Premedication with Oral Dexmedetomidine Alters Hemodynamic Actions of Intravenous Anesthetic Agents in Chronically Instrumented Dogs

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Dexmedetomidine (the β-stereoisomer of medetomidine), a highly selective α₂-adrenoceptor agonist, has been demonstrated to produce analgesia and sedation and attenuate hemodynamic responses to emergence from inhalational anesthetics, which suggests a potential use for this drug as a premedicant for general anesthesia. The authors examined hemodynamic interactions between dexmedetomidine and three commonly used intravenous anesthetic agents with markedly different hemodynamic effects. Conscious, chronically instrumented dogs received intravenous induction doses of ketamine, propofol, or etomidate, followed by continuous infusions of each drug at four different doses for 15-min intervals on different days. Studies in six separate groups (range, 9–12 dogs/group) with and without pre-treatment with oral dexmedetomidine (20 μg/kg) were completed. Heart rate, arterial pressure, left ventricular pressure, rate of increase of left ventricular pressure at 50 mmHg (dP/dt₀), and cardiac output were continuously recorded. Dexmedetomidine administration caused a significant (P < 0.05) decrease in heart rate, rate-pressure product, left ventricular dP/dt₀, and cardiac output. Dexmedetomidine abolished or attenuated the increase in heart rate, rate-pressure product, cardiac output, and arterial pressure produced during induction of anesthesia with ketamine. After the dexmedetomidine pretreatment, continuous infusion of ketamine caused no increase in heart rate or rate-pressure product. However, ketamine significantly reduced left ventricular dP/dt₀ compared to control in dogs premedicated with dexmedetomidine. Except for a significant reduction in systemic vascular resistance, dexmedetomidine did not significantly affect the hemodynamic response to induction of anesthesia with propofol. Similarly, dexmedetomidine did little to alter the hemodynamic response to induction of anesthesia with etomidate. However, in the presence of dexmedetomidine, infusion of etomidate increased systemic vascular resistance and arterial pressure compared to unmedicated dogs. The results demonstrate that oral dexmedetomidine administered 1 h before intravenous induction with ketamine may alter the hemodynamic response observed with these anesthetics. This may provide beneficial actions in certain patients, but caution should be used in patients in whom an increase or maintenance of sympathetic tone during induction of anesthesia with ketamine is desirable. In addition, in certain patients, large increases in peripheral vascular resistance during combined administration of dexmedetomidine and etomidate may be detrimental.

(annual words: Anesthetics, intravenous: etomidate; ketamine; propofol. Premedication: dexmedetomidine. Sympathetic nervous system: α₂-adrenergic agonists; dexmedetomidine. Sympathetic nervous system, receptors: α₂ agonists.)

α₂ ADRENOCEPTOR agonists have been demonstrated to be useful premedicants or adjuncts for general anesthetic agents. Previous studies have demonstrated that α₂-adrenoceptor agonists, including dexmedetomidine, produce sedation with minimal respiratory depression and may decrease the MAC for general anesthetics. Concomitant with these actions, hemodynamic alterations, including a decrease in heart rate and arterial pressure and a reduction in myocardial oxygen demand as estimated from the rate-pressure product, may result. Investigations from this laboratory have demonstrated dose-dependent decreases in cardiac output and the rate of increase of left ventricular pressure at 50 mmHg (dP/dt₀). Such hemodynamic effects probably are mediated at bulbar vasomotor and cardiac centers, which modulate a decrease in sympathetic tone or an increase in parasympathetic outflow. The intravenous administration of α₂-adrenergic agonists has been shown to have a biphasic pressor/depressor response. In contrast, oral administration of dexmedetomidine prevents the initial pressor response while favorably altering systemic hemodynamics.

During induction and maintenance of anesthesia with intravenous anesthetics, alterations in systemic hemodynamics are common. The influence of dexmedetomidine on systemic hemodynamics during induction with various intravenous anesthetics has not been studied in a systematic fashion. Thus, in the current study the hemodynamic effects of dexmedetomidine administered orally as a premedicant to conscious, chronically instrumented dogs was investigated before and during induction and maintenance of anesthesia with several intravenous anesthetic agents. The anesthetics selected for study were ketamine, propofol, and etomidate. Concomitant with the direct actions of anesthetic agents on peripheral cardiovascular...
elements, a disruption of central neural control mechanisms modulating tonic sympathetic and parasympathetic activities and alterations in baroreceptor reflex function contribute to the changes in cardiovascular regulation. The hypothesis of this study was that dexmedetomidine would alter sympathetic or parasympathetic nervous system-mediated responses during induction and maintenance of anesthesia and change the typical hemodynamic responses observed after administration of intravenous anesthetic agents.

Materials and Methods

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

General Preparation

Methods for implantation of instruments have been described in detail. Briefly, conditioned mongrel dogs (n = 14) of either sex weighing between 20 and 30 kg were fasted overnight and anesthetized with sodium thiopental (10 mg/kg, intravenous) and enflurane (2–3%). 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 transit-time ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of cardiac output. A high-fidelity, miniature micromanometer (P7 Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricular cavity through an incision in the apex for measurement of pressure and the dP/dt$_{50}$, an index of global contractility. A heparin-filled catheter was placed in the left atrial appendage. The left ventricular micromanometer was calibrated in vivo against pressures measured via the arterial and left atrial catheters (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 the pneumothorax evacuated by a chest tube. After operation, each dog was treated with procaine penicillin G (25,000 U/kg) and gentamicin (4.5 mg/kg), given analgesics as needed, 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. Systemic vascular resistance was calculated using mean arterial pressure and mean aortic blood flow. All hemodynamic data were continuously recorded on a polygraph (Hewlett Packard 7758A, San Francisco, CA) and digitized via a computer and analog to digital converter.

Experimental Protocol

Six experimental protocols were completed on different days. After the animals were fasted overnight, fluid replacement was accomplished with 500 ml normal saline, and fluid maintenance was continued at 3 ml·kg$^{-1}$·h$^{-1}$ for the duration of each experiment. Baseline hemodynamics were continuously monitored for 30 min, and arterial blood gas tensions (ABL-2, Radiometer, Copenhagen, Denmark) were obtained while the dogs were in the conscious, unanedated state. Dexmedetomidine (20 μg/kg) dissolved in a small amount of normal saline or placebo was administered orally in a gelatin capsule. Hemodynamic data and arterial blood gas tensions were recorded at 60 min in control dogs and in dogs treated with dexmedetomidine. Dogs were anesthetized with ketamine (20-mg/kg bolus followed by 20-, 25-, 50-, and 75-mg·kg$^{-1}$·h$^{-1}$ infusions), propofol (15-mg/kg bolus followed by 15-, 20-, 25-, and 30-mg·kg$^{-1}$·h$^{-1}$ infusions), or etomidate (5-mg/kg bolus followed by 5-, 10-, 15-, and 20-mg·kg$^{-1}$·h$^{-1}$ infusions) with and without pretreatment with oral dexmedetomidine (20 μg/kg) on different days. The same dogs received ketamine (n = 9), propofol (n = 12), or etomidate (n = 11) with and without dexmedetomidine.

Fourteen dogs were used to complete all experiments. Hemodynamic measurements were recorded before and after induction of anesthesia immediately before intubation, when the dogs exhibited no eyelash reflex. Tracheal intubation was performed, and positive pressure ventilation with an air and oxygen mixture adjusted to maintain normal arterial blood gases was established. Infusion of each dose of anesthetic via an infusion/withdrawal pump (model 1941, Harvard Apparatus, Millis, MA) lasted 15 min. At the end of each 15-min anesthetic infusion, hemodynamic measurements were again recorded, and the dose was increased. In this fashion, a cumulative dose–response to each anesthetic was accomplished. Previous studies have demonstrated a stable hemodynamic profile after oral administration of 20 μg/kg dexmedetomidine for the period of intravenous anesthetic administration used in this study. After infusion of the largest dose, the anesthetic was discontinued, and the dogs were allowed...
to emerge from anesthesia. End-tidal carbon dioxide and oxygen concentrations were continuously monitored during all experiments via mass spectrometry (Marquette Advantage 2000, Marquette Electronics, Milwaukee, WI). All dogs were allowed to recover for at least 24 h between experiments.

**Statistical Analysis**

To minimize experimental variability, the same dogs were assigned to each anesthetic drug group. Thus, each dog in each anesthetic group received the same anesthetic with and without prior premedication with dexmedetomidine in a random order. Because of occasional instrument failure, not all dogs received each anesthetic. If a dog was entered into more than one anesthetic group and received dexmedetomidine on several occasions, the hemodynamic effects (secondary to dexmedetomidine) were averaged to obtain the mean effect for that specific dog. These data are summarized in table 1. All data were compared using analysis of variance with repeated measures followed by application of Bonferroni modification of the *t* test. Changes from control within a group or differences at specific intervals between groups (with and without pretreatment of dexmedetomidine for a sole anesthetic) were considered statistically significant when the probability (*P*) value was less than 0.05. Average hemodynamic data before and after dexmedetomidine administration were summarized for all dogs in all groups. All data are expressed as the mean ± SEM.

**Results**

**Hemodynamic Actions of Dexmedetomidine**

Sixty minutes after oral administration, dexmedetomidine (20 μg/kg) decreased heart rate, rate–pressure product, cardiac output, and left ventricular dP/dt<sub>τ</sub>. Although mean arterial blood pressure was unchanged, systemic vascular resistance was significantly (*P* < 0.05) increased (table 1). At 60 min, after administration of dexmedetomidine, arterial blood gas tensions (P<sub>O</sub><sub>2</sub> from 80 ± 3 mmHg to 86 ± 8 mmHg, P<sub>CO</sub><sub>2</sub> from 32 ± 1 mmHg to 27 ± 1 mmHg, and pH from 7.39 ± 0.01 to 7.40 ± 0.01) were unchanged from control.

**Hemodynamic Actions of Ketamine Before and After Dexmedetomidine Administration**

Induction of anesthesia with ketamine in unpremedicated dogs produced significant increases in heart rate, mean arterial pressure, rate–pressure product, and cardiac output. Left ventricular dP/dt<sub>τ</sub> and systemic vascular resistance remained unchanged (fig. 1). During subsequent infusions of ketamine, heart rate and rate–pressure product remained significantly increased (fig. 1), whereas other hemodynamic measurements returned to control.

In dogs premedicated with dexmedetomidine, induction of anesthesia with ketamine also produced an increase in heart rate, but the increase was of smaller magnitude than in untreated dogs. In addition, continued infusion of increasing doses of ketamine was not associated with an increase in heart rate in the presence of dexmedetomidine. Dexmedetomidine pretreatment also prevented the increase in arterial pressure and rate–pressure product caused by ketamine. Left ventricular dP/dt<sub>τ</sub> was significantly reduced by ketamine in premedicated dogs, in contrast to unpremedicated dogs. Vascular resistance remained unchanged by ketamine after dexmedetomidine pretreatment (fig. 1).

**Hemodynamic Actions of Propofol Before and After Dexmedetomidine Administration**

Induction of anesthesia by bolus administration of propofol produced an increase in heart rate and a decrease in mean arterial pressure, cardiac output, and left ventricular dP/dt<sub>τ</sub> in unpremedicated dogs (fig. 2). No significant change in rate–pressure product or systemic vascular resistance was observed. Cardiac output and left ventricular dP/dt<sub>τ</sub> remained decreased during subsequent infusions of propofol; however, heart rate and arterial pressure returned to control. During infusions of

| TABLE 1. Systemic and Coronary Hemodynamics before and 60 Min after Oral Administration of Dexmedetomidine |
|-------------------------------------------------|-----------------|-----------------------------|
|                                & n  & Control  & Dexmedetomidine  |
|                                &    &            & (20 μg/kg orally) |
| Heart rate (beats · min<sup>-1</sup>) & 14 & 88 ± 4 & 64 ± 6* |
| Mean arterial pressure (mmHg) & 13 & 99 ± 3 & 100 ± 4 |
| Rate–pressure product (beats · min<sup>-1</sup> · mmHg · 10<sup>4</sup>) & 14 & 10.6 ± 1.1 & 7.5 ± 0.8* |
| Left ventricular dP/dt<sub>τ</sub> (mmHg/s) & 14 & 2,060 ± 80 & 1,820 ± 110* |
| Cardiac output (l/min) & 14 & 3.1 ± 0.3 & 2.2 ± 0.3* |
| Stroke volume (ml) & 13 & 37 ± 4 & 35 ± 4 |
| Systemic vascular resistance (dyn · s · cm<sup>-5</sup>) & 13 & 2,766.2 ± 263 & 4,646 ± 785* |

Mean ± SEM data.

* Significantly (*P* < 0.05) different from control.
increasing doses of propofol, small increases in systemic vascular resistance occurred. The rate–pressure product was unchanged during anesthetic induction and subsequent maintenance of anesthesia with increasing doses of propofol.

After oral premedication with dexmedetomidine, bolus administration of propofol caused an increase in heart rate and decline in mean arterial pressure and left ventricular dP/dt\(_{50}\). These changes were no different from the responses observed in the absence of dexmedetomidine. Heart rate in unpremedicated dogs during induction of anesthesia was significantly lower in dogs treated with dexmedetomidine. This resulted in a decreased rate-pressure product for animals receiving the combination of propofol and dexmedetomidine (fig. 2). Systemic vascular resistance was significantly reduced in dogs pre-treated with dexmedetomidine during induction of anesthesia but returned to control levels during subsequent propofol infusions.

**Hemodynamic Actions of Etomidate before and after Dexmedetomidine Administration**

Induction of anesthesia with etomidate caused a significant increase in heart rate without other hemodynamic alterations (fig. 3). However, continued infusion of etomidate produced a decline in left ventricular dP/dt\(_{50}\), cardiac output, and the rate–pressure product. No change
in mean arterial pressure or systemic vascular resistance was produced either by bolus administration or by infusion of etomidate.

Bolus administration of etomidate in dexmedetomidine-premedicated dogs also increased heart rate, but the absolute level of heart rate was significantly lower in dogs treated with dexmedetomidine than in untreated dogs. No change in cardiac output, arterial pressure, rate–pressure product, or systemic vascular resistance occurred during induction of anesthesia. In the presence of dexmedetomidine, bolus administration of etomidate produced an abrupt decrease in left ventricular dP/dt50. In contrast to unpremedicated dogs, dogs treated with continued infusions of etomidate in the presence of dexmedetomidine had dramatic increases in mean arterial pressure and systemic vascular resistance (fig. 3). Left ventricular dP/dt50 and cardiac output remained reduced from control during infusion of etomidate in dogs pre-treated with dexmedetomidine.

Discussion

α2-Adrenoceptor agonists such as clonidine have several characteristics that make them attractive as premedications for general anesthesia. These include sedation,1 anxiolysis,14 analgesia,15 diminished airway secretions,16 intraoperative prevention or attenuation of autonomic reflex responses,17 reduced gastric acid production,18 reduced anesthetic requirements,5 decreased postoperative shivering and hypertension,19 attenuation of opioid-induced muscle rigidity20 and the mass autonomic reflex in quadriplegic patients,21 improved intraoperative stability and decreased time to extubation,19 preservation of baroreceptor function,22 and facilitation of induction of anesthesia.23 These beneficial actions occur without significant respiratory depression.2,4 Certain α2 agonists have been shown to be effective orally.5,7 In addition, the α2 agonists have specific antagonists by which their actions can be quickly reversed.24 Although specific α2-adrenergic receptor antagonists are not available for clinical use, they represent an important area of future drug development.

Dexmedetomidine may be superior to clonidine because of greater selectivity at the α2-adrenoceptor and lack of partial antagonism at higher doses.25 Prior studies with dexmedetomidine in this laboratory have demonstrated that when the agent is given orally to chronically instrumented dogs, dexmedetomidine causes a decrease in heart rate, rate–pressure product, left ventricular dP/dt50, cardiac output and plasma norepinephrine within 30 min, which may last as long as 4 h.5 These results were consistent with a central mechanism of action of dexmedetomidine to reduce sympathetic or augment parasympathetic tone and confirmed other studies in animals and humans.14 These hemodynamic effects appear to occur in the absence of significant changes in coronary blood flow.4 The hemodynamic actions of dexmedetomidine may be especially beneficial in patients with coronary artery disease4 or hypertension26 because they reduce primary determinants of myocardial oxygen demand without the respiratory depression observed with other agents, such as opioid agonists. In addition, with oral administration, the initial hypertensive effects of dexmedetomidine that occur during intravenous infusions4 are not observed.

The current investigation examined the effects of oral premedication of dexmedetomidine on the hemodynamic actions of intravenous anesthetics. Ketamine, propofol, and etomidate, agents with widely differing cardiovascular effects, were studied. Chronically instrumented dogs were
used to facilitate comparison of hemodynamic actions of the intravenous anesthetics with and without premedication with dexmedetomidine.

The cardiovascular effects of ketamine are a major distinguishing feature when this drug is compared with other intravenous agents used for induction of anesthesia. Intravenous administration of ketamine is associated with increases in heart rate, systemic arterial pressure, vascular resistance, and pulmonary artery pressure with minimal alterations in baroreceptor function.6,7 These effects are believed to be mediated through central and peripheral sympathomimetic actions27,28 and a central vagolytic action.11 Thus, ketamine often is used in patients with borderline cardiopulmonary reserve in an attempt to maintain hemodynamic stability by increasing sympathetic tone.

In direct contrast to ketamine, propofol has been shown to cause a 15–30% reduction in systolic and diastolic arterial pressure, systemic vascular resistance, stroke volume, cardiac index, and left ventricular stroke work index.29 The mechanism for the decline in cardiovascular function is unknown but has been variously attributed to diminished preload50 or afterload,51 direct negative inotropic properties,52 inhibition of sympathetic vasoconstrictor outflow, and reduced ability of the baroreceptors to respond to hypotension.12 However, propofol is thought to have such attractive characteristics during recovery that it is gaining acceptance for outpatient anesthesia.50

In contrast to ketamine and propofol, etomidate has been reported to have minimal cardiovascular effects.12,53 Etomidate has been shown to be particularly useful as an induction agent in patients with limited cardiovascular reserve.54 This agent has been demonstrated to have negative inotropic effects (approximately half those of thiopental at equianesthetic doses55) and to decrease systemic vascular resistance,8 possibly via a decrease in central sympathetic nervous system tone.9 However, preservation of baroreceptor function may maintain sympathetic vasoconstrictor tone during induction of anesthesia with etomidate.10,12

The current study documents the hemodynamic actions of these intravenous anesthetics in chronically instrumented dogs. Induction of anesthesia with ketamine produced dramatic increases in heart rate, mean arterial pressure, rate–pressure product, and cardiac output without a significant change in left ventricular dP/dt50. In contrast, propofol significantly diminished mean arterial pressure, cardiac output, and dP/dt50 concomitant with an increase in heart rate, which resulted in little effect on systemic vascular resistance or rate–pressure product. Although etomidate had no effect on mean arterial pressure or systemic vascular resistance, a reduction in cardiac output and left ventricular dP/dt50 occurred. Oral premedication with dexmedetomidine in the current study confirmed results obtained using chronically instrumented dogs in previous studies from this laboratory.4,5 Dexmedetomidine decreased heart rate, rate–pressure product, cardiac output, and left ventricular dP/dt50 without altering mean arterial pressure.

Pretreatment with dexmedetomidine had a remarkable effect on the hemodynamic actions of ketamine. The increase in heart rate was attenuated, and the increases in mean arterial pressure, rate–pressure product, and cardiac output were abolished. In addition, left ventricular dP/dt50 decreased after administration of ketamine. The latter effect may represent an unmasking of the direct negative inotropic effect of ketamine,56 with dexmedetomidine pretreatment diminishing central sympathomimetic actions of ketamine. Clinically, a similar decrease in cardiac performance has been described when ketamine has been administered to seriously ill patients with preexisting elevations of sympathetic tone.57

Induction and maintenance of anesthesia with propofol were associated with little additional hemodynamic effect in dogs that had received oral dexmedetomidine compared with dogs that had received no pretreatment. There was a lower heart rate and rate–pressure product in the presence of dexmedetomidine, but the effects of propofol on left ventricular dP/dt50 and mean arterial pressure were unchanged. The decrease in systemic vascular resistance produced by propofol may reflect augmentation of a sympatholytic effect by dexmedetomidine pretreatment.4,5,12 In dogs pretreated with dexmedetomidine, no alteration in cardiac output occurred with propofol. Previous studies have suggested that propofol may produce concentration-dependent decreases in myocardial contractility.50,51 However, in the current study, dexmedetomidine did not appear to enhance any direct depressant effect of propofol.

Administration of etomidate after pretreatment with dexmedetomidine produced unexpected actions. Little change was observed during anesthesia with etomidate, but slight decreases in cardiac output and left ventricular dP/dt50 were observed; these were consistent with a mild negative inotropic action of etomidate, as previously described.55 However, an increase in mean arterial pressure to values well above the baseline control levels in the same dogs anesthetized with etomidate but without pretreatment was observed. The increase in arterial pressure was directly related to an increase in systemic vascular resistance. The mechanism of the increase in systemic vascular resistance remains unknown; however, this action may be related to an unmasked peripheral vasoconstrictor action of etomidate.

An increase in peripheral vascular resistance has been observed with etomidate in pigs after a baseline anesthetic, including metomidate (an imidazoline α2-adrenergic ag-
onist similar in structure to dexmedetomidine).\textsuperscript{38} Etom- 
idate, like dexmedetomidine, is an imidazoline derivative, so an interaction may occur between these compounds. For example, etomidate (like dexmedetomidine) may have direct stimulatory effects on \( \alpha_2 \) receptors in the periphery. These actions may be attenuated in vivo by a central effect of etomidate to reduce sympathetic tone. Previous studies have suggested that the sympatholytic effects of imida-
zoline compounds, including dexmedetomidine and clonidine,\textsuperscript{4,39} may represent actions on putative imidazoline-
binding sites in the ventrolateral medulla, whereas the sedative and anesthetic-sparing actions may represent ac-
tions at \( \alpha_2 \)-adrenergic receptors within the higher central 
nervous system.\textsuperscript{4} Dexmedetomidine may produce a cen-
trally mediated sympatholytic action that results in an en-

hanced pressor effect of etomidate in the peripheral vascu-
lature. Thus, etomidate may have imidazolinelike ac-
tions in the central nervous system that are similar to those 
of dexmedetomidine.

In addition, because the central hemodynamic effects 
of dexmedetomidine to reduce sympathetic tone may be 
related to stimulation of putative central imidazoline re-
ceptors,\textsuperscript{4} antagonism of such actions by the imidazoline 
derivative, etomidate, may occur. However, such an effect 
would be expected to produce an increase in heart rate, 
and this was not observed in the current study. The con-
cept of a drug interaction between dexmedetomidine and 
etomidate at the imidazoline receptor site is speculative 
and warrants further in vitro bindingfunctional studies 
of these agents with the imidazoline receptor.

A limitation of the present experiments is that a true 
dose–response relationship to dexmedetomidine or the 
various intravenous anesthetics was not obtained. Several 
factors may have affected the plasma concentrations of 
each drug during the course of each experiment, includ-
ing a variable absorption of the oral dose of dexmede-
tomidine, in which case some dogs would have lower 
plasma concentrations of dexmedetomidine than others, 
or a changing plasma concentration of dexmedetomidine 
during the study after a single oral dose. However, previ-
uous investigations\textsuperscript{4,5} from this laboratory suggest that 
this investigation was completed within the time course of 
a stable effect of orally administered dexmedetomidine. 
The hemodynamic actions of the dose of dexmedetomi-
dine used in this investigation have been shown to last as 
long as 4 h.\textsuperscript{5} Pharmacokinetics of intravenous anesthetics 
suggest that plasma concentrations may not be at an equi-
librium at the time of measurement of hemodynamics.\textsuperscript{5,7} 
Plasma concentrations of anesthetic agents were not mea-
sured in this study and are likely to be changing despite 
continuous drug infusions. No comparison was made be-
tween different drugs because equianesthetic concentra-
tions were not established. The doses of the intravenous 
anesthetics were chosen from preliminary experiments to 
maintain an unconscious state reliably, and these infusion 
doses may be higher than those used in clinical practice. 
Thus, only the hemodynamic consequences of each an-
esthetic agent in dogs with and without premedication 
with dexmedetomidine were compared in this investiga-
tion. The same doses of anesthetics were used in both 
groups (with and without dexmedetomidine) to facilitate 
direct comparisons of hemodynamic effects. In the clinical 
setting, a reduction in induction and maintenance doses 
of the intravenous agents would be possible because of 
the anesthetic-sparing effect of dexmedetomidine.\textsuperscript{5}

In conclusion, this investigation characterized the he-
modynamic effects of ketamine, propofol, and etomidate 
with and without oral premedication with dexmedetomi-
dine in chronically instrumented dogs. Dogs were chosen 
for study because of ease of instrumentation and training. 
The responses obtained with the intravenous anesthetics 
the dog are similar to those that have been described 
in humans. However, other species might respond differ-
ently to the combination of dexmedetomidine and intra-
venous anesthetic agents. This may depend on the degree 
of resting sympathetic versus parasympathetic tone in the 
specific animal model.

Because of the ability of dexmedetomidine to provide 
sedation, analgesia, and a beneficial effect on systemic he-
modynamics without significant respiratory depression, 
this agent may have a potential role in anesthesia as a 
premedicant, especially in patients with chronic stable ang-
gina pectoris, recent myocardial infarction, hypertension, 
or pulmonary disease. Knowledge of interactions with 
commonly used induction agents is critical for the appro-
priate clinical use of this drug. The current study dem-
onstrates that significant hemodynamic interactions may 
occur. Dexmedetomidine alters the hemodynamic actions 
of ketamine. If the hemodynamic effects of ketamine me-
diated by an increase in sympathetic tone are considered 
beneficial in certain patients, dexmedetomidine may be 
relatively contraindicated. However, if an increase in heart 
rate and mean arterial pressure would be deleterious, 
premedication with dexmedetomidine may be effective 
in blunting these responses and in allowing the use of 
etamine in circumstances in which it usually would not 
be considered. The current study did not examine 
whether or not the combination of these two medications 
causes less respiratory depression in subanesthetic doses, 
such as might be used for short procedures. However, 
the combination of dexmedetomidine and ketamine has 
been used with success in a variety of animal species with 
no changes in arterial blood gases recorded.\textsuperscript{40}

The current investigation also indicates that few un-
toward effects are observed during anesthesia with pro-

propofol after oral dexmedetomidine, so dexmedetomidine
may be an acceptable premedication in patients who would tolerate a propofol induction. Finally, this study confirms the relative lack of hemodynamic effects of etomidate alone and confirms a possible increase in arterial pressure by the combination of dexmedetomidine and etomidate _via_ an increase in systemic vascular resistance. This action may be deleterious in patients with preexisting hypertension. Thus, important interactions between the $\alpha_2$ agonist dexmedetomidine and intravenous anesthetic agents can occur. Knowledge of such interactions can lead to the use of intravenous anesthetics with dexmedetomidine that is tailored to the needs of the individual patient.

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