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The Effects of the Stereoisomers of the α_2-Adrenergic Agonist Medetomidine on Systemic and Coronary Hemodynamics in Conscious Dogs

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The α_2-adrenergic agonist medetomidine produces systemic hemodynamic effects that are mediated by both peripheral and central nervous system actions. The current investigation was designed to characterize coronary and systemic hemodynamic effects of the D- and L-stereoisomers of medetomidine in conscious, chronically instrumented dogs with and without autonomic nervous system blockade. Dogs were instrumented for measurement of aortic pressure, coronary blood flow velocity, cardiac output, left ventricular pressure, rate of change in pressure (dP/dt), and subendocardial systolic shortening. Administration of the D-isomer of medetomidine (doses of 1.25, 2.5, and 5.0 μg/kg, each administered over 10 min, with 60 min between doses) significantly altered systemic hemodynamics, in a biphasic fashion. A decrease in respiratory rate without change in arterial blood gas tensions occurred. With the 5 μg/kg dose of D-medetomidine, an initial pressor response was followed by secondary, significant ($P < 0.05$), and dose-related decreases in heart rate (74 ± 3 to 57 ± 4 beats per min), mean arterial pressure (109 ± 2 to 100 ± 3 mmHg) and the rate–pressure product (10.5 ± 0.4 to 7.0 ± 0.5 beats · min^{-1} · mmHg · 10^3) accompanied by a reduction in plasma concentrations of norepinephrine. No changes in left ventricular end diastolic pressure or coronary blood flow velocity occurred. In contrast to the D-isomer, the L-isomer (1.25, 2.5 and 5.0 μg/kg) produced no changes in hemodynamics or plasma concentrations of norepinephrine. In dogs pretreated with hexamethonium (20 mg/kg), propranolol (2 mg/kg), and atropine methylnitrate (3 mg/kg) to produce autonomic nervous system blockade, D-medetomidine also produced an initial pressor response, but no secondary reduction in heart rate or arterial pressure occurred. The results indicate that the D-isomer of medetomidine is stereospecific for alterations in hemodynamics: the active D-isomer produces decreases in heart rate, arterial pressure, and the rate–pressure product *via* diminished sympathetic and/or augmented parasympathetic tone. This conclusion is supported by the absence of these changes after pharmacologic blockade of the autonomic nervous system. (Key words: Anesthesia: cardiovascular. Premedication: D-medetomidine. Receptors: α_2 agonists. Sympathetic nervous system: α_2-adrenergic agonists; dexmedetomidine; D-medetomidine, L-medetomidine; autonomic blockade.)

PREVIOUS STUDIES[1–5] have demonstrated the ability of a variety of α_2-adrenergic agonists, including clonidine, to alter systemic hemodynamics. Such alterations are believed to be mediated through activation of α_2-adrenergic receptors in the central nervous system.[6] This results in diminished sympathetic tone and a decrease in arterial blood pressure and heart rate. Recent studies[7] have demonstrated that the α_2-adrenergic agonist, medetomidine, possesses a much higher selectivity than does clonidine for the α_2-adrenergic receptor in peripheral tissues as well as in the central nervous system. Additional evidence has suggested also that the active form of medetomidine is the D-isomer.[8] Alpha$_2$-adrenergic agonists, including medetomidine, have been shown to produce a hypnotic–anesthetic–like action on the central nervous system,[9–11] produce a pattern consistent with sedation in the processed electroencephalogram,[12] and diminish the anesthetic requirements for opioid agonists, barbiturates, and volatile anesthetics.[3–5,11,13–15] These actions within the central nervous system may be mediated through specific α_2-adrenergic receptors. Minimal binding and activation of histaminergic, α_1-adrenergic, serotoninergic, or cholinergic receptors occur.[7]

The ability of α_2-adrenergic agonists to activate α_2 receptors in the peripheral vasculature has been demonstrated previously for clonidine and other specific α_2-adrenergic agonists, including azepexole and B-HT920.[16–22] Activation of peripheral α_2-adrenergic receptors results in significant alterations in systemic and coronary hemodynamics.[16–22] The current investigation was conducted because few studies have examined the action of intravenous administration of the stereoisomers of medetomidine on systemic and coronary hemodynamics in the absence of a baseline anesthetic. Because the central nervous system may mediate the hemodynamic alterations of the α_2 agonists, additional experiments were conducted in the presence of pharmacologic blockade of the autonomic nervous system.

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Materials and Methods

General Preparation

All studies were completed with the prior approval of the Animal Care Committee of the Medical College of Wisconsin. All conformed to the Guide for the Care and Use of Laboratory Animals.§ Anesthesia was induced in 11 conditioned, fasted, mongrel dogs of either sex (22–31 kg) with sodium thiamylal (10 mg/kg intravenously). After tracheal intubation, anesthesia was maintained with halothane (1.0–1.5%) in oxygen *via* positive pressure ventilation using a semi-closed circuit. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs gently retracted. An ultrasonic flow transducer (Transonics, Ithaca, NY) was secured around the aortic root (reinforced with a Dacron patch) for determination of cardiac output. The heart was supported in a pericardial cradle, and heparin-filled catheters were inserted into the thoracic aorta and right atrial appendage for measurement of aortic blood pressure and fluid or drug administration, respectively. A catheter was also implanted in the left atrial appendage.

A 1.5–2.0-cm section of the proximal left anterior descending coronary artery (distal to the first diagonal branch) was isolated, and a precalibrated Doppler (20 MHz) ultrasonic flow transducer (Crystal Biotech, Holliston, MA) was positioned around the vessel for measurement of phasic and mean coronary blood flow velocity. Relative mean coronary vascular resistance was determined by dividing mean arterial pressure (in millimeters mercury) by mean coronary blood flow velocity (in hertz $\times 10^2$) and was expressed in resistance units (RU). A high-fidelity miniature micromanometer (P7, Konigsberg, Pasadena, CA) was inserted into the left ventricle through an incision in the apex for subsequent recording 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 differentiation of the ventricular pressure waveform. The differentiator was calibrated by using a triangular wave signal with known slope. The left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured *via* the arterial and left atrial fluid-filled catheters (Oxnard P50 transducer).

Regional contractile function (as percent segment shortening) was measured in the perfusion territory of the left anterior descending coronary artery by pairs of miniature tubular ultrasonic crystals. Crystals (5 MHz) were inserted parallel to muscle fiber orientation perpendicular to the long axis of the left ventricle, within the subendocardium of the left ventricular free wall (10–15 mm apart and 10 mm deep). The leads of each crystal were connected to an ultrasonic amplifier (Crystal Biotech, Holliston, MA), which transformed the sound pulse transmitted into an electronic signal proportional to the distance between the two crystals. All ultrasonic flow and segment length instrumentation was synchronized. All catheters and leads were secured, tunneled subcutaneously, and exteriorized between the scapulae by several small incisions. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket to prevent damage to the instruments and catheters, which were housed in an aluminum box within the jacket pocket. After surgery, each dog was treated with analgesics, procaine penicillin G (25,000 units/kg), and gentamycin (4.5 mg/kg) and was allowed to recover for 7–10 days prior to experimentation.

End-systolic segment length and end-diastolic segment length were derived from the analog signals at points corresponding to maximum rate of decrease in left ventricular pressure (−dP/dt) and the onset of left ventricular isovolumetric contraction, respectively. Percent segment shortening was calculated as: % SS = ([EDL − ESL]/EDL) × 100 (where % SS = percent segment shortening; EDL = end-diastolic segment length; and ESL = end-systolic length). Each measurement of segment function represented the average of eight consecutive cardiac cycles. Systemic vascular resistance (dyne · s · cm^{-5}) was calculated as mean arterial pressure (mmHg) × 80/cardiac output (l/min). During each experiment, hemodynamic data were recorded continuously on a polygraph and digitized with a microcomputer interfaced to an analog-to-digital converter. Arterial blood samples were obtained at various intervals for measurement of blood gas tensions and plasma norepinephrine concentrations.

Determination of Plasma Norepinephrine

The concentration of norepinephrine in plasma was determined by reverse-phase, high-performance liquid chromatography with electrochemical detection using a modification of a method previously described.[23] Briefly, 4.0-ml blood samples were collected in tubes containing anticoagulant (EGTA) and reduced glutathione (Cat-A-Kit® tube, Upjohn Diagnostics, Kalamazoo, MI). The plasma was harvested by centrifugation and stored at −70° C until analyzed. The internal standard, 3,4-dihydroxybenzylamine (2.5 ng/2 ml) was added to each 2.0 ml plasma sample and the norepinephrine and 3,4-dihydroxybenzylamine extracted as described previously.[23] The lower limit of detectibility of norepinephrine was about 30 pg/ml plasma, with a coefficient of variation for the method of 4.2%.

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Experimental Protocols

Three experimental groups (n = 9 each) were completed in the same conscious dogs that were fasted overnight. In two dogs, multiple instrumentation failed before completion of all experiments; these two dogs were not used in subsequent data analysis. Prior to experimentation, fluid replacement was accomplished with 0.9% normal saline (approximately 500 ml), and fluid maintenance was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. In each group, control hemodynamics were continuously recorded for 30 min in the conscious, nonsedated state. Arterial samples were obtained during the control period for measurement of blood gas tensions and plasma norepinephrine.

In the first experimental group, each dog received sequential, increasing doses of D-medetomidine (1.25, 2.5, and 5.0 μg/kg). In this fashion a cumulative dose response was obtained. Each dose was infused slowly over a period of 10 min. Sixty minutes was allowed between doses. Systemic and coronary hemodynamics were assessed at two times for each dose: immediately after completion of drug administration as the peak early effect and 60 min after completion of each drug infusion as the late response. Arterial samples were obtained also 60 min after administration of each dose for measurement of arterial gas tensions and plasma norepinephrine concentrations. The second experimental group was treated in an identical fashion, except that increasing doses of L-medetomidine (1.25, 2.5, and 5.0 μg/kg) were administered. Hemodynamic responses, arterial blood gas tensions, and plasma norepinephrine levels were determined as in the first group.

In the third experimental group, after baseline hemodynamic measurements, arterial gas tensions, and plasma norepinephrine concentrations were obtained, autonomic nervous system blockade was accomplished by intravenous administration of hexamethonium bromide (20 mg/kg), propranolol hydrochloride (2 mg/kg), and atropine methylnitrate (3 mg/kg). Previous studies from this laboratory demonstrated that these doses are sufficient to produce complete autonomic nervous system blockade for the duration of these experiments.[19,24,25] During a stable hemodynamic state 30 min after autonomic nervous system blockade, hemodynamics, arterial gas tensions, and plasma catecholamine concentrations were measured. Two doses of D-medetomidine (1.25 and 2.5 μg/kg) then were administered, and hemodynamic responses, arterial blood gas tensions, and plasma catecholamines determined as in the first and second experimental groups. A period of 3 days was allowed between each experiment performed in each dog.

Drugs

Fresh solutions of all drugs were prepared on the day of each experiment. Hexamethonium bromide, atropine methylnitrate, propranolol hydrochloride, D-medetomidine, and L-medetomidine were dissolved in 0.9% sodium chloride. D-medetomidine, and L-medetomidine were obtained from Orion Corp., Farmos Group Ltd., Turku, Finland.

Statistical Analysis

Statistical analysis of data within and between groups during the conscious state with and without autonomic nervous system blockade and after drug administration was performed by 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 probability (*P*) value was <0.05. All data are expressed as means ± standard error of the means.

Results

Hemodynamic Effects of D-Medetomidine

The effects of cumulative doses of D-medetomidine (1.25, 2.5, and 5.0 μg/kg) on systemic hemodynamics are summarized in table 1. The hemodynamic actions of D-medetomidine were biphasic. Immediately after infusion of D-medetomidine significant increases in mean arterial and left ventricular systolic pressures (table 1) were observed. However, 60 min after the infusion of D-medetomidine (table 1 and fig. 1), there was a dose-dependent decrease in mean arterial and left ventricular systolic pressure as compared to control. Immediately after each infusion of D-medetomidine (during peak increases in arterial pressure), there was a decrease in heart rate. However, 60 min after drug infusion of 2.5 and 5.0 μg/kg D-medetomidine (fig. 1), heart rate remained reduced in the presence of a decrease in arterial pressure. After the 5.0 μg/kg dose of D-medetomidine, heart rate decreased to 77% of control (74 ± 3 to 57 ± 4 beats per min) 60 min after infusion. These hemodynamic alterations resulted in a significant decrease in the rate–pressure product 60 min after 2.5 and 5.0 μg/kg D-medetomidine (fig. 1).

An increase in left ventricular end diastolic pressure was observed early after administration of D-medetomidine (table 1). Immediately after infusion of the 5 μg/kg dose of D-medetomidine, left ventricular end-diastolic pressure increased from 8 ± 1 to 23 ± 3 mmHg. Cardiac output and dP/dt_{50} decreased immediately after admin-

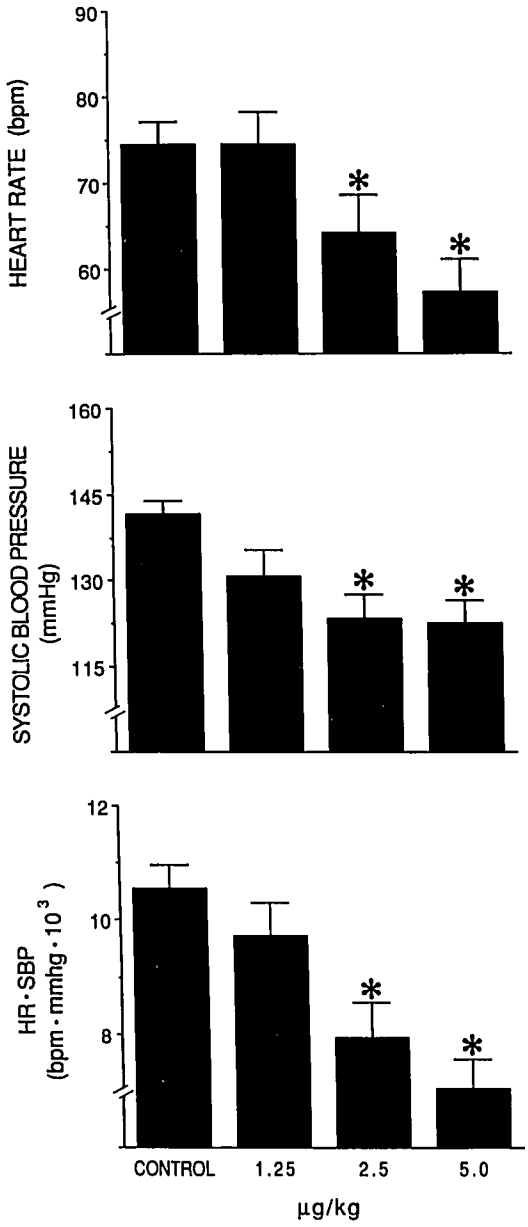

FIG. 1. The effects of D-medetomidine (sequential doses of 1.25, 2.5, and 5.0 μg/kg) on heart rate, systolic blood pressure, and the rate–pressure (HR·SBP) product 60 min after drug administration. *Significantly different ($P < 0.05$) from control.

istration of each sequential dose of D-medetomidine and remained reduced 60 min after drug administration. Systemic vascular resistance increased immediately after each dose of D-medetomidine. However, 60 min after drug infusion there was no change in systemic vascular resistance as compared to control. Percent segment shortening decreased significantly immediately after administration of each dose of D-medetomidine. However, by 60 min after infusion, no changes in percent segment shortening were observed.

The actions of cumulative doses of D-medetomidine on coronary hemodynamics are summarized in table 2. No changes in diastolic and mean coronary blood flow velocity were observed. However, the increases in mean arterial pressure produced by all three doses of D-medetomidine resulted in significant increases in calculated diastolic and mean coronary vascular resistance immediately after each drug infusion. At 60 min after drug infusion, coronary vascular resistance returned to control levels. Administration of D-medetomidine produced a cumulative dose-dependent decrease in respiratory rate (table 3). No alterations in arterial blood gas tensions were observed early or late after any dose of D-medetomidine. D-medetomidine produced significant decreases in plasma norepinephrine concentrations (fig. 2) immediately and 60 min after drug infusion.

HEMODYNAMIC ACTIONS OF L-MEDETOMIDINE

Changes in systemic hemodynamics produced by the administration of cumulative doses of L-medetomidine (1.25, 2.5, and 5.0 μg/kg) are summarized in table 4 and figure 3. In contrast to D-medetomidine, no changes in systemic hemodynamics were observed after any dose of L-medetomidine. Similarly, no changes in coronary blood flow velocity or coronary vascular resistance were observed (table 5). No alterations in arterial blood gas tensions, respiratory rate (table 6), or plasma norepinephrine concentrations (fig. 2) were produced by L-medetomidine.

HEMODYNAMIC EFFECTS OF D-MEDETOMIDINE AFTER AUTONOMIC NERVOUS SYSTEM BLOCKADE

The hemodynamic effects of D-medetomidine (1.25 and 2.5 μg/kg) on systemic hemodynamics after auto-

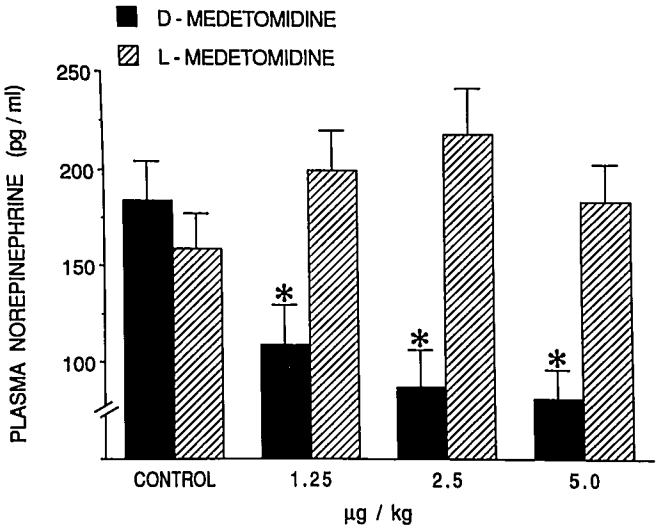

FIG. 2. The effect of D- and L-medetomidine (sequential doses of 1.25, 2.5, and 5.0 μg/kg) on plasma norepinephrine 60 min after drug administration. *Significantly different ($P < 0.05$) from control.

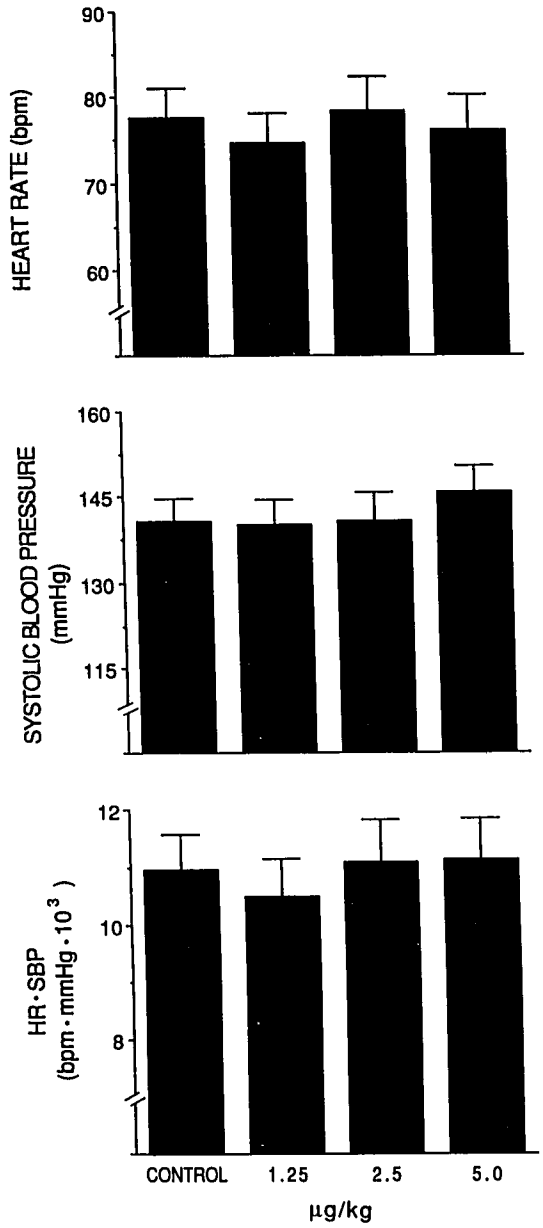

FIG. 3. The effects of L-medetomidine (sequential doses of 1.25, 2.5, and 5.0 μg/kg) on heart rate, systolic arterial blood pressure, and the rate-pressure (HR · SBP) product 60 min after drug administration. *Significantly different ($P < 0.05$) from control.

nomic nervous system blockade are summarized in table 7. After combined ganglionic, cholinergic, and β-adrenergic blockade, significant decreases in mean arterial and left ventricular systolic pressures, dP/dt_{50}, stroke volume, systemic vascular resistance, and segment shortening were observed. Heart rate was increased from 76 ± 4 to 111 ± 8 beats per min. Left ventricular end-diastolic pressure and cardiac output were unchanged. The pressor responses to D-medetomidine immediately after drug infusion were accentuated by autonomic nervous system blockade. The increases in mean arterial and left ventricular systolic pressures were accompanied by increases in heart rate and decreases in segment shortening, dp/dt_{50}, and cardiac output. The increase in mean arterial pressure 60 min after 2.5 μg/kg D-medetomidine administration remained as it had without blockade. Early after infusion of D-medetomidine, significant increases in systemic vascular resistance were observed (table 7).

The actions of D-medetomidine on coronary hemodynamics after autonomic blockade are summarized in table 8. Autonomic blockade alone did not alter coronary blood flow velocity or coronary vascular resistance. In autonomically blocked dogs, administration of D-medetomidine significantly increased diastolic and mean coronary blood flow velocity as well as diastolic and mean coronary vascular resistance. At 60 min after drug infusion, coronary flow velocity and vascular resistance had returned to control. No significant changes in arterial blood gas tensions were observed after autonomic nervous system blockade or after either dose of D-medetomidine (table 9). After autonomic nervous system blockade, a significant decrease in respiratory rate was observed. The administration of D-medetomidine after autonomic blockade resulted in a significant decrease in respiratory rate at the 2.5 μg/kg dose. Autonomic nervous system blockade produced profound decreases in plasma norepinephrine concentrations. Norepinephrine concentrations remained extremely low during subsequent administration of both doses of D-medetomidine.

Discussion

The purpose of the current investigation was to examine the hemodynamic actions of the D- and L-stereoisomers of medetomidine in chronically instrumented dogs with and without concomitant autonomic nervous system blockade. The obtained results were consistent with previous studies[8,13] indicating stereospecificity of the isomers of medetomidine for the sedation and for alterations in hemodynamics. The D-isomer was found to be the active form. In contrast, the L-isomer produced inconsistent sedation and no hemodynamic changes. The intravenous administration of D-medetomidine caused a biphasic pressor–depressor response, characterized by an early hypertensive phase that preceded any beneficial hemodynamic action. After an initial pressor phase, D-medetomidine reduced heart rate, mean arterial pressure, and the rate–pressure product in a dose-dependent manner. No change in coronary blood flow velocity was observed. In dogs with autonomic nervous system blockade, the initial pressor phase remained; however, the late reductions in arterial pressure and heart rate were absent.

Previous studies[1,5–11] demonstrated that α_2-adrenoceptor agonists, including clonidine and medetomidine,

TABLE 5. The Actions of L-Medetomidine on Coronary Hemodynamics in Chronically Instrumented Dogs

	n	Conscious Control	1.25 μg/kg		2.5 μg/kg		5.0 μg/kg	
			Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion
Diastolic coronary blood flow velocity (Hz × 10^2)	6	31 ± 4	35 ± 6	32 ± 5	32 ± 5	31 ± 4	32 ± 5	30 ± 5
Mean coronary blood flow velocity (Hz × 10^2)	6	21 ± 4	21 ± 4	21 ± 4	21 ± 4	21 ± 3	22 ± 4	20 ± 4
Diastolic coronary vascular resistance (RU)	6	3.40 ± 0.60	3.11 ± 0.57	3.20 ± 0.58	3.32 ± 0.67	3.28 ± 0.57	3.25 ± 0.57	3.58 ± 0.60
Mean coronary vascular resistance (RU)	6	5.99 ± 1.09	5.85 ± 0.87	5.96 ± 1.06	6.09 ± 1.14	6.04 ± 1.11	5.81 ± 1.00	6.90 ± 1.43

Mean ± SEM data.

are potentially useful adjuncts to anesthetic management. Putative beneficial effects include improved hemodynamic stability,[3–5] reduction in anesthetic requirements,[3–5,13–15,26] sedation/hypnosis,[10,11] and analgesia.[27] These effects are believed to be mediated through actions within the central nervous system and occur in the absence of significant respiratory depression or alteration of baroreceptor reflexes.[2–3,11–23,26–28] The central antihypertensive, anxiolytic, and antinociceptive actions of the α_2-adrenoceptor agonists may be mediated through binding sites in various noradrenergic and adrenergic brainstem visceral nuclei, the periaqueductal gray region, substantia gelatinosa, intralaminar nuclei of the thalamus, and/or various limbic and infralimbic areas.[29] The initial subclassification of α adrenoceptors was based on anatomical location; the α_1 receptor was that which is located postsynaptically and the α_2 receptor that located presynaptically.[29,30] Presynaptic α_2 receptor stimulation has been demonstrated to decrease catecholamine release from adrenergic neurons in the central nervous system.[30] However, it has been established that α_2 receptors exist both pre- and postsynaptically and that the preponderance of α_2 adrenoceptors in the central nervous system may be located postsynaptically.[31]

Paradoxically, although α_2-adrenergic agonists are centrally acting antihypertensive agents,[32] peripheral effects of these drugs may include intense vasoconstriction with initial transient increases in systemic arterial pressure.[33,34] This pressor effect occurs through vascular postsynaptic α_2-adrenoceptor activation and consequent mediation of an influx of extracellular calcium.[19,35,36] The longer-lasting hypotensive action, in combination with bradycardia, is mediated at bulbar vasomotor and cardiac centers,[37–39] with contributions from the supracollicular central nervous system.[40–42]

The current investigation supports previous studies[8,13,43] that have demonstrated that the D-isomer of medetomidine (or "dexmedetomidine") is the active drug form for production of vasoactive and sedative responses. However, in the current experiments, despite initial pressor responses after administration of D-medetomidine, subsequent decreases in systemic arterial pressure and heart rate were relatively small. This may have been related to a low sympathetic tone in trained, chronically instrumented dogs. Previous studies have demonstrated that while clonidine is a mixed partial α_2 agonist, D-medetomidine is a more selective (α_2/α_1 selectivity ratio of 1,620) and efficacious agent. Bousquet *et al.*[44] and Ernsberger *et al.*[45] recently proposed that imidazoline-sensitive, catecholamine-insensitive membrane receptors located in the ventrolateral area of the medulla are important sites in the mediation of the hemodynamic actions of several centrally acting antihypertensive agents. Rilmenidine, a new centrally acting antihypertensive agent with minimal sedative actions, has a much higher α_2/α_1 selectivity ratio and is two and one half times more selective than clonidine for these imidazoline receptors.[45–47] The specific binding characteristics of D-medetomidine for these imidazoline receptors has not yet been investigated. However, while the sedative and anesthetic-sparing actions of D-medetomidine may represent actions at α_2-adrenergic receptors within higher central nervous system loci and the initial pressor responses may represent actions at similar receptors in the peripheral vasculature, the central sympatholytic effects may be mediated at imidazoline-binding sites in the central nervous system where D-medetomidine may be a less efficacious agent.

In the current experiments, no changes in diastolic or mean coronary blood flow velocity were observed after D- or L-medetomidine. After autonomic blockade, however, increases in diastolic or mean coronary blood flow velocity or both occurred immediately after the intravenous administration of D-medetomidine, concomitant with the profound systemic pressor response and increase in oxygen demand. However, after the peripheral pressor response resolved, no significant changes in coronary blood flow velocity had occurred. Whereas myocardial perfusion is predominantly metabolically autoregulated,

TABLE 6. The Actions of L-Medetomidine on Arterial Blood Gas Tensions, Respiratory Rate, and Plasma Norepinephrine Concentration in Chronically Instrumented Dogs

	n	Conscious Control	1.25 μg/kg		2.5 μg/kg		5.0 μg/kg	
			Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion
pH	9	7.40 ± 0.01	7.41 ± 0.01	7.42 ± 0.01	7.41 ± 0.01	7.41 ± 0.01	7.43 ± 0.02	7.43 ± 0.02
Pa_{CO_2} (mmHg)	9	32 ± 1	30 ± 1	31 ± 1	30 ± 1	30 ± 1	30 ± 1	31 ± 1
Pa_{O_2} (mmHg)	9	84 ± 2	87 ± 3	85 ± 4	84 ± 3	82 ± 2	85 ± 3	86 ± 1
Respiratory rate (breaths per min)	8	25 ± 2	25 ± 3	24 ± 2	23 ± 3	27 ± 2	20 ± 2	27 ± 3
Plasma norepinephrine (pg/ml)	8	159 ± 18	209 ± 17	200 ± 20	199 ± 16	218 ± 24	170 ± 16	183 ± 19

Mean ± SEM data.

neurogenic modulation of coronary blood flow has been shown to occur.[48] Previous work[21-22] has suggested the presence of both α_1- and α_2- adrenoceptors in coronary epicardial, resistance and collateral vessels. Other studies[20-22] have demonstrated a predominance of α_2 receptors in mediating coronary vasoconstrictor responses to cardiac nerve stimulation or α adrenergic agonists. Furthermore, intracoronary infusion of the α_2-adrenergic agonist B-HT920 has been shown to cause vasoconstriction.[49,50] In the current investigation, coronary vascular resistances were elevated only immediately after infusion of D-medetomidine, reflecting the transient elevation of systemic arterial pressure. After autonomic nervous system blockade, D-medetomidine initially increased both mean and diastolic coronary artery blood flow velocities during abrupt increases in aortic pressure. At 60 min after administration of D-medetomidine there were no significant differences in coronary artery blood flow velocities or in calculated vascular resistances.

These results are in sharp contrast to a recent report[51] that demonstrated a dose-dependent decrease in coronary blood flow and an increase in regional myocardial oxygen extraction immediately after D-medetomidine in dogs anesthetized with thiopental, halothane, and nitrous oxide. However, a recent report[1] that used chronically instrumented dogs demonstrated that the oral administration of D-medetomidine eliminates the initial pressor response and produces similar late systemic hemodynamic changes without altering coronary blood flow velocities.[1] Differences in experimental methodologies, use of acute versus chronic experimental animals, and the confounding presence of other anesthetic agents, including barbiturates and volatile anesthetics, both of which have been demonstrated to alter α-adrenergic responses,[52-54] may explain these discrepancies in results. It is possible also that large increases in myocardial oxygen demand during the early pressor phase may have offset any direct peripheral vasoconstrictor actions of D-medetomidine through metabolic autoregulatory phenomena.

Previous studies in experimental animals[55,56] and in humans[57] have demonstrated that D-medetomidine has minimal effects on arterial blood gas tensions but produces a small depression of the carbon dioxide–ventilation response curve, perhaps secondary to the profound sedation rather than to a specific α_2-adrenergic-modulated action on respiration.[58] The current results confirm these previous findings.[55-58] The L-isomer had no effect, and the D-isomer, though depressing respiratory rate, did not alter arterial blood gas tensions. A decrease in respiratory rate occurred immediately after the infusion of D-medetomidine during the period of increased systemic arterial pressure, suggesting that D-medetomidine may have produced effects within the central nervous system concurrent with the peripheral pressor response.

TABLE 7. The Actions of D-Medetomidine on Systemic Hemodynamics after Autonomic Nervous System Blockade in Chronically Instrumented Dogs

	n	ANS Block		D-Medetomidine			
				1.25 μg/kg		2.5 μg/kg	
		Before	After	Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion
Heart rate (beats per min)	9	76 ± 4*	111 ± 8	121 ± 9	115 ± 8	123 ± 7*	114 ± 7
Mean arterial pressure (mmHg)	9	111 ± 2*	85 ± 6	181 ± 8	93 ± 5	207 ± 6*	98 ± 6*
Left ventricular systolic pressure (mmHg)	9	145 ± 4*	104 ± 7	192 ± 8	109 ± 5	214 ± 5*	112 ± 6
Left ventricular end-diastolic pressure (mmHg)	8	8 ± 1	8 ± 1	20 ± 3	8 ± 1	26 ± 2*	9 ± 1
$+dP/dt_{50}$ (mmHg/s)	9	2,069 ± 92*	1,588 ± 83	1,401 ± 95	1,579 ± 59	1,152 ± 163*	1,524 ± 60
Cardiac output (l/min)	5	2.4 ± 0.2	2.6 ± 0.2	1.9 ± 0.3	2.2 ± 0.2	1.5 ± 0.3*	1.9 ± 0.2*
Stroke volume (ml)	5	30 ± 2*	23 ± 3	16 ± 2	20 ± 4	12 ± 2*	17 ± 3*
Systemic vascular resistance (dyne · s · cm^{-5})	5	3,921 ± 285	2,618 ± 84	8,738 ± 1,597	3,586 ± 397	13,079 ± 2,308*	4,404 ± 513
Segment shortening (%)	9	19.6 ± 1.6*	15.5 ± 1.9	7.3 ± 0.8	16.5 ± 1.7	5.6 ± 1.0*	15.4 ± 1.5

Mean ± SEM data.
ANS block = autonomic nervous system blockade (hexamethonium [2 mg/kg], propranolol [2 mg/kg], and atropine methylnitrate [3 mg/kg]).
* Significantly different from after ANS block ($P < 0.05$).

Other investigators have studied the actions of α_2-adrenergic agonists in autonomically blocked animals. Laubie and Schmitt,[59] studying dogs with various combinations of reserpine, vagotomy, β-adrenergic blockade, muscarinic receptor blockade, and carotid sinus denervation, concluded that alterations in both sympathetic and parasympathetic tone were responsible for the changes in heart rate and cardiac output produced by intravenous clonidine. However, the clonidine-induced changes in systemic arterial pressure represented a primarily sympatholytic action within the central nervous system. Recently, Flacke *et al.*[60] investigated the effects of D-medetomidine in dogs anesthetized with thiopental, isoflurane, and nitrous oxide. Autonomic blockade was produced by vagal transection and an epidural blockade of the thoracolumbar areas by injection of tetracaine. Observed after D-medetomidine were significant increases in mean arterial pressure, systemic vascular resistance index, and left ventricular end-diastolic pressure; a decrease in the cardiac index; and no change in heart rate. Flacke *et al.*[60] interpreted this data as supportive of a direct myocardial depressant action of D-medetomidine.

In the current investigation, similar hemodynamic effects were observed immediately after administration of D-medetomidine. An abrupt increase in arterial pressure would be expected to cause a reduction in afterload-dependent indices of contractility, such as cardiac output, dP/dt, or segment shortening. Furthermore, an increase

TABLE 8. The Actions of D-Medetomidine on Coronary Hemodynamics after Autonomic Nervous System Blockade in Chronically Instrumented Dogs

	n	ANS Block		D-Medetomidine			
				1.25 μg/kg		2.5 μg/kg	
		Before	After	Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion
Diastolic coronary blood flow velocity (Hz × 10^2)	6	33 ± 4	34 ± 7	48 ± 10	31 ± 4	42 ± 6*	30 ± 4
Mean coronary blood flow velocity (Hz × 10^2)	6	23 ± 3	25 ± 4	32 ± 6*	22 ± 4	30 ± 4*	21 ± 4
Diastolic coronary vascular resistance (RU)	6	3.21 ± 0.57	2.54 ± 0.60	4.05 ± 0.89*	2.95 ± 0.48	4.80 ± 0.64*	3.04 ± 0.43
Mean coronary vascular resistance (RU)	6	5.36 ± 0.90	4.08 ± 1.06	6.35 ± 1.30*	4.58 ± 0.80	7.13 ± 0.97*	4.81 ± 0.74

Mean ± SEM data.
ANS block = autonomic nervous system blockade (hexamethonium [20 mg/kg], propranolol [2 mg/kg], and atropine methyl nitrate [3 mg/kg]).
* Significantly different from after ANS block ($P < 0.05$).

TABLE 9. The Actions of D-Medetomidine on Arterial Blood Gas Tensions Respiratory Rate, and Plasma Norepinephrine Concentration after Autonomic Nervous System Blockade in Chronically Instrumented Dogs

	n	ANS Block		D-Medetomidine			
				1.25 μg/kg		2.5 μg/kg	
		Before	After	Postinfusion	60 min Postinfusion	Postinfusion	60 min Postinfusion
*p*H	9	7.41 ± 0.01	7.3 ± 0.02	7.38 ± 0.02	7.40 ± 0.01	7.40 ± 0.01	7.41 ± 0.01
Pa_{CO_2} (mmHg)	9	31 ± 1	32 ± 1	31 ± 1	32 ± 1	31 ± 1	33 ± 2
Pa_{O_2} (mmHg)	9	86 ± 2	86 ± 2	87 ± 3	85 ± 2	87 ± 3	82 ± 3
Respiratory rate (breaths per min)	9	28 ± 3	21 ± 3	16 ± 2	22 ± 2	15 ± 1*	17 ± 2
Plasma norepinephrine (pg/ml)	8	238 ± 19	70 ± 23	56 ± 21	56 ± 23	108 ± 28	74 ± 27

Mean ± SEM data.
ANS block = autonomic nervous system blockade (hexamethonium [20 mg/kg], propranolol [2 mg/kg], and atropine methyl nitrate [3 mg/kg]).
* Significantly different from after ANS block ($P < 0.05$).

in left ventricular end-diastolic pressure also would be expected during an abrupt increase in impedance to left ventricular ejection. Other studies[61,62] using the selective α_2-adrenergic agonists B-HT920 and azepexole were unable to demonstrate decreases in cardiac output. In addition, a recent *in vitro* investigation by Housmans[63] showed that D-medetomidine has no direct negative inotropic actions in isolated ferret papillary muscle.

In summary, the current investigation documents the ability of the D-isomer of medetomidine, but not the L-isomer, to produce a biphasic alteration in systemic hemodynamics after intravenous administration. Pressor responses were observed immediately after intravenous infusion, but within 1 h, a decrease in heart rate and arterial pressure was observed. No changes in coronary blood flow or arterial blood gas tensions occurred. After autonomic nervous system blockade, the initial pressor responses were augmented and the secondary central nervous system-mediated sympatholytic action eliminated. The augmented pressor responses may indicate the absence of baroreceptor modulation after autonomic nervous system blockade. Similarly, for D-medetomidine to produce a beneficial hemodynamic effect, some preexisting sympathetic tone may be required. The current study does not support a direct myocardial depressant action of D-medetomidine. Specific studies to examine the action of D-medetomidine on myocardial contractile function in the presence and absence of alterations in preload and afterload are necessary to characterize fully such an action. Therefore, the results do indicate that D-medetomidine produces beneficial hemodynamic effects dependent on an intact autonomic nervous system and that these effects may provide a useful adjunct for general anesthesia.

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