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Oral Dexmedetomidine Attenuates Hemodynamic Responses during Emergence from General Anesthesia in Chronically Instrumented Dogs

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This investigation evaluated the hemodynamic effects of orally administered dexmedetomidine in chronically instrumented dogs in the conscious state, during enflurane anesthesia, and after emergence. Four experimental groups (n = 9 each) were completed. In groups 1 and 2, dexmedetomidine (10 or 20 μg/kg, respectively) was administered orally, and hemodynamics, arterial blood gas tensions, and plasma norepinephrine concentrations were monitored for 6 h. Animals in groups 3 and 4 were given dexmedetomidine (20 μg/kg) or placebo orally, and hemodynamics, arterial blood gas tensions, and plasma norepinephrine concentrations were measured 1 h later with animals in the conscious state, after 30 min of enflurane anesthesia (1.0 MAC), and 2 and 7 min after extubation. Oral administration of dexmedetomidine resulted in sedation with significant decreases in heart rate (76 ± 4 to 49 ± 4 beats per min), rate–pressure product (11,500 ± 650 to 6,100 ± 600 mmHg · beats per min), cardiac output (2.2 ± 0.2 to 1.2 ± 0.4 l/min), and plasma norepinephrine concentrations (290 ± 50 to 135 pg/ml). Peak effects occurred within 30 min and lasted approximately 3 h. No reduction in coronary blood flow velocity, decrease in regional contractile function, or respiratory depression was observed. Administration of dexmedetomidine before enflurane anesthesia also was associated with a reduction in heart rate and rate–pressure product, and dexmedetomidine prevented the increase in heart rate (146 ± 9 *vs.* 60 ± 7 beats per min) and arterial pressure (117 ± 7 *vs.* 98 ± 7 mmHg) during emergence from anesthesia. The results of this investigation indicate that oral administration of dexmedetomidine favorably alters systemic hemodynamics without a reduction in coronary blood flow velocity or contractile function or a depression of respiratory function. Oral dexmedetomidine also diminishes the hemodynamic response to emergence from general anesthesia. The lack of an initial pressor response, the sedation without respiratory depression, and the favorable hemodynamic actions suggest that oral dexmedetomidine may be a useful premedication for general anesthesia. (Key words: Anesthesia: cardiovascular; emergence. Animals: dogs. Pharmacodynamics: dexmedetomidine, oral. Premedication: dexmedetomidine. Sympathetic nervous system: alpha-2 adrenergic agonists, dexmedetomidine; receptors, alpha-2 agonists.)

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PREVIOUS STUDIES have demonstrated that administration of alpha-2 adrenergic receptor agonists, including clonidine, produce sedation and may decrease the anesthetic requirements for barbiturates, opioids, and volatile agents.[1–5] Postulated sites of action for the modulation of anesthetic requirements by alpha-2 agonists include presynaptic and postsynaptic alpha-2 adrenoceptors in the central nervous system[6] and a specific antinociceptive action in the spinal cord.[7] Concomitant with sedative effects and a reduction in anesthetic requirements, alpha-2 adrenergic receptor agonists diminish sympathetic outflow and decrease heart rate, systemic arterial pressure, and the rate–pressure product[8] without significant respiratory depression.[9] These properties suggest that such alpha-2 adrenergic agonists may be useful adjuncts to general anesthetics in patients with coronary artery disease. Indeed, clonidine has been demonstrated to be effective in improving intraoperative hemodynamics, reducing intraoperative plasma catecholamines, and decreasing post–coronary artery bypass graft hypertension, shivering, and requirement for ventilatory support.[2] Unfortunately, clinical studies have been limited by lack of specific alpha-2 adrenergic receptor selectivity of the compounds previously used and by the mixed agonist/antagonist activity, in which higher doses of the drugs show partial reversal of effects.

The D isomer of medetomidine, dexmedetomidine, has been shown to be a highly selective agonist of alpha-2 receptors,[10] and as a result is a potentially useful compound for delineating the physiologic and pharmacologic actions of alpha-2 adrenergic receptor agonists. However, intravenous (iv) administration of dexmedetomidine has been associated with initial, transient increases in arterial pressure mediated through direct stimulation of postsynaptic alpha-2 receptors in the peripheral vasculature.[10,11] Additionally, stimulation of postsynaptic alpha-2 receptors in coronary arteries has been shown to cause direct coronary artery vasoconstriction.[12] Whether such hemodynamic actions occur after oral administration of dexmedetomidine has not been previously examined. The current study was designed to evaluate the effects of orally administered dexmedetomidine on coronary and systemic hemodynamics in chronically instrumented dogs. Additionally, emergence from general anesthesia may be accompanied by an increase in heart rate and arterial pres-

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sure. Because the alpha-2 agonists may attenuate such responses, the effects of oral administration of dexmedetomidine during and after general anesthesia with a volatile anesthetic also were evaluated in the current investigation.

Materials and Methods

All experimental procedures and protocols used in this investigation were approved by the Animal Care Committee of the Medical College of Wisconsin and conformed to the Guiding Principals 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 previously been described in detail.[13] Briefly, conditioned mongrel dogs (n = 11) of either sex weighing between 20 and 30 kg were fasted overnight and anesthetized with sodium thiamylal (10 mg/kg, iv). After tracheal intubation, anesthesia was maintained with enflurane (2.0–3.0%) in 100% oxygen by positive-pressure ventilation. 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 drug administration, respectively. A 1.5–2.0-cm segment of the proximal left anterior descending coronary artery was isolated, and a Doppler ultrasonic flow velocity transducer (20 MHz) was placed around the vessel 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.** A pair of miniature cylindric ultrasonic length transducers (5 MHz) were implanted in the left ventricular subendocardium (10–15 mm apart and 7–9 mm deep) in a circumferential plane within the perfusion territory of the left anterior descending coronary artery for measurement of contractile function. A high-fidelity miniature micromanometer (model P7, Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricular cavity through an incision in the apex for measurement of pressure and the rate of increase of ventricular pressure at 50 mmHg (dP/dt_{50}). A heparin-filled catheter was placed in the left atrial appendage. The left ventricular micromanometer was calibrated *in vivo* against pressures measured through the arterial and left atrial catheters (Gould P50® Pressure Transducer, Oxnard, CA).

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. After surgery, each dog was treated with analgesics, procaine penicillin G (25,000 U/kg), and gentamycin (4.5 mg/kg) and 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.

Segment length and coronary blood flow velocity signals were driven and monitored by ultrasonic amplifiers (Crystal Biotech, Boston, MA). 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 described by Theroux *et al.*[14] Percent segment shortening (%SS) was calculated with the following equation:

$$\%SS = \frac{EDL - ESL}{EDL} \times 100$$

Relative mean or diastolic vascular resistances were calculated as the quotients of mean or diastolic arterial pressures and mean or diastolic coronary blood flow velocities (Hz × 10^2), respectively. All hemodynamic data were continuously recorded on a polygraph (Hewlett Packard 7758A®, San Francisco, CA) and digitized with a computer and analog to digital converter.

Measurement of Plasma Norepinephrine

The method used for the determination of concentration of norepinephrine in plasma has been previously described.[15] Briefly, norepinephrine concentrations were measured from arterial blood samples with the use of reverse-phase, high-performance liquid chromatography. All samples were extracted with the use of alumina. The internal standard was 3,4 dihydroxybenzylamine. The mobile phase consisted of 1.0 l buffer (NaH_2PO_4 [6.9 g], sodium octyl sulfate [0.611 g], Na_2EDTA [0.25 g] adjusted to *p*H 3.0), 67 ml methanol, and 17 ml tetrahydrofuran. Absolute retention times of norepinephrine and dihydroxybenzylamine were 8.7 and 14.5 min, respectively. The lower limit of detectability of norepinephrine was approximately 50 pg/ml, with a coefficient of variation for the method of 4.2%.

Experimental Protocol

Four separate experimental groups were completed. On separate days, after the animals were fasted overnight,

¶ Guide for the Care and Use of Laboratory Animals, Department of Health and Human Services publication no. (NIH) 85-23, revised 1985.

** Hartman J, Koerner J, Lancaster L, Gorczynski R: In vivo calibration of a transit time ultrasound system for measuring aortic blood flow (abstract). Pharmacologist 27:A572, 1985.

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baseline hemodynamic function was monitored continuously for 30 min and plasma norepinephrine concentrations and arterial blood gas tensions (ABL-2®, Radiometer Copenhagen, Copenhagen, Denmark) were obtained in dogs in the conscious, unsedated state. In groups 1 (n = 9) and 2 (n = 9), dexmedetomidine (10 and 20 μg/kg, respectively) dissolved in a small amount of normal saline was then administered orally in a gelatin capsule. Hemodynamics were monitored continuously for 6 h after drug administration. Arterial blood gas tensions and plasma norepinephrine concentrations were obtained at various intervals. To minimize experimental variability, the same dogs were randomly assigned to groups 1 and 2. Between experiments, each dog was allowed a recovery period of at least 3 days.

In group 3 (n = 9), dexmedetomidine (20 μg/kg) dissolved in normal saline was administered orally in a gelatin capsule after measurement of hemodynamics during control conditions. Hemodynamics were monitored continuously, and arterial blood gas tensions were measured 60 min after drug administration. Inhalation induction of anesthesia, with the use of 3–5% enflurane in 100% oxygen, was then accomplished. Tracheal intubation was performed and anesthesia maintained at 1.0 MAC enflurane (2.2%; end-tidal mass spectrometry, Advantage 2000®, Marquette Electronics, Milwaukee, WI) in 100% oxygen for 30 min by positive-pressure ventilation. After 30 min, hemodynamics and arterial blood gas tensions were measured and enflurane was discontinued. During emergence from enflurane anesthesia, hemodynamics were monitored continuously, and the trachea of each animal was extubated immediately on apparent return of consciousness as manifested by spontaneous ventilation, response to verbal stimuli, and mastication of the endotracheal tube. Experiments in group 4 (n = 9) were completed in a similar fashion to those in group 3; however, animals were given placebo before anesthesia. The same dogs were randomly assigned to groups 3 and 4.

Statistical Analysis

All data were compared with the use of analysis of variance with repeated measures followed by application of Bonferroni's modification of the *t* test. Changes from control within a group or between groups were considered statistically significant when the *P* value was less than 0.05. All data are expressed as mean ± SEM.

Results

Hemodynamic Actions of Dexmedetomidine

The hemodynamic effects of orally administered dexmedetomidine are summarized in figure 1. Dexmedetomidine significantly decreased heart rate, rate–pressure product, cardiac output, and left ventricular dP/dt_{50}. These actions were observed by 30 min after oral administration and lasted approximately 3 h. The higher dose (20 μg/kg) demonstrated a more prolonged action than the lower dose (10 μg/kg). Heart rate and rate–pressure product of dogs receiving 10 μg/kg of dexmedetomidine recovered to control levels by 3 h as opposed to 4 h in dogs receiving 20 μg/kg. In addition, recovery of cardiac output and dP/dt_{50} to control levels took 1 h longer than did recovery of heart rate and rate–pressure product. Oral dexmedetomidine did not alter mean arterial pressure, left ventricular end-diastolic pressure, coronary blood flow velocity, or systolic shortening. Hemodynamic actions oc-

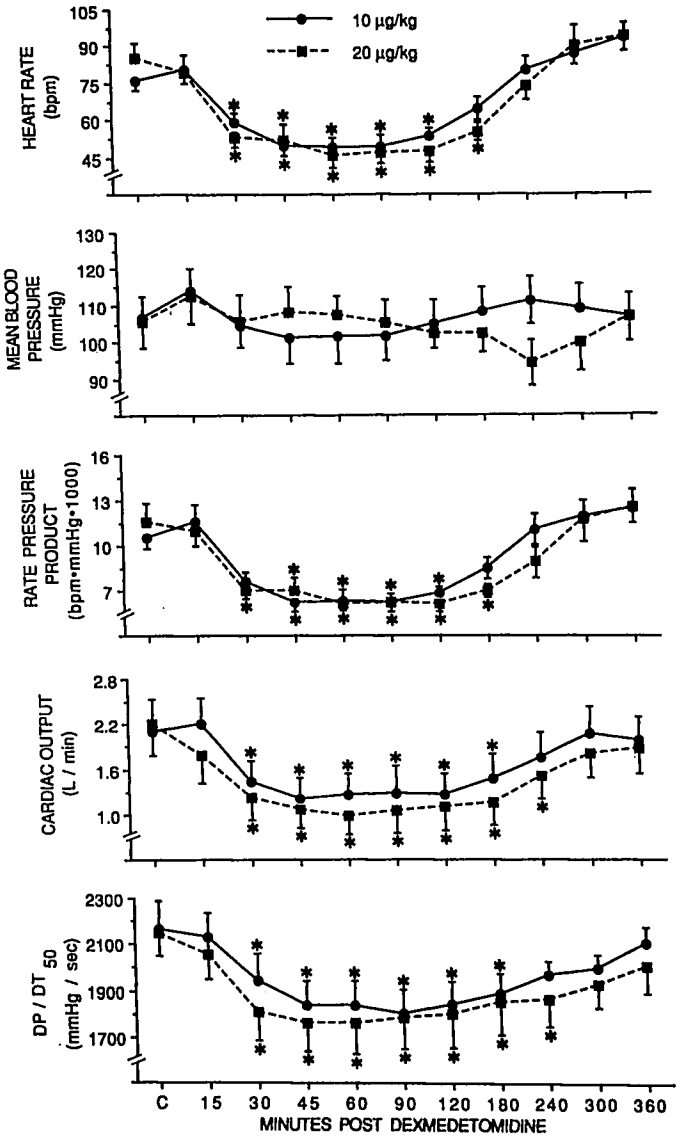

FIG. 1. Time course of effects of dexmedetomidine (circles, 10 μg/kg; squares, 20 μg/kg) on hemodynamics after oral administration. dP/dt_{50} = rate of increase of left ventricular pressure at 50 mmHg. *Significant ($P < 0.05$) difference from control.

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TABLE 1. Effects of Dexmedetomidine on Respiratory Rate, Arterial Blood Gas Tensions, and Norepinephrine

	Dose (μg/kg)	Control	Time After Oral Dexmedetomidine (h)					
			1	2	3	4	5	6
RR (breaths per min)	10	21 ± 2	14 ± 1*	15 ± 2*	18 ± 2	20 ± 2	21 ± 3	22 ± 3
	20	24 ± 2	13 ± 2*	13 ± 1*	15 ± 2*	19 ± 2*	21 ± 3	22 ± 2
*p*H	10	7.44 ± 0.01	7.43 ± 0.01	7.42 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01
	20	7.43 ± 0.01	7.42 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.42 ± 0.01	7.43 ± 0.01
P_{CO_2} (mmHg)	10	31 ± 1	31 ± 1	32 ± 1	31 ± 1	31 ± 1	32 ± 1	32 ± 1
	20	31 ± 1	30 ± 1	30 ± 1	31 ± 1	33 ± 2	31 ± 1	30 ± 1
P_{O_2} (mmHg)	10	87 ± 3	83 ± 2	85 ± 3	84 ± 2	83 ± 3	82 ± 3	80 ± 2
	20	82 ± 2	85 ± 3	88 ± 3	86 ± 3	82 ± 4	83 ± 1	83 ± 2
NE (pg/ml)	10	280 ± 50	120 ± 30*	135 ± 15*	150 ± 22*	223 ± 27	256 ± 19	254 ± 25
	20	265 ± 61	77 ± 28*	109 ± 23*	123 ± 30*	184 ± 29*	204 ± 38	276 ± 50

RR = respiratory rate; NE = norepinephrine.
All values are mean ± SEM (n = 9).

* Significant ($P < 0.05$) difference from control.

curred concomitantly with readily observed sedation, as indicated by the dogs sleeping comfortably in the sling. All animals, however, remained easily arousable.

The actions of dexmedetomidine on arterial blood gas tensions, respiratory rate, and plasma norepinephrine concentrations are summarized in table 1. Oral administration of dexmedetomidine resulted in a decline in respiratory rate but did not affect arterial *p*H, P_{CO_2}, or P_{O_2}. The slowing of respiratory rate was present at 1 h after drug administration and persisted for 2 h after the 10 μg/kg dose and 4 h after the 20 μg/kg dose. A decrease in plasma norepinephrine concentration was observed (table 1) concomitant with alterations in hemodynamics, respiratory rate, and sedation.

DEXMEDETOMIDINE AND EMERGENCE FROM ANESTHESIA

Hemodynamic data from dogs treated with oral dexmedetomidine or placebo before enflurane anesthesia are summarized in figure 2. Dexmedetomidine produced a decrease in heart rate, rate–pressure product, cardiac output, and dP/dt_{50} before induction of anesthesia. There was, however, no difference in systemic and coronary hemodynamics between dogs pretreated with placebo and those treated with dexmedetomidine during enflurane anesthesia except for a slightly diminished rate–pressure product in the dexmedetomidine-treated group. During emergence from enflurane anesthesia, dogs receiving dexmedetomidine had a significantly lower heart rate, rate–pressure product, cardiac output, and dP/dt_{50} than placebo-treated dogs. Dexmedetomidine prevented the increase in heart rate and arterial pressure during emergence from anesthesia that occurred in placebo-treated dogs (fig. 2). All dogs in both groups met the same criteria for extubation. Dexmedetomidine did not change coronary blood flow velocity or systolic shortening either before induction or after extubation, when compared with controls or those dogs not receiving dexmedetomidine.

Arterial blood gas tensions and respiratory rate in dogs before, during, and after enflurane anesthesia are summarized in table 2. Oral administration of dexmedetomidine decreased respiratory rate before inhalation induction and after emergence from anesthesia without affecting arterial *p*H, P_{CO_2}, or P_{O_2}.

Discussion

The purpose of this investigation was two-fold—to examine the time course and hemodynamic effects of orally

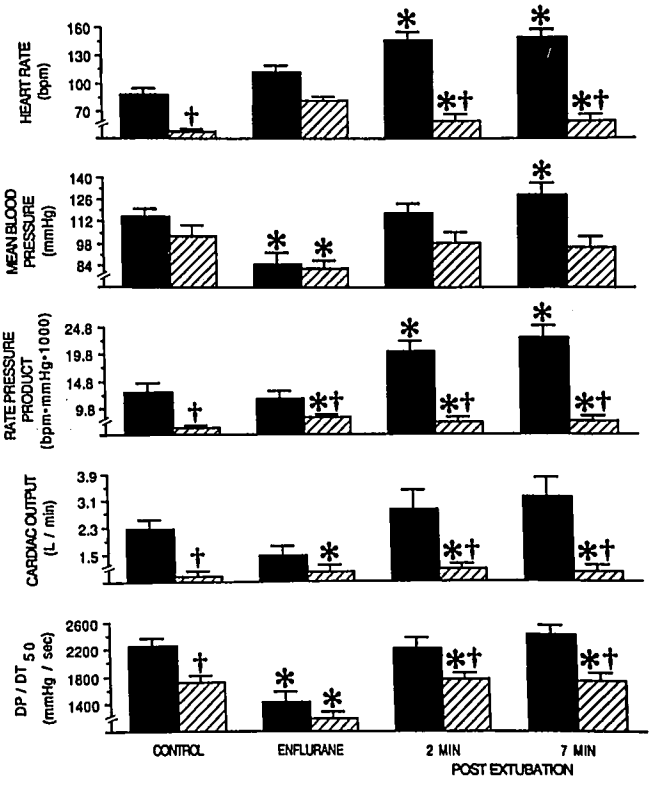

FIG. 2. Effects of enflurane anesthesia and emergence (2 and 7 min postextubation) from anesthesia on hemodynamics in placebo (solid bars) and dexmedetomidine (20 μg/kg, shaded bars) pretreated dogs. *Significant ($P < 0.05$) difference from conscious control. †Significant ($P < 0.05$) difference from placebo group.

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TABLE 2. Effects of Dexmedetomidine on Respiratory Rate and Arterial Blood Gas Tensions Before, During, and After Enflurane Anesthesia

		Control	1 h Post-D	30 min Enflurane	Time Postextubation (min) 2	7
RR (breaths per min)	P	22 ± 2	—	14 ± 2*	23 ± 2	24 ± 2
	D	22 ± 2	14 ± 2*†	14 ± 2*	14 ± 2*†	15 ± 2*†
*p*H	P	7.43 ± 0.02	—	7.36 ± 0.02	7.39 ± 0.02	7.40 ± 0.02
	D	7.43 ± 0.01	7.41 ± 0.01	7.37 ± 0.02	7.39 ± 0.01	7.39 ± 0.02
P_{CO_2} (mmHg)	P	31 ± 1	—	36 ± 1	33 ± 1	32 ± 1
	D	31 ± 1	32 ± 1	35 ± 1	35 ± 1	36 ± 2
P_{O_2} (mmHg)	P	87 ± 2	—	339 ± 15	95 ± 5	89 ± 3
	D	84 ± 2	85 ± 2	329 ± 22	88 ± 2	85 ± 2

All values are mean ± SEM (n = 9).
RR = respiratory rate; P = placebo; D = dexmedetomidine (20 μg/kg, po).

All values are mean ± SEM (n = 9).
* Significant ($P < 0.05$) difference from control.
† Significant ($P < 0.05$) difference from placebo group.

administered dexmedetomidine and to evaluate hemodynamic responses during emergence from general anesthesia after preanesthetic medication with oral dexmedetomidine. The results demonstrated that dexmedetomidine reduces heart rate and plasma norepinephrine concentrations during sedation and blunts the hemodynamic response during emergence from anesthesia.

Alpha-2 adrenoceptor agonists have been shown to have multiple beneficial effects in the perioperative period. Sympathetic reflex activation to intubation[16] has been shown to be diminished, and intraoperative hemodynamics have been reported to have greater stability[2] after administration of alpha-2 adrenergic agonists. Studies in humans and animals indicate that alpha-2 adrenoceptor agonists provide sedation[17] and analgesia[4] and preserve baroreceptor reflexes[18]; they also do not produce significant respiratory depression.[9] Intraoperative effects of alpha-2 adrenoceptor stimulation include prevention of opioid-induced muscle rigidity[19] and of the mass autonomic reflex in quadriplegic patients.[20] There is also a significant reduction in intraoperative anesthetic requirements as reflected by a reduced MAC for halothane[3] and isoflurane.[5]

Analgesia and sedation produced by alpha-adrenergic agonists appear to be mediated by activation of alpha-2 receptors in the brain and spinal cord.[6] Presynaptic alpha-2 receptor stimulation decreases catecholamine release from central adrenergic neurons and therefore decreases peripheral sympathetic neuronal activity and serum catecholamines.[21] Alpha-2 agonists also may act through stimulation of antinociceptive pathways within the spinal cord, an action that depresses neuronal excitability.[7]

Clonidine is a well-established antihypertensive agent that acts through stimulation of central alpha-2 receptors. The utility of this drug as a preanesthetic medication has been demonstrated to be limited by a "ceiling effect," followed by a partial reversal of drug effects at higher doses.[22] The latter action has been attributed to partial antagonist properties of clonidine.[3] The D isomer of medetomidine, dexmedetomidine, has been shown to be a more selective agonist at the alpha-2 adrenoceptor,[23] retaining the advantages of alpha-2 stimulation without attenuation of effects with increasing dosage. This high selectivity for alpha-2 adrenoceptors may be responsible for the greater "anesthetic-sparing effect" observed with dexmedetomidine as compared with other alpha-2 agonists.[10]

Previous investigations from this laboratory[24] have shown a biphasic blood pressure response to the iv administration of dexmedetomidine characterized by an initial hypertensive phase that is dose-dependent and precedes any beneficial hemodynamic effect. The pressor effect has been postulated to be the result of direct stimulation of alpha-2 receptors in the peripheral vasculature. This pressor response may limit the utility of intravenously administered alpha-2 agonists. The current investigation demonstrates that oral administration of dexmedetomidine does not produce the initial pressor phase before centrally mediated sedation and diminished sympathetic tone. These results suggest that the absorption profile of orally administered dexmedetomidine minimizes the stimulation of peripheral alpha-2 adrenoceptors while nevertheless permitting activation of central nervous system alpha-2 receptors.

The current study demonstrated that oral administration of dexmedetomidine to chronically instrumented dogs caused a decrease in heart rate, rate–pressure product, left ventricular dP/dt_{50}, cardiac output, and plasma norepinephrine within 30 min that lasted for 3–4 h. The reduction in plasma norepinephrine concentrations coincided with the peak hemodynamic effects of dexmedetomidine. These alterations were consistent with a central mechanism of action of dexmedetomidine and confirm prior studies in animals and humans.[17,25] These changes occurred without an initial pressor response or change in coronary blood flow velocity, mean arterial pressure, or arterial blood gas tensions. In this investigation, dexmedetomidine was also shown to attenuate the

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hemodynamic changes occurring during emergence from anesthesia. The increase in heart rate, arterial pressure, and rate–pressure product occurring during emergence in control experiments was significantly reduced by pretreatment with dexmedetomidine.

This investigation did reveal dexmedetomidine to significantly reduce left ventricular dP/dt_{50}, a reduction that possibly reflects a decline in global myocardial contractility. Left ventricular dP/dt_{50} may be subject to changes in preload and afterload, however, but few alterations in these parameters occurred in this study. Thus, dexmedetomidine may compromise cardiac function in patients with a limited contractile reserve and dependence on sympathetic tone. Furthermore, the hemodynamic consequences of dexmedetomidine may depend on the preexisting level of sympathetic tone, and in previously hypertensive patients or in hypovolemic states a greater decrease in arterial pressure may be observed. The effects of dexmedetomidine in these conditions require additional investigation.

The protocol used in this study did not include any evaluation of the "anesthetic-sparing properties" of dexmedetomidine because both control and dexmedetomidine-treated groups of dogs were anesthetized with equal end-tidal concentrations of enflurane. This was done to demonstrate any potential deleterious hemodynamic effects of the combination of alpha-2 adrenoceptor agonists with potent inhalational anesthetics. The finding that hemodynamics were the same in both groups during anesthesia except for a slightly lower rate–pressure product in the dexmedetomidine-treated group may reflect the preservation of baroreceptor responsiveness observed with alpha-2 agonists.[18] In studies comparing depths of anesthesia, the MAC of volatile anesthetics was reduced 60–90% after pretreatment with dexmedetomidine.[21] As a result of this additive effect, the combination of enflurane and dexmedetomidine may have resulted in a greater depth of anesthesia and may have blunted the hemodynamic response to emergence and extubation on that basis. However, all dogs in both groups met the same clinical criteria for extubation—criteria chosen to reflect the clinical situation, and by application of the same criteria to both groups, to imply a similar level of alertness in each. If "dexmedetomidine anesthesia" accounted for the stable hemodynamics after extubation rather than decreased sympathetic tone, patients nevertheless may benefit from this effect.

This study used arterial blood gas tensions to show significant respiratory depression. Arterial blood gases are a relatively insensitive indicator and would not show minor respiratory depressant effects. For example, Bloor *et al.*[9] measured carbon dioxide response curves in chronically tracheostomized dogs treated with dexmedetomidine and found some depression of the hypercapnic response, despite normal blood gas values.

The ability of orally administered dexmedetomidine to provide sedation, analgesia, and a favorable effect on coronary and systemic hemodynamics without significant respiratory depression or an initial pressor response suggests that this agent may have a potential therapeutic role in anesthesia as a premedicant. It may be especially beneficial in patients with chronic angina pectoris, recent myocardial infarction, or hypertension by reducing primary determinants of myocardial oxygen demand such as heart rate without the respiratory depression observed with narcotic agonists. In addition, emergence from general anesthesia is a period when significant alterations in hemodynamics (such as dramatic increases in heart rate and arterial pressure) occur that may be detrimental to patients with ischemic heart disease. As demonstrated in the current investigation, such potentially hazardous changes may be minimized by pretreatment with dexmedetomidine.

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