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Oral Dexmedetomidine Preserves Baroreceptor Function and Decreases Anesthetic Requirements of Halothane-anesthetized Dogs

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Background: The α_2 -adrenergic agonist, dexmedetomidine, alters hemodynamics by diminishing sympathetic and/or augmenting parasympathetic neurogenic tone to the heart and peripheral vasculature. However, the specific actions of dexmedetomidine on baroreceptor function are unknown. The purpose of the current investigation was to determine baroreceptor function during an anesthetic state produced by halothane and a similar anesthetic state produced by halothane after dexmedetomidine pretreatment.

Methods: Dogs were instrumented for measurement of arterial and left ventricular pressures, coronary blood flow velocity, segment shortening and cardiac output. Five experimental conditions were studied in the same dogs ($n = 8$). Measurements of baroreceptor sensitivity (*via* abrupt decreases and increases in arterial pressure resulting in changes in the cardiac cycle) and hemodynamics were made in the conscious state in dogs in conditions 1 and 2 before and after 25 and 50 $\mu\text{g} \cdot \text{kg}^{-1}$ of oral dexmedetomidine, respectively. Dogs in conditions 3 and 4 received the same doses of dexmedetomidine and were then anesthetized with halothane. Baroreceptor sensitivity was determined after 60 min of halothane anesthesia. For comparison, dogs in condition 5 had baroreceptor sensitivity measured after 60 min of halothane anesthesia in the absence of dexmedetomidine.

Results: Dexmedetomidine decreased heart rate, rate-pressure product, rate of increase of left ventricular pressure at 50 mmHg, cardiac output and percent segment shortening. Diastolic coronary vascular resistance and systemic vascular resistance were increased with both oral doses. In addition, diastolic coronary blood flow velocity and stroke volume were significantly reduced by the high dose of dexmedetomidine. Anesthesia with halothane increased heart rate and decreased mean arterial pressure, left ventricular systolic pressure, rate of increase of left ventricular pressure at 50 mmHg, stroke volume and segment shortening. Administration of dexmedetomidine before halothane anesthesia in dogs pretreated with dexmedetomidine resulted in small increases in heart rate and decreases mean arterial pressure and left ventricular systolic pressure. Both doses of dexmedetomidine demonstrated anesthetic-sparing effects. The end-tidal concentration of halothane to maintain dogs unconscious and unresponsive was reduced by 30% and 40% ($1.03 \pm 0.08\%$ to $0.67 \pm 0.09\%$ and to $0.58 \pm 0.06\%$ end-tidal, respectively) at 25 and 50 $\mu\text{g} \cdot \text{kg}^{-1}$, respectively. Baroreceptor sensitivity was profoundly depressed by halothane alone. Dexmedetomidine did not significantly change the slope of the baroreflex response when compared with conscious control measurements. After pretreatment with dexmedetomidine, the reduction in halothane concentration required for a comparable level of anesthesia resulted in significant preservation of baroreceptor sensitivity.

Conclusions: The results indicate that dexmedetomidine alone does not alter baroreflex sensitivity. In addition, possibly through an anesthetic-sparing action, dexmedetomidine preserves baroreflex responses during halothane anesthesia. Such a preservation of the baroreceptor reflex by dexmedetomidine might provide an important mechanism for maintenance of cardiovascular stability by retaining buffer reflexes during general anesthesia. (Key words: Anesthetics, volatile: halothane. Premedication: dexmedetomidine. Sympathetic nervous system: baroreflex; dexmedetomidine. Sympathetic nervous system, receptors: α_2 agonists.)

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A variety of homeostatic control systems are intimately involved in the reflex regulation of the cardiovascular system.¹⁻⁴ Short-term regulatory mechanisms involve multiple neuronal reflex arcs, including baroreceptor responses, whereas longer-term adjustments usually are mediated by the renal and endocrine systems. General anesthetics may adversely affect cardiovascular ho-

meostasis by altering the function of these controlling systems as well as by direct actions on the heart and peripheral vasculature.¹⁻⁴

The autonomic nervous system regulates circulatory reflexes *via* various pressure sensor elements located in the major blood vessels. Low pressure (cardiopulmonary baroreceptors) are primarily located at the junction of the vena cavae and right atrium, within the right atrium and in the pulmonary blood vessels. These receptors respond to alterations in central blood volume and predominately initiate adjustments of sympathetic outflow. High pressure or arterial baroreceptor reflex responses are predominantly mediated by pressure sensors located in the aortic arch and carotid sinus. These reflexes modulate both heart rate through efferent parasympathetic and sympathetic activities and systemic arterial pressure through sympathetic neuronal activity to the peripheral vasculature. Inhalational anesthetics including halothane, enflurane and isoflurane, have been previously demonstrated to depress or abolish baroreceptor responses.¹⁻³

α_2 -Adrenergic agonists, such as clonidine, azepexole and dexmedetomidine, have been shown to produce sedation, analgesia and decrease anesthetic requirements in both human and animal studies without significantly depressing respiratory regulation.⁵⁻¹⁹ α_2 -Adrenergic agonists have also been reported to improve perioperative hemodynamic stability by diminishing reflex sympathetic outflow in response to noxious stimuli, decreasing heart rate and rate-pressure product, and preserving systemic arterial pressure.⁵⁻²² Other beneficial effects of α_2 agonists include decreased intraocular pressure, attenuation of hemodynamic responses to laryngoscopy,¹⁷ reduction of "shivering" upon emergence from general anesthesia,²⁰ and an antiarrhythmic action on epinephrine induced ventricular ectopy during halothane anesthesia.²¹

Dexmedetomidine is at least seven times more specific for α_2 -adrenoceptors than clonidine,²³ and has been demonstrated to result in favorable hemodynamic responses without direct myocardial depression.^{15,18-20,24} However, the direct actions of dexmedetomidine on baroreceptor reflex sensitivity have not been studied. The current investigation was designed to determine baroreceptor function in chronically instrumented dogs before and after two doses of oral dex-

medetomidine, in the presence of an anesthetic concentration of halothane, and during a combination of both agents that resulted in a similar anesthetic state. In addition, concurrent with baroreceptor evaluation, the systemic and coronary hemodynamic effects of oral dexmedetomidine with and without halothane were also evaluated.

Materials and Methods

All the experimental procedures and protocols used in this study were approved by the Animal Care Committee of the Medical College of Wisconsin. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were in accordance with the Guide for the Care and Use of Laboratory Animals.||

General Preparation

Methods for implantation of instruments have been previously described in detail.^{18,19} Conditioned mongrel dogs ($n = 8$) of either sex were fasted overnight and anesthetized with sodium thiamylal ($10 \text{ mg} \cdot \text{kg}^{-1}$ intravenously). Anesthesia was maintained with enflurane (2-3%) in 100% oxygen by positive pressure ventilation after tracheal intubation. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space. Heparin-filled catheters were placed in the descending thoracic aorta and right atrium for measurement of aortic blood pressure and fluid and drug administration, respectively. A Doppler (20-MHz) ultrasonic flow velocity transducer (Crystal Biotech, Holliston, MA) was placed around the proximal left anterior descending coronary artery for measurement of phasic and mean coronary blood flow velocity. A transit-time ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of cardiac output (minus coronary flow). Two pairs of miniature, ultrasonic 5-MHz crystals (Crystal Biotech, Holliston, MA) were implanted in the left ventricular anterior wall subendocardium (10-15 mm apart and 7-9 mm deep) for measurement of contractile function. A high-fidelity, miniature micromanometer (P7, Konigsberg Instruments, Pasadena, CA) was inserted in the left ventricular cavity through an incision in the apex for measurement of left ventricular pressure. The rate of increase of left ventricular pressure at 50 mmHg (dP/dt_{50}), an index of global left ventricular contractility, was obtained by electronic

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differentiation of the ventricular pressure waveform. A heparin-filled catheter was placed in the left atrial appendage. The left ventricular micromanometer was calibrated *in vivo* against pressures measured *via* the arterial and left atrial catheters (P50 pressure transducers, Gould, Oxnard, CA).

End-systolic segment length was determined at the maximum rate of decrease in left ventricular pressure. End-diastolic segment length was determined at the onset of left ventricular isovolumic contraction. The lengths were normalized according to the method described by Theroux *et al.*²⁵ Percent segment shortening was calculated with the following equation:

$$\%SS = [(EDL - ESL) \times EDL^{-1}] \times 100$$

where ESL = end-systolic segment length; EDL = end-diastolic segment length; and %SS = percent segment shortening.

Diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood velocity ($\text{hertz} \times 10^{-2}$). All hemodynamic data were continuously recorded on a polygraph (7758A, Hewlett-Packard, San Francisco, CA) and digitized with a computer and analog-to-digital converter.

All instrumentation was secured, tunneled between the scapulae, and exteriorized through several small incisions. The chest wall was closed in layers and pneumothorax evacuated by a chest tube. Each dog was treated with analgesics, procaine penicillin G ($25,000 \text{ U} \cdot \text{kg}^{-1}$), and gentamicin ($4.5 \text{ mg} \cdot \text{kg}^{-1}$) and was allowed to recover for a minimum of 7 days before experimentation. During the postoperative period, the dogs were trained to stand quietly in a sling during hemodynamic monitoring.

Determination of Baroreceptor Sensitivity

Baroreceptor reflex control of heart rate was studied by modification of the method of Smyth *et al.*²⁶ Each dog received bolus injections of sodium nitroprusside ($50 \mu\text{g} \cdot \text{kg}^{-1}$) and phenylephrine ($10 \mu\text{g} \cdot \text{kg}^{-1}$) to decrease and increase the systemic arterial pressure, respectively, by at least 30 mmHg. All responses were recorded on FM tape for off-line computer analysis of baroreceptor responses with software written in this laboratory. Left ventricular pressure and systemic arterial pressure were digitized at 256 Hz using a 12-bit analog-to-digital converter and an IBM clone 486 microcomputer. The alterations in systemic pressure were displayed, and a portion of the curve devoid of sinus

arrhythmia selected for analysis. Cardiac interval (R-R interval) was obtained simultaneously from the left ventricular pressure tracing and plotted as a function of the mean aortic pressure from the preceding cardiac cycle. A subsequent linear regression was performed from the point of the first noticeable change of R-R interval to the maximal change in arterial pressure (fig. 1). Baroreflex sensitivity was expressed as the slope of the linear regression line obtained (change in R-R interval [milliseconds] *vs.* change in mean aortic pressure [millimeters mercury]).

Experimental Protocol

Five experimental conditions were completed in the same chronically instrumented dogs ($n = 8$), using a Latin square design. Dogs were fasted overnight before experimentation. Fluid replacement was accomplished with normal saline ($200\text{--}300 \text{ ml}$) and fluid maintenance continued at $3.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for the duration of the experiment. Each experiment was performed at a similar time on a separate day. In all conditions, hemodynamics, baroreflex sensitivity and arterial blood gas tensions (ABL-2, Radiometer, Copenhagen, Denmark) were recorded in the conscious, unanesthetized state. After stabilization of hemodynamics with a full recovery from the effects of nitroprusside and phenylephrine (minimum 20 min), dogs received oral dexmedetomidine or inhalational induction with halothane, or both, as described below.

In the first and second experimental conditions, each dog received 25 or $50 \mu\text{g} \cdot \text{kg}^{-1}$ dexmedetomidine dis-

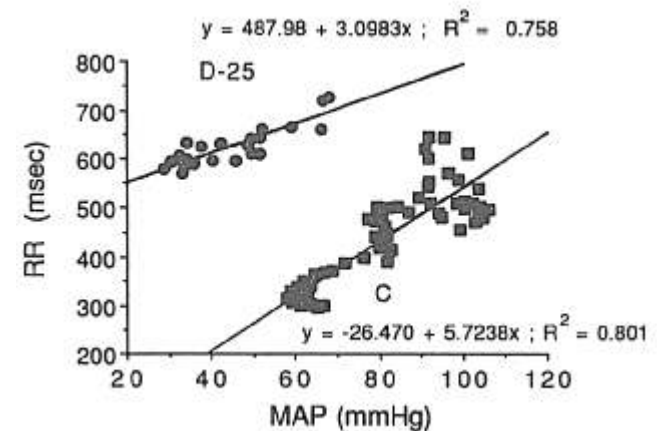


Fig. 1. Sample linear regression for determination of baroreceptor response (R-R interval *vs.* mean aortic pressure [MAP]) to sodium nitroprusside induced decrease in arterial pressure in an individual dog during control (C) and after pretreatment with $25 \mu\text{g} \cdot \text{kg}^{-1}$ dexmedetomidine (D-25).

Table 1. Hemodynamic Effects of Oral Dexmedetomidine

	Control	Dexmedetomidine 25 µg/kg	Control	Dexmedetomidine 50 µg/kg
HR (beats/min)	84 ± 3	58 ± 4*	77 ± 5	53 ± 5*
MAP (mmHg)	100 ± 4	108 ± 7	95 ± 6	106 ± 8
LVSP (mmHg)	135 ± 4	137 ± 6	128 ± 4	129 ± 7
LVEDP (mmHg)	11 ± 1	12 ± 2	10 ± 1	11 ± 2
HR/SBP (beats/min · mmHg · 10 ³)	10.9 ± 0.8	7.7 ± 0.8*	9.6 ± 1	7 ± 0.9*
dP/dt ₅₀ (mmHg/s)	2,177 ± 115	1,961 ± 108*	2,210 ± 78.1	2,013 ± 147*
DCBFV (Hz · 10 ²)	38 ± 6	35 ± 6	43 ± 8	29 ± 4*
DCVR (ru)	2.2 ± 0.2	3.0 ± 0.3*	2.2 ± 0.4	3.6 ± 0.5*
CO (L/min)	2.3 ± 0.1	1.7 ± 0.2*	1.9 ± 0.1	1.4 ± 0.2*
SVR (dyne · s · cm ⁻⁵)	3,454 ± 290	5,479 ± 670*	4,209 ± 413	6,579 ± 810*
SV (ml)	29.4 ± 3	27.2 ± 2.9	25.3 ± 2.6	22.3 ± 2.5*
SS (%)	16.6 ± 1.7	15.1 ± 1.8*	19.1 ± 3	15.2*

Values are mean ± SEM (n = 8).

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; HR/SBP = double product; SBP = systolic blood pressure; DCBFV and DCVR = diastolic coronary blood flow velocity and vascular resistance, respectively; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; SS = segment shortening.

solved in a small amount of normal saline in a gelatin capsule on separate days. Hemodynamics were continuously recorded, and 90 min after administration of dexmedetomidine, baroreflex sensitivity was again determined. In the third and fourth conditions, each dog received 25 or 50 µg · kg⁻¹ dexmedetomidine orally and 30 min later, inhalational induction was performed with halothane. Dogs were tracheally intubated, and anesthesia was maintained for 60 min with halothane during positive pressure ventilation with room air supplemented by oxygen. Baroreflex sensitivity in the presence of halothane and dexmedetomidine was determined 90 min after administration of dexmedetomidine. Dogs in condition 5 were unpremedicated and were anesthetized with halothane. Baroreflex sensitivity was subsequently determined 60 min after establishing a stable end-tidal concentration of halothane.

Each dog in conditions 3, 4, and 5 received an individualized concentration of halothane. The minimal concentration producing an anesthetic state characterized by: the absence of response (gross movement, hemodynamic alterations, onset of spontaneous respiration) to tail clamp and to movement of the tracheal tube, was delivered to each dog. The tail clamp consisted of a hemostat closed to the first ratchet position near the base of the tail for 60 s (modification of the method by Eger *et al.*²⁷) while the tracheal tube was moved in and out approximately 1.0 cm. If the dog moved, initiated spontaneous respiration or exhibited greater than a 20% increase in heart rate or systemic

arterial pressure, the end-tidal halothane concentration was increased until the response was abolished. Hence, an end-tidal concentration of halothane that resulted in this anesthetic state was determined for each dog in conditions 3, 4 and 5. End-tidal carbon dioxide, oxygen, nitrogen and halothane concentrations were continuously monitored during all experiments *via* mass spectrometry (Marquette Advantage 2000, Marquette Electronics, Milwaukee, WI).

Statistical Analysis

Statistical analysis of hemodynamic and baroreflex sensitivity data within and between conditions during the conscious state and after drug administration was performed by analysis of variance with repeated measures, followed by application of Duncan's modification of the *t* test. Changes from control within a condition or between conditions were considered statistically significant when the probability (*P*) value was less than 0.05. All data are expressed as means ± standard error of the mean.

Results

Hemodynamic Effects of Oral Dexmedetomidine

The hemodynamic effects of dexmedetomidine (25 and 50 µg · kg⁻¹; conditions 1 and 2, respectively) 90 min after oral administration are summarized in table 1. Both doses of dexmedetomidine significantly (*P* <

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0.05) decreased heart rate, rate-pressure product, dP/dt_{50} , cardiac output and percent segment shortening. Diastolic coronary vascular resistance and systemic vascular resistance were significantly elevated in both conditions, whereas diastolic coronary blood flow velocity and stroke volume were significantly lower only in the high dose group. Mean arterial pressure, left ventricular systolic pressure and left ventricular end diastolic pressure, were not changed from the respective control in either condition.

Hemodynamic Effects of Halothane with and Without Pretreatment with Oral Dexmedetomidine

Coronary and systemic hemodynamics during halothane anesthesia alone and during halothane anesthesia 90 min after pretreatment with either 25 or 50 $\mu\text{g} \cdot \text{kg}^{-1}$ dexmedetomidine are summarized in table 2. Halothane caused a significant increase in heart rate and a decrease in mean arterial pressure, left ventricular systolic pressure, dP/dt_{50} , stroke volume and percent segment shortening, when compared with the conscious control.

Halothane after pretreatment with dexmedetomidine decreased cardiac output and dP/dt_{50} , when compared with conscious control. Heart rate, left ventricular systolic pressure, rate pressure product and percent segment shortening were significantly decreased only in the 50 $\mu\text{g} \cdot \text{kg}^{-1}$ dexmedetomidine pretreated condition. In both dexmedetomidine (25 and 50 $\mu\text{g} \cdot \text{kg}^{-1}$) pretreatment conditions, heart rate was significantly lower (108 ± 9 vs. 73 ± 13 and 65 ± 7 beats/min, respectively) and left ventricular systolic pressure significantly higher (101 ± 4 vs. 115 ± 5 and 116 ± 5 , mmHg, respectively), than the same variables in the condition in which halothane was used alone. Mean arterial pressure was also significantly higher in the dexmedetomidine 50 $\mu\text{g} \cdot \text{kg}^{-1}$ pretreatment condition during halothane anesthesia. Diastolic coronary blood flow velocity and stroke volume were significantly decreased in the low dose dexmedetomidine with halothane condition.

The Effects of Dexmedetomidine and Halothane on Baroreceptor Responses

Conscious control baroreceptor responses were highly reproducible in individual animals. The slopes of the conscious control baroreceptor response curves (R-R interval vs. mean arterial pressure) and the Y-intercepts were not significantly different between con-

Table 2. Hemodynamic Effects of Oral Dexmedetomidine with Halothane

	Dexmedetomidine 25 $\mu\text{g}/\text{kg}$ + Halothane		Dexmedetomidine 50 $\mu\text{g}/\text{kg}$ + Halothane	
	Control	Halothane	Control	Halothane
HR (beats/min)	84 \pm 3	108 \pm 9*	80 \pm 4	73 \pm 13†
MAP (mmHg)	92 \pm 2	79 \pm 5*	94 \pm 5	90 \pm 5
LVSP (mmHg)	127 \pm 3	101 \pm 4*	128 \pm 3	115 \pm 5†
LVEDP (mmHg)	11 \pm 1	10 \pm 1	10 \pm 1	11 \pm 2
HR/SBP (beats/min \cdot mmHg \cdot 10 ⁻³)	9.9 \pm 0.3	9.8 \pm 1	9.4 \pm 0.5	7.9 \pm 1.2
dP/dt_{50} (mmHg/s)	2,121 \pm 116	1,383 \pm 85*	2,199 \pm 122	1,351 \pm 161*
DCBFV (Hz \times 10)	29 \pm 3	30 \pm 5	34 \pm 7	27 \pm 4*
DCVR (ru)	2.8 \pm 0.2	2.5 \pm 0.3	3.2 \pm 0.8	3.4 \pm 0.4
CO (l/min)	2.2 \pm 0.2	2.0 \pm 0.3	2.2 \pm 0.1	1.3 \pm 0.3*
SVR (dyne \cdot s \cdot cm ⁻⁵)	3,475 \pm 298	3,397 \pm 387	3,547 \pm 351	6,816 \pm 1,715*
SV (ml)	27.1 \pm 2.8	18.4 \pm 3*	29.4 \pm 2.6	19 \pm 3.3*
SS (%)	18.6 \pm 3.2	11.8 \pm 2.3*	18 \pm 2.9	12.4 \pm 1.9
			Control	Dexmedetomidine 50 $\mu\text{g}/\text{kg}$ + Halothane
			83 \pm 4	65 \pm 7†
			101 \pm 5	93 \pm 3†
			132 \pm 3	116 \pm 5†
			12 \pm 1	13 \pm 3
			10.4 \pm 0.6	7.0 \pm 0.9*
			2,107 \pm 134	1,421 \pm 104*
			32 \pm 5	29 \pm 2
			3.4 \pm 1	3 \pm 0.3
			2.4 \pm 0.2	1.4 \pm 0.2*
			3,378 \pm 237	5,934 \pm 1,011*
			27.6 \pm 2.2	22.7 \pm 4.4
			20.8 \pm 2.9	14.2 \pm 1.7*

Values are mean \pm SEM (n = 8).

HR = heart rate; MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures, respectively; HR/SBP = double product; SBP = systolic blood pressure; DCBFV and DCVR = diastolic coronary blood flow velocity and vascular resistance, respectively; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; SS = segment shortening.

* Significantly different from respective conscious control.

† Significantly different from halothane only.

ditions (figs. 2–5). Baroreflex sensitivity to an increase in systemic arterial pressure elicited by phenylephrine (figs. 2 and 4) was greater than that to a decrease in pressure elicited by nitroprusside (figs. 3 and 5). Dexmedetomidine (25 and 50 $\mu\text{g}\cdot\text{kg}^{-1}$) alone did not change baroreflex sensitivity when compared with conscious control (figs. 2 and 3). Similar results were obtained between baroreceptor responses secondary to increases or decreases in arterial pressure.

Halothane, at the predetermined definition of anesthetic state, produced a significant depression of baro-

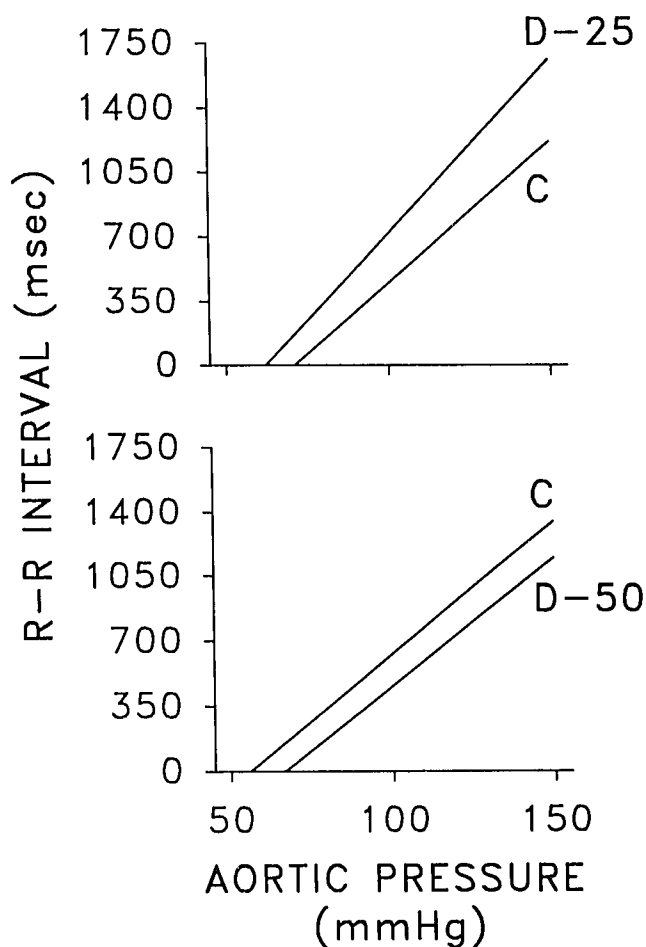


Fig. 2. Linear regression baroreceptor responses (R-R interval vs. aortic pressure) determined during an increase in pressure in the conscious control (C) state and after 25 $\mu\text{g}\cdot\text{kg}^{-1}$ (D-25) or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (D-50) dexmedetomidine. Dexmedetomidine did not alter the slope or the intercept at either 25 (control: $m = 15.4 \pm 3.5$, $y = -1,094 \pm 330$, $R^2 = 0.76 \pm 0.04$; D-25: $m = 18.9 \pm 5.8$, $y = -1,176 \pm 509$, $R^2 = 0.79 \pm 0.04$) or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (control: $m = 14.3 \pm 4.4$, $y = -802 \pm 387$, $R^2 = 0.74 \pm 0.05$; and D-50: $m = 12.0 \pm 3.7$, $y = -915 \pm 469$, $R^2 = 0.72 \pm 0.03$).

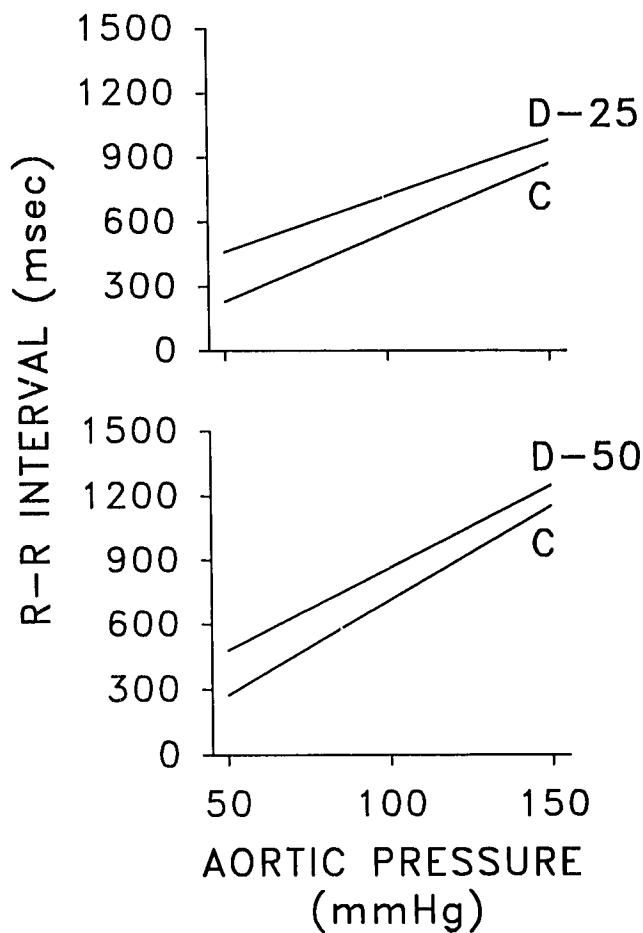


Fig. 3. Linear regression baroreceptor responses (R-R interval vs. aortic pressure) determined during a decrease in pressure in the conscious control (C) state and after 25 $\mu\text{g}\cdot\text{kg}^{-1}$ (D-25) or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (D-50) dexmedetomidine. Dexmedetomidine did not alter the slope at either 25 (control: $m = 6.4 \pm 0.8$; D-25: $m = 5.2 \pm 1.1$) or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (control: $m = 8.8 \pm 1.5$; D-50: $m = 7.7 \pm 1.2$). Intercept was reset to higher than control level in the D-25 group (control: $y = -91 \pm 46$, $R^2 = 0.85 \pm 0.02$ vs. D-25: $y = 199 \pm 68$, $R^2 = 0.78 \pm 0.05$), but remained at the control level in the D-50 group (control: $y = -168 \pm 72$, $R^2 = 0.92 \pm 0.03$; and D-50: $y = 91 \pm 119$, $R^2 = 0.78 \pm 0.03$).

receptor response (figs. 4 and 5). Pretreatment with dexmedetomidine resulted in significant preservation of baroreceptor responses to increases or decreases in arterial pressure as compared with halothane anesthesia without pretreatment (fig. 5).

Anesthetic-sparing Actions of Dexmedetomidine

The end-tidal halothane concentrations that resulted in the predetermined anesthetic state, with and without

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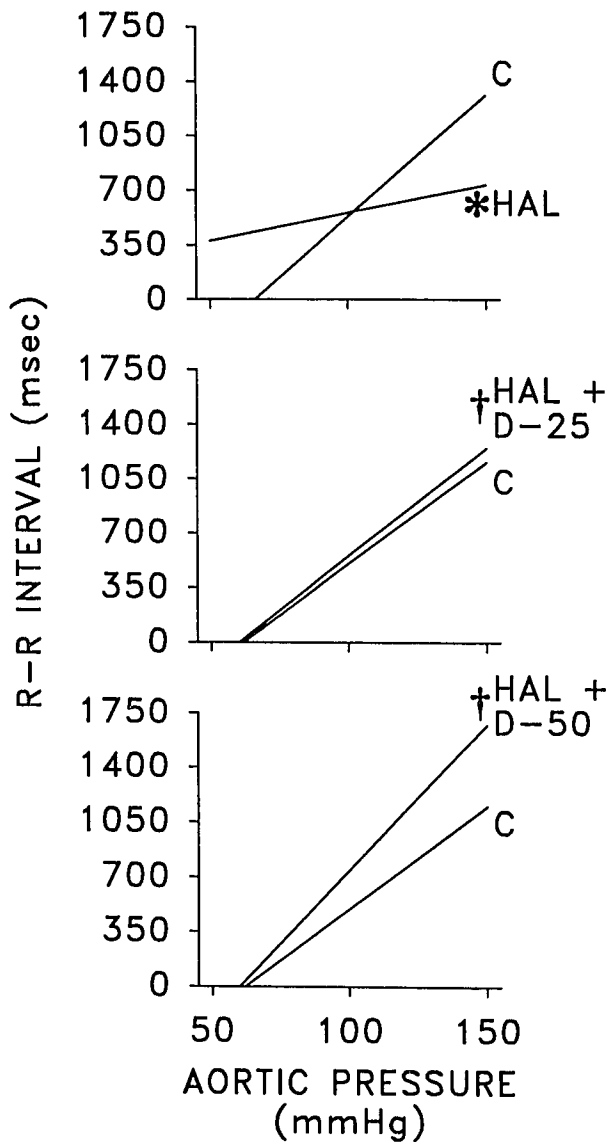


Fig. 4. Linear regression baroreceptor responses (R-R interval vs. aortic pressure) determined during an increase in pressure in the conscious control (C) state, during 1.0 MAC halothane anesthesia (HAL) after pretreatment with 25 (D-25) or 50 $\mu\text{g} \cdot \text{kg}^{-1}$ (D-50) dexmedetomidine. Halothane alone significantly altered baroreceptor responses (control: $m = 15.7 \pm 31$, $y = -1,038 \pm 252$, $R^2 = 0.76 \pm 0.03$; HAL: $m = 3.6 \pm 1.0$, $y = 196 \pm 75$, $R^2 = 0.77 \pm 0.04$). Halothane produced less alteration in baroreceptor responses after dexmedetomidine at 25 $\mu\text{g} \cdot \text{kg}^{-1}$ (control: $m = 13.1 \pm 2.4$, $y = -808 \pm 164$, $R^2 = 0.72 \pm 0.03$; HAL + D-25: $m = 13.9 \pm 3.3$, $y = -835 \pm 321$, $R^2 = 0.75 \pm 0.05$) or at 50 $\mu\text{g} \cdot \text{kg}^{-1}$ (control: $m = 13.1 \pm 3.5$, $y = -812 \pm 326$, $R^2 = 0.78 \pm 0.02$; and HAL + D-50: $m = 18.6 \pm 5.4$, $y = -1,119 \pm 506$, $R^2 = 0.75 \pm 0.02$). *Significantly different ($P < 0.05$) from conscious control; †Significantly different ($P < 0.05$) from HAL alone.

pretreatment with dexmedetomidine, are summarized in table 3. The 25 and 50 $\mu\text{g} \cdot \text{kg}^{-1}$ doses of dexmedetomidine significantly reduced the end-tidal concentration of halothane from $1.03 \pm 0.08\%$ to $0.67 \pm 0.09\%$ and $0.58 \pm 0.06\%$, respectively.

Discussion

The current study demonstrates that pretreatment with oral dexmedetomidine before administration of halothane results in a potentially beneficial hemodynamic profile at similar levels of anesthesia when compared with halothane anesthesia alone. In the presence of dexmedetomidine significantly less halothane was required to produce a similar anesthetic depth. When compared with halothane anesthesia alone, heart rate, left ventricular systolic pressure and mean arterial pressure were significantly less altered by dexmedetomidine in combination with halothane. In addition, oral dexmedetomidine alone did not significantly affect baroreceptor responses. In contrast, whereas halothane depressed baroreceptor function during both depressor and pressor tests, pretreatment with dexmedetomidine resulted in a significant preservation of baroreceptor function at the predetermined anesthetic levels, presumably secondary to reduced concentrations of halothane. Hemodynamic effects of oral dexmedetomidine, including decreases in heart rate, double product and dP/dt_{50} with maintenance of systemic arterial pressures, observed in the current study were consistent with previously published results.¹⁸ The decreases in cardiac output, stroke volume and percent segment shortening may have occurred secondarily to peripheral α_2 -adrenergic receptor mediated increases in systemic vascular resistance.

Dexmedetomidine is a centrally acting, highly selective α_2 -adrenergic agonist. Previous studies have delineated the cardiovascular and central nervous system actions of dexmedetomidine.^{5-23,28-32} An investigation from this laboratory documented the biphasic pressor-depressor response to intravenous dexmedetomidine in intact and autonomically denervated, chronically implanted dogs.¹⁹ The initial increase in arterial pressure with a concurrent reflex decrease in heart rate was attributed to peripheral α_2 -adrenoceptor activation in the vasculature, and a later reduction in heart rate and arterial pressure was mediated, presumably, through actions in the central nervous system. In contrast, previous studies of oral administration of dexmedetomidine demonstrated only the depressor responses with

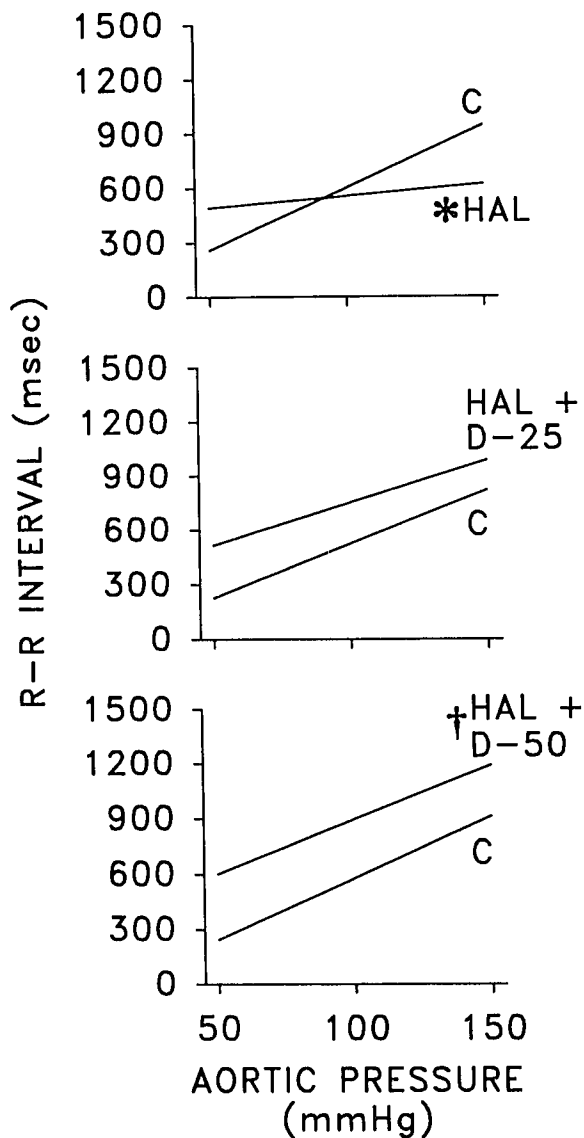


Fig. 5. Linear regression baroreceptor responses (R-R interval vs. aortic pressure) determined during a decrease in pressure in the conscious control (C) state, during the halothane anesthetic state (HAL) and during the halothane anesthetic state after pretreatment with 25 (D-25) or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (D-50) dexmedetomidine. Halothane alone significantly altered baroreceptor responses (control: $m = 6.9 \pm 0.9$, $y = -88 \pm 85$, $R^2 = 0.82 \pm 0.04$; Halothane: $m = 1.3 \pm 0.6$, $y = 425 \pm 57$, $R^2 = 0.79 \pm 0.08$). Dexmedetomidine pretreatment resulted in less depression of the baroreceptor response at 25 $\mu\text{g}\cdot\text{kg}^{-1}$ (control: $m = 6.0 \pm 1.0$, $y = -72 \pm 64$, $R^2 = 0.84 \pm 0.03$; HAL + D-25: $m = 4.7 \pm 1.3$, $y = 277 \pm 90$, $R^2 = 0.81 \pm 0.06$) and 50 $\mu\text{g}\cdot\text{kg}^{-1}$ (control: $m = 6.7 \pm 0.9$, $y = -88 \pm 82$, $R^2 = 0.82 \pm 0.04$; and HAL + D-50: $m = 5.9 \pm 1.7$, $y = 307 \pm 111$, $R^2 = 0.91 \pm 0.03$). *Significantly different ($P < 0.05$) from conscious control; †Significantly different ($P < 0.05$) from HAL alone.

a decrease in heart rate, double product, cardiac output and dP/dt_{50} but without changes in mean arterial pressure, diastolic coronary blood flow velocity and percent segment shortening from control levels.¹⁸ The current results are consistent with this latter study.

In a recent study¹² of the hemodynamic actions of dexmedetomidine in humans, the two largest intravenous doses of dexmedetomidine (1 and 2 $\mu\text{g}\cdot\text{kg}^{-1}$) resulted in a biphasic early pressor-late depressor response. The initial increase in mean arterial pressure was transient and occurred concomitantly with prominent reductions in cardiac output and heart rate. However, the initial pressor phase was not observed with two lower doses (0.25 and 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$) of dexmedetomidine used in this study.¹² Therefore, as previously suggested,¹⁹ it appears likely that with high doses of dexmedetomidine activation of α_2 -adrenergic receptors in the peripheral vasculature may result in apparent decrements in cardiac performance secondary to increases in afterload and impedance to left ventricular ejection. After the transient, peripheral α_2 -adrenoceptor stimulation by dexmedetomidine diminishes, elaboration of the beneficial, centrally mediated actions of dexmedetomidine becomes apparent.

The anesthetic-sparing action of dexmedetomidine and other α_2 -adrenergic agonists has been the subject of numerous animal and clinical studies.^{7,9-11,14-17} Intravenous administration of dexmedetomidine is associated with prominent sedation without significant decreases in minute ventilation or hypercapnic ventilatory response.^{16,32} Previous studies have suggested that major site of action for the hypnotic effects of dexmedetomidine lies in the locus ceruleus where the actions may be mediated through pertussis toxin sensitive

Table 3. End-tidal Halothane Concentration Resulting in Anesthetic State

Dog	Halothane Only (%)	Halothane (%) + 25 $\mu\text{g}/\text{kg}$ Dexmedetomidine	Halothane (%) + 50 $\mu\text{g}/\text{kg}$ Dexmedetomidine
1	0.95	0.35	0.40
2	0.95	0.65	0.35
3	1.10	0.75	0.60
4	1.10	0.90	0.70
5	0.60	0.65	0.50
6	1.40	1.10	0.90
7	1.00	0.55	0.55
8	1.10	0.40	0.60
Mean \pm SEM	1.03 \pm 0.08	0.67 \pm 0.09*	0.58 \pm 0.06*

* Significantly different ($P < 0.05$) from halothane only.

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G-protein coupling of the α -adrenergic receptor to effector mechanisms.^{10,14,33} It also appears that the hypnotic effects of α_2 -adrenergic agonists may be partially mediated through actions on central α_1 -adrenergic receptors.³⁴ In the current investigation, the anesthetic-sparing actions of dexmedetomidine were evident: the concentration of halothane producing a similar anesthetic state decreased by 30% after 25 $\mu\text{g} \cdot \text{kg}^{-1}$ and by 40% after 50 $\mu\text{g} \cdot \text{kg}^{-1}$ dexmedetomidine. A previous study has demonstrated an even more impressive anesthetic-sparing action of dexmedetomidine in halothane-anesthetized dogs.³¹ This may be related to a different route of administration and temporal determination of MAC or anesthetic state (10 min after intravenous infusion *versus* 90 min after oral dosing). Differences in the methodologic determination of MAC or anesthetic state may also underlie the discrepancies.

The nucleus tractus solitarius (NTS) serves as the primary relay nucleus for cardiovascular afferents arising from both the baroreceptors and cardiopulmonary afferents.³⁵⁻³⁷ It is well established that both electrical and chemical stimulation of the NTS will elicit changes in hemodynamics similar to activation of the baroreceptor reflex.³⁶ Direct application of α_2 -adrenergic agents in *in vivo* and *in vitro* preparations has been demonstrated to alter spontaneous and evoked activity of single neurons in the NTS.^{38,39} Other studies suggest that α_2 -adrenergic agonists may also exert actions at more rostral areas in the central nervous system that project to the NTS.⁴⁰ At these rostral areas, an activation of inhibitory and an inhibition of excitatory projections to medullary regions, as well as a direct action at medullary centers, may all contribute to a decrease in sympathetic activity and an increase in parasympathetic activity, mimicking activation of the baroreceptor reflex arc. Therefore, the hemodynamic changes produced by α_2 -adrenergic agonists have been referred to as a central activation of the baroreceptor reflex.⁴⁰

Studies have also demonstrated an enhancement of baroreceptor-mediated reflex slowing of the heart after intravenous and intracisternal administration of clonidine in anesthetized or conscious dogs.^{41,42} Both phenylephrine and clonidine potentiated baroreflex-mediated systemic vasoconstriction induced by mild hemorrhage.⁴³ However, paradoxically, intravenous administration of clonidine has been demonstrated to inhibit reflex bradycardia and decreases in systemic arterial pressure caused by increases in intrasinus pressure of the autoperfused carotid sinus in anesthetized dogs.⁴² However, in this study,⁴² clonidine potentiated

reflex bradycardia after norepinephrine infusion. The enhancement of the baroreceptor reflex produced by clonidine was present in chronically sinusectomized and absent in aortically denervated dogs, suggesting an action on a second reflex arc, presumably mediated *via* high pressure aortic baroreceptors. However, Muzi *et al*⁴⁴ reported that oral clonidine did not alter baroreflex regulation of the cardiac cycle or efferent sympathetic nerve activity in humans. Similarly, both azepexole⁴⁵ and rilmenidine,^{46,47} (both centrally acting α_2 -adrenergic agonists) have been shown not to enhance baroreflex sensitivity. In the current investigation, no facilitation of baroreceptor responses was observed.

Other important areas of the caudal brain stem involved in reflex control of systemic arterial pressure include the rostral ventrolateral medulla (C1 area), which receives innervation from the NTS, largely unilaterally, and projects directly to the sympathetic preganglionic cell bodies in the intermedial lateral cell column.³⁶ The C1 area may be involved in the tonic maintenance of arterial pressure through sympathetic efferents and may mediate vasodepressor reflex responses to baroreceptor activation. An additional important site of cardiovascular control is the caudal ventrolateral medulla (A1 area). The A1 area provides afferent projections to the supraoptic and paraventricular hypothalamic nuclei and may mediate vasopressin and posterior pituitary regulatory mechanisms.³⁷ It has been demonstrated that the ventrolateral medulla may be a primary site of action for hemodynamic alterations produced by centrally active antihypertensive agents, including clonidine and rilmenidine.⁴⁸⁻⁵⁰ Previous studies have suggested that the sedative and anesthetic-sparing actions of dexmedetomidine might represent actions at α_2 -adrenergic receptors located within the higher central nervous system but that the central sympatholytic and parasympathomimetic effects might be mediated at putative imidazoline-binding sites, presumably in the brain stem where dexmedetomidine may be a less efficacious agonist.¹⁹ The current results are consistent with such a concept. Although dexmedetomidine administration resulted in preservation of baroreceptor responses, similar to previous results with rilmenidine and clonidine, no augmentation of reflex responses was observed.

Anesthetic agents, particularly halothane, have been shown to depress baroreflex sensitivity in both human and animal species.^{1-4,51,52} However, considerable controversy exists over the primary site of this depressant action. Attenuation of baroreceptor responses pro-

duced by halothane, isoflurane and enflurane is mediated at both peripheral sites and within the central nervous system.^{3,52} By using single-fiber carotid sinus afferent nerve activity, a sensitization of the baroreceptors has been demonstrated and may involve an alteration in sinus wall tension and a direct calcium-dependent effect on the baroreceptors.⁵¹ Reflex-induced changes in preganglionic sympathetic nerve activity are significantly attenuated by both isoflurane and halothane, consistent with the depression of central nervous system centers.^{51,52} Other studies have demonstrated alterations in both pressor and depressor responses to stimulation of multiple cardiovascular regulatory centers within the central nervous system.⁵³ However, although significant blunting of baroreceptor reflex responses occurs during volatile anesthesia, some residual baroreflex response remains. Whether this action of the volatile anesthetics is mediated at the C1, A1, or NTS regions is unknown. Presumably, the preservation of baroreceptor reflex response with dexmedetomidine pretreatment during halothane anesthesia resulted solely from the anesthetic-sparing action of dexmedetomidine, with a resultant lowered concentration of halothane producing a similar anesthetic state, and thus minimizing baroreceptor disruption, rather than an opposing interaction of these two agents in the central nervous system.

There may be several limitations to the current investigation associated with the methodology. Only a single concentration of halothane resulting in the production of an anesthetic state, both in the presence and absence of dexmedetomidine, was used to determine baroreceptor responses. This concentration, in the absence of dexmedetomidine, essentially eliminated baroreceptor responses. Higher concentrations would, presumably, have produced similar results. Significantly, dexmedetomidine alone did not significantly alter baroreceptor responses. In addition, pretreatment with dexmedetomidine diminished the halothane concentration producing a similar anesthetic state while concurrently significantly preserving baroreceptor function. This preservation, presumably, reflected the diminished halothane concentration. However, a dexmedetomidine/halothane interaction cannot be totally excluded. Ideally, several concentrations of halothane with and without dexmedetomidine pretreatment could be studied. Unfortunately, concentrations less than those resulting in the anesthetic state, as defined in these experiments, could not be used in these chronically instrumented animals without a baseline anesthetic.

In conclusion, in the current investigation, pretreatment of dogs with dexmedetomidine produced a decrease in halothane anesthetic requirements concurrent with preservation of baroreflex sensitivity. Potentiation of baroreceptor reflex sensitivity as observed with some other less specific α_2 -adrenergic agonists was not apparent in the current study. Baroreceptor slopes in the presence of dexmedetomidine were not significantly different from control. Such preservation of baroreceptor function during anesthesia might have important clinical consequences. However, because of the significant action of dexmedetomidine on cardiovascular hemodynamic parameters, careful administration and dosage titration may be necessary in patients with underlying cardiovascular disease processes. Paradoxically, such high risk cardiac patients are likely to represent the patient group that might benefit the most from the central nervous system-mediated beneficial actions of this α_2 -adrenergic agonist.

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