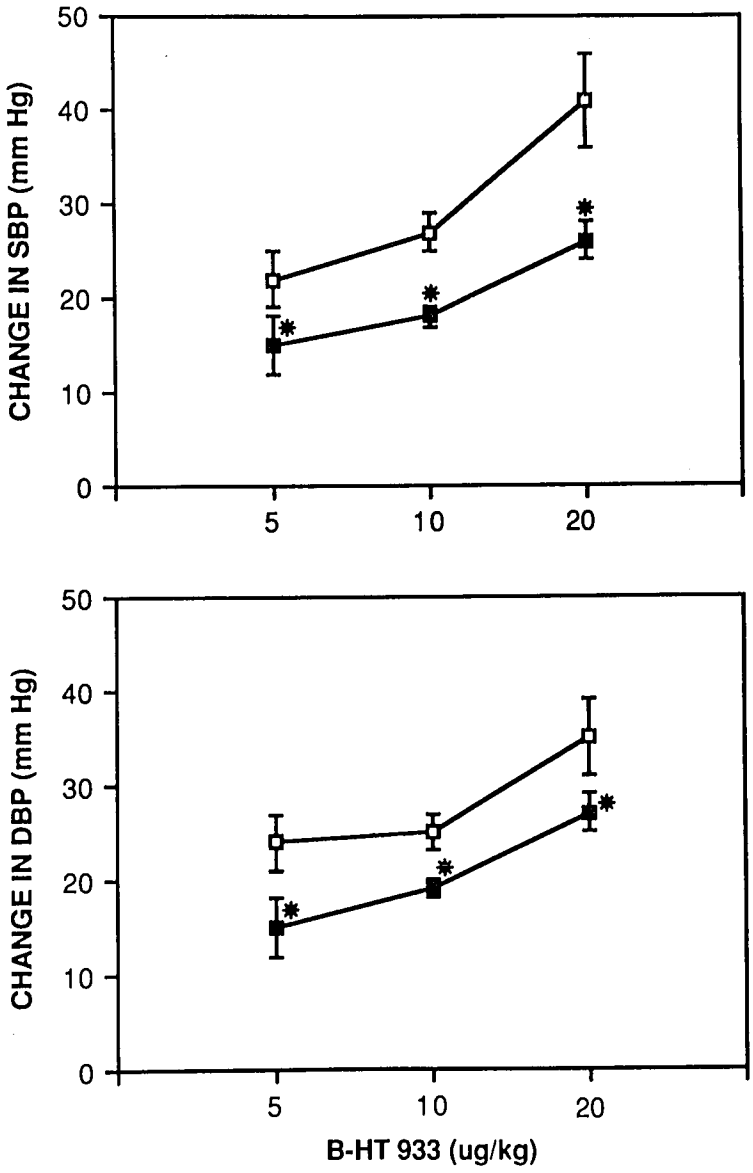

FIG. 3. Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) produced by azepexole (5, 10, and 20 μg/kg) (mean ± SEM; N = 10) before (open squares) and after (closed squares) 1 h of isoflurane anesthesia. *Significantly ($P < 0.05$) different: before *vs.* after isoflurane.

results obtained in the conscious dog may be closer to the human than in the pithed rat.

In the present investigation, the dose response curves for phenylephrine and azepexole were shifted to the right by both halothane and isoflurane. Such a shift is consistent with the anesthetics acting as functional antagonists to phenylephrine and azepexole. These results are similar to those obtained by Woodman *et al.*[8] and Wynsen *et al.*[3] which demonstrated that nifedipine attenuated the pressor responses to both $alpha_1$ and $alpha_2$ adrenoceptor agonists in the conscious dog without selectivity for either receptor subtype. Although halothane and isoflurane have important effects on calcium metabolism in cardiac muscle,[31] and have a direct relaxing action on vascular smooth muscle,[16] the volatile anesthetics probably do not act as classic calcium channel-blocking agents.[32] While the mechanism of calcium utilization in vasoconstriction induced by alpha adrenergic activation is unresolved,[17] it is possible that halothane and isoflurane interfere with changes in calcium in vascular smooth muscle following alpha adrenoceptor stimulation, but further experiments are required to determine the precise mechanisms involved.

Although this study has demonstrated that $alpha_1$ and $alpha_2$ pressor responses are attenuated by halothane and isoflurane in the chronically instrumented dog, it is unclear if this inhibitory action is confined to the alpha receptor or represents a nonspecific action of these anesthetics. Halothane has been shown to inhibit norepinephrine release from sympathetic nerve endings[33] and to reduce the oxidative deamination of norepinephrine in canine saphenous vein.[34] This would not explain the pres-

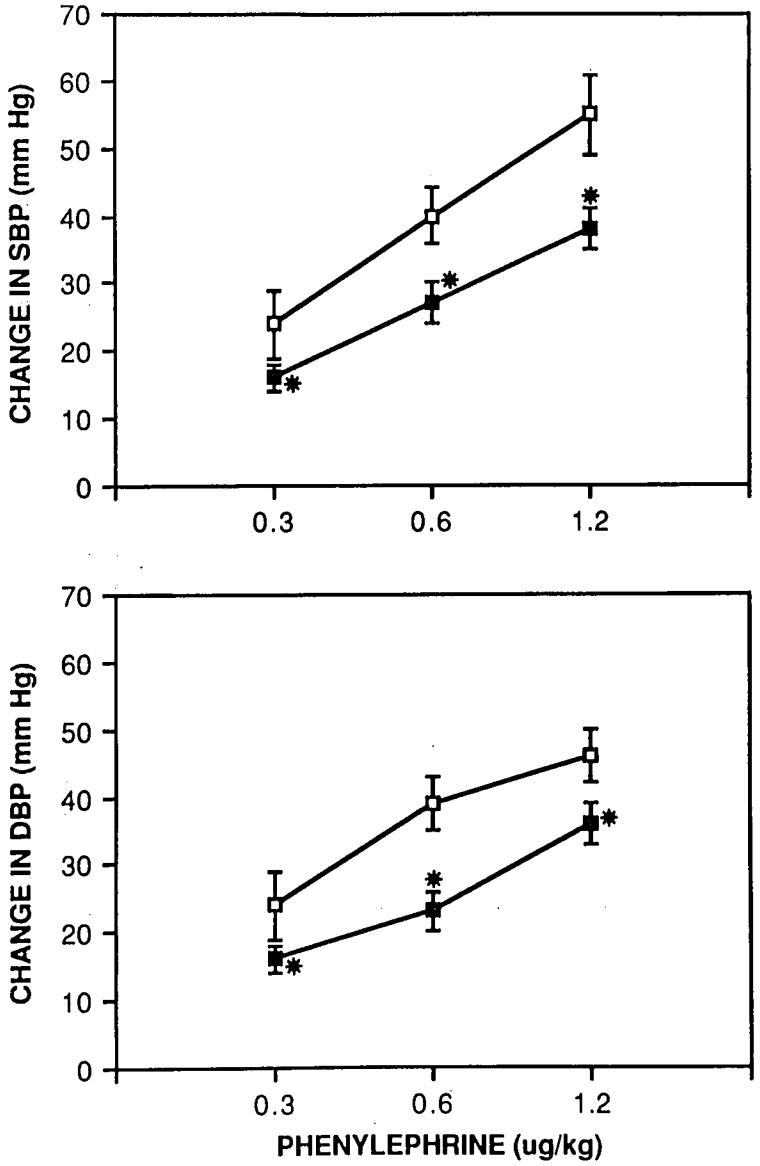

FIG. 4. Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) produced by phenylephrine (3, 6, and 1.2 μg/kg) (mean ± SEM; N = 10) before (open squares) and after (closed squares) 1 h of isoflurane anesthesia. *Significantly ($P < 0.05$) different: before *vs.* after isoflurane.

ent results since phenylephrine and azepexole are specific agonists which act directly on the alpha adrenergic receptor. Blaise *et al.*[35] have previously demonstrated that isoflurane attenuated vasoconstriction induced by serotonin, phenylephrine, and prostaglandin F2α in isolated canine arteries. These investigators reported that the only direct effect of isoflurane on vascular smooth muscle was a moderate alpha adrenergic inhibitory action since isoflurane depressed contractions evoked by phenylephrine in rings of coronary arteries devoid of endothelium. Furthermore, it was also demonstrated[35] that isoflurane had no effect on the tension generated by isolated coronary arteries contracted with potassium. This may suggest that the effect of isoflurane on $alpha_1$ and $alpha_2$ pressor responses in the present investigation is specific. Muldoon *et al.*[36] have shown that contractions induced by norepinephrine in canine carotid and rabbit aortic arch preparations were significantly diminished by halothane, although halothane did cause an increase in the tension induced by norepinephrine in isolated canine femoral arteries. Vatner and Smith[37] also observed variable responses of halothane in different vascular beds in chronically instrumented dogs. Regional variation[38] in alpha adrenergic receptor subtype in the dog may explain such results. In general, the present study demonstrates that $alpha_1$ and $alpha_2$ pressor responses are attenuated by halothane and isoflurane in the chronically instrumented dog.

Thus, the mechanism of inhibition of alpha$_1$ and alpha$_2$ adrenoceptors by halothane and isoflurane remains unclear; however, the present investigation demonstrates that both volatile anesthetics interfere with the vasoconstriction produced by alpha$_1$ and alpha$_2$ adrenoceptor stimulation in a nonselective manner in the canine model.

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