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Sedative and echocardiographic effects of dexmedetomidine combined with butorphanol in healthy dogs

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Abstract *Objectives:* To evaluate the echocardiographic variables and sedation after two dosages of dexmedetomidine combined with butorphanol in healthy dogs.
Animals: Fourteen healthy dogs.
Methods: The dogs received dexmedetomidine 5 mcg/kg IM and butorphanol 0.4 mg/kg (low dose (LD), n = 6) or dexmedetomidine 10 mcg/kg IM and butorphanol 0.4 mg/kg (recommended dose (RD), n = 8). Sedation scoring, noninvasive blood pressure measurement, and echocardiography were performed before sedation at baseline, at 20 minutes (T20), and 60 minutes (T60) after drug administration.
Results: The median sedation scores were increased at both T20 and T60 in the RD group, and at T60 in the LD group, compared with baseline ($p < 0.0001$, $p = 0.012$). At T60, the RD dogs were more sedated than the LD dogs ($p = 0.0093$). The median cardiac output (CO) decreased at both T20 (63%) and T60 (65%) in the RD group and at T60 (42%) in the LD group, compared with baseline ($p = 0.0011$, $p = 0.0055$). The median heart rate (HR) was decreased at both T20 and T60 in the RD group and at T60 in the LD group, compared with baseline ($p = 0.0009$, $p = 0.0001$). In both RD and LD dogs, valvular regurgitation developed and was identified by color Doppler imaging.
Conclusions: There were significant hemodynamic changes, mainly related to HR and indices of systolic function, following administration of dexmedetomidine in

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these healthy dogs. The changes also included decreases in systolic function and CO, as well as appearance of 'new' valvular regurgitation. Caution should be used when considering dexmedetomidine for sedation in dogs with, or being screened for, cardiovascular disease.

Abbreviations

2D	two-dimensional
A	late, diastolic mitral valve inflow velocity
A′	peak, late diastolic velocity (tissue Doppler imaging)
Ao	aorta
AR	aortic regurgitation
AV	aortic valve
BL	baseline
BP	blood pressure
CO	cardiac output
CSA	cross-sectional area
E	early, diastolic mitral valve inflow velocity
E′	peak, early diastolic velocity (tissue Doppler imaging)
ECG	electrocardiogram
EF	ejection fraction
FS	fractional shortening
HR	heart rate
IVS	interventricular septum
IVS_d	interventricular septum in diastole
IVS_s	interventricular septum in systole
LA	left atrium
LD	low dose
LV	left ventricle
$LVvol_d$	left ventricular volume in diastole
$LVvol_s$	left ventricular volume in systole
LVID	left ventricular internal diameter
$LVID_d$	left ventricular internal diameter in diastole
$LVID_s$	left ventricular internal diameter in systole
LVPW	left ventricular posterior wall
$LVPW_d$	left ventricular posterior wall in diastole
$LVPW_s$	left ventricular posterior wall in systole
MR	mitral regurgitation
MV	mitral valve
PV	pulmonic valve
RD	recommended dose
RR	respiratory rate
S′	peak systolic velocity (tissue Doppler imaging)
SV	stroke volume
T0	time zero
T20	time 20 minutes
T60	time 60 minutes
TDI	tissue Doppler imaging
TR	tricuspid regurgitation
VTI	velocity time integral

Introduction

Sedation is often necessary in dogs and cats for the purpose of restraint during diagnostic procedures, including: physical examination, radiography, ultrasound examination, and echocardiography. Sedation is also common prior to intravenous catheter placement and induction of general anesthesia. Fractious animals might require profound sedation, regardless of underlying health concerns, in order for diagnostic tests to be performed.

The alpha-2 agonist class of drugs is commonly used in veterinary medicine. These drugs are well known for providing dose-dependent and generally reliable sedation. This class of drugs generally provides profound sedation when used alone, or in combination with opioids. The R-isomer of medetomidine — dexmedetomidine — is commercially available, and is now commonly used for sedation of dogs and cats, with or without opioids, by many veterinary practitioners. Dexmedetomidine, like other alpha-2 agonists, centrally produces sedation by reducing sympathetic outflow from the central nervous system.[1] Because of their affinity to alpha-receptors, these drugs also cause profound vasoconstriction by activating vascular postsynaptic receptors, increasing systemic vascular resistance, and inducing reflex bradycardia. In addition, there is a centrally mediated bradycardia from the effects of alpha-2 agonist receptor stimulation. In dogs, the effects of dexmedetomidine on heart rate (HR), blood pressure (BP), and temperature have been well documented and include bradycardia, systemic hypertension and reduced body temperature. Cardiac output (CO) decreases when dexmedetomidine is administered to dogs.[2]

Echocardiographic examinations are an integral part of the management of cardiac disease in dogs, and may be performed on sedated patients. In these cases, the effect of sedative drugs on echocardiographic findings must be taken into account during assessment of the examination. The purpose of this study was to investigate the sedative and echocardiographic effects of the label-recommended sedative dose of dexmedetomidine in healthy dogs, and to compare these effects to those of dogs given a lower dosage of dexmedetomidine. In both treatment groups, background sedation with butorphanol was also included. The low dose of dexmedetomidine is the standard dose used by the anesthesia department at the University of Wisconsin, and the authors hypothesized that the same level of sedation would be achieved with high-dose and low-dose dexmedetomidine, yet with more cardiovascular depression at the higher dose.

Methods

The School of Veterinary Medicine Animal Care and Use Committee approved this double-blinded, randomized clinical trial. Fourteen healthy dogs, which were presented to the clinical Orthopedic Service for evaluation of lameness, were included in the study after informed owner consent. The dogs were examined by a veterinarian on the Orthopedic Service and identified as healthy based on physical examination and history. Prior to sedation, all dogs underwent a baseline (BL) thoracic auscultation, temperature, sedation score[2] (Table 1), lead II electrocardiogram (ECG),[c] oscillometric BP measurement,[d] and echocardiogram[e] by a board-certified cardiologist (HBK or RLS). Heart rates were recorded from both the auscultation and the ECG, but the HR used in data analysis was the HR obtained by ECG. The respiratory rate was recorded for each dog; if the patient was panting, the RR was recorded as 100 rpm. Dogs were excluded from the study if a cardiac murmur was detected, systolic BP was $\geq$160 mmHg or a cardiac rhythm other than sinus rhythm was present on the ECG.

After the BL measurements were taken, the dogs were randomized (via an internet randomization table categorizing dogs as odd or even) to receive either the higher, manufacturer-recommended dose (RD, 10 mcg/kg dexmedetomidine hydrochloride[f]) or the lower dose (LD, 5 mcg/kg dexmedetomidine hydrochloride) in combination with 0.4 mg/kg butorphanol tartrate.[g] A technician who was not involved in data collection administered sedation, and none of the investigators involved in data collection were aware of the drug treatments. All drugs were administered intra-muscularly in the epaxial muscles, with the time of administration being recorded as time 0 (T0) minutes.

At time 20 (T20) minutes and time 60 (T60) minutes, temperature, auscultation, sedation scoring[2] (Table 1), lead II ECG, oscillometric BP

[c] MAC 5000 Electrocardiogram, General Electric, Waukesha, WI, USA.
[d] Cardell® Veterinary Monitor 9401 BP, Sharn Veterinary Inc., FL, USA.
[e] Vivid 7 Echocardiographic System, General Electric, Waukesha, WI, USA.
[f] Dexdomitor, Pfizer Inc., New York, USA.
[g] Torbugesic, Pfizer Inc., New York, USA.

Table 1 Sedation score.[2,a]

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 or moves 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 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

[a] Total sedation score was assigned as a sum of scores for each variable. Bright, alert, responsive dogs would have received a score of 0. The maximum score was 13 and indicated the deepest level of sedation.

measurement and echocardiogram were again recorded by the same individuals as at BL. The dogs underwent any appropriate orthopedic radiographic imaging between T20 and T60 for the purpose of their orthopedic evaluation. After 60 (T60) minutes, when data collection was complete, the dexmedetomidine was reversed in all dogs, by a technician who was not involved in data collection, using atipamezole hydrochloride[h] IM at a volume equal to that of the administered dose of dexmedetomidine.

Blood pressure measurement

All BP measurements were recorded in the same room on the exam table. The BP cuff was premeasured and sized such that the width of the cuff was approximately 40% of the circumference of the limb at the level of cuff placement. The cuff was positioned around the mid-metatarsus at the level of the superficial plantar arterial arch of the left hind limb when the dog was in right or left lateral recumbency. The cuffed leg was positioned level with the heart during measurements. Six replicate measurements were recorded at 1-minute intervals. The first value was discarded and the remaining values were averaged to yield a representative value for the time point.

Echocardiography

A board-certified cardiologist (HBK or RLS) recorded standardized transthoracic echocardiograms[3] in right and left lateral recumbent positions using a phased-array transducer with a 5.0 MHz frequency and continuous ECG monitoring. Echocardiographic recordings from each patient at each time point were analyzed in random order at a later date on a digital workstation[i] by a sole observer (HBK) who was unaware of treatment or

[h] Atipamezole, Pfizer Inc., New York, USA.

[i] EchoPAC PC, General Electric, Waukesha, WI, USA.

time point at the time of analysis. Each echocardiographic measurement was made by averaging three consecutive cardiac cycles.

M-mode echocardiographic measurements

The M-mode echocardiographic measurements of the left ventricle were made from the right parasternal short-axis view at the level of the papillary muscles. Left ventricular (LV) interventricular septum in diastole (IVSd), LV internal diameter in systole and diastole (LVIDs and LVIDd), and LV posterior wall in diastole (LVPWd) were measured. Each LV M-mode measurement value was normalized according to the methods of Cornell et al.[4] and were reported in mm. Fractional shortening (FS) was calculated from the formula:

$$FS = ([LVIDd - LVIDs]/LVIDd) \times 100.$$

Two-dimensional echocardiographic measurements

Two-dimensional (2D) echocardiographic measurements of the left atrium (LA), aorta (Ao) and LV ejection fraction (EF), as calculated by the single-plane Simpson rule of disc summation method, were made from the right parasternal short-axis basilar view (LA and Ao) and long-axis four-chamber view (EF). The LA/Ao ratio was calculated by the Swedish method[5] and EF was calculated by the formula:

$$EF = ([LVvol_d - LVvol_s]/LVvol_d) \times 100.$$

Doppler echocardiographic measurements

Doppler echocardiographic measurements of mitral valve (MV) inflow velocities during early (E) and late (A) diastole, and tissue Doppler imaging (TDI) of the lateral MV annulus in early (E′) and late (A′) diastole and systole (S′) were obtained from the left parasternal four-chamber view. Aortic valve (AV) peak velocity, peak pressure gradient, and velocity time integral (VTI) were measured from the most optimal alignment through the aortic valve from the left parasternal five-chamber view. The peak pulmonic valve (PV) velocity and peak pressure gradient were measured and calculated from the modified Bernoulli equation from the PV optimally aligned from the right parasternal basilar short-axis view.

Estimation of CO by echocardiogram was performed by using the AV cross-sectional area (CSA), Ao VTI, and HR. The AV CSA was calculated from the AV diameter measurement obtained from the left parasternal five-chamber view. The HR was calculated from the average of three cardiac cycles, where each R—R interval was measured preceding each Ao VTI measurement. The following formulas were used to calculate the echocardiographic estimated stroke volume (SV) and CO:

$$SV(mL) = \text{Ao CSA}(cm^2) * \text{Ao VTI}(cm)$$

$$CO(L/min) = SV(mL) * HR(bpm)/1000.$$

Evaluation for valvular insufficiency of all four valves was performed on both the right and left sided views, and was reported as present or not present. Spontaneous echo contrast (i.e. 'smoke') was also documented as present or not present if seen in the left atrium and/or left ventricle, in addition to the right-sided chambers, on any of the views.

Statistical analysis

Data analysis was performed using standard statistical calculation software.[j] Normal distribution could not be assumed due to the small sample size, and all variables were analyzed with non-parametric methods. A Friedman test with the Dunn's post hoc analysis was used to compare values for each variable over time (BL, T20 and T60) in both the RD and LD groups. A Mann—Whitney U test was used to compare all variables at the same time point (BL, T20 and T60) between the RD and LD groups. p-Values <0.05 were considered significant for all tests. Results were given as the median (range) for all data.

Results

The median weight for the LD dogs was 36.6 kg (range 14.4—43.5), and for RD dogs it was 35 kg (range 19.8—43.4); there was no significant difference between the two groups ($p = 0.651$). The median age of the LD dogs was 6 years (range 2—8) and for the RD dogs it was 2.5 years (range 1—4); there was a significant difference between the two groups ($p = 0.0286$). There were three male neutered, one male intact and two female spayed dogs in the LD group, and seven male neutered and one female spayed dog in the RD group.

[j] GraphPad Prism 5.0b, GraphPad Software Inc., San Diego, CA, USA.

Sedation score, heart rate, respiratory rate and temperature

The sedation score, HR, RR and temperature data are summarized in Table 2. Dogs in both groups had sedation scores of 0 at BL. The RD dogs attained maximal sedation scores by T20, and these were maintained through T60. The RD group's median heart rate and RR decreased at T20 and T60 compared with BL, but there was no change in rectal temperature. In the LD group, the sedation score was significantly higher, but not maximal, at T20 and T60. The LD group's median heart rate was significantly decreased at T60 compared with BL. The median respiratory rate did not change at T20, but was significantly decreased at T60 compared with BL and T20. The median temperature decreased at T60 compared with T20. The sedation score of the RD group's dogs was significantly higher than the LD dogs at T60. There was no significant difference between median heart rate, respiratory rate, or temperature between the RD and LD groups at BL, T20 or T60.

Blood pressure measurement

The blood pressure measurements are presented in Table 2. In the RD group, there was no change in median systolic, diastolic or mean BP across all time points. In the LD group, the median systolic and mean BP were both significantly lower at T20 compared with BL. In the RD group, the median mean arterial pressure based on oscillometric measurement at T20 was significantly higher in the RD group compared with same time point in the LD group.

M-mode echocardiographic measurements

The normalized M-mode echocardiographic measurements are shown in Table 3. In the RD group, the median normalized LVIDs (mm) was significantly increased, and FS was significantly decreased at T20 compared with BL — these effects were maintained at T60. The normalized LVPWs followed a similar pattern, although decreases in IVSd and IVSs did not reach significance until T60. In the LD group, the only significant change in M-mode echocardiographic measurements was a decrease in the median FS at T60 compared with BL. Normalized IVSd at BL was greater in the RD group than in the LD group, but there were no significant differences in all of the other M-mode echocardiographic measurements between the two dosing groups at any time point.

Two-dimensional echocardiographic measurements

The aortic diameter, LA diameter, LA:Ao ratio and LV ejection fraction results are presented in Table 4. In the RD group, the median ejection fraction was significantly decreased at T20 compared with BL, and this lower value was maintained at T60. The aortic diameter, LA diameter and LA:Ao were unchanged. In contrast, in the LD group, the median LA diameter (mm) and median LA diameter (mm/kg) were enlarged at T20 and T60 compared with BL. There was no significant difference for 2D echocardiographic measurements between the groups at any time point.

Doppler echocardiographic measurements

The Doppler echocardiographic measurements are presented in Table 5. In the RD group, of the diastolic and tissue Doppler measures analyzed, mitral E and A wave, and A′ velocities were significantly decreased at T20 and remained decreased at T60. The mitral E/A ratio was significantly increased at T20 and T60. In the LD group, similar changes were noted, with A-wave velocity decreased at T20 compared with BL, and maintained at T60. The decrease in mitral E-wave velocity did not achieve significance, but the E/A ratio increased at T20 and T60 compared with BL. Tissue Doppler values did not change in the LD group. Mitral E-wave velocity and E/E′ differed at BL between the groups, but not at any other time point.

The aortic systolic velocity in the RD group was decreased at T20 and the decrease was statistically significant at T60. The pulmonic systolic velocity was significantly decreased at T20 and this decrease was maintained at T60. In the LD group, peak aortic and pulmonic systolic velocities trended down, but were not significantly different from BL at T20 and T60. There was no difference between RD and LD group aortic or pulmonic systolic velocities at any time point.

Cardiac output estimate measurements

In the RD group, the median HR and CO were both decreased at T20 compared with BL, and this decrease was maintained at T60 (Table 5). In the LD group, the HR and CO trended down at T20, but were both significantly lower at T60 compared with BL. There was no significant difference between the calculated SV and CO, and the echocardiographic variables used to calculate

Table 2 Sedation score, clinical exam variables and blood pressure (RD: 10 mcg/kg, n = 8) (LD: 5 mcg/kg, n = 6).

	Baseline		T20		T60		*p*-value	
	RD	LD	RD	LD	RD	LD	RD	LD
Sedation Score	0	0	13[a] (4–13)	9 (0–13)	13[a,b] (10–13)	9.5[a] (3–12)	<0.0001	0.012
Temperature (F)	101.8 (99.5–102.8)	102.3 (101.5–103.2)	102 (100.5–103.1)	102.6 (101.2–103.1)	100.5 (100.2–103)	100.9[b] (100.2–102.4)	0.9640	0.0289
Heart Rate (bpm)	116 (95–140)	100 (90–112)	44[a] (30–70)	60 (44–70)	38[a] (36–50)	41[a] (30–50)	0.0009	0.0001
Respiratory Rate (rpm)	100 (30–100)	52 (42–100)	22[a] (9–80)	50 (24–66)	19[a] (8–40)	30[a,b] (16–36)	0.0009	0.0017
Systolic BP (mmHg)	152 (122–157)	151 (133–157)	147 (120–188)	126[a] (91–154)	125 (105–162)	125 (99–142)	0.1197	0.0055
Diastolic BP (mmHg)	89 (65–111)	91 (69–95)	88 (78–146)	75 (42–95)	80 (56–111)	81 (57–126)	0.5306	0.4297
Mean BP (mmHg)	112 (83–124)	111 (100–114)	111[b] (90–151)	91[a] (57–112)	95 (79–126)	96 (74–106)	0.2359	0.0289

The *p*-values reported are calculated from the Friedman's analysis.
BP, blood pressure; LD, low dose; RD, recommended dose; T20, time 20 minutes; T60, time 60 minutes.
[a] Significant difference ($p < 0.05$) compared with baseline in same dosing group.
[b] Significant difference ($p < 0.05$) compared with 5 mcg dose at same time point.

Table 3 Normalized[4] M-mode echocardiographic measurements (RD: 10 mcg/kg, n = 8) (LD: 5 mcg/kg, n = 6).

	Baseline		T20		T60		*p*-value	
	RD	LD	RD	LD	RD	LD	RD	LD
IVSd ($mm/kg^{0.241}$)	4.7[b] (4.12–5.43)	4.25 (3.71–4.43)	4.005 (3.73–5.05)	4.16 (3.44–5.12)	3.995[a] (3.29–4.72)	4.21 (3.83–4.33)	0.0303	0.9563
LVIDd ($mm/kg^{0.294}$)	15.48 (13.69–19.53)	14.4 (13.16–15.43)	15.83 (13.51–20.35)	14.29 (13.22–16.1)	15.39 (12.67–19.64)	14.09 (12.58–15.61)	0.5306	0.4297
LVPWd ($mm/kg^{0.232}$)	4.235 (3.99–4.9)	4.06 (3.79–4.39)	4.095 (3.45–4.97)	3.805 (3.35–4.67)	4.25 (3.91–4.63)	3.99 (3.81–4.45)	0.1495	0.4297
IVSs ($mm/kg^{0.24}$)	5.92 (5.14–8.4)	5.15 (3.85–6.62)	5.16 (4.64–7.02)	5.37 (4.24–5.85)	5.395[a] (3.98–5.91)	5.32 (4.2–5.86)	0.0469	0.7402
LVIDs ($mm/kg^{0.315}$)	9.8 (8.37–13.92)	10.04 (8.96–10.47)	11.52[a] (8.51–17.52)	10.81 (9.1–13.19)	11.51[a] (9.86–16.18)	10.98 (8.64–12.7)	0.0011	0.4297
LVPWs ($mm/kg^{0.222}$)	6.16 (5.21–6. 674)	5.52 (5.18–6.43)	5.21[a] (4.22–6.66)	5.205 (4.56–6.47)	5.35[a] (4.83–6.17)	5.075 (4.49–6.85)	0.008	0.2522
FS (%)	31.5 (22–34)	28 (16–31)	19.5[a] (8–33)	22.5 (12–28)	16.5[a] (9–27)	20[a] (11–27)	0.0011	0.012

The *p*-values reported are calculated from the Friedman's analysis.
FS, fractional shortening; IVSd, interventricular septum in diastole; IVSs, interventricular septum in systole; LD, low dose; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; LVPWd, left ventricular posterior wall in diastole; LVPWs, left ventricular posterior wall in systole; RD, recommended dose; T20, time 20 minutes; T60, time 60 minutes.
[a] Significant difference ($p < 0.05$) compared with baseline in same dosing group.
[b] Significant difference ($p < 0.05$) compared with 5 mcg dose at same time point.

Table 4 2D echocardiographic and cardiac output values (RD: 10 mcg/kg, n = 8) (LD: 5 mcg/kg, n = 6).

	Baseline		T20		T60		*p*-value	
	RD	LD	RD	LD	RD	LD	RD	LD
LA/Ao	1.2 (0.9–1.5)	1.3 (1.1–1.4)	1.2 (1.1–1.8)	1.2 (1.1–1.4)	1.3 (1–1.5)	1.3 (1.1–1.5)	0.2851	0.7402
LA diameter (mm)	39 (33.5–42.9)	37.1 (31.5–45.8)	41.7 (35.2–50.7)	42.2[a] (31.9–48.1)	40.6 (32.9–50)	42.5[a] (33.7–46.5)	0.0789	0.0081
Ao diameter (mm)	21.4 (17.7–28.2)	21.2 (18.3–23.3)	21.4 (18.5–25.7)	23.1 (18.3–24.7)	21 (16.7–26.1)	23.5 (17.3–26.2)	0.2359	0.1416
EF (%)	64 (49–72)	64 (43–70)	48[a] (18–68)	50 (36–76)	48[a] (30–62)	51 (33–53)	0.008	0.1416

The *p*-values reported are calculated from the Friedman's analysis.
Ao, aorta; EF, ejection fraction; LA, left atrium; RD, recommended dose; LD, low dose; T20, time 20 minutes; T60, time 60 minutes.
[a] Significant difference ($p < 0.05$) compared with baseline in same dosing group.

Table 5 Doppler echocardiographic measurements (RD: 10 mcg/kg, n = 8) (LD: 5 mcg/kg, n = 6).

	Baseline		T20		T60		*p*-value	
	RD	LD	RD	LD	RD	LD	RD	LD
E velocity (m/s)	0.87[b] (0.63—1.02)	0.67 (0.54—0.73)	0.66 (0.53—0.84)	0.61 (0.42—0.68)	0.665 (0.46—0.8)	0.57 (0.5—0.69)	0.0375 (no post-hoc)	0.4297
A velocity (m/s)	0.575 (0.44—0.77)	0.56 (0.36—0.97)	0.3 (0.16—0.41)	0.25[a] (0.21—0.7)	0.205[a] (0.12—0.41)	0.27[a] (0.15—0.54)	<0.0001	0.0081
E/A	1.405 (1.150—1.77)	1.1 (0.7—1.6)	2.185 (1.56—3.31)	2.1[a] (1—2.5)	3.11[a] (1.95—4.58)	2.45[a] (0.93—4.08)	<0.0001	0.0081
E/E′	7.465[b] (5.770—9.34)	5.1 (4.3—7.4)	6.84 (4.29—11.1)	4.9 (3.8—7.8)	7.105 (4.47—8.44)	4.86 (4.11—6.26)	0.3553	0.742
E′ velocity (m/s)	0.11 (0.09—0.15)	0.13 (0.1—0.16)	0.095 (0.06—0.13)	0.12 (0.08—0.13)	0.1 (0.09—0.14)	0.13 (0.08—0.16)	0.1197	0.2522
A′ velocity (m/s)	0.1 (0.07—0.12)	0.1 (0.09—0.12)	0.06[a] (0.04—0.08)	0.09 (0.04—0.13)	0.06[a] (0.04—0.09)	0.07 (0.05—0.1)	0.0001	0.5705
S′ velocity (m/s)	0.15 (0.07—0.24)	0.16 (0.1—0.18)	0.08[a] (0.06—0.16)	0.12 (0.09—0.16)	0.1[a] (0.06—0.14)	0.11 (0.06—0.13)	0.0011	0.0721
AV Vmax (m/s)	1.585 (1.13—2.16)	1.4 (1.2—1.9)	0.93 (0.73—2.23)	1.1 (1.0—1.6)	0.92[a] (0.78—1.69)	1.185 (1.11—1.39)	0.0048	0.1416
PV Vmax (m/s)	1.045 (0.95—1.52)	1.1 (0.9—1.3)	0.75[a] (0.46—1.23)	0.7 (0.6—0.9)	0.785[a] (0.58—1.07)	0.745 (0.61—1.52)	0.0009	0.0521
SV (mL)	67.1 (44—95.6)	59.8 (41.9—66.2)	62.4 (39.6—81)	60.5 (37.2—76.4)	63.9 (24.7—107.5)	84.9 (40—97.1)	0.2359	0.0521
HR (bpm)	100 (72—137)	96 (71—128)	52[a] (29—86)	50 (42—65)	40[a] (28—83)	43[a] (27—60)	0.0009	0.0017
CO (L/min)	6.5 (4.9—9.5)	5.7 (3.0—8.2)	2.4[a] (2—6.5)	2.9 (1.8—5)	2.3[a] (0.8—4.3)	3.3[a] (1.4—5.4)	0.0011	0.0055

The *p*-values reported are calculated from the Friedman's analysis.

A, late diastolic mitral valve inflow velocity; A′, peak late diastolic velocity (tissue Doppler imaging); AV, aortic valve; CO, cardiac output; E, early diastolic mitral valve inflow velocity; E′, peak early diastolic velocity (tissue Doppler imaging); LD, low dose; PV, pulmonic valve; RD, recommended dose; S′, peak systolic velocity (tissue Doppler imaging); T20, time 20 minutes; T60, time 60 minutes; Vmax, maximum velocity.

[a] Significant difference ($p < 0.05$) compared with baseline in same dosing group.

[b] Significant difference ($p < 0.05$) compared with 5 mcg dose at same time point.

them, between the RD and LD groups for any time point.

Valvular insufficiency and spontaneous echocardiographic contrast

The occurrence of valvular regurgitation and spontaneous echo contrast was noted after sedation in both groups (Table 6). There was no evidence of mitral regurgitation (MR), tricuspid regurgitation (TR), aortic regurgitation (AR) or spontaneous echo contrast in either group at BL. At T20, the majority of the RD group dogs had MR and TR noted, and spontaneous contrast ('smoke') was noted in 50%; these changes were maintained at T60. In the LD dogs, TR was more commonly noted than MR at both time points, and spontaneous contrast was noted in 33% of the dogs at both time points.

Discussion

The hemodynamic effects of dexmedetomidine used for sedation in healthy dogs have previously been described,[2,6–10] and the results of this study are generally in agreement with previous findings at similar doses. This is the first study, however, that has evaluated the echocardiographic findings associated with dexmedetomidine sedation. Specifically, in this study, the dexmedetomidine dosage recommended on the label (10 mcg/kg) administered IM with standard and hemodynamically insignificant doses of butorphanol[11] caused a decrease in CO accompanied by a markedly decreased HR. At a lower dose of 5 mcg/kg, similar findings were seen at 60 min, but at 20 min, the decline in HR was not as severe and not statistically significant. At T20, the decrease in CO, although not significant, was greater for the RD group (63%) compared with the LD group (50%), and both doses caused a significant decrease in CO (RD 65%, LD 42%) at T60 compared with baseline.

Table 6 Valvular insufficiency and smoke (RD: 10 mcg/kg, n = 8) (LD: 5 mcg/kg, n = 6).

	Baseline		T20		T60	
	RD	LD	RD	LD	RD	LD
MR	0	0	5 (63%)	2 (33%)	6 (75%)	2 (33%)
TR	0	0	6 (75%)	4 (67%)	7 (88%)	5 (83%)
AR	0	0	2 (25%)	1 (17%)	4 (50%)	1 (14%)
PR	2	0	1 (13%)	1 (17%)	2 (25%)	1 (17%)
Smoke	0	0	4 (50%)	2 (33%)	4 (50%)	2 (33%)

The *p*-values reported are calculated from the Friedman's analysis.
AR, aortic regurgitation; LD, low dose; MR, mitral regurgitation; PR, pulmonic regurgitation; RD, recommended dose; T20, time 20 minutes; T60, time 60 minutes; TR, tricuspid regurgitation.

The sedative effects of dexmedetomidine in dogs can be profound,[2,6,12–15] and in this study they appeared to be dose related. At the RD, the median sedation score was at the maximal score possible at both T20 and T60. In contrast, although the sedation score at T60 was significantly higher than at BL in the LD dogs, 2/6 (33%) dogs had the maximal sedation score recorded at T20, and both of these dogs had slightly lower than maximal scores at T60. Further, at T60, the sedation scores for RD dogs were significantly higher than for dogs given the LD. These results suggest that lower doses of dexmedetomidine may be associated with acceptable sedation for orthopedic manipulation and radiographs, and less depression of CO for short-term (20 min) procedures, but that similar cardiovascular effects will be seen at either dose by 60 min.

The hypertensive effects of alpha-2 agonists have been documented in other studies using invasive BP measurements.[2,6–10] In the present study, the hypertensive effects were not documented after sedation by non-invasive methods, and wide variability in the measurements within each group may have obscured differences between time points. In the LD group, a significant decrease in systolic BP at T20 with non-significant decreases in HR may imply true changes in systemic vascular resistance, but the RD (higher) dose of dexmedetomidine was associated with BP values that were essentially unchanged at T20 despite a significant decrease in HR. Because no measure of systemic vascular resistance was obtained, it remains unclear if dexmedetomidine at the higher of the two tested doses had a 'supportive' effect on BP at T20, which was overcome by the additional decrease in HR at T60.

While Doppler measures of diastolic function, including tissue Doppler values, were largely unchanged, there were some effects of the sedation noted on some of the values that might be recorded as part of a typical Doppler examination (e.g. E wave, A wave, E/A ratio). The increase in LAD for both time points in the LD group, and the significant decreases of the A wave in both the RD and LD groups, suggest decreased LA function following dexmedetomidine administration. Left atrial

enlargement and the appearance of LV restrictive physiology could negatively affect the prognosis of a dog while sedated with dexmedetomidine.

Of greater clinical significance was the effect of sedation with dexmedetomidine on several measures of systolic function. Many echocardiographic diagnoses depend on assessment of systolic function as well as assessment of flow velocities obtained by Doppler-echocardiographic examination. While it is occasionally necessary to sedate canine patients in order to perform echocardiography, sedative medications have been shown to affect Doppler velocities and echocardiographic measures of systolic function. This could complicate the diagnosis of mild degrees of congenital valvular obstruction as well as affect the assessment of systolic function in patients with congenital and acquired heart disease.[16–18] The results of this small study in healthy dogs suggests that the effects of dexmedetomidine on the echocardiographic findings of dogs may be diagnostically significant at the dosage recommended on the label. In the RD group, the dogs displayed increased LVIDs and decreased EF at both T20 and T60. In addition, FS, a simple and commonly used indicator of systolic function, was significantly decreased at T60 in both dosage groups, and was significantly decreased at T20 when the RD was used. These changes, if noted on echocardiographic examination and interpreted without regard for sedative effects, may suggest systolic dysfunction in a healthy patient. Similarly, the label dose of dexmedetomidine was associated with lower maximal aortic and pulmonary systolic velocities at T20, which reached statistical significance at T60 compared with BL values, potentially affecting the assessment of possible congenital valve disease patients.

The valvular regurgitation seen at both RD and LD dexmedetomidine sedation in these healthy dogs was qualitatively similar to that seen in degenerative (myxomatous) valvular disease in dogs. In the present study, no dog had echocardiographic evidence of regurgitation of the mitral, tricuspid or aortic valve at BL, but more than half in the LD group and $>$80% of those in the RD group showed at least one of these abnormalities after dexmedetomidine was administered. Such findings in dogs sedated with dexmedetomidine may complicate screening echocardiograms performed for the purpose of breeding suitability in breeds predisposed to abnormalities of these valves. In addition, spontaneous echocardiographic contrast ('smoke') was documented in 50% of the RD dogs and 33% of the LD dogs. The finding of smoke in concert with otherwise normal echocardiographic findings might be dismissed as secondary to bradycardia in patients sedated with dexmedetomidine. However, this finding may be considered suggestive of blood stasis and prethrombus-like conditions[19–21] in a patient with cardiac abnormalities. The finding of spontaneous contrast in a patient with cardiac disease that has been sedated with dexmedetomidine might lead to inappropriate medication with anticoagulants.

There were several limitations to the present study, including a small sample size. There are inherent flaws in estimating CO and SV from echo measurements vs. direct invasive measurements.[22] Despite evaluating the echocardiograms in a blinded fashion, there is an inevitable bias towards knowing which dogs received dexmedetomidine because of the dramatic decreases in HR. The present study was evaluating the effects of dexmedetomidine in healthy dogs, and the effects of dexmedetomidine are not known in the population of dogs with cardiovascular disease and cannot be directly extrapolated from the current study. An additional limitation to this study was the noninvasive methodology used to measure blood pressure. The wide variability in the values at each time point may have obscured the true differences among groups. Oscillometric BP measurement methods are known to consistently produce lower and perhaps more variable systolic BP readings than invasive methods,[23] but the placement of arterial catheters was not possible in this population of normal, client-owned animals.

Conclusions

There are significant cardiovascular and echocardiographic changes associated with administration of dexmedetomidine at the label dosage and lower than recommended dose for sedation in healthy canine patients. These echocardiographic changes, including decreases in systolic function indicators and calculated CO, as well as the appearance of 'new' valvular regurgitation, may affect the clinical evaluation of disease. Caution should be used when considering dexmedetomidine for sedation, particularly in canine patients with, or being screened, for cardiovascular disease. Further studies are needed to determine if similar effects are seen with dexmedetomidine administration in dogs with cardiovascular disease.

Conflicts of interest

None.

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References

1. Murrell JC, Hellebrekers LJ. Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth Analg 2005; 32:117—127.
2. Congdon JM, Marquez M, Niyom S, Boscan P. Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs. J Am Vet Med Assoc 2011;239:81—89.
3. Thomas W, Gaber CE, Jacobs GJ, Kaplan PM, Lombard CW, Moïse NS, Moses BL. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine. J Vet Intern Med 1993;7:247—252.
4. Cornell CC, Kittleson MD, Torre Della P, Haggstrom J, Lombard CW, Pedersen HD, Vollmar A, Wey A. Allometric scaling of M-mode cardiac measurements in normal adult dogs. J Vet Intern Med 2004;18:311—321.
5. Hansson K, Haggstrom J, Kvart C, Lord P. Left atrial to aortic root indices using two-dimensional and M-mode echocardiography in Cavalier King Charles spaniels with and without left atrial enlargement. Vet Radiol Ultrasound 2002;43:568—575.
6. Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M. Hemodynamic and sedative effects of dexmedetomidine in dog. J Pharmacol Exp Ther 1992;263: 690—697.
7. Congdon KM, Marquez M, Niyom S, Boscan P. Cardiovascular, respiratory, electrolyte and acid-base balance during continuous dexmedetomidine infusion in anesthetized dogs. Vet Anaesth Analg 2013;40:464—471.
8. Keating SCJ, Kerr CL, Valverde A, Johnson RJ, McDonell WN. Cardiopulmonary effects of intravenous fentanyl infusion in dogs during isoflurane anesthesia and with concurrent acepromazine or dexmedetomidine administration during anesthetic recovery. Am J Vet Res 2013;74:672—682.
9. Ko JC, Barletta M, Sen I, Weil AB, Krimms RA, Payton ME, Constable P. Influence of ketamine on the cardiopulmonary effects of intramuscular administration of dexmedetomidine-buprenorphine with subsequent reversal with atipamezole in dogs. J Am Vet Med Assoc 2013;242:339—345.
10. Silva FDC, Hatschbach E, Carvalho YK, Minto BW, Massone F, Nascimento PD. Hemodynamics and bispectral index (BIS) of dogs anesthetized with midazolam and ketamine associated with medetomidine or dexmedetomidine and submitted to ovariohysterectomy. Acta Cir Bras 2010;25:181—189.
11. Dodam JR, Cohn LA, Durham HE, Szladovits B. Cardiopulmonary effects of medetomidine, oxymorphone, or butorphanol in selegiline-treated dogs. Vet Anaesth Analg 2004;31:129—137.
12. Carter JE, Lewis C, Beths T. Onset and quality of sedation after intramuscular administration of dexmedetomidine and hydromorphone in various muscle groups in dogs. J Am Vet Med Assoc 2013;243:1569—1572.
13. Hunt JR, Grint NJ, Taylor PM, Murrell JC. Sedative and analgesic effects of buprenorphine, combined with either acepromazine or dexmedetomidine, for premedication prior to elective surgery in cats and dogs. Vet Anaesth Analg 2013;40:297—307.
14. Pinelas R, Alibhai HIK, Mathis A, Jimenez Lozano A, Brodbelt DC. Effects of different doses of dexmedetomidine on anaesthetic induction with alfaxalone—a clinical trial. Vet Anaesth Analg 2014;41:378—385.
15. Raszplewicz J, MacFarlane P, West E. Comparison of sedation scores and propofol induction doses in dogs after intramuscular premedication with butorphanol and either dexmedetomidine or medetomidine. Vet Anaesth Analg 2013;40:584—589.
16. Monteiro ER, Teixeira Neto FJ, Castro VB, Campagnol D. Effects of acepromazine on the cardiovascular actions of dopamine in anesthetized dogs. Vet Anaesth Analg 2007;34: 312—321.
17. Saponaro V, Crovace A, De Marzo L, Centonze P, Staffieri F. Echocardiographic evaluation of the cardiovascular effects of medetomidine, acepromazine and their combination in healthy dogs. Res Vet Sci 2013;95:687—692.
18. Lehmkuhl L, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. J Vet Intern Med 1994;8:2—17.
19. Cheng TO. Spontaneous echo contrast in mechanical valve prosthesis. Ann Thorac Surg 1997;63:1826—1827.
20. Lee TM, Chou NK, Su SF, Lin YJ, Chen MF, Liau CS, Lee YT, Chu SH. Left atrial spontaneous echo contrast in asymptomatic patients with a mechanical valve prosthesis. Ann Thorac Surg 1996;62:1790—1795.
21. Wang XF, Liu L, Cheng TO, Li ZA, Deng YB, Wang JE. The relationship between intracardiovascular smoke-like echo and erythrocyte rouleaux formation. Am Heart J 1992;124: 961—965.
22. Lopes PCF, Sousa MG, Camacho AA, Carareto R, Nishimori CTD, Santos PSP, Nunes N. Comparison between two methods for cardiac output measurement in propofol-anesthetized dogs: thermodilution and Doppler. Vet Anaesth Analg 2010;37:401—408.
23. Bodey AR, Michell AR, Bovee KC, Buranakurl C, Garg T. Comparison of direct and indirect (oscillometric) measurements of arterial blood pressure in conscious dogs. Res Vet Sci 1996;61:17—21.