Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs

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Objective—To evaluate degree of sedation and cardiovascular, respiratory, acid-base excess, and electrolyte variables in response to IM administration of dexmedetomidine or dexmedetomidine with atropine.

Design—Randomized crossover study.

Animals—5 healthy 1- to 2-year-old sexually intact male Treeing Walker Coonhounds.

Procedures—Dogs were instrumented with catheters placed in the dorsal pedal artery and lateral saphenous vein. All dogs received dexmedetomidine (10 µg/kg [4.5 µg/lb], IM) or dexmedetomidine with atropine (0.02 mg/kg [0.009 mg/lb], IM). Variables were measured at baseline (time 0) and 5, 15, 30, and 60 minutes after drug administration.

Results—In all dogs, lithium dilution cardiac output decreased from a mean ± SD baseline value of 5.07 ± 1.0 L/min to 2.1 ± 0.9 L/min. Cardiac output was not different between dexmedetomidine group dogs and dexmedetomidine-atropine group dogs. Mean arterial pressure increased from baseline in both groups but was significantly higher in dexmedetomidine-atropine group dogs, compared with dexmedetomidine group dogs. Heart rate in dexmedetomidine group dogs decreased from 110 ± 14.2 beats/min to 49.4 ± 10.4 beats/min by 15 minutes. No differences were seen in blood gas values, electrolyte concentration, or hemoglobin values over time or between groups. Arrhythmias were detected in dexmedetomidine-atropine group dogs and included atrioventricular block, ventricular premature contractions, and ventricular bigeminy.

Conclusions and Clinical Relevance—Administration of atropine at 0.02 mg/kg, IM, with dexmedetomidine at 10 µg/kg, IM, resulted in an increase in mean arterial blood pressure and heart rate; deleterious cardiac arrhythmias were also observed. Use of atropine with dexmedetomidine is not recommended in dogs. (*J Am Vet Med Assoc* 2011;239:81–89)

Dexmedetomidine is an α_2-adrenergic receptor agonist that is routinely used in the clinical setting for sedation and analgesia in a wide variety of species. Dexmedetomidine is the dextro isomer of medetomidine and has been shown to have most, if not all, of the potent sedative and analgesic effects of the parent drug.[1] The sedative effects of dexmedetomidine in dogs have not been fully evaluated at a low dose such as 10 µg/kg (4.5 µg/lb), IM. Although α_2-adrenergic receptor agonists are among the most potent sedatives we have available for small animals,[2] they have substantial cardiovascular adverse effects, namely a potent albeit transient vasoconstriction, reflex bradycardia, and decrease in cardiac output.[3,4] There has been controversy about the use of anticholinergics to either prevent[5–8] or treat[4,9] α_2-adrenergic receptor agonist–mediated bradycardia. Previous studies[3,4,10] involving the use of a variety of doses of α_2-adrenergic receptor agonists have shown a 50% to 60% decrease in cardiac output.

Abbreviations

DAP	Diastolic arterial pressure
MAP	Mean arterial pressure
RPP	Rate pressure product
SAP	Systolic arterial pressure

The purpose of the study reported here was to evaluate effects of dexmedetomidine on sedation, cardiovascular, respiratory, acid-base, and electrolyte variables when used alone or in conjunction with the anticholinergic atropine in awake but deeply sedated dogs. It was hypothesized that atropine when administered with dexmedetomidine would increase heart rate, blood pressure, and cardiac output, compared with dexmedetomidine administration alone. It was also hypothesized that IM administration of dexmedetomidine at 10 µg/kg would provide potent sedation such that minor clinical procedures would be possible in dogs. This was evaluated on the basis of the degree of seda-

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tion observed with the sedation scoring system as well as with our clinical judgment based on experience with dexmedetomidine.

Materials and Methods

The design and execution of this study were approved by Colorado State University's Institutional Animal Care and Use Committee. Five 1- to 2-year old adult male sexually intact Treeing Walker Coonhounds with a mean weight of 25.4 ± 1.6 kg (55.8 ± 3.52 lb) were used in both phases of this study. They were housed in temperature-controlled kennels in the hospital for 3 days before the experiments and were brought to the laboratory twice daily to familiarize themselves with the environment for 1 week before the first testing day. On the day of the study, dogs were brought to the laboratory and allowed to acclimate for 20 to 30 minutes before restraint and onset of instrumentation and testing. Measurements were performed at baseline (time 0) and repeated at 5, 15, 30, and 60 minutes after injection of dexmedetomidine alone or dexmedetomidine and atropine.

By use of sterile technique, all dogs had an 18-gauge catheter placed in the lateral saphenous vein, and after blocking with 0.2 mL of lidocaine, a 20-gauge catheter was placed in the dorsal pedal artery. Dogs were monitored and measurements were taken before drug administration and for the duration of the study with a commercially available digital data acquisition system and software.[a] This included a transducer[b] to measure arterial blood pressure (systolic, mean, and diastolic) and an ECG for heart rate and rhythm. Rate pressure product was calculated at all time points for each patient as the product of heart rate and SAP, as previously reported.[11–14] Pressure transducers were zeroed to ambient atmospheric pressure and centered at the level of the heart, which was considered to be the sternum in lateral recumbency. Respiratory rates were manually counted and recorded. Body temperature was measured rectally at baseline, and subsequently, body temperature was continuously monitored by use of an esophageal temperature probe beginning at the 5-minute time point. At all measurement time points, an arterial blood sample was collected for measurements of blood gas tension, electrolyte concentration,[c] co-oximeter–derived hemoglobin values,[d] PCV, and total protein concentration. Arterial blood samples were tested immediately after collection. Cardiac output was measured via lithium dilution[e] through the peripheral arterial catheter, as previously reported.[15–19]

A modification of a previously reported sedation scoring system[8] was used at all time points to score the sedation at baseline and after IM injection (**Appendix**); all scores were assigned by a single individual (JMC). Included in sedation scoring was the response to environmental stimuli, which included a toe pinch to evaluate the response of the patient to a mildly painful stimulus. All environmental stimuli were applied after measurement and recording of all other variables. Dogs were placed in lateral recumbency for arterial and lateral saphenous catheter placement, and time was taken to calm them before catheter placement. Thirty minutes after catheter placement, baseline measurements for all variables were taken before any injections of sedative. Dogs were then given dexmedetomidine (10 µg/kg; dexmedetomidine group dogs) or dexmedetomidine (10 µg/kg) and atropine (0.02 mg/kg [0.01 mg/lb]; dexmedetomidine-atropine group dogs). All dogs were injected by use of 3-mL syringes with 22-gauge, 1.25-inch needles in the semitendinosus muscle. All dogs received both treatments at a minimum of 3 days apart, applied in a randomized order. Randomization of dogs to first treatment group as either dexmedetomidine alone or dexmedetomidine-atropine groups was determined by a coin flip. Dogs received the alternate treatment on the following research day, no less than 3 days after first treatment. No efforts were made to control for volume of injectate of dexmedtomidine or dexmedetomidine-atropine between treatment groups for 2 reasons. First, in keeping with the goal of clinical application to the private practitioner, we wanted the volume of drug injected to reflect the dosage used, not an arbitrarily selected volume. Second, after calculation of dexmedetomidine at 10 µg/kg and atropine at 0.02 mg/kg, volumes of drug for either dexmedetomidine or atropine are equal across all dogs on a per kilogram basis, with the dexmedetomidine dose being given at a final volume of 0.02 mL/kg and the atropine dose being given at a final volume of 0.04 mL/kg.

Statistical analysis—Mean ± SD values are reported for each treatment group across time. Outcome variables were evaluated for assumptions of linear regression within each treatment group. Normality was determined by use of the Shapiro-Wilk statistic and a probability plot. A bivariable linear regression analysis with the generalized estimating equation method[f] was used to determine the association between the time and outcome variable within each treatment group. Repeated measurements on the same dogs were taken into account during the analysis.

A multivariable linear regression analysis with the generalized estimating equation method[f] was used to determine the association between treatment and time with each outcome. Repeated measurements on the same dogs were taken into account during the analysis. A value of $P < 0.05$ was considered significant. A type

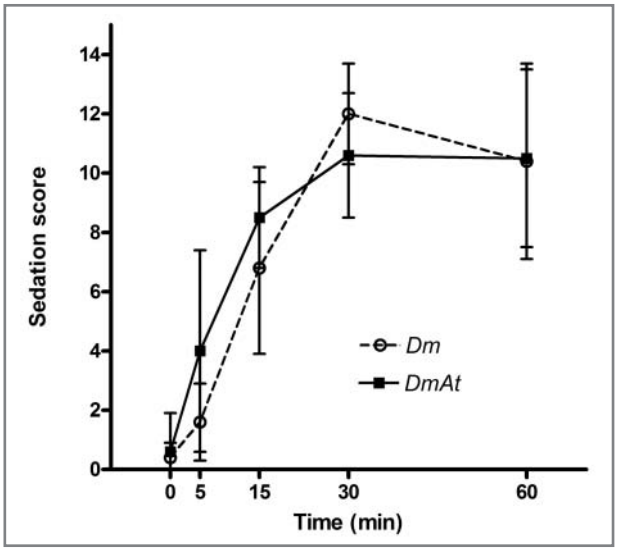

Figure 1—Mean ± SD sedation score in dexmedetomidine (Dm) and dexmedetomidine-atropine (DmAt) group dogs (n = 5) over a 60-minute study period.

III *P* value was calculated to indicate the overall significance of the association between the independent variable and the outcome for each treatment group. Paired *t* tests were used to evaluate the baseline data for all measured variables between the dexmedetomidine and dexmedetomidine-atropine group dogs.

Results

Sedation—No difference was seen in baseline sedation scores between groups. Dogs were equally sedated in both groups over time, and sedation scores increased significantly from baseline in dexmedetomidine group dogs at 15 minutes ($P = 0.01$) and in dexmedetomidine-atropine group dogs at 5 minutes ($P = 0.048$; **Figure 1**). There was no difference in the onset time or degree of sedation between groups through the study period. Sedation was assessed to be sufficient to maintain lateral recumbency with no restraint by 15 minutes after injection, and subjects were unresponsive to stimuli as outlined in the sedation scoring system description.

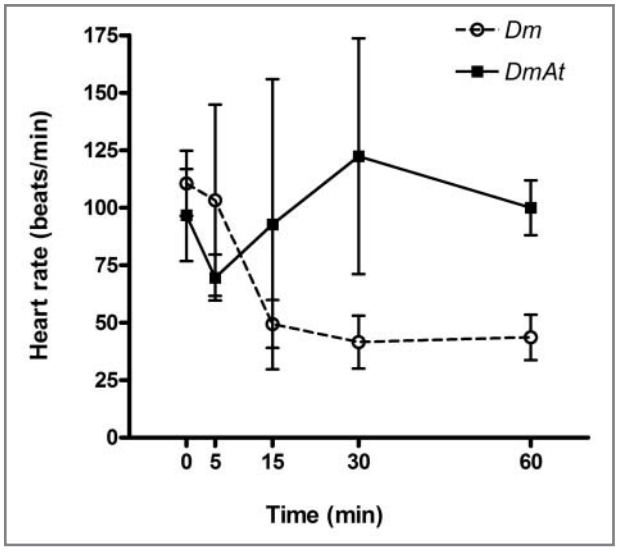

Figure 2—Mean ± SD heart rate in Dm and DmAt group dogs (n = 5) over a 60-minute study period.

Heart rate—Baseline heart rate was not different between groups (**Figure 2**). In dexmedetomidine group dogs, heart rate significantly ($P = 0.003$) decreased from a mean of 110.6 ± 14 beats/min at baseline to a mean of 49.4 beats/min at 15 minutes and remained decreased through the end of the study period. Heart rate in dexmedetomidine-atropine group dogs at baseline was 96.8 ± 20 beats/min and significantly ($P = 0.045$) decreased to 69.6 ± 10 beats/min at 5 minutes. However, heart rate returned to baseline by the 15-minute time point (92.8 beats/min; $P = 0.91$) and remained similar to baseline during the rest of the study. When compared between treatment groups as a whole, heart rate was significantly ($P = 0.018$) lower in the dexmedetomidine group dogs than in dexmedetomidine-atropine group dogs.

Blood pressure—Baseline SAP was not different between groups (**Figure 3**). Systolic arterial pressure in dexmedetomidine group dogs increased significantly ($P = 0.003$) from a baseline of 143.8 ± 13.1 mm Hg to a maximum of 157.2 ± 17 mm Hg at 15 minutes and remained increased through the end of the study period. In dexmedetomidine-atropine group dogs, mean SAP was significantly ($P < 0.001$) higher than baseline at 15 through 60 minutes. Baseline SAP in dexmedetomidine-atropine group dogs was 150.8 ± 4.4 mm Hg and significantly ($P < 0.001$) increased to 229.8 ± 47.9 mm Hg. Systolic arterial pressure significantly ($P = 0.001$) increased in both groups by the 15-minute time point. Systolic arterial pressure was significantly ($P = 0.039$) higher overall in dexmedetomidine-atropine group dogs, compared with dexmedetomidine-group dogs.

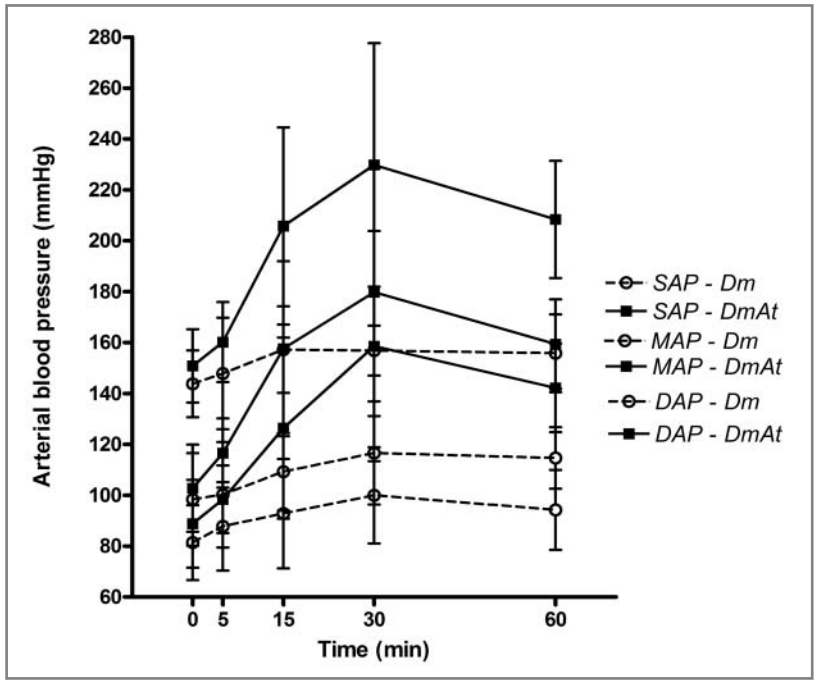

Figure 3—Mean ± SD direct blood pressure (SAP, MAP, and DAP) in Dm and DmAt group dogs (n = 5) over a 60-minute study period.

There was no difference between groups in baseline measurements for MAP. Mean arterial pressure in dexmedetomidine group dogs was 98.4 ± 18.2 mm Hg, increased significantly ($P < 0.001$) by the 5-minute time point to a maximum of 116.2 ± 20.3 mm Hg at 30 minutes, and remained high to the end of the study. Mean arterial pressure in dexmedetomidine-atropine group dogs at baseline was 102.8 ± 17.1 mm Hg and increased significantly ($P < 0.001$) by 5 minutes to a maximum of 179.8 ± 48.7 mm Hg at the 30-minute time point. Mean MAP was significantly ($P = 0.039$) higher overall in dexmedetomidine-atropine group dogs, compared with dexmedetomidine group dogs.

There was also no difference between groups in baseline measurements for DAP. Diastolic arterial pressure in

dexmedetomidine group dogs was 81.4 ± 14.7 mm Hg and significantly (P = 0.002) increased by 15 minutes to the maximum of 100 ± 18.9 mm Hg at the 30-minute time point. Diastolic arterial pressure significantly ($P < 0.001$) increased from 88.8 ± 17.3 mm Hg by 5 minutes to a maximum of 158 ± 45.2 mm Hg at the 30-minute time point in the dexmedetomidine-atropine group dogs. Diastolic arterial pressure was significantly (P = 0.034) higher overall in dexmedetomidine-atropine group dogs, compared with dexmedetomidine group dogs.

RPP—No difference was seen between groups in baseline measurements of RPP (**Table 1**). Rate pressure product significantly (P = 0.048) increased from baseline in dexmedetomidine-atropine group dogs with peak difference from the baseline at 30 minutes. Rate pressure product decreased in dexmedetomidine group dogs by 15 minutes and remained low at a stable plateau through the end of the study period from this point forward. Given this finding, all data were combined from the 15-, 30-, and 60-minute time points to compare the overall effect on RPP between the dexmedetomidine and dexmedetomidine-atropine group dogs. For combined data, mean RPP in dexmedetomidine group dogs (7,040 ± 460 mm Hg/beats/min) was significantly (P = 0.003) different than in dexmedetomidine-atropine group dogs (23,380 ± 3,020 mm Hg/beats/min).

Cardiac output—Baseline cardiac output was not different between groups. Cardiac output significantly decreased within 5 minutes after either dexmedetomidine (P = 0.004) or dexmedetomidine-atropine ($P < 0.001$) administration and remained low for the duration of the study period (**Figure 4**). However, there was no significant (P = 0.60) difference between groups over time. Mean cardiac output in dexmedetomidine group dogs was 5.38 ± 0.77 L/min at baseline and reached a maximum significant ($P < 0.001$) decrease at 30 minutes of 1.68 ± 0.39 L/min. Baseline cardiac output in dexmedetomidine-atropine group dogs was 4.75 ± 1.19 L/min and reached maximum significant ($P < 0.001$) decrease at 15 minutes of 1.88 ± 1.13 L/min.

Respiratory rate—Respiratory rate did not differ significantly (P = 0.66) between groups, but decreased significantly from baseline to 15 minutes in dexmedetomidine (P = 0.001) and dexmedetomidine-atropine (P = 0.037) group dogs. Respiratory rate decrease was maximal by 30 minutes (**Table 2**). Mean baseline respiratory rate in the dexmedetomidine (51.2 ± 41.7 breaths/min) and dexmedetomidine-atropine (58.4 ± 45.5 breaths/min) group dogs decreased by 15 minutes and plateaued by 30 minutes (dexmedetomidine group dogs, 12.8 ± 4.4 breaths/min; dexmedetomidine-atropine group dogs, 15.2 ± 5.2 breaths/min) through the study period.

Arterial blood gas values and co-oximeter analysis—Acid-base analysis included pH, $Paco_2$, and bicarbonate, acid-base excess, and lactate concentrations (Table 2). Oxygenation included Pao_2 and oxygen saturation percentage (**Table 3**). Electrolyte evaluation included sodium, potassium, chloride, ionized calcium, and glucose concentrations (**Table 4**). Packed cell volume and total protein concentration were measured manually on the arterial blood sample after blood gas and co-oximeter analysis. Co-oximeter values included total hemoglobin, hemoglobin saturation, carboxyhemoglobin, methemoglobin, oxygen content, oxyhemoglobin, and reduced hemoglobin. For all of these measured variables, there were no differences either within groups (dexmedetomidine or dexmedetomidine-atropine over time) or between groups in baseline measurements or over the 60-minute study period.

Body temperature—Body temperature decreased slightly over time in both groups, but no difference was found in baseline measurements, over the study period, or between the 2 groups. Body temperature change in dexmedetomidine group dogs was from 39 ± 0.4°C (102.1 ± 0.6°F) at baseline to 38.3 ± 0.5°C (100.9 ± 0.9°F) at 60 minutes, and in dexmedetomidine-atropine group dogs, baseline body temperature was 39.3 ± 0.2°C (102.8 ± 0.4°F) and decreased to 38.7 ± 0.3°C (101.7 ± 0.6°F).

Arrhythmias—Given the nature of ECG interference and lack of a completely continuous ECG for all

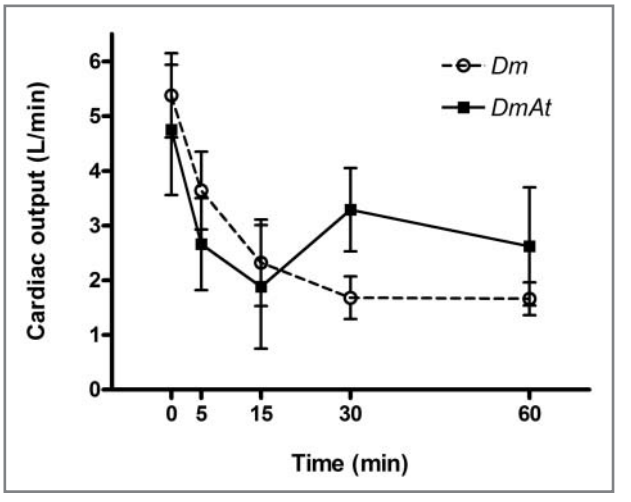

Figure 4—Mean ± SD cardiac output in Dm and DmAt group dogs (n = 5) over a 60-minute study period.

Table 1—Mean ± SD RPP measured (mm Hg/beats/min) over time in dexmedetomidine (Dm) and dexmedetomidine-atropine (DmAt) group dogs (n = 5) during a 60-minute study period.

Treatment	Baseline	5 min	15 min	30 min	60 min	*P* value
Dm	16,000 ± 3,180	15,200 ± 6,100	7,780 ± 1800	6,590 ± 2,100	6,760 ± 1,500	< 0.01
DmAt	14,800 ± 4,300	11,000 ± 900	19,700 ± 1,400*	29,500 ± 1,390*	21,000 ± 4,600*	0.093

Type III *P* value indicating overall significance between the treatment group and the individual outcome variable.
*Significant ($P < 0.05$) difference from baseline to selected data point within a treatment group.

Table 2—Mean ± SD acid-base measurements over time in arterial blood samples from Dm and DmAt group dogs (n = 5) during a 60-minute study period.

Variable	Treatment	Baseline	5 min	15 min	30 min	60 min	*P* value
pH	Dm	7.43 ± 0.02	7.4 ± 0.02	7.39 ± 0.03	7.4 ± 0.04	7.4 ± 0.04	0.3369
	DmAt	7.42 ± 0.04	7.38 ± 0.02	7.4 ± 0.02	7.39 ± 0.02	7.39 ± 0.03	0.3364
$Paco_2$ (mm Hg)	Dm	32.5 ± 3.8	36.7 ± 2.4	34.7 ± 2.1	34.8 ± 2.5	34.5 ± 3	0.813
	DmAt	31 ± 0.9	34.9 ± 1.2	32.8 ± 2.3	34.1 ± 1.8	35.8 ± 1	0.0046
HCO_3^- (mmol/L)	Dm	21.1 ± 3	22.5 ± 2.4	20.4 ± 2.1	21.2 ± 2.3	20.8 ± 2.8	0.6608
	DmAt	19.7 ± 2.5	20.3 ± 1.2	19.9 ± 1.1	20.4 ± 1.7	20.7 ± 1.1	0.3349
Acid-base excess (mmol/L)	Dm	–3 ± 3.2	–1.75 ± 2.6	–3.8 ± 2.2	–3.08 ± 2.6	–3.34 ± 3.3	0.6556
	DmAt	–4.54 ± 2.8	–4.02 ± 1.4	–4.46 ± 1.2	–3.94 ± 1	–3.74 ± 1.3	0.4913
Respiratory rate (breaths/min)	Dm	51.2 ± 41.7	33.2 ± 14.5	19.2 ± 9.9*	12.8 ± 4.4*	10.4 ± 2.2*	0.288
	DmAt	58.4 ± 45.5	37.4 ± 26.3	24.2 ± 10.6*	15.2 ± 5.2*	10.8 ± 1.8*	0.381
Body temperature (°C)	Dm	39 ± 0.4	38.8 ± 0.2	38.7 ± 0.2	38.6 ± 0.4	38.3 ± 0.5	0.408
	DmAt	39.3 ± 0.2	39.2 ± 0.4	39.3 ± 0.3	39.0 ± 0.3	38.7 ± 0.3	0.287

See Table 1 for key.

Table 3—Mean ± SD oxygenation and co-oximeter variables over time in arterial blood samples from Dm and DmAt group dogs (n = 5) during a 60-minute study period.

Variable	Treatment	Baseline	5 min	15 min	30 min	60 min	*P* value
Pao_2 (mm Hg)	Dm	72.6 ± 7.9	67.8 ± 2.2	65.7 ± 4.2	70.4 ± 7.5	72.6 ± 4.8	0.4611
	DmAt	81.3 ± 7.9	64.1 ± 2.3	69.8 ± 4.2	70.5 ± 7.5	67.7 ± 4.8	0.4006
Tot Hgb (G%)	Dm	16.5 ± 0.9	14.9 ± 0.7	15.5 ± 0.9	15.8 ± 0.5	15.4 ± 1.4	0.4735
	DmAt	16.3 ± 0.7	15.2 ± 0.5	15.8 ± 0.8	16.4 ± 0.7	16.9 ± 0.4	0.0049
Hgb Sat (%)	Dm	94.4 ± 1.6	91.8 ± 1.2	90.6 ± 1.3	92.2 ± 2.2	93.1 ± 1.7	0.995
	DmAt	94.1 ± 2.3	90.9 ± 1.9	91.9 ± 1.1	92.4 ± 1.9	91.1 ± 2.1	0.189
Hgb-CO (%)	Dm	2.7 ± 3	1 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	1 ± 0.1	0.8175
	DmAt	1.1 ± 0.1	2.3 ± 2.8	0.9 ± 0.2	1 ± 0	1 ± 0.1	0.4445
Met-Hgb (%)	Dm	0.1 ± 0.3	0.1 ± 0.1	0 ± 0.1	0.1 ± 0.1	0 ± 0.1	0.3496
	DmAt	0 ± 0.1	0.1 ± 0.2	0 ± 0	0 ± 0	0 ± 0	0.3847
O_2 Ct (vol%)	Dm	21 ± 1.6	18.8 ± 0.8	19.3 ± 1.2	20.4 ± 0.4	19.7 ± 1.9	0.7109
	DmAt	21.1 ± 0.7	18.7 ± 1.4	20 ± 1	20.9 ± 1	21.2 ± 0.5	0.0613

Hgb-CO = Percent carboxyhemoglobin. Hgb Sat = Percentage oxygen saturation of hemoglobin. Met-Hgb = Percentage methemoglobin. O_2 Ct = Oxygen content. Tot Hgb = Total measured hemoglobin.
See Table 1 for remainder of key.

Table 4—Mean ± SD electrolyte and selected variables over time in arterial blood samples from Dm and DmAt group dogs (n = 5) during a 60-minute study period.

Variable	Treatment	Baseline	5 min	15 min	30 min	60 min	*P* value
Na^+ (mEq/L)	Dm	148 ± 1.2	148 ± 1.4	175 ± 0.6	147.6 ± 1.7	147.2 ± 0.8	0.2429
	DmAt	149.2 ± 0.8	147.8 ± 1.5	147.2 ± 1.6	147.7 ± 0.9	149 ± 2.5	0.6355
K^+ (mEq/L)	Dm	3.72 ± 0.4	3.72 ± 0.2	3.5 ± 0.2	3.72 ± 0.3	3.7 ± 0.4	0.9235
	DmAt	3.58 ± 0.3	3.8 ± 0.3	3.78 ± 0.3	3.7 ± 0.2	3.68 ± 0.3	0.9517
Cl^- (mEq/L)	Dm	117.8 ± 1.9	116.5 ± 1.5	117.7 ± 2.2	117.6 ± 1.5	118.4 ± 2.8	0.3797
	DmAt	119.2 ± 2.8	118.4 ± 1.8	118.2 ± 1.3	118 ± 2.2	119 ± 1.6	0.9358
iCa^{++} (mEq/L)	Dm	1.28 ± 0.1	1.3 ± 0	1.29 ± 0.1	1.34 ± 0.1	1.35 ± 0	0.4361
	DmAt	1.22 ± 0.1	1.3 ± 0.1	1.31 ± 0.1	1.33 ± 0	1.37 ± 0	0.3698
Glucose (mg/dL)	Dm	104.8 ± 5.4	103.4 ± 1.3	105.5 ± 4.2	101.6 ± 18.1	109.4 ± 8	0.4361
	DmAt	95.6 ± 8.6	103.2 ± 7	102.4 ± 12.8	102.4 ± 12.8	104.6 ± 8.7	0.3698
Lactate (mmol/L)	Dm	0.72 ± 0.2	0.88 ± 0.3	0.78 ± 0.4	0.84 ± 0.4	0.88 ± 0.5	0.5733
	DmAt	0.82 ± 0.3	1.02 ± 0.3	2.5 ± 3.1	1.1 ± 0.3	1.12 ± 0.3	0.9578
PCV (%)	Dm	48.2 ± 2.8	43 ± 2.1	45.3 ± 3.5	45.4 ± 1.1	44.8 ± 1.6	0.0833
	DmAt	46.6 ± 2.1	44 ± 1.4	45 ± 1.4	46.2 ± 1.3	41.8 ± 16	0.3927
Total protein (g/dL)	Dm	5.8 ± 0.3	5.0 ± 0.4	5.1 ± 0.7	5.7 ± 1.3	5.0 ± 0.9	0.4266
	DmAt	5.4 ± 0.3	5.1 ± 0.2	5.1 ± 0.2	5.3 ± 0.4	5.7 ± 0.4	0.0788

iCa^{++} = Ionized calcium.
See Table 1 for remainder of key.

dogs for the duration of the study, formal statistical analysis was not able to be performed on incidence or frequency of arrhythmias between groups or over time. In place of this, the ECG was reviewed for the presence or absence of particular arrhythmias. In dexmedetomidine group dogs, all dogs had sinus bradycardia or sinus arrhythmia; 3 of 5 dogs had second-degree AV block that began at 5 to 15 minutes and continued to the conclusion of the study. No ventricular arrhythmias were seen in dexmedetomidine group dogs. In dexmedetomidine-atropine group dogs, no second-degree atrioventricular block was seen and 3 of 5 dogs developed ventricular premature contractions, of which 1 dog had evidence of ventricular bigeminy. Onset of ventricular premature contractions was developed between 5 and 15 minutes and continued to the end of the study period in those dogs developing ventricular premature contractions. The dog that developed ventricular bigeminy developed the arrhythmia 9 minutes after dexmedetomidine and atropine administration, and the arrhythmia was detected intermittently for the duration of the study period.

Discussion

In the present study, we evaluated the sedative, cardiovascular, respiratory, acid-base excess, and electrolyte changes resulting from a clinically relevant dose of dexmedetomidine administered IM with or without concurrent IM administration of atropine.

Of clinical interest is the quality and depth of sedation and also the onset time and duration of sedation that one could expect following dexmedetomidine administration IM. Our data indicated that the onset time of sedation following IM administration of dexmedetomidine is 5 to 15 minutes, with its peak sedative effect occurring at approximately 30 minutes and lasting through the end of our study period, similar to findings reported previously.[8] Though not tested in our experimental design, in our clinical experience of using this dose of dexmedetomidine IM, we feel that the degree of sedation would be sufficient for minor procedures such as laceration repairs and radiography in otherwise healthy patients. To evaluate the degree of sedation, we did evaluate response to painful stimuli by applying a toenail pinch after scoring the sedation according to our scoring outline. This allowed us more insight into our assessment of response to painful stimuli and depth of sedation as would be required for minor procedures.

We have adapted a previously published sedation scoring system (Appendix)[8] to semi-objectively assess the degree of sedation from dexmedetomidine administration alone and from dexmedetomidine concurrently with atropine. Completely objective evaluation of degree of sedation is problematic. Objective measurements of vital variables have been included; however, these are subject to influence of a number of variables and cannot be used alone to evaluate the degree of sedation. Therefore, degree of sedation in the patient is evaluated by the observer, which introduces subjectivity and variability into the assessment. The study design used 2 means of reducing this subjectivity. First, 1 observer evaluated the degree of sedation for all study subjects to minimize interobserver variation. Secondly, a previously accepted and published scoring system used for evaluating dexmedetomidine sedation after acepromazine or atropine administration was adapted.[8] Four of 7 categories for scoring were included in the present study. All categories of assessment in the original system included some degree of observer interpretation and subsequent subjectivity. Although the subjectivity of this type of system will continue to be problematic, it was effective in the overall goal of the study to show the onset, duration, and degree of sedation a clinician may expect from these doses of dexmedetomidine and atropine.

It is well established in the veterinary literature that α_2-adrenergic receptor agonists including dexmedetomidine cause an increase in systemic vascular resistance.[4,10,20–22] This vasoconstriction can significantly increase blood pressure; thus, a reflex bradycardia develops. In the present study, heart rate decreased from a mean of 110.6 ± 14 beats/min at baseline to a mean of 49.4 beats/min 15 minutes after injection in dexmedetomidine group dogs. With the bradycardia that develops after dexmedetomidine administration, there are varying recommendations to treat α_2-adrenergic receptor agonist–mediated bradycardia with an anticholinergic.[6,8,20,23] Our data indicated that atropine appears to reverse the dexmedetomidine–induced bradycardia as heart rate initially decreased after dexmedetomidine administration and then returned to baseline by the 15-minute time point in dexmedetomidine-atropine group dogs. There is strong concern, however, that although heart rate returns to baseline values, there is a concurrent increase in arterial blood pressures with a peak SAP of 229.8 ± 47.9 mm Hg and peak MAP of 179.8 ± 48.7 mm Hg at about 30 minutes in dexmedetomidine-atropine group dogs. The authors are unaware of any scientific studies in veterinary medicine evaluating short-term hypertension and secondary changes in organ function; however, the degree of systemic hypertension seen in the present study may become clinically relevant. In addition to this finding, our data indicated that although heart rate is increased to baseline levels by the addition of atropine, there is no parallel increase in cardiac output. Therefore, the use of atropine with dexmedetomidine must be questioned if the only benefit of its use from a cardiovascular standpoint is simply a more normal heart rate and not a substantial increase in cardiac output. Avoidance of concomitant use of α_2-adrenergic receptor agonist with anticholinergics has been recommended previously.[4,7,8,23]

The concern for cardiovascular function is also underlined by the dramatic increase in the calculated RPP. The RPP is a calculated variable used in human medicine and increasingly in veterinary medicine[11–14] that is the product of heart rate and SAP. The RPP gives a good estimate or indication of myocardial oxygen demand.[24–26] Admittedly, its clinical usefulness is controversial in that although it is a good estimate for an increase in oxygen demand, it is not well correlated with documented myocardial ischemia.[24] Despite this controversy, an RPP below 12,000 mm Hg/beats/min in humans is considered within reference range.[24] Our data revealed over a 3-fold increase in RPP between

groups from 15 to 60 minutes. Widely accepted RPP values do not appear to be established for clinically normal dogs; however, RPP has been previously reported for dogs, and baseline values range from 9,200 to 18,500 mm Hg/beats/min.[11–14,27,28] Combined data for the 15- to 60-minute time points resulted in a mean RPP in dexmedetomidine-atropine group dogs of 23,378 ± 3,024 mm Hg/beats/min and a peak RPP in dexmedetomidine-atropine group dogs of 29,463.2 ± 13,880 mm Hg/beats/min at the 60-minute time point. These results give us concern that there is a severe increase in myocardial oxygen demand, which could be the origin of the ventricular arrhythmias seen in dexmedetomidine-atropine group dogs.

Cardiac output in this study was measured by use of the lithium dilution cardiac output technique, an indicator dilution technique that is based on the injection of a calculated lithium chloride dose into a central catheter and measured via continuous arterial blood sampling at a peripheral arterial catheter past a lithium sensitive sensor.[29] The lithium dilution cardiac output technique has been shown to provide similar cardiac output measurements when a peripheral catheter is used for lithium injection in place of a central catheter, with a difference in cardiac output measurement of 0.098 ± 0.336 L/min between central and peripheral lithium injections.[30] There is the potential for lithium accumulation in our study dogs given the number of injections of lithium in a short time span. This carries the risk of elevating background lithium concentrations and thus introducing error into cardiac output measurements or the risk of preventing the computer used in lithium dilution cardiac output from sensing a difference between background lithium and lithium injection during cardiac output measurement and not providing a lithium curve and cardiac output calculation. This question has been investigated, and results indicated that to increase serum lithium concentrations to an amount that the equipment may not be able to differentiate from background lithium (0.2 mmol/L according to the manufacturer),[31] up to 34 injections can be given in a 3- to 7-hour period before serum concentrations reach 0.2 mmol/L. Dogs receiving dexmedetomidine had a mean of 6.6 ± 2.4 lithium injections for cardiac output measurement over 78.4 ± 24.5 minutes, and dogs receiving dexmedetomidine and atropine had a mean of 6.6 ± 2.1 lithium injections over 73.8 ± 11.3 minutes.

Another source of error in the present study is the 3-day interval in drug dosing and the concern for drug effects in the body remaining from the first randomized dexmedetomidine or atropine dosing. The authors are unaware of any pharmacokinetic studies of IM administration of dexmedetomidine or atropine in dogs. In humans given dexmedetomidine at 0.5 to 2.0 µg/kg, IM, elimination half-life varied from 1.6 ± 0.42 hours to 2.5 ± 0.6 hours.[32,33] Similarly, elimination half-life of atropine at 0.01 mg/kg, IM, in humans is 2.56 hours.[34] If elimination of dexmedetomidine or atropine parallels findings in humans, then it is unlikely that there is any influence of dexmedetomidine from the dosing on day 1 when dogs were retested 3 days later, given that 99% of the drug will be eliminated in 5 to 7 half-lives.

Dexmedetomidine at 10 µg/kg, IM, with or without the inclusion of atropine at 0.02 mg/kg, IM, did not have any effect on arterial blood gas measurements, electrolyte concentrations, PCV, and total protein, glucose, lactate concentrations, and co-oximeter measurements of hemoglobin. A significant decrease in respiratory rate was observed in both groups without a concomitant increase in arterial carbon dioxide measurements. Potential explanations for this observation include an increase in tidal volume such that minute ventilation was maintained with a lower respiratory rate or a decrease in carbon dioxide production. Decreases in minute ventilation with the use of atropine and medetomidine have been reported, although causes for this observation were unclear.[20] To our knowledge, the ability of dexmedetomidine to depress metabolism as measured by a decrease in $Paco_2$ production has not been evaluated.

In the present study, a higher number of cardiac arrhythmias were witnessed in dexmedetomidine-atropine group dogs, compared with dexmedetomidine group dogs. This has been previously reported,[8] and many correlate the increased myocardial oxygen demand with a calculated RPP. Humans have been shown to develop electrocardiographic evidence of myocardial ischemia at an RPP > 12,000.[4,24,25] We found that while inclusion of atropine in the sedation protocol decreased the frequency of second-degree atrioventricular block, there was a higher number of ventricular arrhythmias and a period of ventricular bigeminy in our dogs. This could represent more evidence to avoid the combination of dexmedetomidine and atropine given IM at these doses.

In conclusion, the change in heart rate, cardiac output, and blood pressures from IM administration of dexmedetomidine reported for both groups of dogs in our study is not unexpected and agrees with findings in previous studies.[8,20,35] Findings in the present study suggest that ultimately there is no benefit to the use of atropine to treat dexmedetomidine-induced bradycardia. Heart rate may increase or prevent the dexmedetomidine-induced bradycardia, but no increase in cardiac output was observed with the concurrent use of atropine with dexmedetomidine.

a. PowerLab for LabChart 6, AD Instruments, Colorado Springs, Colo.
b. MLT844 Physiological Pressure Transducer, AD Instruments, Colorado Springs, Colo.
c. ABL 800, Radiometer, Copenhagen, Demark.
d. OSM-3 Co-oximeter, Radiometer, Copenhagen, Denmark.
e. LiDCO Group Plc, London, England.
f. PROC GENMOD, SAS version 9.2, SAS Institute Inc, Cary, NC.

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Continued on next page.

Appendix

Criteria for scoring depth of sedation in dogs.

Variable	Score*	Description
Posture	0	Standing, normal proprioception, and no ataxia
	1	Animal remains in sternal or lateral position; able to stand when stimulated verbally
	2	Remains in sternal recumbency
	3	Lateral recumbency; eventually lifts or moves head
	4	Lateral recumbency; if not verbally stimulated, does not move or lift its head
Response to sound	0	Alert attitude; readily reacts (looks, lifts head) to the stimulus
	1	Reduced reaction (discrete movement, lifting of the head), but the animal appears sedated
	2	No reaction or movement
Resistance to physical restraint in lateral recumbency	0	Animal resists; readily returns to standing position or sternal recumbency after being released
	1	Offers little resistance, but readily returns to standing position or sternal recumbency
	2	Does not offer resistance, but eventually moves or lifts its head and returns to sternal recumbency
	3	Remains in lateral recumbency; does not offer resistance
General appearance	0	Alert, normal consciousness
	1	Animal lightly sedated; promptly reacts or moves in response to environmental stimulus
	2	Animal moderately sedated; eventually reacts to environmental stimulus
	3	Animal appears moderately to deeply sedated; reduced reaction to environmental stimulation
	4	Animal appears to be deeply sedated; does not react to environmental stimulation

*Total sedation score was assigned as a sum of scores for each variable. Bright, alert, responsive dogs would have received a score of zero. Maximum score was 13 and indicated deepest level of sedation.