Effects of a combination of acepromazine maleate and butorphanol tartrate on conventional and two-dimensional speckle tracking echocardiography in healthy dogs

Giorgia Santarelli DVM, MSc

Jesús Talavera López DVM, PhD

Josefa Fernández del Palacio DVM, PhD

Received January 20, 2016.
Accepted May 17, 2016.

From the Division of Veterinary Cardiology-Pulmonology, Veterinary Teaching Hospital, and the Department of Veterinary Medicine and Surgery, Faculty of Veterinary Medicine, University of Murcia, Campus Espinardo, 30100, Murcia, Spain.

Address correspondence to Dr. Santarelli (giorgia.santarelli1@um.es).

OBJECTIVE
To determine effects of a combination of acepromazine maleate and butorphanol tartrate on conventional echocardiographic variables and on strain values obtained by use of 2-D speckle tracking echocardiography (STE) in healthy dogs.

ANIMALS
18 healthy medium- and large-size adult dogs.

PROCEDURES
Transthoracic echocardiographic examination (2-D, M-mode, color flow, spectral Doppler, and tissue Doppler ultrasonography) and high-definition oscillometric blood pressure measurement were performed before and after dogs were sedated by IM administration of a combination of acepromazine (0.02 mg/kg) and butorphanol (0.2 mg/kg). Adequacy of sedation for echocardiographic examination was evaluated. Circumferential and longitudinal global and segmental strains of the left ventricle (LV) were obtained with 2-D STE by use of right parasternal short-axis and left parasternal apical views. Values before and after sedation were compared.

RESULTS
The sedation combination provided adequate immobilization to facilitate echocardiographic examination. Heart rate and mean and diastolic blood pressures decreased significantly after dogs were sedated. A few conventional echocardiographic variables differed significantly from baseline values after sedation, including decreased end-diastolic LV volume index, peak velocity of late diastolic transmitral flow, and late diastolic septal mitral and tricuspid annulus velocities, increased ejection time, and increased mitral ratio of peak early to late diastolic filling velocity; global strain values were not affected, but 1 segmental (apical lateral) strain value decreased significantly.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that acepromazine and butorphanol at the doses used in this study provided sedation adequate to facilitate echocardiography, with only mild influences on conventional and 2-D STE variables. (*Am J Vet Res* 2017;78:158–167)

Use of tranquilizers or sedatives is sometimes necessary to aid in and simplify echocardiographic examination of dogs[1,2] and to enable researchers and clinicians to obtain quality ultrasonographic images. The ideal sedative regimen for cardiovascular diagnostic procedures should reduce anxiety, provide adequate immobilization, and preserve hemodynamic conditions as much as possible.[1,3]

Phenothiazine agents and opioid analgesics are frequently used in veterinary medicine to facilitate the handling of small animals. The effects of some of these sedatives on cardiovascular variables have been assessed in dogs[3–7] and cats.[8] The influence of acepromazine, alone[3] or in combination with pethidine[5] or buprenorphine,[6] on conventional echocardiographic measurements of healthy dogs has been determined. Acepromazine alone caused a reduction in LV wall stress, which was associated with a decrease in systolic and mean systemic arterial blood

ABBREVIATIONS

DAP	Diastolic arterial blood pressure
EDV	End-diastolic volume
EDVI	End-diastolic volume index
ESV	End-systolic volume
ESVI	End-systolic volume index
HR	Heart rate
LV	Left ventricle
LVAd	Left ventricle luminal area at end diastole
LVAs	Left ventricle luminal area at end systole
LVIDd	Left ventricle internal diameter at end diastole
LVIDs	Left ventricle internal diameter at end systole
MAP	Mean arterial blood pressure
ROI	Region of interest
SAP	Systolic arterial blood pressure
STE	Speckle tracking echocardiography
Vmax	Peak velocity

pressures.[3] When acepromazine was combined with pethidine, the combination induced a decrease in systolic and diastolic LV internal dimensions in healthy Greyhounds.[5] In addition, a combination of acepromazine and buprenorphine decreased ESVI and Vmax of late transmitral diastolic flow (A wave) in healthy Beagles, which was associated with a reduction in HR.[6]

In healthy cats, a combination of acepromazine and butorphanol induced mild and clinically unimportant changes of conventional echocardiographic variables, including decreased LV end-diastolic dimension and increased LV end-diastolic wall thickness.[8] The combination of acepromazine and butorphanol is commonly used for and tolerated well by healthy dogs, and good sedation has been achieved,[4,7] which is associated with minimal cardiovascular depression usually characterized by a transient decrease in HR,[4] decrease in systemic arterial blood pressure,[9,10] or both.[7] However, to the authors' knowledge, the influence of acepromazine-butorphanol combinations on echocardiographic variables of dogs has not been investigated.

Two-dimensional STE represents a relatively novel ultrasonographic technique that has been introduced in veterinary medicine to aid in the noninvasive assessment of LV function. Specifically, 2-D STE can be used to measure, among other indices, myocardial strain, which represents deformation of a myocardial segment over time.[11] Deformation analysis with 2-D STE is based on the formation of speckles (ie, a series of ultrasonographic components attributable to reflection, scattering, and interference between tissue and ultrasound beams that can be tracked over time in 2-D echocardiograms).[12–14] Deformation measurements derived by use of 2-D STE have been validated in dogs against measurements obtained by use of sonomicrometry and MRI,[13,14] and adequate feasibility,[14,15] reproducibility, and repeatability[13] for their use in healthy subjects have been reported. Furthermore, various 2-D STE indices have been evaluated in canine patients with differing severities of myxomatous mitral valve disease[16–19] and in dogs with Duchenne muscular dystrophy.[6]

Effects of sedation on some 2-D STE indices were assessed in 6 healthy Beagles.[6] In that study,[6] dogs were sedated with a combination of acepromazine and buprenorphine. To the authors' knowledge, the influence of sedation on 2-D STE variables has not been investigated for a combination of acepromazine and butorphanol or in large populations of dogs.

The objective of the study reported here was to determine effects of sedation with a combination of acepromazine and butorphanol on conventional echocardiographic variables and on strain values obtained by use of 2-D STE in healthy dogs. We hypothesized that this combination of drugs would have only minimal influence on echocardiographic variables.

Materials and Methods

Animals

Apparently healthy adult dogs with no history of heart or respiratory tract disease and that were not receiving medications were prospectively recruited from among the pets of staff and students of the University of Murcia. Dogs were eligible for inclusion if they were medium to large size (body weight, 15 to 50 kg) and > 1 year old. Dogs were confirmed healthy on the basis of the medical history and results of physical examination, a CBC, blood biochemical analysis, noninvasive blood pressure measurement, electrocardiography, and conventional echocardiography. Owner consent was obtained for each dog before it was enrolled in the study. The study protocol was approved by the Ethics Committee of the University of Murcia.

Experimental procedures

Dogs were allowed to acclimate to the examination room for at least 15 minutes before the experiments began. A baseline echocardiographic examination was performed before dogs were sedated. The sedation protocol consisted of a combination of acepromazine maleate (0.02 mg/kg) and butorphanol tartrate (0.2 mg/kg) administered IM. Drug doses were chosen on the basis of published information that they would result in an ambulatory dog with mild to moderate sedation.[20] The degree of sedation was considered adequate for echocardiographic examination when dogs voluntarily maintained lateral recumbency with no attempts to change position and breathed calmly, which reduced respiration artifacts and allowed the operator to comfortably perform a quality diagnostic procedure. Echocardiographic examinations were repeated 30 to 40 minutes after drug administration.

Blood pressure measurement

Immediately before echocardiographic examinations were performed, noninvasively obtained indirect estimates of blood pressure were recorded by use of a high-definition oscillometric device.[a] Dogs were gently restrained in sternal or lateral recumbency (according to each dog's preference) for 5 minutes before measurements were obtained by use of a cuff positioned at the base of the tail. Three to 5 indirect estimates were collected, and values for SAP, MAP, and DAP were obtained. Quality and reliability of recordings were assessed by visual inspection of the blood pressure waveforms on a computer monitor. The mean value for ≥ 3 reliable measurements was calculated and used for statistical analysis.

Echocardiographic examination

All echocardiographic examinations were performed by use of a commercially available ultrasound unit[b] equipped with a multifrequency 1- to 5-MHz phased-array sector transducer with simultaneous ECG recording. All echocardiograms were obtained and

measured by a single experienced operator (MJFP), who used standard methods described elsewhere.[21–24] During examination, all dogs were positioned first in right and then in left lateral recumbency. All data were obtained for at least 4 consecutive cardiac cycles during stable sinus rhythm and at the end of expiration. Each echocardiographic examination was stored digitally for analysis offline. The operator was not aware of the sedation status of each dog when performing offline measurements. Mean values over 3 cardiac cycles were calculated and used for statistical analysis.

M-mode measurements

The M-mode measurements of LVIDs, LVIDd, interventricular septum during systole and diastole, and posterior wall of the LV during systole and diastole were obtained from 2-D–guided M-mode images recorded at the level of the chordae tendinae, in accordance with the leading edge-to-leading edge method. The percentage of fractional shortening was calculated as ([LVIDd – LVIDs]/LVIDd) × 100. The M-mode measurements of E-point to septal separation were achieved by use of parasternal transverse mitral valve views.

2-D measurements

Measured conventional echocardiographic variables included LV ESV and EDV obtained with the modified single-plane Simpson method by use of images acquired from a right parasternal 4-chamber long-axis view. The LV ejection fraction was calculated as ([EDV – ESV]/EDV) × 100. The LV ESVI and EDVI were derived, respectively, from ESV and EDV measurements (obtained from 2-D images) and divided by body surface area. Aortic annulus diameter was obtained from the right parasternal long-axis view by use of the inner edge-to-inner edge method. Cross-sectional area of the aortic annulus, which subsequently was used to determine cardiac output, was calculated as πr^2, where $\pi = 3.14$ and r is the annulus radius (corresponding to half of the diameter). Right parasternal short-axis views at the level of the papillary muscles were used to calculate LVAs and LVAd, and LV shortening area was then calculated as ([LVAd – LVAs]/LVAd) × 100. Measurements of left atrium and aorta dimensions were obtained on 2-D parasternal short-axis views at the level of the aortic valve in early ventricular diastole at the first frame after aortic valve closure. The left atrium-to-aorta ratio was then calculated.

Spectral Doppler ultrasonography measurements

Pulmonary artery flow was recorded with pulsed-wave Doppler ultrasonography from the right parasternal short-axis view at the level of the pulmonary artery. Pulmonary artery Vmax and transpulmonary pressure gradient were determined. Continuous-wave Doppler ultrasonography was used to record aorta flow from the subcostal 3-of-5 chamber view. The aorta Vmax, transaortic pressure gradient, LV preejection period, LV ejection time, and velocity time integral were measured. The LV preejection period-to-LV ejection time ratio was also calculated. Cardiac output was determined as HR × cross-sectional area of the aortic annulus × velocity time integral. Transmitral flow was recorded from the left parasternal apical 4-chamber view with pulsed-wave Doppler ultrasonography; variables measured included Vmax of early diastolic flow (E wave), deceleration time of early diastolic flow, A wave, and duration of late diastolic flow. Thereafter, the ratio of the peak of the E wave to peak of the A wave was calculated.

Spectral pulsed tissue Doppler ultrasonography measurements

Myocardial (peak systolic, early diastolic, and late diastolic) velocities were obtained from left apical parasternal 4-chamber views by use of tissue Doppler ultrasonographic imaging, with the pulsed Doppler ultrasonography sample volume positioned on the lateral and septal walls of the mitral annulus. The ratio of early diastolic transmitral flow velocity to tissue Doppler ultrasonography early diastolic lateral mitral annulus velocity was then calculated. The LV myocardial performance index was also derived by

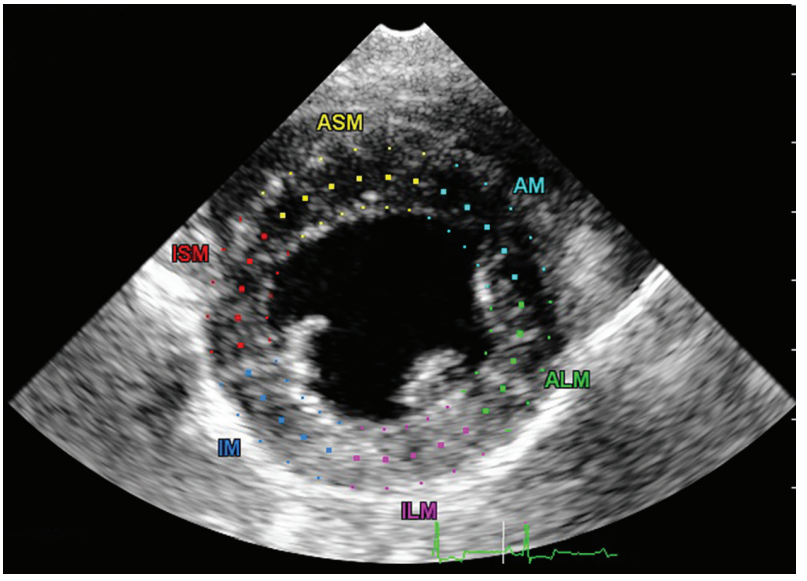

Figure 1—Representative 2-D echocardiographic image obtained from a healthy dog providing a right parasternal short-axis view of the LV at the level of the papillary muscles in which there is a circular ROI drawn by the software that has been adjusted manually. The myocardium has been divided automatically into 6 segments for strain analysis in accordance with the anatomy classification for humans. The 6 segments are as follows: anteroseptal (ASM [yellow]), anterior (AM [light blue]), lateral (ALM [green]), posterior (ILM [purple]), inferior (IM [dark blue]), and septal (ISM [red]). Notice the simultaneously recorded ECG tracing at the bottom of the image (green line). Tick marks on the right side are at intervals of 5 mm.

use of tissue Doppler ultrasonographic imaging and calculated as (isovolumic contraction time + isovolumic relaxation time)/LV ejection time. Tricuspid lateral annular (peak systolic, early diastolic, and late diastolic) velocities were also determined.

2-D STE

For analysis of 2-D STE data, images were recorded at rates of 60 to 90 Hz for a minimum of 4 consecutive cardiac cycles. The LV strain analysis was performed offline on a separate personal computer by use of software.[c] Recordings of good quality 2-D cine loops of the LV recorded from the left parasternal apical 4-chamber view and the right parasternal short-axis view at the level of the papillary muscle were used for analysis of longitudinal and circumferential strain.

To calculate circumferential strain, the software drew a circular ROI in each short-axis view. The operator adjusted the ROI manually to best incorporate the entire myocardial thickness **(Figure 1)**. The software algorithm automatically segmented the LV short-axis and performed speckle tracking on 6 segments (anteroseptal, anterior, lateral, posterior, inferior, and septal), which were in accordance with standard segmentation models used for humans. Six circumferential strain profiles were obtained that corresponded to the average values of each myocardial segment. Global strain values were automatically calculated by the software and corresponded to the peak of the global strain curve prior to aortic valve closure **(Figure 2)**.

Global longitudinal strain was obtained by manual placement of 3 reference points (one on each side of the mitral valve annulus and the third at the apical endocardial border). The software then created an ROI with the automatic delineation of endocardial and epicardial borders. The operator subsequently adjusted the ROI to best incorporate the entire myocardial thickness **(Figure 3)**. The LV was divided into 7 segments (basal septal, midseptal, apical septal, apical, apical lateral, midlateral, and basal lateral) by the software in accordance with standard segmentation models used for humans. The operator inspected the adequacy of segmentation and verified that the ROI followed the movements of each segment of the myocardium throughout the cardiac cycle. The software algorithm performed speckle tracking and derived segmental and global strain values. Global longitudinal strain was calculated from the entire ROI, which was considered as a single segment **(Figure 4)**.

Event timing for aortic valve closure was recorded from the flow profile of the LV outflow tract obtained by use of pulsed-wave Doppler ultrasonography.

Between-day intraobserver repeatability of 2-D STE variables was determined by use of 6 unsedated dogs and strain analysis performed on 2 days over a 2-week period. Each variable was measured 3 times during 3 consecutive cardiac cycles by use of the same loop, and the mean value was used to determine between-day repeatability.

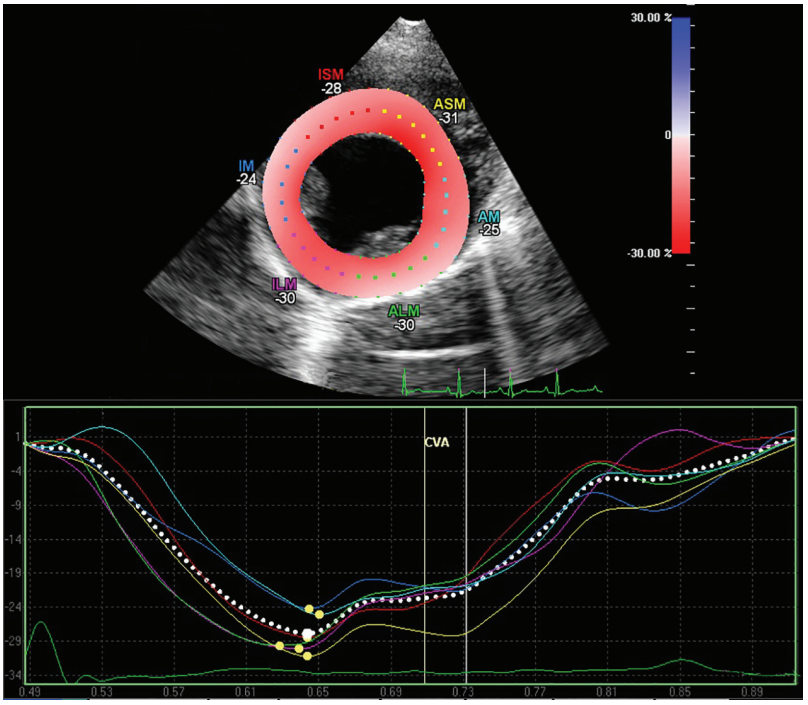

Figure 2—Representative 2-D echocardiographic image obtained from a healthy dog (top) and a circumferential time-strain curve obtained by use of 2-D STE (bottom). In the 2-D image, an ROI has been drawn by the software and the myocardium has been divided into 6 segments. Strain values for each segment are indicated and represent the corresponding percentage. Notice the simultaneously recorded ECG tracing at the bottom of the 2-D image (green line). The bottom panel provides color-coded circumferential strain curves for each of the 6 segments and a global strain curve (dotted white line), with strain value percentages on the y-axis and time in seconds on the x-axis. Yellow circles on the strain curves represent peak circumferential systolic strain values. The global circumferential strain value (white circle) is –28% and corresponds to the peak of the global strain curve prior to aortic valve closure (CVA). ***See*** Figure 1 for remainder of key.

Statistical analysis

Statistical analysis was performed with commercially available software.[25,d,e] An a priori power analysis by use of a *t* test between means (α = 0.05 and power = 0.8) indicated that 14 dogs would be needed to detect large effects (d = 0.8) and 33 dogs would be needed to detect medium effects (d = 0.5).

Distribution of variables was tested for normality by use of the Shapiro-Wilk test (α = 0.05). Data were normally distributed, and mean and SD for each normally distributed variable were calculated. A paired Student *t* test was used to compare variables between nonsedated and sedated states. Adjustments for multiple comparisons were made by use of the Benjamini-Hochberg procedure to control the false discovery rate.[26,27] Variables were considered

significantly affected by sedation when the corresponding value was $P < 0.01$ (false discovery rate, < 5%). Correlations between HR and echocardiographic variables that had a significant treatment effect were examined by use of Pearson correlation analysis. Values of $P < 0.05$ were considered significant.

Between-day intraobserver variability for global strain values was quantified as follows: coefficient of variation = (mean difference between measurements/mean of measurements) X 100.

Results

Animals

The study population comprised 18 medium- to large-sized healthy dogs that consisted of 5 Labrador Retrievers, 5 mixed-breed dogs, 3 Dalmatians, 1 American Staffordshire Bull Terrier, 1 Golden Retriever, 1 Irish Setter, 1 Spanish Podenco, and 1 Weimaraner. Seven dogs were spayed females, 6 were sexually intact females, 3 were castrated males, and 2 were sexually intact males. Age of the dogs ranged from 2 to 10 years (median, 5 years), and body weight ranged from 16 to 48 kg (median, 26.5 kg).

Sedation

The degree of sedation was considered adequate to facilitate echocardiography in all dogs. Panting was observed in 1 dog during the baseline examination and continued after the dog was sedated.

Cardiovascular variables

Mean ± SD HR after sedation (80 ± 19 beats/min) was significantly ($P < 0.01$) lower than the mean HR before sedation (107 ± 22 beats/min). Mean noninvasively measured DAP and MAP after sedation (59 ± 10 mm Hg and 80 ± 10 mm Hg, respectively) were significantly ($P < 0.01$) lower than values obtained before sedation (69 ± 12 mm Hg and 91 ± 10 mm Hg, respectively).

Standard and spectral pulsed tissue Doppler echocardiography

Results for conventional echocardiographic variables were determined **(Tables 1 and 2)**. The majority (38/44 [86%]) of variables measured were not significantly different from baseline values after treatment. The EDVI, A wave, late diastolic velocity for the septal wall of the mitral annulus, and late diastolic velocity for the tricuspid lateral annulus decreased after sedation, and ejection time and peak of the E wave-to-peak of the A wave ratio increased after sedation.

Pearson correlation analysis revealed significant correlations between HR and several variables. There was a significant positive correlation between HR and the A wave ($r = 0.58$; $P < 0.001$), late diastolic velocity for the septal wall of the mitral annulus ($r = 0.43$; $P = 0.01$), and late diastolic velocity for the tricuspid lateral annulus ($r = 0.39$; $P = 0.024$), and a significant negative correlation between HR and ejection time ($r = -0.59$; $P < 0,001$) and peak of the E wave-to-peak of the A wave ratio ($r = -0.61$; $P < 0.001$).

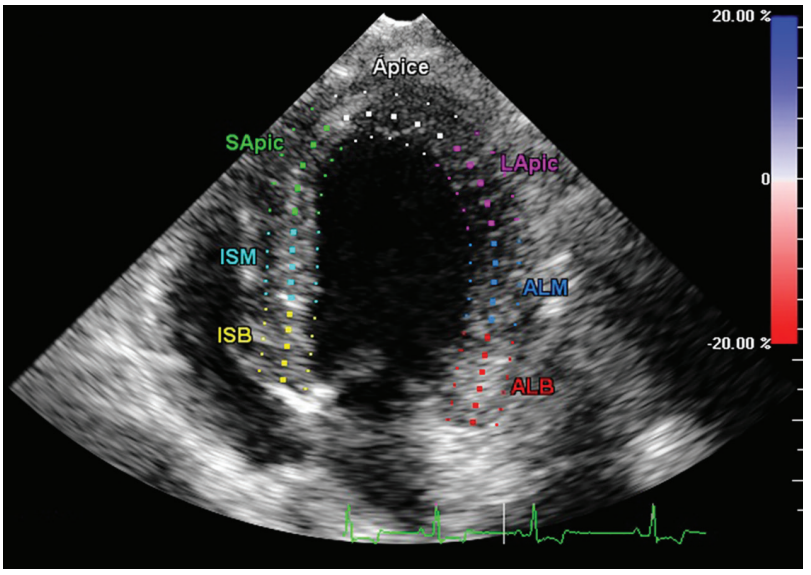

Figure 3—Representative 2-D echocardiographic image obtained from a healthy dog providing a left apical 4-chamber view of the LV in which an ROI (drawn by the software) with delineation of endocardial and epicardial borders has been adjusted manually. The myocardium has been automatically divided into 7 segments for strain analysis in accordance with standard segmentation models used for humans. The 7 segments are as follows: basal septal (ISB [yellow]), midseptal (ISM [light blue]), apical septal (SApic [green]), apical (Apice [white]), apical lateral (LApic [purple]), midlateral (ALM [dark blue]), and basal lateral (ALB [red]). Notice the simultaneously recorded ECG tracing at the bottom of the image (green line). Tick marks on the right side are at intervals of 5 mm.

2-D STE

Results for 2-D STE variables were determined **(Table 3)**. All segments could be tracked and used for strain analysis. The frame rate used to analyze STE indices ranged from 60 to 90 Hz. Between-day coefficient of variation values ranged from 8.8% to 9.77%. The majority (14/15) of 2-D STE variables measured did not differ significantly when strain indices after sedation were compared with baseline values. Specifically, global strain values were not affected by sedation, whereas among segmental strain values, apical lateral strain was significantly decreased in sedated dogs. No significant correlation was found between apical lateral strain and HR.

Discussion

The present study was the first in which effects of a combination of acepromazine and butorphanol on conventional echocardiographic variables and on strain values obtained by use of 2-D STE were evaluated in healthy dogs. Results indicated that aceproma-

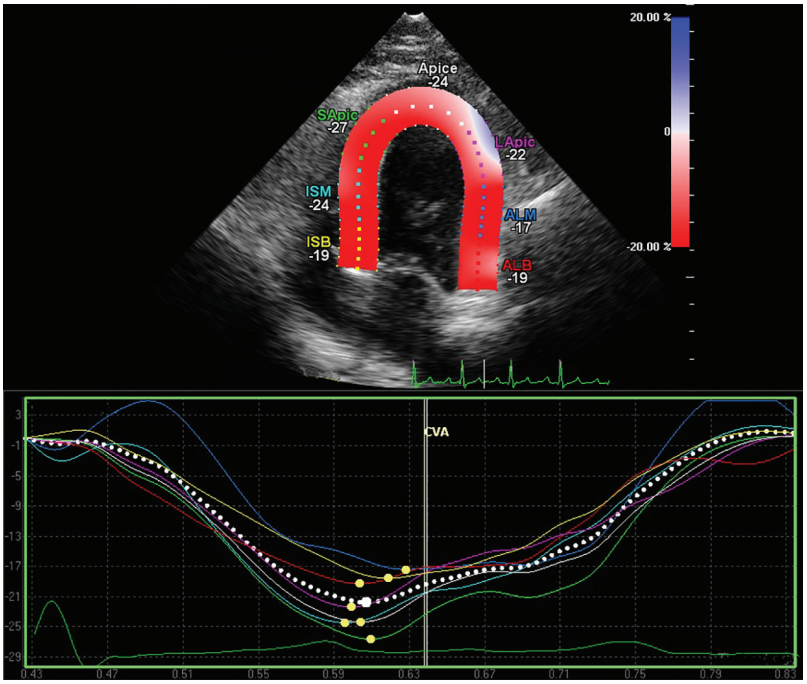

Figure 4—Representative 2-D echocardiographic image obtained from a healthy dog (top) and a longitudinal time-strain curve obtained by use of 2-D STE (bottom). In the 2-D image, an ROI drawn by the software has been manually adjusted and the myocardium has been divided into 7 segments. Strain values for each segment are indicated and represent the corresponding percentage. Notice the simultaneously recorded ECG tracing at the bottom of the 2-D image (green line). Tick marks on the right side are at intervals of 1 cm. The bottom panel provides color-coded longitudinal strain curves for each of the 7 segments and a global circumferential strain curve (dotted white line), with strain value percentages on the y-axis and time in seconds on the x-axis. Yellow circles on the strain curves represent peak longitudinal systolic strain values. The global circumferential strain value (white circle) is –22% and corresponds to the peak of the global strain curve prior to aortic valve closure (CVA). ***See*** Figure 3 for remainder of key.

zine and butorphanol at the doses used in this study provided sedation adequate to facilitate echocardiographic examination with only mild influence on conventional and 2-D STE echocardiographic variables.

Transient decreases in HR[4] or arterial blood pressure[9,10] (or both[7]) after administration of various combinations of acepromazine and butorphanol have been described. The use of opioid-tranquilizer combinations makes it difficult to attribute cardiovascular effects to either drug alone.[7] In healthy dogs, a reduction of HR and SAP[3,4] or MAP[3] has been described after administration of acepromazine alone. The decrease in HR may be attributable to a central vagal effect,[7] whereas the reduction in arterial blood pressure would be mediated through peripheral α_1-adrenoceptor blockade and depression of the hypothalamic vasomotor center.[4] Reductions in HR and arterial blood pressures have also been reported for dogs treated with butorphanol alone,[28,29] with the reduction in HR probably related to an increase in vagal tone[4] and the reduction in arterial blood pressures to a decrease in peripheral vascular tone.[7,29]

In the present study, 3 of 18 dogs had bradycardia (HR < 60 beats/min) after acepromazine-butorphanol treatment. Bradycardia was a common finding in another study[29] in which healthy dogs received butorphanol IV at doses of 0.1 or 0.4 mg/kg; bradycardia was recorded up to 60 minutes after drug injection, even if it was easily reversible with verbal stimulation.[29] In a later study[28] that involved use of halothane-anesthetized dogs, the reduction of HR observed after IV administration of butorphanol (0.2 mg/kg) was considered clinically relevant, and the concurrent use of an anticholinergic agent to prevent bradycardia was suggested. Specifically because of its anticholinergic effects, the use of acepromazine before opioid administration to reduce the incidence of bradycardia was supported by results of another study[7] in which acepromazine (0.22 mg/kg) and butorphanol (0.22 mg/kg) were administered IV or IM. Interestingly, in that study,[7] no significant differences in mean HR were detected when comparing the 2 routes of administration. However, in a subsequent study,[4] bradycardia was detected in 3 of 6 dogs after IV administration of butorphanol (0.15 mg/kg) despite pretreatment with acepromazine (0.05 mg/kg). Therefore, it can be concluded on the basis of results of the present study and of other studies that bradycardia might occur in healthy dogs treated with acepromazine and butorphanol, regardless of the dose and route of administration. Thus, the possibility of bradycardia should be considered before this combination of drugs is used.

Mild changes in arterial blood pressure were detected in dogs of the present study after acepromazine-butorphanol treatment. These changes were characterized by a decrease of 14% in DAP and a decrease of 12% in MAP. Even though mean blood pressure values obtained after sedation in the present study were in the normotensive range, an SAP < 90 mm Hg was recorded in one dog, and an MAP < 70 mm Hg was recorded in another dog. Hypotension (SAP < 90 mm Hg and MAP < 70 mm Hg) was not detected after acepromazine administration alone in healthy awake dogs,[3,4] nor was it detected after injection of butorphanol alone in another population of healthy dogs,[28,29] whereas the effects of various combinations of the 2 drugs are variable.[4,7,10] More specifically, hypotension has not been reported after IV or IM administration of various doses of acepromazine-butorphanol when acepromazine was administered 15 minutes before the administration of butorphanol.[4,7] Mild arterial and pulmonary arterial hypotension was observed in another study[10] that involved

Table 1—Mean ± SD values for 2-D and M-mode echocardiographic variables measured in 18 healthy dogs before (baseline) and after sedation by IM administration of a combination of acepromazine maleate (0.02 mg/kg) and butorphanol tartrate (0.2 mg/kg).

Variable	Baseline	Sedation
HR (beats/min)	107 ± 22	80 ± 19*
SAP (mm Hg)	131 ± 10	118 ± 14
DAP (mm Hg)	69 ± 12	59 ± 10*
MAP (mm Hg)	91 ± 10	80 ± 10*
LV outflow tract (cm)	1.80 ± 0.21	1.83 ± 0.21
ESVI (mL/m^2)	30.9 ± 6.5	29.4 ± 7.3
EDVI (mL/m^2)	65.6 ± 11	59.1 ± 12.2*
LV ejection fraction (%)	53 ± 4	50 ± 7
LVAs (cm^2)	7.9 ± 2.0	7.9 ± 2.4
LVAd (cm^2)	14.1 ± 3.0	13.5 ± 3.6
LV shortening area (%)	44 ± 5	42 ± 6
IVSs (cm)	1.33 ± 0.20	1.31 ± 0.21
IVSd (cm)	1.04 ± 0.33	0.99 ± 0.14
LVIDs (cm)	2.89 ± 0.51	2.80 ± 0.42
LVIDd (cm)	4.03 ± 0.58	3.81 ± 0.45
LVPWs (cm)	1.31 ± 0.18	1.36 ± 0.33
LVPWd (cm)	0.91 ± 0.13	0.96 ± 0.12
Fractional shortening (%)	30 ± 6	28 ± 5
EPSS (cm)	0.32 ± 0.10	0.34 ± 0.13
Left atrium-to-aorta ratio	1.34 ± 0.19	1.35 ± 0.19

*Within a row, value differs significantly ($P < 0.01$) from the baseline value.

EPSS = E-point to septal separation. IVSd = Interventricular septum at end diastole. IVSs = Interventricular septum at end systole. LVPWd = Left ventricular posterior wall at end diastole. LVPWs = Left ventricular posterior wall at end systole.

Table 2—Mean ± SD values for Doppler ultrasonography–derived echocardiographic variables measured in 18 healthy dogs before (baseline) and after sedation by IM administrat ion of a combination of acepromazine maleate and butorphanol tartrate.

Variable	Baseline	Sedation
Pulmonary artery Vmax (m/s)	1.12 ± 0.27	0.99 ± 0.23
Pulmonary artery PG (mm Hg)	5.30 ± 2.48	4.17 ± 2.17
Aorta Vmax (m/s)	1.66 ± 0.25	1.56 ± 0.33
Aorta PG (mm Hg)	11.30 ± 3.68	10.20 ± 4.50
LV PEP (ms)	52 ± 12	57 ± 14
LV ejection time (ms)	162 ± 18	184 ± 27*
LV velocity time integral (cm)	17.7 ± 2.86	18.0 ± 3.55
LV PEP-to-ejection time ratio	6.67 ± 1.03	6.27 ± 1.34
Stroke volume (mL)	44.9 ± 9.6	47.9 ± 14.6
Cardiac output (L/min)	4.8 ± 1.2	3.9 ± 1.6
E wave (m/s)	0.78 ± 0.15	0.74 ± 0.13
DcT (ms)	103 ± 21	106 ± 30
A wave (m/s)	0.58 ± 0.23	0.41 ± 0.13*
Adur (ms)	80 ± 9	87 ± 14
E:A	1.46 ± 0.41	1.92 ± 0.43*
S lat (cm/s)	14.4 ± 6.0	12.7 ± 4.5
E' lat (cm/s)	12.2 ± 3.1	10.6 ± 3.3
A' lat (cm/s)	7.9 ± 2.1	6.5 ± 2.0
E:E' lat	0.07 ± 0.02	0.08 ± 0.02
Isovolumic relaxation time (ms)	86 ± 36	87 ± 29
Isovolumic contraction time (ms)	57 ± 18	52 ± 19
LV myocardial performance index	0.88 ± 0.19	0.77 ± 0.24
S sep (cm/s)	12.3 ± 4.1	11.0 ± 3.3
E' sep (cm/s)	8.5 ± 2.6	7.1 ± 2.0
A' sep (cm/s)	7.9 ± 2.5	5.3 ± 1.1*
S tric (cm/s)	16.2 ± 7.6	15.6 ± 4.5
E' tric (cm/s)	11.2 ± 3.8	11.6 ± 3.5
A' tric (cm/s)	11.9 ± 3.8	7.7 ± 1.9*

A wave = The Vmax of late transmitral diastolic flow. Adur = Duration of late transmitral diastolic flow. A' lat = Late diastolic velocity of annulus motion for the lateral wall of the mitral annulus. A' sep = Late diastolic velocity of annulus motion for the septal wall of the mitral annulus. A' tric = Late diastolic velocity of annulus motion for the tricuspid annulus. DcT = Deceleration time of early transmitral diastolic flow. E wave = The Vmax of early transmitral diastolic flow. E:A = Peak of E wave to peak of A wave ratio. E:E' lat = Ratio of peak of E wave to early diastolic velocity of annulus motion for the lateral wall of the mitral annulus. E' lat = Early diastolic velocity of annulus motion for the lateral wall of the mitral annulus. E' sep = Early diastolic velocity of annulus motion for the septal wall of the mitral annulus. E' tric = Early diastolic velocity of annulus motion for the tricuspid annulus. PEP = Pre-ejection period. PG = Transpulmonary pressure gradient. S lat = Peak systolic velocity of annulus motion for the lateral wall of the mitral annulus. S sep = Peak systolic velocity of annulus motion for the septal wall of the mitral annulus. S tric = Peak systolic velocity of annulus motion for the tricuspid annulus.

See Table 1 for remainder of key.

use of acepromazine and butorphanol administered simultaneously IM, as in the present study. Considering the results of previous studies, hypotension does not appear to be exacerbated by the use of a particular route of administration or by higher doses of the drugs. It remains to be determined whether hypotension can be fully avoided by first administering acepromazine alone followed subsequently by administration of butorphanol. However, this may be impractical for clinical purposes. In fact, 2 invasive procedures (injections) would be needed, and the diagnostic procedure (eg, echocardiography) could be delayed. Regardless, changes of arterial blood pressures observed in the present study were considered mild, and the sedation protocol was considered adequate to facilitate echocardiographic examination of healthy animals.

In the present study, 6 of 44 conventional echocardiographic variables (EDVI, ejection time, A wave, late diastolic velocity for the septal wall of the mitral annulus, late diastolic velocity for the tricuspid lateral annulus, and peak of the E wave-to-peak of the A wave ratio) were significantly affected by sedation. Variables altered by sedation reflected both systolic and diastolic function. The EDVI after sedation was decreased from the baseline value, which suggested a reduction in preload that could have been related to diminished vascular resistance induced by the combination of drugs.

The increase in ejection time detected after sedation in the present study could have been secondary to a reduced afterload. In fact, even if a reduction in HR can increase ejection time, this would be related to an increase in preload, not supported by the changes observed for other echocardiographic variables. However, the influence of HR on duration of ejection time cannot be completely excluded because of the moderate negative correlation between the 2 variables. A moderate positive correlation between HR and the A wave and a strong negative correlation between HR and peak of the E wave-to-peak of the A wave ratio were also found. However, because a slow HR is expected to increase flow velocity of the A wave,[30] the reduction in A wave and subsequent increase in the peak of the E wave-to-peak of the A

Table 3—Mean ± SD values for STE-derived variables measured in 18 healthy dogs before (baseline) and after sedation by IM administration of a combination of acepromazine maleate and butorphanol tartrate.

Variable	Baseline	Sedation
Global circumferential strain	–26 ± 3	–25 ± 4
Global longitudinal strain	–20 ± 3	–20 ± 4
Anteroseptal strain	–30 ± 7	–30 ± 8
Anterior strain	–30 ± 5	–28 ± 6
Lateral strain	–25 ± 6	–25 ± 7
Posterior strain	–27 ± 7	–22 ± 6
Inferior strain	–27 ± 5	–24 ± 7
Septal strain	–25 ± 6	–24 ± 7
Basal septal strain	–18 ± 4	–18 ± 5
Midseptal strain	–25 ± 8	–22 ± 4
Apical septal strain	–25 ± 8	–25 ± 6
Apical strain	–23 ± 6	–21 ± 4
Apical lateral strain	–22 ± 6	–18 ± 4*
Midlateral strain	–18 ± 6	–23 ± 7
Basal lateral strain	–20 ± 5	–21 ± 7

Values reported are percentages.
See Table 1 for remainder of key.

wave ratio observed in the present study could have been the effect of a reduced preload, as has been suggested for EDVI. A decreased A wave, associated with a reduction in HR, has been also reported for healthy Beagles sedated with a combination of acepromazine and buprenorphine.[6]

Two pulsed-wave tissue Doppler ultrasonographic imaging variables (late diastolic velocity for the septal wall of the mitral annulus and late diastolic velocity for the tricuspid lateral annulus) were significantly decreased after sedation in the present study. Although preload can affect pulsed-wave tissue Doppler ultrasonographic imaging variables of healthy dogs, with an increase of velocities for increased preloads, these variables appear to be less affected by HR.[30] Therefore, results of the present study might have reflected a reduced preload. Although positive correlations were found between HR and late diastolic velocity for the septal wall of the mitral annulus and between HR and late diastolic velocity for the tricuspid lateral annulus, and even if these findings could have been spurious, the contribution of HR to their reduction cannot be excluded.

In the present study, the majority (14/15) of 2-D STE variables did not differ significantly when baseline and postsedation values were compared. In particular, global strain indices were unaffected by treatment, whereas only 1 segmental strain value (apical lateral) decreased significantly after sedation. The fact that global strain values were not affected by treatment is probably more interesting than the small decrease in 1 segmental strain value. Significant differences among 2-D STE–derived segmental longitudinal strain and strain rate values were not found in a previous study[31] in which investigators compared 2-D STE and color tissue Doppler ultrasonography imaging for healthy dogs. In addition, average global values are considered an acceptable representation of the entire LV deformation and are more commonly used than are segmental values.[16,17] Furthermore, the segmentation used in the present study and in most studies of dogs is created automatically by the software taking into account anatomy of the LV in humans, which does not necessarily correspond to the anatomy of the LV in dogs.[16]

The small decrease in apical lateral strain observed in the present study after treatment could have been induced by the aforementioned suggested decrease in preload or afterload (or both). Some deformation indices reportedly reflect LV function at least in part independently of hemodynamic load in clinically normal awake dogs.[13] However, results of other studies[15,18] have not supported load independency of these measurements. A decrease in strain variables may also be the result of a longer R-R interval caused by a decrease in vagal tone.[32] The influence of HR on 2-D STE–derived strain indices of dogs is variable. In a study[33] conducted to assess myocardial deformations at pacing rates of 120, 140, 160, and 180 beats/min in healthy anesthetized dogs, results indicated that longitudinal, circumferential, and radial strain values were not affected by increases in HR. However, other studies[16–19,32] have revealed correlations between HR and 2-D STE–derived indices. In the present study, no correlations between HR and apical lateral strain after sedation were found; therefore, it cannot be excluded that such a decrease was dependent on altered loading conditions.

The values obtained for global strain in the baseline examination were similar to those previously reported for healthy awake dogs in other studies.[19,32] However, the segmental longitudinal strain values appeared less comparable to those of another study[31] in which different equipment and segmentation analysis were used. Algorithms used to perform deformation analysis are proprietary, and it is not clear whether values obtained with one software system can be used interchangeably with those obtained by use of another.[11,16,34,35] Studies[35,36] in human medicine have revealed significant differences between strain values obtained by use of software products from various manufacturers, and attempts have been made to improve strain concordance among vendors. Furthermore, results of a study[35] in which investigators compared longitudinal strain values attained with equipment from 2 manufacturers indicated good agreement for global longitudinal strain but not for segmental values, which supports the use of global longitudinal strain for clinical practice. In veterinary medicine, information regarding agreement in strain measurements among vendors is lacking, but it might be speculated that similar limitations exist and that the use of global values may partially reduce interpretation errors until standardization is achieved.

The present study had limitations. The sample size needed to achieve statistical power for a medium or small effect was larger than the study population of 18 dogs; thus, caution should be used when extrapolating findings to larger populations. Large effects

were considered more clinically relevant, and the related statistical power was adequate for the purposes of the present study. Another limitation was that the population of dogs differed with regard to sex and age, and only medium- to large-sized dogs were included; thus, results may not represent the overall dog population. However, dogs had a body weight range of 15 to 50 kg, which was important considering that strain is a measurement of systolic function that can be especially useful to assess medium- and large-sized dogs predisposed to cardiomyopathies such as dilated cardiomyopathy. Furthermore, the study subjects were healthy dogs, and sedation may have a different influence on echocardiographic variables in dogs with cardiac disease. The sedative combination may be less safe for use in unhealthy animals, with potential adverse effects other than those detected in the present study. Therefore, clinicians should be cautious when such a sedative combination is administered to unhealthy dogs, especially those with cardiac disease.

The use of acepromazine in combination with butorphanol at the doses administered in the present study provided sedation adequate to facilitate echocardiography in healthy dogs. It resulted in only minimal changes to conventional echocardiographic variables and 2-D STE–derived strain measurements. Therefore, the sedative combination used in this study could be considered for clinical use in healthy dogs when pharmacological means are required to aid echocardiographic assessment, including strain analysis performed with 2-D STE. However, clinicians and researchers must take into account the fact that small echocardiographic changes probably attributable to reduced preload or afterload (or both) might be detected and that bradycardia could be a common adverse effect.

Acknowledgments

Presented as an oral communication at the 23rd European College of Veterinary Internal Medicine Congress, Liverpool, England, September 2013.

The authors thank Antonio Maurandi López for assistance with the statistical analysis.

Footnotes

a. Memo Diagnostic Pro, S+B MedVet GmBH, Babenhausen, Germany.
b. iE33 ultrasound system, Philips Medical Systems, Andover, Mass.
c. Qlab 2D Strain software, version 9.0, Philips Medical Systems, Andover, Mass.
d. R, version 3.1.2, The R Foundation for Statistical Computing. Available at: www.cran.r-project.org/. Accessed Jul 7, 2015.
e. IBM SPSS statistics for Windows, version 19.0, IBM Corp, Armonk, NY.

References

1. Stepien RL. Sedation for cardiovascular procedures. In: Bonagura JD, ed. *Kirk's current veterinary therapy XII*. Philadelphia: WB Saunders Co, 1995;773–780.
2. Kellihan HB, Stepien RL, Hassen KM, et al. Sedative and echocardiographic effects of dexmedetomidine combined with butorphanol in healthy dogs. *J Vet Cardiol* 2015;17:282–292.
3. Saponaro V, Crovace A, De Marzo L, et al. Echocardiographic evaluation of the cardiovascular effects of medetomidine, acepromazine and their combination in healthy dogs. *Res Vet Sci* 2013;95:687–692.
4. Monteiro ER, Junior AR, Assis HM, et al. Comparative study on the sedative effects of morphine, methadone, butorphanol or tramadol, in combination with acepromazine, in dogs. *Vet Anaesth Analg* 2009;36:25–33.
5. Page A, Edmunds G, Atwell RB. Echocardiographic values in the Greyhound. *Aust Vet J* 1993;70:361–364.
6. Takano H, Fujii Y, Yugeta N, et al. Assessment of left ventricular regional function in affected and carrier dogs with Duchenne muscular dystrophy using speckle tracking echocardiography. *BMC Cardiovasc Disord* 2011;11:23–28.
7. Cornick JL, Hartsfield SM. Cardiopulmonary and behavioral effects of combinations of acepromazine/butorphanol and acepromazine/oxymorphone in dogs. *J Am Vet Med Assoc* 1992;2000:1952–1956.
8. Ward JL, Schober KE, Luis Fuentes V, et al. Effects of sedation on echocardiographic variables of left atrial and left ventricular function in healthy cats. *J Feline Med Surg* 2012;14:678–685.
9. Kojima K, Nishimura R, Mutoh T, et al. Comparison of cardiopulmonary effects of medetomidine-midazolam, acepromazine-butorphanol and midazolam-butorphanol in dogs. *Zentralbl Veterinarmed A* 1999;46:353–359.
10. Kojima K, Nishimura R, Mutoh T, et al. Effects of medetomidine-midazolam, acepromazine-butorphanol, and midazolam-butorphanol on induction dose of thiopental and propofol and on cardiopulmonary changes in dogs. *Am J Vet Res* 2002;63:1671–1679.
11. Armstrong WF, Ryan T. Evaluation of systolic function of the left ventricle. In: Armstrong WF, Ryan T, eds. *Feigenbaum's echocardiography*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2010;123–157.
12. Armstrong WF, Ryan T. Specialized echocardiographic techniques and methods. In: Armstrong WF, Ryan T, eds. *Feigenbaum's echocardiography*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2010;39–66.
13. Chetboul V, Serres F, Gouni V, et al. Radial strain and strain rate by two-dimensional speckle tracking echocardiography and the tissue velocity based technique in the dog. *J Vet Cardiol* 2007;9:69–81.
14. Carnabuci C, Hanås S, Ljungvall I, et al. Assessment of cardiac function using global and regional left ventricular endomyocardial and epimyocardial peak systolic strain and strain rate in healthy Labrador Retriever dogs. *Res Vet Sci* 2013;95:241–248.
15. Culwell NM, Bonagura JD, Schober KE. Comparison of echocardiographic indices of myocardial strain with invasive measurements of left ventricular systolic function in anesthetized healthy dogs. *Am J Vet Res* 2011;72:650–660.
16. Smith DN, Bonagura JD, Culwell NM, et al. Left ventricular function quantified by myocardial strain imaging in small-breed dogs with chronic mitral regurgitation. *J Vet Cardiol* 2012;14:231–242.
17. Zois NE, Tidholm A, Nägga KM, et al. Radial and longitudinal strain and strain rate assessed by speckle-tracking echocardiography in dogs with myxomatous mitral valve disease. *J Vet Intern Med* 2012;26:1309–1319.
18. Zois NE, Olsen NT, Moesgaard SG, et al. Left ventricular twist and circumferential strain in dogs with myxomatous mitral valve disease. *J Vet Intern Med* 2013;27:875–883.
19. Suzuki R, Matsumoto H, Teshima T, et al. Clinical assessment of systolic myocardial deformations in dogs with chronic mitral valve insufficiency using two-dimensional speckle-tracking echocardiography. *J Vet Cardiol* 2013;15:41–49.
20. Armitage-Chan E. Anesthesia and analgesia in dogs and cats. In: Fish RE, Brown MJ, Danneman PJ, et al, eds. *Anesthesia and analgesia in laboratory animals*. 2nd ed. Amsterdam: Academic Press, 2008;365–384.
21. Thomas WP, Gaber CE, Jacobs GJ, et al. 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.
22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.
23. Quiñones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167–184.
24. Hansson K, Haggstrom J, Kvart C, et al. 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.
25. R Core Team. *R: a language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing, 2014.
26. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995;57:289–300.
27. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol* 2014;67:850–857.
28. Greene SA, Hartsfield SM, Tyner CL. Cardiovascular effects of butorphanol in halothane-anesthetized dogs. *Am J Vet Res* 1990;51:1276–1279.
29. Trim CM. Cardiopulmonary effects of butorphanol tartrate in dogs. *Am J Vet Res* 1983;44:329–331.
30. Boon J. Evaluation of size, function, and hemodynamics. In: Boon J, ed. *Veterinary echocardiography*. 2nd ed. Oxford: Blackwell Publishing, 2011;153–266.
31. Wess G, Keller LJM, Klausnitzer M, et al. Comparison of longitudinal myocardial tissue velocity, strain, and strain rate measured by two-dimensional speckle tracking and by color tissue Doppler imaging in healthy dogs. *J Vet Cardiol* 2011;13:31–43.
32. Takano H, Fujii Y, Ishikawa R, et al. Comparison of left ventricular contraction profiles among small, medium, and large dogs by use of two-dimensional speckle tracking echocardiography. *Am J Vet Res* 2010;71:421–427.
33. Suzuki R, Matsumoto H, Teshima T, et al. Influence of heart rate on myocardial function using two-dimensional speckle-tracking echocardiography in healthy dogs. *J Vet Cardiol* 2013;15:139–146.
34. Biaggi P, Carasso S, Garceau P, et al. Comparison of two different speckle tracking software systems: does the method matter? *Echocardiography* 2011;28:539–547.
35. Castel AL, Szymanski C, Delelis F, et al. Prospective comparison of speckle tracking longitudinal bidimensional strain between two vendors. *Arch Cardiovasc Dis* 2014;107:96–104.
36. Yang H, Marwick TH, Fukuda N, et al. Improvement in strain concordance between two major vendors after the strain standardization initiative. *J Am Soc Echocardiogr* 2015;28:642–8.e7.