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Dexmedetomidine Alters the Hemodynamic Effects of Desflurane and Isoflurane in Chronically Instrumented Dogs

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Background: **Previous studies have shown that desflurane and isoflurane produce similar hemodynamic actions. This investigation examined the cardiovascular effects of desflurane and isoflurane in the presence or absence of dexmedetomidine, a highly selective α_2-adrenergic agonist that may be clinically useful as a premedicant or anesthetic adjuvant.**

Methods: **Four groups, comprising 40 experiments, were performed using ten dogs that were chronically instrumented for measurement of aortic and left ventricular pressure, the maximum rate of increase of left ventricular pressure (dP/dt_{max}), diastolic coronary blood flow velocity, cardiac output, and subendocardial segment length. On separate experimental days, systemic and coronary hemodynamics were recorded, and plasma concentrations of catecholamines were measured with or without oral dexmedetomidine pretreatment (30 μg/kg) in the conscious state and after 15 min of equilibration at 1.0, 1.3, and 1.6 end-tidal MAC desflurane or isoflurane in a random fashion.**

Results: **In conscious dogs, dexmedetomidine significantly decreased heart rate, cardiac output, percent segment shortening (%SS), left ventricular dP/dt_{max}, myocardial oxygen consumption (as estimated by the pressure-work index), and plasma norepinephrine concentration. Concomitant increases in systemic and diastolic coronary vascular resistance were observed. Pretreatment with dexmedetomidine decreased peak increases in heart rate during desflurane and isoflurane anesthesia. Mean arterial pressure was reduced less by desflurane than by isoflurane in the absence of dexmedetomidine. This difference was abolished in dogs pretreated with dexmedetomidine. Desflurane, but not isoflurane, decreased cardiac output in dexmedetomidine-pretreated dogs when compared with untreated dogs. Concomitantly, systemic vascular resistance was greater in desflurane- *versus* isoflurane-anesthetized dogs pretreated with dexmedetomidine. No differences in myocardial contractility, as assessed by left ventricular dP/dt_{max} and %SS, were observed between desflurane and isoflurane groups in the absence or presence of dexmedetomidine.**

Conclusions: **The results indicate that the cardiovascular actions of desflurane or isoflurane are similar in the absence or presence of dexmedetomidine; however, some differences between anesthetic groups were noted. In the presence of dexmedetomidine, systemic vascular resistance during desflurane anesthesia was higher when compared with that during isoflurane anesthesia, indicating that desflurane produces less pronounced direct effects on peripheral vascular tone. The concomitant greater reductions in cardiac output are consistent with greater impedance to left ventricular outflow in desflurane-anesthetized dogs pretreated with dexmedetomidine, because no differences in contractile function were observed between volatile anesthetics. In contrast, cardiac output during isoflurane anesthesia after pretreatment with oral dexmedetomidine is better maintained secondary to the peripheral vasodilator actions of this agent.** **(Key words: Anesthetics, volatile: desflurane; isoflurane. Heart: blood flow; cardiac output; cardiovascular physiology; coronary hemodynamics. Pharmacodynamics: dexmedetomidine, oral. Sympathetic nervous system, α-adrenergic agonists: dexmedetomidine. Sympathetic nervous system, receptor: α_2 agonists.)**

α_2-ADRENOCEPTOR agonists have been shown to be useful premedicants and anesthetic adjuvants. Dexmedetomidine, a highly selective α_2 agonist,[1,2] produces sedation in laboratory animals[1,3] and humans.[4] Premedication with α_2 agonists, including clonidine or dexmedetomidine, produces minimal respiratory depression,[5] reduces anesthetic requirements,[6–9] improves intraoperative hemodynamic stability,[6,7,10,11] and attenuates the hemodynamic response to tracheal intubation[8] and emergence from anesthesia.[12] These effects result from decreased central sympathetic ner-

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vous system outflow secondary to α_2 adrenoceptor stimulation in medullary bulbar vasomotor and cardiac centers.[1] This mechanism of action is indirectly supported by the observation that stress hormone responses, as indicated by serum epinephrine, norepinephrine, and vasopressin concentrations, are blunted by treatment with clonidine before aortic surgery.[10] The systemic and coronary hemodynamic actions and stress hormone responses have been previously characterized after premedication with α_2 agonists during isoflurane and enflurane anesthesia,[6,9,12,13] in the presence of intravenous anesthetic infusions,[14] and during fentanyl anesthesia.[8,10,11]

Desflurane has been demonstrated to produce cardiovascular effects that are remarkably similar to those produced by isoflurane, with only slight differences.[15–18] However, the interactions between α_2-adrenoceptor agonists such as dexmedetomidine and desflurane are unknown. The current investigation examined and compared the systemic and coronary hemodynamic actions of desflurane or isoflurane anesthesia in the presence and absence of dexmedetomidine, to test the hypothesis that differences between desflurane and isoflurane are eliminated by pretreatment with dexmedetomidine. In addition, plasma norepinephrine concentrations were measured to assess the degree of autonomic nervous system tone before and during anesthesia with each agent. A chronically instrumented canine model was chosen to eliminate the impact of acute surgical intervention, and to provide the advantage of a baseline conscious state for comparison.

Materials and Methods

Animal Instrumentation

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. Furthermore, all conformed to the *Guiding Principles in the Care and Use of Animals of the American Physiologic Society*, and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (DHEW [DHHS] publication no. [NIH] 85-23, revised 1985).

Conditioned mongrel dogs (n = 10) weighing 25 ± 1 kg (mean ± SEM) were anesthetized and instrumented under sterile conditions, as previously described.[16] Catheters were placed in the descending thoracic aorta and the right atrium for measurement of aortic blood pressure and fluid administration, respectively. A precalibrated Doppler ultrasonic flow transducer was placed around the proximal left anterior descending coronary artery for measurement of blood flow velocity. A pair of miniature ultrasonic segment-length transducers (5 MHz) were inserted in the left ventricular subendocardium for measurement of regional contractile function. A high-fidelity micromanometer (Model P7; Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricular cavity for measurement of left ventricular pressure and the peak rate of increase of left ventricular pressure (dP/dt_{max}). An ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of relative cardiac output (minus coronary blood flow). All instruments were tunneled subcutaneously and exteriorized between the scapulae through a small incision.

Antibiotic prophylaxis consisted of intravenous 40 mg/kg cephazolin and 5 mg/kg gentamicin. All dogs were treated with intramuscular analgesics as needed (fentanyl-droperidol; Pitman-Moore, Mundelein, IL) for 2–3 days in the immediate postoperative period. Dogs were allowed to recover for a minimum of 7 days before experimentation, and were trained to stand quietly in a sling during hemodynamic monitoring. Segment length and coronary blood flow velocity signals were monitored by ultrasonic amplifiers (Crystal Biotech, Hopkinton, MA). End-systolic segment length (ESL) was determined at maximum negative left ventricular dP/dt, and end-diastolic length (EDL) was determined at the onset of left ventricular isovolumic contraction. The lengths were normalized according to the method described by Theroux *et al.*[19] Percent segment shortening (%SS) was calculated using the formula: %SS = (EDL − ESL) × 100/EDL. Relative coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow velocity (Hz × 10^2). The pressure-work index, an estimate of myocardial oxygen consumption, was calculated using the formula of Rooke and Feigl,[20] as previously described.[21] Hemodynamic data were continuously recorded on a Hewlett-Packard polygraph (model 7758A; Hewlett-Packard, San Francisco, CA) and digitized by a computer interfaced with an analog-to-digital converter.

Measurement of Plasma Norepinephrine

The method used to determine the concentration of norepinephrine in plasma has been previously described.[22] Briefly, norepinephrine concentrations were measured from arterial blood samples by reverse-phase, high-performance liquid chromatography. All samples were extracted with the use of alumina. The internal standard consisted of 3,4 dihydroxybenzylamine. The mobile phase consisted of 1 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 178 ml tetrahydrofuran. Absolute retention times of norepinephrine and 3,4 dihydroxybenzylamine were 8.7 and 14.5 min, respectively. The lower limit of detectability of norepinephrine was approximately 30 pg/ml, with a coefficient of variation for the method of 4.2%.

Experimental Protocol

All dogs were fasted overnight, and fluid deficits were replaced with crystalloid (500 ml, 0.9% saline) before experimentation. Maintenance fluids were continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ (0.9% saline) for the duration of each experiment. All dogs were randomly assigned to receive desflurane or isoflurane anesthesia with or without pretreatment of oral dexmedetomidine (30 μg/kg) on 4 different days. In two groups of experiments, inhalation induction was accomplished with desflurane or isoflurane in 100% O_2 after baseline systemic and coronary hemodynamics, arterial blood gases, and plasma norepinephrine concentrations were obtained in the conscious state. Hemodynamics were recorded, and, after inhalation induction and tracheal intubation, anesthesia was maintained at 1, 1.3, and 1.6 end-tidal MAC in a nitrogen (70%)/oxygen (30%) mixture. Arterial blood gases were maintained at conscious levels during anesthesia by adjustment of nitrogen and oxygen concentrations and respiratory rate. End-tidal concentrations of volatile anesthetics were measured with an anesthetic gas analyzer (Datex Capnomac, Helsinki, Finland). The gas analyzer was calibrated with known standards before and during experimentation. Canine MAC values for desflurane and isoflurane used in this investigation were 7.2 and 1.28%, respectively.[23,24] Systemic and coronary hemodynamics were recorded, and plasma norepinephrine concentrations were measured after 15 min of equilibration at each anesthetic concentration.

In two additional groups of experiments, desflurane or isoflurane was administered after pretreatment with oral dexmedetomidine (30 μg/kg). Systemic and coronary hemodynamics, arterial blood gases, and plasma concentrations of norepinephrine were measured in the conscious state and 60 min after administration of dexmedetomidine. Inhalation induction was then accomplished, and anesthesia was maintained at 1, 1.3, and 1.6 end-tidal MAC desflurane or isoflurane in a random fashion. Hemodynamics and plasma norepinephrine concentrations were obtained at each anesthetic concentration, as described above. The anesthetic agent was discontinued and emergence allowed to occur at the completion of all experiments. The dogs were allowed to recover for 2 days before subsequent experimentation. Thus, a total of 40 experiments were performed in 4 separate groups (desflurane and isoflurane alone or after pretreatment with dexmedetomidine) in which the same 10 dogs were used.

Statistical Analysis

Statistical analysis of the data within and between groups in the conscious state, with and without dexmedetomidine pretreatment, and during all anesthetic interventions was performed by multiple ANOVA (MANOVA) with repeated measures followed by Duncan's modification of the Student's *t* test. Changes within and between groups were considered statistically significant when $P < 0.05$. All data are reported as mean ± SEM.

Results

Desflurane anesthesia produced significant ($P < 0.05$) increases in heart rate and decreases in mean arterial pressure, left ventricular systolic pressure, and stroke volume (table 1). Dose-related decreases in myocardial contractility, as assessed by peak positive left ventricular dP/dt_{max} (2,246 ± 158 during the conscious state to 1,213 ± 145 mmHg/s at 1.6 MAC) and %SS (21 ± 4 during the conscious state to 10 ± 3% during 1.6 MAC), were observed during administration of desflurane. No change in cardiac output, systemic vascular resistance, diastolic coronary blood flow velocity, coronary vascular resistance, rate pressure product, pressure work index, or plasma norepinephrine concentration, as compared with the conscious state, was observed (table 1, figs. 1–3).

The systemic and coronary hemodynamic actions of isoflurane were similar to those produced by desflurane. Isoflurane anesthesia produced increases in heart rate and decreases in mean arterial pressure, left ventricular systolic pressure, left ventricular dP/dt_{max}, %SS, and stroke volume (table 2). In contrast to desflurane, isoflurane caused decreases in systemic vascular resistance,

Table 1. Systemic and Coronary Hemodynamic Effects of Desflurane

	n	Conscious	Desflurane (MAC)		
			1.0	1.3	1.6
HR (beats · min^{-1})	10	77 ± 4	118 ± 10*	126 ± 7*	127 ± 5*
MAP (mmHg)	8	89 ± 4	73 ± 3*	71 ± 4*	69 ± 5*
LVSP (mmHg)	9	115 ± 3	91 ± 3*	86 ± 4*	81 ± 5*
LVEDP (mmHg)	9	10 ± 2	10 ± 2	9 ± 2	9 ± 1
dP/dt_{max} (mmHg · s^{-1})	8	2,246 ± 158	1,640 ± 179*	1,378 ± 114*,†	1,213 ± 145*,†
DCBFV (Hz · 10^2)	9	43 ± 10	41 ± 9	40 ± 6	36 ± 7
CVR (ru)	8	2.2 ± 0.4	2.4 ± 0.7	2.0 ± 0.4	2.9 ± 1.1
SV (ml)	8	33 ± 2	20 ± 2*	17 ± 2*	17 ± 2*
SS (%)	8	21.4 ± 3.6	16.1 ± 4.9*	12.8 ± 4.2*	9.6 ± 3.1*,†
CO (l · min^{-1})	8	2.5 ± 0.1	2.4 ± 0.2	2.2 ± 0.2	2.2 ± 0.2
SVR (dyn · s · cm^{-5})	7	2,811 ± 80	2,433 ± 215	2,515 ± 245	2,442 ± 278
RPP (beats · min^{-1} · mmHg · 10^3)	9	8.7 ± 0.7	9.8 ± 1.1	10.2 ± 0.7	9.8 ± 0.7
NE (pg · ml^{-1})	7	220 ± 52	214 ± 32	207 ± 32	236 ± 40
*p*H	9	7.40 ± 0.01	7.43 ± 0.01	7.41 ± 0.01	7.39 ± 0.01
P_{CO_2} (mmHg)	9	33 ± 1	28 ± 1*	29 ± 1*	30 ± 1*
P_{O_2} (mmHg)	9	84 ± 3	116 ± 6*	120 ± 5*	125 ± 6*
ET (%)	10	—	7.2 ± 0.1	9.4 ± 0.1	11.3 ± 0.2

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; dP/dt_{max} = maximum rate of increase in pressure; DCBFV and CVR = diastolic coronary blood flow velocity and coronary vascular resistance, respectively; ru = resistance units; SV = stroke volume; SS = segment shortening; CO = cardiac output; SVR = systemic vascular resistance; RPP = rate–pressure product; NE = plasma norepinephrine concentration; ET = end-tidal anesthetic concentration.

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

† Significantly ($P < 0.05$) different from 1.0 MAC desflurane.

coronary vascular resistance (table 2, fig. 1), and cardiac output (fig. 3). When compared with desflurane, isoflurane anesthesia caused a significantly smaller increase in heart rate at 1.6 MAC (tables 1 and 2). Isoflurane also reduced mean arterial pressure to a greater degree than did desflurane at equivalent end-tidal MAC. In addition, indices of myocardial oxygen consumption (rate pressure product and pressure work index) were significantly lower in isoflurane- *versus* desflurane-anesthetized dogs at 1.3 and 1.6 MAC (tables 1 and 2, fig. 2).

Oral administration of dexmedetomidine produced significant declines in heart rate, left ventricular dP/dt_{max}, %SS, cardiac output, rate pressure product, pressure work index, and plasma norepinephrine concentration, and increases in left ventricular end-diastolic pressure, systemic vascular resistance, and coronary vascular resistance (tables 3 and 4, figs. 1–3). Desflurane anesthesia in dexmedetomidine-pretreated dogs caused increases in heart rate and decreases in mean arterial pressure, left ventricular systolic and end-diastolic pressures, left ventricular dP/dt_{max}, %SS, cardiac output, stroke volume, systemic vascular resistance, and coronary vascular resistance (table 3, figs. 1 and 3). The increase in heart rate after administration of desflurane in dexmedetomidine-pretreated dogs was significantly less than that observed in unpremedicated dogs. In addition, the rate pressure product, pressure work index, and plasma norepinephrine concentration were less at equi-MAC desflurane in dexmedetomidine-pretreated compared with untreated dogs (table 3, fig. 2). In the presence of dexmedetomidine, desflurane anesthesia was accompanied by dose-dependent decreases in systemic vascular resistance, in contrast to the findings when desflurane was administered alone (table 3, fig. 1); however, systemic resistance remained significantly higher in dexmedetomidine-pretreated *versus* untreated dogs. Cardiac output was significantly lower in dexmedetomidine-pretreated dogs at all anesthetic concentrations (fig. 3).

Administration of isoflurane to dexmedetomidine-pretreated dogs resulted in systemic and coronary hemodynamic effects that were similar to those caused by desflurane in the presence of dexmedetomidine (table 4). Increases in heart rate during isoflurane anesthesia were significantly attenuated by dexmedetomidine. Decreases in mean arterial pressure, left ventricular systolic and end-diastolic pressures, left ventricular dP/dt_{max}, %SS, cardiac output, systemic vascular resistance, and coronary vascular resistance were observed during isoflurane anesthesia after pretreatment with dexmedetomidine. No differences in these variables were observed at any isoflurane concentration when dexmedetomidine-pretreated *versus* untreated dogs were compared. In contrast, the rate pressure product and pressure work index were significantly less at 1 and 1.3 MAC isoflurane in dexmedetomidine-pretreated *versus* untreated dogs (fig. 2).

Systemic vascular resistance was maintained at higher levels during desflurane anesthesia than during isoflurane anesthesia at all three anesthetic concentrations (tables 3 and 4, fig. 1) after pretreatment with dexmedetomidine. In dexmedetomidine-pretreated dogs, cardiac output was maintained to a greater degree with isoflurane than with desflurane (fig. 3). In addition, differences between desflurane and isoflurane in heart rate and mean arterial pressure in untreated dogs were abolished after pretreatment with dexmedetomidine.

Discussion

α_2-Adrenoceptor agonists are clinically useful antihypertensive agents that reduce heart rate and arterial blood pressure. These agents alter autonomic nervous system reflex responses by reducing sympathetic, or augmenting parasympathetic, tone.[25–28] Such systemic hemodynamic effects of α_2 agonists are an additional benefit when using these drugs as anesthetic premedicants in patients with coronary artery disease, because α_2 agonists reduce multiple determinants of myocardial oxygen demand. Premedication with clonidine has been demonstrated to decrease hemodynamic lability during surgery for coronary artery bypass grafting,[7] during isoflurane anesthesia for abdominal and head and neck operations,[6] and during aortic surgery.[10,11] Pretreatment with α_2 agonists has been shown to favorably modify intraoperative cardiovascular and endocrine responses to surgical stimuli and laryngoscopy.[7,9–11,13] α_2 Agonists produce sedation[4,7] and analgesia,[29] and reduce intraoperative anesthetic requirements, while having little effect on respiratory function.[5–9] Thus, the use of α_2 agonists has been advocated for patients at risk for cardiovascular and neurologic complications resulting from perioperative tachycardia or hypertension.[28,30]

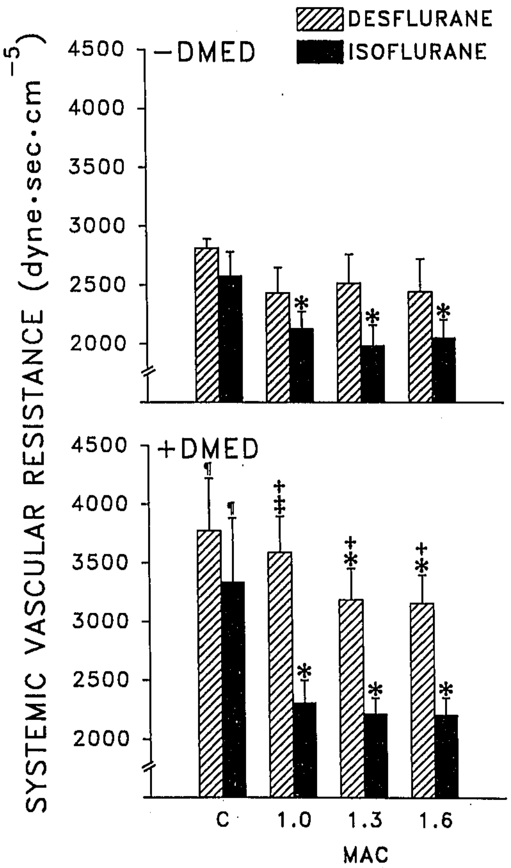

Fig. 1. Effects of desflurane and isoflurane on systemic vascular resistance in the presence (+DMED) or absence (−DMED) of dexmedetomidine. ¶Significantly (P < 0.05) different from the conscious control without dexmedetomidine; *significantly (P < 0.05) different from the respective conscious control (C); ‡significantly (P < 0.05) different from the same anesthetic at the same concentration without dexmedetomidine pretreatment; †significantly (P < 0.05) different from isoflurane with dexmedetomidine pretreatment at the same anesthetic concentration.

The hemodynamic and endocrine effects of enflurane[12] and halothane[31] after pretreatment with dexmedetomidine have been previously studied, as have the effects of dexmedetomidine in conscious dogs.[12,14,32] However, the cardiovascular effects of isoflurane compared with the new volatile anesthetic agent desflurane after pretreatment with this highly selective α_2 agonist have not been characterized. The results of the current investigation indicate that dexmedetomidine decreases heart rate, calculated estimates of myocardial oxygen consumption (rate pressure product and pressure work index), cardiac output, indices of myocardial contractility (left ventricular dP/dt_{max} and %SS),

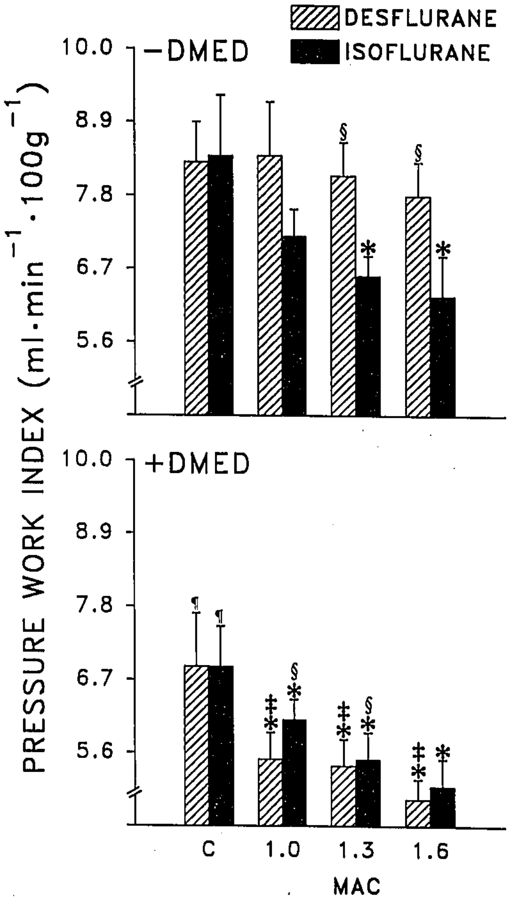

Fig. 2. Effects of desflurane and isoflurane on myocardial oxygen consumption as reflected by the pressure work index, in the presence (+DMED) or absence (−DMED) of dexmedetomidine. ¶Significantly ($P < 0.05$) different from the conscious control without dexmedetomidine; *significantly ($P < 0.05$) different from the respective conscious control (C); ‡significantly ($P < 0.05$) different from the same anesthetic at the same concentration without dexmedetomidine pretreatment; §significantly ($P < 0.05$) different from isoflurane without dexmedetomidine pretreatment at the same anesthetic concentration.

and plasma norepinephrine concentration, and causes increases in systemic vascular resistance and left ventricular end-diastolic pressure when administered to conscious dogs. These cardiovascular actions occurred in the absence of significant changes in coronary blood flow velocity. The current findings confirm the observations of several previous investigations,[12,14,32] and are consistent with α_2 agonist-induced decreases in sympathetic, or increases in parasympathetic, nervous system tone. In addition, although initial pressor effects of dexmedetomidine resulting from direct peripheral α_2-mediated vasoconstriction[31,33] have been described during intravenous infusions, these actions were not observed after oral administration of dexmedetomidine in the current, or prior, investigations.[12,14] Whether the pressor effects during intravenous infusion of dexmedetomidine are caused by more rapid changes in effector site concentration, as compared with a slower rise in concentration after oral administration, is unknown.

The results of this investigation indicate that desflurane and isoflurane produce similar cardiovascular actions in chronically instrumented dogs;[16,34] however,

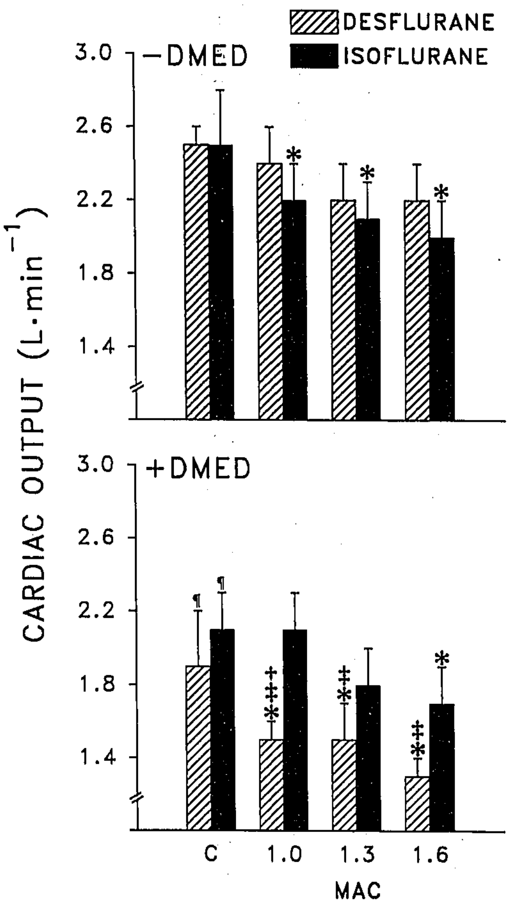

Fig. 3. Effects of desflurane and isoflurane on cardiac output in the presence (+DMED) or absence (−DMED) of dexmedetomidine. ¶Significantly ($P < 0.05$) different from the conscious control without dexmedetomidine; *significantly ($P < 0.05$) different from the respective conscious control (C); ‡significantly ($P < 0.05$) different from the same anesthetic at the same concentration without dexmedetomidine pretreatment; †significantly ($P < 0.05$) different from isoflurane with dexmedetomidine pretreatment at the same anesthetic concentration.

Table 2. Systemic and Coronary Hemodynamic Effects of Isoflurane

			Isoflurane (MAC)		
	n	Conscious	1.0	1.3	1.6
HR (beats · min^{-1})	10	81 ± 5	123 ± 5*	116 ± 3*	113 ± 4*,†
MAP (mmHg)	8	89 ± 5	62 ± 2*,†	58 ± 2*,†	54 ± 4*,†
LVSP (mmHg)	9	116 ± 5	79 ± 3*,†	73 ± 4*	69 ± 4*
LVEDP (mmHg)	9	9 ± 1	8 ± 2	8 ± 2	7 ± 2
dP/dt_{max} (mmHg · s^{-1})	8	2,497 ± 218	1,385 ± 154*	1,199 ± 122*	1,040 ± 139*,‡
DCBFV (Hz · 10^2)	9	44 ± 11	48 ± 10	46 ± 8	44 ± 9
CVR (ru)	8	2.3 ± 0.5	1.5 ± 0.3*	1.3 ± 0.2*	1.3 ± 0.2*
SV (ml)	8	32 ± 3	18 ± 2*	18 ± 2*	17 ± 2*
SS (%)	8	19.0 ± 1.7	12.9 ± 2.6*	12.8 ± 2.9*	11.0 ± 2.5*
CO (l · min^{-1})	8	2.5 ± 0.3	2.2 ± 0.2*	2.1 ± 0.2*	2.0 ± 0.2*
SVR (dyn · s · cm^{-5})	7	2,577 ± 205	2,133 ± 142*	1,989 ± 174*	2,056 ± 153*
RPP (beats · min^{-1} · mmHg · 10^3)	9	9.1 ± 1.0	9.4 ± 0.4	8.1 ± 0.3†	7.5 ± 0.6†
NE (pg · ml^{-1})	7	211 ± 36	176 ± 31	186 ± 41	178 ± 34
*p*H	9	7.40 ± 0.01	7.40 ± 0.02	7.36 ± 0.01	7.36 ± 0.01
P_{CO_2} (mmHg)	9	33 ± 1	33 ± 1	34 ± 1	35 ± 1
P_{O_2} (mmHg)	9	85 ± 5	128 ± 5*	120 ± 5*	123 ± 5*
ET (%)	10	—	1.29 ± 0.01	1.67 ± 0.01	2.03 ± 0.01

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; dP/dt_{max} = maximum rate of increase in pressure; DCBFV and CVR = diastolic coronary blood flow velocity and coronary vascular resistance, respectively; ru = resistance units; SV = stroke volume; SS = segment shortening; CO = cardiac output; SVR = systemic vascular resistance; RPP = rate-pressure product; NE = plasma norepinephrine concentration; ET = end-tidal anesthetic concentration.

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

† Significantly ($P < 0.05$) different from equi-MAC desflurane (table 1).

‡ Significantly ($P < 0.05$) different from 1.0 MAC isoflurane.

some differences between these agents were observed. Mean arterial pressure was maintained more closely to the conscious state with desflurane *versus* isoflurane at equivalent MAC, consistent with the observations of previous investigations from this laboratory.[16,35] Calculated estimates of myocardial oxygen consumption, the rate pressure product and pressure work index, were also greater in dogs anesthetized with desflurane *versus* isoflurane. Premedication with dexmedetomidine abolished these differences in mean arterial pressure and estimated myocardial oxygen consumption between anesthetic groups. This occurred because dexmedetomidine caused attenuation of the increases in heart rate observed during maintenance of anesthesia with both desflurane and isoflurane. The current results extend previous findings that also demonstrated a reduction in heart rate in dogs anesthetized with other volatile (halothane and enflurane) or intravenous (propofol, etomidate, and ketamine) anesthetics after dexmedetomidine pretreatment.[12,14,31] Isoflurane, but not desflurane, decreased systemic vascular resistance and cardiac output when administered alone. In the presence of dexmedetomidine, however, both agents caused declines in systemic vascular resistance and cardiac output. Systemic vascular resistance was greater, and cardiac output lower, in desflurane- compared with isoflurane-anesthetized dogs premedicated with dexmedetomidine.

Volatile anesthetics are known to produce differential suppression of autonomic reflexes and exert actions on systemic hemodynamics mediated *via* an intact autonomic nervous system.[36,37] Pagel *et al.*[16] compared and contrasted the systemic and coronary hemodynamic effects of desflurane, isoflurane, halothane, and enflurane in chronically instrumented dogs with or without pharmacologic blockade of the autonomic nervous system, to indirectly examine the relative actions of volatile anesthetics on autonomic function. These investigators[16] demonstrated that greater mean arterial pressure, rate pressure product, and left ventricular dP/dt_{50} observed in desflurane- *versus* isoflurane-anesthetized dogs were eliminated by autonomic nervous system blockade. Subsequent investigations showed that desflurane and isoflurane depress intrinsic con-

Table 3. Systemic and Coronary Hemodynamic Effects of Desflurane in Dogs Pretreated with Dexmedetomidine

	n	Conscious	After Dexmedetomidine	Desflurane (MAC)		
				1.0	1.3	1.6
HR (beats · min^{-1})	10	79 ± 4	59 ± 5*	78 ± 9†,‡	87 ± 7†,‡	93 ± 4†,‡
MAP (mmHg)	8	84 ± 4	92 ± 6	69 ± 3*,†	62 ± 4*,†	56 ± 4*,†,§
LVSP (mmHg)	9	116 ± 4	120 ± 6	90 ± 3*,†	79 ± 4*,†,§	71 ± 4*,†,§
LVEDP (mmHg)	9	10 ± 1	13 ± 2*	7 ± 2*,†	7 ± 2*,†	7 ± 2*,†
dP/dt_{max} (mmHg · s^{-1})	8	2,362 ± 145	2,080 ± 185*	1,585 ± 168*,†	1,197 ± 103*,†,§	898 ± 78*,†,§,‖
DCBFV (Hz · 10^2)	9	38 ± 8	33 ± 6	33 ± 5	35 ± 6	33 ± 6
CVR (ru)	8	2.3 ± 0.4	2.9 ± 0.5*	2.2 ± 0.4†	1.8 ± 0.3†	1.9 ± 0.3†
SV (ml)	8	34 ± 2	36 ± 6	21 ± 3*,†	18 ± 2*,†	14 ± 2*,†
SS (%)	8	20.2 ± 1.9	17.4 ± 1.7*	13.1 ± 2.9*,†	11.1 ± 2.6*,†,§	8.9 ± 2.3*,†,§,‖
CO (l · min^{-1})	8	2.6 ± 0.2	1.9 ± 0.3*	1.5 ± 0.1*,†,‡	1.5 ± 0.2*,†,‡	1.3 ± 0.1*,†,‡
SVR (dyn · s · cm^{-5})	7	2,556 ± 108	3,771 ± 448*	3,590 ± 305*,‡	3,186 ± 265†	3,156 ± 242†,§
RPP (beats · min^{-1} · mmHg · 10^3)	9	8.8 ± 0.7	7.1 ± 1.0*	6.3 ± 0.7*,‡	6.4 ± 0.5*,‡	6.1 ± 0.4*,‡
NE (pg · ml^{-1})	7	248 ± 53	76 ± 15*	76 ± 18*,‡	74 ± 25*,‡	45 ± 14*,‡
*p*H	9	7.40 ± 0.01	7.40 ± 0.01	7.41 ± 0.01	7.40 ± 0.01	7.39 ± 0.01
P_{CO_2} (mmHg)	9	33 ± 1	32 ± 1	30 ± 2	31 ± 1	30 ± 2
P_{O_2} (mmHg)	9	88 ± 4	84 ± 3	117 ± 5*,†	120 ± 5*,†	125 ± 7*,†
ET (%)	10	—	—	7.2 ± 0.1	9.4 ± 0.1	11.6 ± 0.2

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; dP/dt_{max} = maximum rate of increase in pressure; DCBFV and CVR = diastolic coronary blood flow velocity and coronary vascular resistance, respectively; ru = resistance units; SV = stroke volume; SS = segment shortening; CO = cardiac output; SVR = systemic vascular resistance; RPP = rate–pressure product; NE = plasma norepinephrine concentration; ET = end-tidal anesthetic concentration.

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

† Significantly ($P < 0.05$) different from after dexmedetomidine.

‡ Significantly ($P < 0.05$) different from desflurane alone (table 1).

§ Significantly ($P < 0.05$) different from 1.0 MAC desflurane.

‖ Significantly ($P < 0.05$) different from 1.3 MAC desflurane.

tractile function to equivalent degrees, independent of autonomic nervous system activity.[35,38] These results indicated that desflurane may produce less depression of sympathetic nerve activity and autonomic reflexes than isoflurane, and, therefore, result in a greater maintenance of mean arterial pressure and peripheral vascular tone at equivalent MAC. This supposition is supported by Ebert *et al.*'s[39] recent findings that sympathetic nerve activity is increased in desflurane- compared with isoflurane-anesthetized volunteers.

In the current investigation, oral premedication with dexmedetomidine also eliminated the differential effects of desflurane and isoflurane on mean arterial pressure and indices of myocardial oxygen consumption. The findings may indicate that antagonism of central sympathetic outflow by dexmedetomidine (presumably *via* α_2 receptor stimulation of medullary nuclei[25,26]) has more profound effects on the vascular consequences of desflurane than isoflurane. Alternatively, desflurane may attenuate direct α_2-mediated vasoconstriction less effectively than isoflurane. Pagel *et al.*[16] demonstrated that the differential ability of desflurane *versus* isoflurane to maintain mean arterial pressure closer to levels present in the conscious state was eliminated by autonomic nervous system blockade. The current results show that decreases in central sympathetic outflow produced by dexmedetomidine similarly attenuate maintenance of mean arterial pressure by desflurane. However, despite similar degrees of central sympatholysis, differential effects on systemic vascular resistance were demonstrated. While the direct peripheral vasodilator properties of both agents were observed in the presence of dexmedetomidine, systemic vascular resistance was maintained to a greater degree during desflurane *versus* isoflurane anesthesia. This finding would support the contention that dexmedetomidine unmasks the greater peripheral vasodilator actions of isoflurane as compared with desflurane, because the confounding effects of central sympathetic outflow have been reduced.

Table 4. Systemic and Coronary Hemodynamic Effects of Isoflurane in Dogs Pretreated with Dexmedetomidine

	n	Conscious	After Dexmedetomidine	Isoflurane (MAC) 1.0	1.3	1.6
HR (beats · min^{-1})	10	78 ± 4	62 ± 4*	88 ± 6†,‡	97 ± 4*,†,‡	100 ± 4*,†,‡
MAP (mmHg)	8	85 ± 3	92 ± 8	67 ± 5*,†	58 ± 5*,†	52 ± 3*,†,§
LVSP (mmHg)	9	114 ± 3	118 ± 6	85 ± 4*,†	75 ± 4*,†,§	67 ± 3*,†,§
LVEDP (mmHg)	9	10 ± 1	15 ± 2*	9 ± 2†	8 ± 1†	8 ± 1†
dP/dt_{max} (mmHg · s^{-1})	8	2,277 ± 145	1,875 ± 147*	1,286 ± 126*,†	1,032 ± 102*,†,§	860 ± 74*,†,§
DCBFV (Hz · 10^2)	9	45 ± 10	38 ± 7	42 ± 8	46 ± 8	45 ± 7
CVR (ru)	8	2.1 ± 0.4	2.6 ± 0.5	1.7 ± 0.4†	1.3 ± 0.3*,†	1.2 ± 0.1*,†
SV (ml)	8	37 ± 4	36 ± 5	22 ± 2*,†	18 ± 1*,†	17 ± 2*,†
SS (%)	8	20.7 ± 2.6	19.6 ± 2.0	13.9 ± 2.4*,†	11.5 ± 2.0*,†	10.3 ± 2.0*,†,§
CO (l · min^{-1})	8	2.7 ± 0.2	2.1 ± 0.2*	2.1 ± 0.2*,∥	1.8 ± 0.2*	1.7 ± 0.2*,†,§
SVR (dyn · s · min^{-5})	7	2,471 ± 215	3,337 ± 543*	2,310 ± 188†,∥	2,216 ± 134†,∥	2,208 ± 144†,∥
RPP (beats · min^{-1} · mmHg · 10^3)	9	8.7 ± 0.6	7.0 ± 0.8*	6.7 ± 0.4*,‡	6.5 ± 0.4*,‡	6.1 ± 0.4*
NE (pg · ml^{-1})	7	256 ± 64	103 ± 24*	107 ± 27*	90 ± 32*	113 ± 31*
*p*H	9	7.39 ± 0.01	7.39 ± 0.01	7.36 ± 0.01	7.35 ± 0.01	7.33 ± 0.02
P_{CO_2} (mmHg)	9	32 ± 1	33 ± 1	35 ± 1	35 ± 2	37 ± 2
P_{O_2} (mmHg)	9	88 ± 2	90 ± 5	124 ± 7*,†	123 ± 8*,†	114 ± 7*,†
ET (%)	10	—	—	1.29 ± 0.01	1.67 ± 0.01	2.02 ± 0.01

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; dP/dt_{max} = maximum rate of increase in pressure; DCBFV and CVR = diastolic coronary blood flow velocity and coronary vascular resistance, respectively; ru = resistance units; SV = stroke volume; SS = segment shortening; CO = cardiac output; SVR = systemic vascular resistance; RPP = rate-pressure product; NE = plasma norepinephrine concentration; ET = end-tidal anesthetic concentration.

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

† Significantly ($P < 0.05$) different from after dexmedetomidine.

‡ Significantly ($P < 0.05$) different from equi-MAC isoflurane (table 2).

§ Significantly ($P < 0.05$) different from 1.0 MAC isoflurane.

∥ Significantly ($P < 0.05$) different from equi-MAC desflurane with dexmedetomidine (table 3).

Intravenously administered dexmedetomidine produces brief elevations in mean arterial pressure secondary to α_2-mediated vasocontraction.[32] Oral administration of dexmedetomidine in this study produced no direct pressor effects. However, absence of an increase in arterial pressure does not preclude the presence of α_2-mediated vasoconstriction, because elevated systemic vascular resistance was accompanied by concomitant reductions in cardiac output. Therefore, an alternative hypothesis for the findings of this study is that isoflurane attenuates α_2-mediated vasoconstriction to a greater extent than desflurane, resulting in lower systemic vascular resistance and better maintenance of cardiac output. This hypothesis is consistent with the results of Pagel *et al.*,[16] which indicated that cardiac output was not lower in desflurane- *versus* isoflurane-anesthetized dogs after autonomic nervous system blockade. The sympatholytic effect of dexmedetomidine did, however, result in differential effects on both systemic vascular resistance and cardiac output during desflurane and isoflurane anesthesia in this investigation. This observation is consistent with a greater attenuation of α_2-mediated peripheral vasoconstriction by isoflurane than desflurane.

The results of the current investigation must be interpreted within the constraints of several limitations. A dose-response relationship to dexmedetomidine was not established. The dose of dexmedetomidine (30 μg/kg) was chosen to provide reliable and stable hemodynamic and endocrine effects over the time course of this investigation, and was based on previous studies from this laboratory.[12] Multiple factors may have altered the plasma concentration of dexmedetomidine in each experiment, including variable absorption and metabolism of the oral dose of this agent between animals. Plasma concentrations of dexmedetomidine may have been changing during each experiment, or some dogs may have had lower plasma concentrations of dexmedetomidine than others. Proctor *et al.*[12] demonstrated that the hemodynamic actions of the dose of dexmedetomidine used in this investigation lasted as long as 4 h, far exceeding the time required for completion of an experiment in the current study. Nevertheless, individual variation in pharmacokinetics between animals represents a potential limitation of the current investigation. Furthermore, applicability of results to humans must be made with caution. Hemodynamic responses to combinations of dexmedetomidine and inhalational anesthetics will depend on resting sympathetic *versus* parasympathetic tone that may be different in humans and dogs. Individuals with a higher sympathetic tone may be expected to exhibit a more profound hemodynamic effect after premedication with dexmedetomidine.

In addition, the protocol in this study did not include any evaluation of the "anesthetic-sparing" properties of dexmedetomidine, because the investigation was designed to evaluate hemodynamic differences between desflurane and isoflurane at equivalent MAC. Other studies have demonstrated that the requirement for volatile anesthetics is reduced by as much as 90% after treatment with dexmedetomidine.[13] Whether the MAC of desflurane or isoflurane is depressed equivalently by pretreatment with dexmedetomidine is unknown. If such depression of MAC is not equivalent, the clinically observed hemodynamic effects of desflurane and isoflurane in the presence of dexmedetomidine may differ from those observed in this study.

In summary, this investigation characterized the systemic and coronary hemodynamic actions and neuroendocrine effects of desflurane and isoflurane in the absence and presence of oral premedication with dexmedetomidine in chronically instrumented dogs. The current investigation indicates that few untoward effects were observed during anesthesia with desflurane or isoflurane after oral administration of dexmedetomidine, indicating that this α_2 agonist may be an acceptable premedicant in patients undergoing general anesthesia with these agents. Although the cardiovascular and endocrine actions of desflurane and isoflurane anesthesia are similar in the presence and absence of dexmedetomidine, the results also indicate that peripheral vascular resistance is maintained at higher levels with desflurane than with isoflurane in the presence of dexmedetomidine. This finding may be consistent with the contention that desflurane produces less direct peripheral vasodilator actions than isoflurane. Concomitant modest reductions in cardiac output are also produced by desflurane in the presence of dexmedetomidine secondary to increased impedance to left ventricular outflow.

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