Cardiopulmonary effects of fentanyl in conscious dogs and dogs sedated with a continuous rate infusion of medetomidine

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Objective—To determine the hemodynamic consequences of the coadministration of a continuous rate infusion (CRI) of medetomidine with a fentanyl bolus in dogs.

Animals—12 healthy sexually intact male dogs weighing 30.3 ± 4.2 kg (mean ± SD).

Procedure—Dogs received either fentanyl alone (15.0 µg/kg, IV bolus) or the same dose of fentanyl during an 11-hour CRI of medetomidine (1.5 µg/kg/h, IV). Prior to drug administration, dogs were instrumented for measurement of cardiac output, left atrial pressure, and systemic arterial blood pressures. Additionally, blood samples were collected from the pulmonary artery and left atrium for blood gas analysis.

Results—Medetomidine infusion reduced the cardiac index, heart rate, and O_2 delivery while increasing left atrial pressure. Subsequent fentanyl administration further decreased the cardiac index. The Pao_2 was not significantly different between the 2 treatment groups; however, fentanyl transiently decreased Pao_2 from baseline values in dogs receiving a CRI of medetomidine.

Conclusions and Clinical Relevance—Because of the prolonged hemodynamic changes associated with the CRI of medetomidine, its safety should be further evaluated before being clinically implemented in dogs. (*Am J Vet Res* 2005;66:1222–1226)

The combination of α_2-adrenergic receptor agonists with opioids has been shown to result in additive or synergistic analgesia as well as prolonged duration of action and improved consistency of individual response.[1,2] Because medetomidine has a relatively short duration of effect (ie, 60 to 90 minutes), its use for pain control in dogs has been limited to the immediate perianesthetic period.[3] The use of **continuous rate infusions (CRIs)** of low doses of α_2-adrenergic receptor agonists has been recommended by some; however, there have been few reports[4-6] of the hemodynamic effects of this dosage regimen in dogs.

Medetomidine is a synthetic α_2-adrenergic receptor agonist that is approved by the FDA's Center for Veterinary Medicine as a sedative-analgesic for dogs. Dexmedetomidine (the active stereoisomer of medetomidine) is approved for use in human patients, but bolus administration has been reported[7] to cause dose-dependent reductions in tissue blood flow in dogs. Medetomidine administration is associated with decreased cardiac output, decreased heart rate, increased peripheral vascular resistance, and time-dependent alterations in arterial blood pressure, when administered IM or as an IV bolus.[6-9]

Fentanyl citrate is a µ-opioid receptor agonist used to treat moderate to severe pain. When given at high doses, fentanyl can be used as an anesthetic adjunct that has minimal hemodynamic effects. The aim of this study was to quantify changes in cardiopulmonary indices following fentanyl administration alone and with a CRI of medetomidine in dogs.

Materials and Methods

Animals—This study was approved by local institutional animal care and use committees and was in compliance with local and federal guidelines governing laboratory animal care and housing. Twelve sexually intact male mixed-breed hounds weighing (mean ± SD) 30.3 ± 4.2 kg, all free of disease, were randomly assigned to 1 of 2 treatment groups. Group I dogs (n = 6) were given the equivalent of 15.0 µg of fentanyl base/kg, administered as citrate salt,[a] IV, over 60 seconds. Group II dogs (n = 6) received the same dose of fentanyl, but 2 hours prior to fentanyl administration, a CRI of medetomidine hydrochloride[b] (1.5 µg/kg/h, IV) was begun and continued throughout the experimental period (total of 11 hours). Prior to administration, the medetomidine was diluted in 60 mL of saline (0.9% NaCl) solution. The medetomidine was administered via a calibrated syringe infusion pump. Dogs that did not receive medetomidine received the same volume of saline solution over the study period.

Catheterization—On the morning of the experiment, dogs were mask induced with and maintained on isoflurane in O_2 for catheter placement under fluoroscopic guidance.

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Following anesthetic induction, the right jugular vein was aseptically prepared, and a 110-cm-long balloon-tipped wedge pressure catheter was placed transvenously across the atrial septum via the jugular vein, according to the method of Phillips et al.[10] Catheter placement was verified by fluoroscopic visualization and measurement of Pa_{O_2} from a sample of blood obtained through the catheter. Heparinized saline (0.9% NaCl with 10 U of heparin/mL) solution was continuously infused through the catheter at a rate of 5 mL/h to reduce thrombus formation.

Through the same jugular vein, a 7-F 110-cm-long thermodilution cardiac output catheter[c] was positioned with the tip in the pulmonary artery for determination of cardiac output, pulmonary artery pressure, and core body temperature and for sample collection to measure mixed-venous blood gas tensions. An arterial catheter for measurement of heart rate and arterial blood pressure and for sample collection to measure arterial blood gas tensions was placed in the descending thoracic aorta via the femoral artery.[d] A cephalic catheter[e] was also aseptically placed to allow administration of fentanyl and medetomidine.

All catheters were secured in place, and dogs were allowed to recover from anesthesia. Two hours were allowed between recovery from isoflurane anesthesia and initial hemodynamic measurements, to allow for body temperature and hemodynamic variables to normalize. Following measurements, the CRI of medetomidine was begun in group II dogs and continued for the remainder of the study. Baseline hemodynamic measurements for both groups were taken immediately before bolus injection of fentanyl, which occurred approximately 4 hours following recovery from anesthesia. Cardiopulmonary measurements were recorded until 540 minutes after administration of fentanyl.

Hemodynamic measurements—Cardiac output was measured by thermodilution[f] following injection of 5 mL of iced 5% dextrose solution through the proximal port of the thermodilution catheter. Three injections were performed with the dogs in lateral recumbency, and the mean was calculated and recorded for each time point.

Systemic arterial blood pressure, pulmonary arterial pressures, and left atrial pressures were measured with the dogs in lateral recumbency by use of calibrated pressure transducers[g] zeroed to the level of the right atrium. The transducers were connected to a physiograph with zero and gain adjustments for the observed pressure range.[h]

Left atrial, arterial, and mixed-venous blood gas analyses were performed by use of a calibrated blood gas analyzer.[i] Samples were collected anaerobically into heparinized 1-mL syringes from the distal port of the thermodilution and left atrial catheters. Samples were analyzed immediately after collection. Percent **arterial O_2 saturation of hemoglobin (Sa_{O_2})** and percent mixed-venous saturation of hemoglobin were calculated from the analyzer output. All hemodynamic and blood gas measurements were performed immediately before and at 15, 60, and 540 minutes following fentanyl administration.

Statistical analysis—Data for hemodynamic variables and blood gas tensions were analyzed by use of a software program[j] by running a 2-way ANOVA with treatment as a between-animal factor and time of response as a within-animal, repeated-measures factor.[11] When appropriate, a post hoc Bonferroni multiple comparisons *t* test was applied by use of a Bonferroni correction to the overall *P* value. Data for cardiac index were log transformed prior to analysis. For all statistical tests, a P value ≤ 0.05 was considered significant.

Results

Evaluation of interactions—Treatment by time interactions were observed for heart rate, systolic arterial blood pressure, diastolic arterial blood pressure, mean pulmonary blood pressure, mean left atrial pressure, cardiac index, systemic and pulmonary vascular resistance index, O_2 delivery and consumption, body temperature, Pa_{O_2} and Pa_{CO_2}, Sa_{O_2}, arterial pH, **partial pressure of CO_2 in mixed-venous blood (Pmv_{CO_2})**, and mixed-venous blood pH (**Appendix**). Results of pairwise comparisons across treatment and time follow. Reported results are mean ± SD values.

Effect of the CRI of medetomidine alone—Following the 2-hour anesthetic recovery period and prior to initiating treatment, variables did not differ between treatment groups (summarized data not shown). Contrasts made between treatment groups before fentanyl bolus administration allowed comparison of the effect of a CRI of medetomidine alone on reported variables. Following initiation of the CRI of medetomidine, heart rate was lower in the treated dogs, compared with dogs that did not receive medetomidine (60 ± 12 beats/min vs 103 ± 19 beats/min; **Table 1**). Systemic and mean pulmonary arterial blood pressures were unchanged by medetomidine administration; however, the mean left atrial pressure was higher (17 ± 4 mm Hg vs 8 ± 6 mm Hg) and cardiac index lower (0.10 ±

Table 1—Mean ± SD values of hemodynamic variables before (baseline) and after fentanyl administration to dogs receiving fentanyl alone or fentanyl coadministered with a continuous rate infusion (CRI) of medetomidine.

		Hemodynamic variables									
Treatment group	**Time (min)**	**Heart rate (beats/min)**	**SAP (mm Hg)**	**DAP (mm Hg)**	**MAP (mm Hg)**	**MPAP (mm Hg)**	**MLAP (mm Hg)**	**CI (L/min/kg)**	**SVI (mL/beat/kg)**	**SVRI (dynes•s/cm^5/kg)**	**PVRI (dynes•s/cm^5/kg)**
Fentanyl alone (n = 6)	Baseline	103 ± 19*	181 ± 23	100 ± 8	127 ± 11	18 ± 7	8 ± 6*	0.17 ± 0.04*	1.7 ± 0.4	75.2 ± 36.8	6.0 ± 3.8
	15	72 ± 13*†	174 ± 23	89 ± 16	121 ± 18	21 ± 5	10 ± 3*	0.14 ± 0.54*	1.9 ± 0.6	108.5 ± 91.4	9.0 ± 4.8
	60	82 ± 6*	156 ± 19†	82 ± 14†	111 ± 18	18 ± 7	6 ± 2*	0.17 ± 0.03*	2.0 ± 0.3	63.7 ± 20.7*	7.7 ± 3.8
	540	117 ± 21*	159±18†	98 ± 11	119 ± 13	17 ± 6	4 ± 2*†	0.16 ± 0.027*	1.4 ± 0.4	73.8 ± 30.9*	8.9 ± 4.0
Medetomidine and fentanyl (6)	Baseline	60 ± 12	159 ± 19	100 ± 14	124 ± 16	21 ± 3	17 ± 4	0.10 ± 0.015	1.7 ± 0.4	106.1 ± 28.3	4.1 ± 4.4
	15	48 ± 13	159 ± 27	90 ± 15	115 ± 22	27 ± 5†	18 ± 5	0.07 ± 0.013	1.6 ± 0.5	132.1 ± 36.5	11.4 ± 2.6†
	60	47 ± 10	151 ± 29	85 ± 7†	111 ± 16	25 ± 6	13 ± 6	0.07 ± 0.014	1.6 ± 0.4	126.1 ± 24.5	13.5 ± 6.5†
	540	52 ± 11	153 ± 20	88 ± 9	114 ± 13	21 ± 6	11 ± 5	0.08 ± 0.011	1.6 ± 0.3	118.9 ± 22.4	12.4 ± 4.8†

*Significant ($P < 0.05$) difference between treatment groups at that time point. †Significant ($P < 0.05$) difference from baseline within treatment group.

SAP = Systolic arterial blood pressure. DAP = Diastolic arterial blood pressure. MAP = Mean arterial blood pressure. MPAP = Mean pulmonary arterial blood pressure. MLAP = Mean left atrial pressure. CI = Cardiac index. SVI = Stroke volume index. SVRI = Systemic vascular resistance index. PVRI = Pulmonary vascular resistance index.

0.015 L/min/kg vs 0.17 ± 0.04 L/min/kg) in dogs that received the CRI of medetomidine, compared with dogs that did not receive medetomidine. Stroke volume index was not lower, suggesting the change in cardiac index was related to lower heart rates in the dogs that received medetomidine. Oxygen delivery was also significantly lower in dogs receiving medetomidine, compared with untreated dogs (**Table 2**). No other variables were significantly different between groups (**Table 3**).

Comparison of fentanyl alone and fentanyl in combination with medetomidine—Following fentanyl administration, most dogs in either group were recumbent for up to 60 minutes. The administration of medetomidine in combination with fentanyl resulted in lower heart rates, cardiac index values, and calculated O_2 delivery at all times, compared with dogs that only received fentanyl (Tables 1 and 2). Systemic and pulmonary blood pressures did not differ between treatment groups; however, mean left atrial blood pressure was significantly higher at all time points in dogs that received medetomidine and fentanyl. Systemic vascular resistance index and $Pmvco_2$ (Table 3) were greater in dogs that received medetomidine with fentanyl at 60 and 540 minutes but not at earlier time points. The $Paco_2$ was significantly greater only at 60 minutes in the group receiving the CRI of medetomidine and fentanyl bolus, compared with dogs receiving the fentanyl bolus alone. Core body temperature was higher at 15 and 60 minutes in dogs receiving the CRI of medetomidine and fentanyl bolus, compared with dogs receiving the fentanyl bolus alone. The Sao_2 was transiently lower at 15 minutes in dogs that received medetomidine with fentanyl, compared with dogs that received fentanyl alone. All other variables did not differ significantly between treatment groups.

Table 2—Mean ± SD values of O_2 delivery and consumption before (baseline) and after fentanyl administration to dogs receiving fentanyl alone or fentanyl coadministered with a CRI of medetomidine.

		O_2 variables	
Treatment group	**Time (min)**	**O_2 delivery (mL/min)**	**O_2 consumption (mL/min)**
Fentanyl alone (n = 6)	Baseline	766 ± 274*	226 ± 121
	15	639 ± 319*	125 ± 55†
	60	699 ± 280*	111 ± 30†
	540	553 ± 142*	160 ± 45
Medetomidine and fentanyl (6)	Baseline	447 ± 131	164 ± 51
	15	345 ± 63	113 ± 38
	60	357 ± 55	104 ± 18
	540	302 ± 58	121 ± 41

See Table 1 for key.

Effect of fentanyl bolus administration over time—Responses recorded at 15, 60, and 540 minutes after fentanyl bolus administration were compared with baseline responses within treatment groups. Pairwise comparisons from baseline reflected the effect of fentanyl bolus administration on measured and calculated variables over time in the fentanyl alone and medetomidine with fentanyl treatment groups. Bolus administration of fentanyl to dogs that did not receive medetomidine decreased heart rate at 15 minutes, compared with baseline. This effect was not observed in dogs receiving a CRI of medetomidine during fentanyl administration (Table 1). Systolic blood pressure was decreased at 60 and 540 minutes, compared with the baseline value, in dogs receiving fentanyl alone. These differences were not observed in dogs that received the CRI of medetomidine. Compared with their baseline values, diastolic blood pressures were lower at 60 minutes in both treatment groups. Mean blood pressures did not change from baseline in either treatment group. Mean left atrial pressure was lower at 540 minutes, compared with baseline, only in dogs that received fentanyl alone. Mean pulmonary pressure was elevated from baseline at 15 minutes only in dogs given the fentanyl bolus during the CRI of medetomidine. Pulmonary vascular resistance was increased at all times, compared with the baseline value, in dogs receiving fentanyl and medetomidine but did not change in dogs receiving fentanyl alone. Core body temperature was decreased from baseline at 60 minutes only in dogs that received fentanyl alone (Table 3).

The Pao_2 and Sao_2 decreased from baseline values at 15 minutes only in dogs that received fentanyl and medetomidine (Table 3). In this same group, the $Paco_2$ and $Pmvco_2$ increased at 15 and 60 minutes, compared with their respective baseline values; no changes from baseline were observed for corresponding responses in dogs that received fentanyl alone. Arterial blood pH decreased in both groups at 15 minutes, but that decrease persisted at 60 minutes only in dogs that

Table 3—Mean ± SD values of pulmonary variables and body temperatures before (baseline) and after fentanyl administration to dogs receiving fentanyl alone or fentanyl coadministered with a CRI of medetomidine.

		Pulmonary variables and body temperatures							
Treatment group	**Time (min)**	**Temp (°C)**	**Pao_2 (mm Hg)**	**Sao_2 (%)**	**$Paco_2$ (mm Hg)**	**Arterial pH**	**$Pmvo_2$ (mm Hg)**	**$Pmvco_2$ (mm Hg)**	**Mixed-venous pH**
Fentanyl alone (n = 6)	Baseline	37.8 ± 0.5	95.3 ± 6.8	96.7 ± 0.7	33.2 ± 3.6	7.37 ± 0.02	40.5 ± 5.3	43.0 ± 2.6	7.34 ± 0.02
	15	37.5 ± 1.1*	86.4 ± 7.0	95.1 ± 0.7*	38.3 ± 1.8	7.30 ± 0.02†	50.7 ± 11.9	47.6 ± 2.1	7.27 ± 0.05†
	60	36.9 ± 1.1*†	96.0 ± 6.2	97.0 ± 0.8	31.1 ± 8.0*	7.35 ± 0.03	49.7 ± 4.8	42.0 ± 2.4*	7.30 ± 0.04†
	540	38.0 ± 0.4	94.0 ± 5.7	97.1 ± 0.3	27.7 ± 5.7	7.40 ± 0.03	42.2 ± 4.0	37.6 ± 2.9*	7.36 ± 0.02
Medetomidine and fentanyl (6)	Baseline	38.4 ± 0.9	96.8 ± 10.1	97.1 ± 0.6	30.8 ± 3.2	7.39 ± 0.04	38.1 ± 1.6	42.9 ± 4.6	7.34 ± 0.06
	15	38.7 ± 1.0	76.4 ± 10.7†	91.7 ± 3.5†	38.3 ± 4.1†	7.30 ± 0.06†	40.9 ± 6.5	50.3 ± 5.3†	7.27 ± 0.06†
	60	38.4 ± 0.9	90.1 ± 6.4	95.6 ± 0.7	40.0 ± 2.2†	7.32 ± 0.04†	44.1 ± 8.6	50.1 ± 4.2†	7.28 ± 0.06
	540	38.5 ± 1.3	91.0 ± 9.6	96.4 ± 0.9	30.4 ± 3.7	7.39 ± 0.02	37.1 ± 5.7	43.6 ± 5.4	7.33 ± 0.03

Temp = Core body temperature. Sao_2 = O_2 saturation of hemoglobin in arterial blood. $Paco_2$= Partial pressure of CO_2 in arterial blood. $Pmvo_2$ = Partial pressure of O_2 in mixed-venous blood. $Pmvco_2$ = Partial pressure of CO_2 in mixed-venous blood.
See Table 1 for remainder of key.

received fentanyl and medetomidine. The Pmv_{CO_2} was increased at 60 and 540 minutes in dogs that received fentanyl and medetomidine, compared with dogs that received only fentanyl. Mixed-venous pH decreased at 15 and 60 minutes for dogs that received fentanyl alone but at 15 minutes only for dogs that received medetomidine and fentanyl. Calculated global O_2 consumption was decreased from baseline at 15 and 60 minutes only in dogs receiving fentanyl alone (Table 2). No changes from baseline were observed in either treatment group for cardiac stroke volume and systemic vascular indices (Table 1), O_2 delivery, and **partial pressure of o_2 in mixed-venous blood ($Pmvo_2$)**.

Discussion

Methods to assess cardiovascular and pulmonary system function in dogs include measurement of heart rate, pulse quality, and respiratory rate. However, to conclude on the basis of interpretation of these variables that tissue O_2 delivery, blood pressure, or myocardial performance are adequate to meet physiologic requirements relies on assumptions that are often oversimplified, especially when applied to drugs that can have complex effects on the cardiopulmonary system, such as α_2-adrenergic receptor agonists.

In this study, the CRI of medetomidine (1.5 µg/kg/h) decreased heart rate and enhanced sinus arrhythmia in most dogs. This change occurred in most dogs within 15 to 30 minutes of the beginning of the infusion. By 1 hour, all dogs had reduced heart rate values, compared with baseline values. Second-degree atrioventricular block did not occur in any dog. However, pronounced sinus pauses occurred in all dogs, compatible with increased vagal efferent activity. Systemic blood pressure did not change noticeably prior to fentanyl administration in dogs receiving medetomidine. The decrease in cardiac output allowed mean arterial blood pressure to be maintained in a physiologically normal range, even though the vasculature was constricted. Similar responses have been documented[8,12-17] for dogs and other species following the administration of α_2-adrenergic receptor agonists. What is interesting in the current study is the rapidity and intensity of the effect on heart rate. The dose of 1.5 µg/kg/h was chosen on the basis of several pilot studies that indicated it was as effective as 10 and 15 µg/kg/h at inducing cardiovascular and sedative changes. Even without a loading dose, infusion of medetomidine induced pronounced hemodynamic effects, suggesting that low-dose long-term CRI of α_2-adrenergic receptor agonists should be monitored carefully in dogs.

The administration of fentanyl without concurrent administration of medetomidine resulted in a mild, short-lived decrease in heart rate. This decrease was not associated with a significant change in mean arterial blood pressure. Opioids, including fentanyl, are known to enhance vagal efferent activity. At least 3 different mechanisms have been proposed including central inhibition of sympathetic activity, direct effects on vagal efferents, and possibly direct agonist activity on cardiac opioid receptors.[18-20]

Fentanyl administration alone was not associated with a decrease in cardiac index. However, when coadministered with medetomidine, a significant decrease in cardiac index occurred. This observation has been previously reported[21] for dexmedetomidine and fentanyl coadministration in dogs. The decrease in cardiac index in the present study was not associated with a change in stroke volume index or mean arterial blood pressure but did parallel changes in heart rate.

Pulmonary arterial blood pressure was increased 15 minutes after fentanyl injection in dogs concurrently receiving medetomidine. Similar increases in pulmonary arterial pressure have been reported[22] with oxymorphone (0.4 mg/kg, IV), suggesting the effect may be common to µ-opioid receptor agonists and not unique to fentanyl. One mechanism of increasing pulmonary arterial blood pressure is an increase in pulmonary vascular resistance associated with hypoxic pulmonary vasoconstriction. Pulmonary vascular resistance was increased in the medetomidine-treated dogs following fentanyl administration, and this was reflected in higher pulmonary arterial pressures. At the same time, mean Pa_{O_2} had decreased significantly (at 15 minutes) or was lower following fentanyl administration during the CRI of medetomidine. The pattern of change was similar with fentanyl alone, but the change was not as large in magnitude and not significant. Hypoxic pulmonary vasoconstriction is usually a local response to alveolar hypoxia (partial pressure of o_2 in the alveoli of < 70 mm Hg); however, the mean Pa_{O_2} nadir for dogs receiving medetomidine and fentanyl in the present study was 76.4 mm Hg.[23]

Body temperature was better maintained in dogs receiving medetomidine than in dogs given fentanyl alone. Vasoconstriction and reduced flow to peripheral tissues would reduce distribution of core body heat to the body surface where radiation, conduction, convection, and evaporative losses occur. Following fentanyl administration, most dogs were recumbent for up to 60 minutes. During this time, metabolic activity was likely reduced, contributing to the decrease in body temperature. Following resumption of normal amounts of activity, dogs that received fentanyl alone had their body temperatures increase to baseline values.

Respiratory variables reflected fentanyl-associated respiratory depression and hypoventilation. The Pa_{CO_2} increased at 15 and 60 minutes following fentanyl administration in dogs that were also receiving medetomidine. The magnitude of the change was neither large nor associated with adverse clinical effects. Although Pa_{O_2} decreased in dogs receiving medetomidine and fentanyl, even the most severely affected dog did not appear cyanotic. The Sa_{O_2} decreased in parallel with Pa_{O_2}, as would be expected when Sa_{O_2} is calculated from Pa_{O_2} as in this study. Arterial pH decreased transiently following the administration of fentanyl in both groups, but the pattern paralleled changes in Pa_{CO_2} and was presumably associated with respiratory acidemia.

Results of mixed-venous blood gas analysis can provide information about global O_2 utilization and offer insight into the adequacy of O_2 delivery to tissues. The Pmv_{O_2} did not differ in the current study between dogs that received fentanyl alone or fentanyl with medetomidine. Comparison of O_2 delivery between the 2 treatment groups revealed an overall O_2 delivery to the systemic circulation that was reduced with a CRI of

medetomidine, primarily a function of decreased cardiac output. Mean O_2 delivery, even in its lowered state, still exceeded mean global consumption of conscious dogs in the present study. These global measures of systemic O_2 delivery and extraction do not provide enough information about events in specific tissues to determine whether local ischemia may have occurred. However, because medetomidine induces α_2-adrenergic receptor–mediated tissue blood flow distribution alterations that maintain perfusion of visceral organs at the expense of nonvital tissues such as skin and inactive muscle, it is reasonable to assume the temporary decrease in O_2 delivery is not associated with tissue hypoxia in vital tissues and thus is generally tolerated in healthy dogs.[7]

In conclusion, the administration of medetomidine (1.5 µg/kg/h, IV; CRI) reduced cardiac index, heart rate, and tissue O_2 delivery. Fentanyl (15.0 µg/kg, IV) administration, either alone or to dogs receiving a CRI of medetomidine, transiently reduced indices of oxygenation and enhanced respiratory depression. The use of medetomidine at 1.5 µg/kg/h as a continuous rate IV infusion results in pronounced reductions in cardiac index and heart rate as well as an increase in left atrial blood pressure. As such, and in the authors' opinion, the prolonged administration of medetomidine in dogs should be further evaluated for its adverse cardiopulmonary effects before its use can be recommended by this method. The current study was performed on healthy young dogs. The use of a CRI of dexmedetomidine in human patients is often reserved for sedating patients in intensive care units. The same use of medetomidine in dogs with a high degree of pain or stress or older dogs in the intensive care unit may alter the hemodynamic responses found in this study.

a. Elkins-Sinn, Cherry Hill, NJ.
b. Domitor, Pfizer Animal Health, New York, NY.
c. 131F7 Swan-Ganz catheter, Edwards Lifesciences, Irvine, Calif.
d. Arrow International Inc, Reading, Pa.
e. Angiocath, Becton-Dickinson, Sandy, Utah.
f. COM-1, American Edwards, Santa Ana, Calif.
g. TruWave, Edwards Lifesciences, Irvine, Calif.
h. Gould Inc, Cleveland, Ohio.
i. Ciba Corning 288 blood gas system, Ciba Corning Diagnostics, Medfield, Mass.
j. PROC GLM, SAS Institute Inc, Cary, NC.

References

1. Meert TF, De Kock M. Potentiation of the analgesic properties of fentanyl-like opioids with alpha 2-adrenoceptor agonists in rats. *Anesthesiology* 1994;81:677–688.
2. Grimm KA, Tranquilli WJ, Thurmon JC, et al. Duration of nonresponse to noxious stimulation after intramuscular administration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. *Am J Vet Res* 2000;61:42–47.
3. Cullen LK. Medetomidine sedation in dogs and cats: a review of its pharmacology, antagonism and dose. *Br Vet J* 1996;152:519–535.
4. Benson GJ, Thurmon JC, Tranquilli WJ, et al Cardiopulmonary effects of an intravenous infusion of guaifenesin, ketamine, and xylazine in dogs. *Am J Vet Res* 1985;46:1896–1898.
5. Tranquilli WJ, Grimm KA, Lamont LA. *Pain management for the small animal practitioner*. 2nd ed. Jackson, Wyo: Teton New Media, 2004.
6. Willigers HM, Prinzen FW, Roekaerts PM, et al. Dexmedetomidine decreases perioperative myocardial lactate release in dogs. *Anesth Analg* 2003;96:657–664.
7. Lawrence CJ, Prinzen FW, de Lange S. The effect of dexmedetomidine on nutrient organ blood flow. *Anesth Analg* 1996;83:1160–1165.
8. Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. *Vet Surg* 1998;27:612–622.
9. Klide AM, Calderwood HW, Soma LR. Cardiopulmonary effects of xylazine in dogs. *Am J Vet Res* 1975;36:931–935.
10. Phillips HR, Stack RS, Rembert JC, et al. A technique to inject microspheres into the left atrium of awake dogs without thoracotomy. *Am J Physiol* 1982;243:H488–H490.
11. Glantz SA, Slinker BK. Two-way analysis of variance. In: *Primer of applied regression and analysis of variance*. New York: McGraw-Hill Book Co, 2000;339–507.
12. Lamont LA, Bulmer BJ, Grimm KA, et al. Cardiopulmonary evaluation of the use of medetomidine hydrochloride in cats. *Am J Vet Res* 2001;62:1745–1749.
13. Jalonen J, Halkola L, Kuttila K, et al. Effects of dexmedetomidine on coronary hemodynamics and myocardial oxygen balance. *J Cardiothorac Vasc Anesth* 1995;9:519–524.
14. Flacke WE, Flacke JW, Bloor BC, et al. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993;7:41–49.
15. Bloor BC, Frankland M, Alper G, et al. Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992;263:690–697.
16. Weitz JD, Foster SD, Waugaman WR, et al. Anesthetic and hemodynamic effects of dexmedetomidine during isoflurane anesthesia in a canine model. *Nurse Anesth* 1991;2:19–27.
17. Flacke JW, Flacke WE, Bloor BC, et al. Hemodynamic effects of dexmedetomidine, an alpha 2-adrenergic agonist, in autonomically denervated dogs. *J Cardiovasc Pharmacol* 1990;16:616–623.
18. Reitan JA, Stengert KB, Wymore ML, et al. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. *Anesth Analg* 1978;57:31–36.
19. Inoue K, Samodelov LF, Arndt JO. Fentanyl activates a particular population of vagal efferents which are cardioinhibitory. *Naunyn Schmiedebergs Arch Pharmacol* 1980;312:57–61.
20. Gautret B, Schmitt H. Multiple sites for the cardiovascular actions of fentanyl in rats. *J Cardiovasc Pharmacol* 1985;7:649–652.
21. Salmenpera MT, Szlam F, Hug CCJ. Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. *Anesthesiology* 1994;80:837–846.
22. Copland VS, Haskins SC, Patz JD. Oxymorphone: cardiovascular, pulmonary, and behavioral effects in dogs. *Am J Vet Res* 1987;48:1626–1630.
23. Stoelting PK. Pulmonary circulation. In: *Pharmacology and physiology in anesthetic practice*. 2nd ed. Philadelphia: JB Lippincott Co, 1991;685–691.

Appendix

Hemodynamic calculations.

Calculations	Equations
Cardiac index (L/min/kg)*	CO/BW
O_2 delivery†	$CO \times ([1.34 \times Sa_{O_2} \times Hb] + [Pa_{O_2} \times 0.003])$
O_2 consumption†	$CO \times ([\{1.34 \times Sa_{O_2} \times Hb\} + \{Pa_{O_2} \times 0.003\}] - [\{1.34 \times Sm_{VO_2} \times Hb\} + \{Pm_{VO_2} \times 0.003\}])$

*Cardiac output (CO) expressed in L/min. †CO expressed in dL/min.
BW = Body weight (kg). Sa_{O_2} = O_2 saturation of hemoglobin in arterial blood (%). Hb = Hemoglobin concentration (g/dL). Pa_{O_2} = Partial pressure of O_2 in arterial blood (mm Hg). Sm_{VO_2} = O_2 saturation of Hb in mixed-venous blood (%). Pm_{VO_2} = Partial pressure of O_2 in mixed-venous blood (mm Hg).