Accuracy of point-of-care lung ultrasonography for the diagnosis of cardiogenic pulmonary edema in dogs and cats with acute dyspnea

Jessica L. Ward DVM

Gregory R. Lisciandro DVM

Bruce W. Keene DVM, MSc

Sandra P. Tou DVM

Teresa C. DeFrancesco DVM

From the Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27607 (Ward, Keene, Tou, DeFrancesco); and Hill Country Veterinary Specialists, Spicewood, TX 78669 (Lisciandro). Dr. Ward's present address is Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA 50011.

Address correspondence to Dr. DeFrancesco (tdefranc@ncsu.edu).

OBJECTIVE
To determine the accuracy of a point-of-care lung ultrasonography (LUS) protocol designed to diagnose cardiogenic pulmonary edema (CPE) in dyspneic dogs and cats.

DESIGN
Diagnostic test evaluation.

ANIMALS
76 dogs and 24 cats evaluated for dyspnea.

PROCEDURES
Dogs and cats were evaluated by LUS; B lines were counted at 4 anatomic sites on each hemithorax. A site was scored as positive when > 3 B lines were identified. Animals with ≥ 2 positive sites identified on each hemithorax were considered positive for CPE. Medical records were evaluated to obtain a final diagnosis (reference standard) for calculation of the sensitivity and specificity of LUS and thoracic radiography for the diagnosis of CPE.

RESULTS
Dogs and cats with a final diagnosis of CPE had a higher number of positive LUS sites than did those with noncardiac causes of dyspnea. Overall sensitivity and specificity of LUS for the diagnosis of CPE were 84% and 74%, respectively, and these values were similar to those of thoracic radiography (85% and 87%, respectively). Use of LUS generally led to the misdiagnosis of CPE (ie, a false-positive result) in animals with diffuse interstitial or alveolar disease. Interobserver agreement on LUS results was high ($\kappa > 0.85$).

CONCLUSIONS AND CLINICAL RELEVANCE
LUS was useful for predicting CPE as the cause of dyspnea in dogs and cats, although this technique could not be used to differentiate CPE from other causes of diffuse interstitial or alveolar disease. Point-of-care LUS has promise as a diagnostic tool for dyspneic dogs and cats. (*J Am Vet Med Assoc* 2017;250:666–675)

Emergency diagnosis of congestive heart failure can be challenging, particularly when a dog or cat has respiratory distress that limits the diagnostic evaluation. Thoracic radiography is considered a fairly high-yield test for identifying CPE; however, findings are sometimes equivocal and the process of obtaining radiographs can exacerbate respiratory distress in a compromised patient.

A recent advancement in the diagnostic imaging of dyspneic patients is point-of-care LUS.[1-10] Lung ultrasonography can be conceptualized as a visual stethoscope that can be used to supplement auscultation findings and improve the diagnostic accuracy of physical examination[9] prior to thoracic radiography.

ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
CPE	Cardiogenic pulmonary edema
LUS	Lung ultrasonography
NT-proBNP	N-terminal pro-B-type natriuretic peptide
Vet BLUE	Veterinary bedside lung ultrasound exam

The LUS technique can be used to detect pulmonary edema through the identification of ultrasound artifacts (B lines; also called ring-down artifacts, comet tails, lung rockets, and other terms) caused by an increase in the amount of water within the lungs.[3,5] The B lines (the terminology advocated in a recent international consensus statement[3]) are created when small fluid-filled alveoli, which are below the resolution threshold of the ultrasound beam, are surrounded by air, creating a high impedance gradient. These artifacts are identified ultrasonographically as discrete narrow-based vertical hyperechoic artifacts that extend from the pleural-pulmonary interface to the far aspect of the ultrasound screen without fading, and that move synchronously with respiration.[3,5-8,11,12]

Findings in human emergency patients suggest that LUS can be used to differentiate cardiogenic from noncardiogenic causes of dyspnea with high sensitivity and specificity[3,7,8,10,11,13-16] and similar or greater positive predictive value than measurement of blood NT-proBNP concentration[8,11,13,17] or thorac-

ic radiography.[3–5,7,18,19] The number of B lines is also positively and linearly correlated with amount of lung water and pulmonary capillary wedge pressure.[20,21] An international consensus panel[3] and meta-analysis[10] confirmed the usefulness of LUS for dyspneic patients and its accuracy for the diagnosis of CPE.

In veterinary medicine, protocols for point-of-care ultrasonography (thoracic- and abdominal-focused assessment with sonography for trauma) have been developed to evaluate the thorax and abdomen for the presence of free fluid and pneumothorax.[12,22] Lung ultrasonography is now emerging as an extension of point-of-care ultrasonography in veterinary patients. Two studies[23,24] have shown that B lines are fairly rare in clinically normal dogs but are common and widely distributed in dogs with CPE.[23,24] However, to the authors' knowledge, no studies have been conducted to prospectively evaluate the diagnostic accuracy of LUS in clinically dyspneic veterinary patients.

The primary objective of the study reported here was to evaluate the accuracy of a protocol for point-of-care LUS (the Vet BLUE protocol) for the diagnosis of CPE in a group of dyspneic dogs and cats. Secondary objectives were to evaluate the diagnostic accuracy of LUS in dogs versus cats, to characterize types of noncardiac disease that were correctly or incorrectly identified by use of LUS, and to determine interobserver agreement on LUS results.

Materials and Methods

Ethics statement

All study procedures were approved by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, North Carolina State University. Informed owner consent was obtained for each participating dog and cat.

Animals

Dogs and cats were prospectively enrolled from the Small Animal Emergency and Critical Care Service or Cardiology Service of North Carolina State University over a 16-month period (September 2013 through January 2015). To be included in the study, patients were required to have dyspnea (tachypnea or increased respiratory effort) on physical examination, a trained examiner available to perform LUS, and 2- or 3-view thoracic radiography performed by hospital staff or by the referring veterinarian within 6 hours before or after LUS examination. Patients were excluded when they had a respiratory disturbance suspected to be a pain response (ie, obvious nonrespiratory and noncardiac cause of pain), a recent history of trauma, or moderate-to-severe pleural effusion (fluid accumulation of > 1 cm) identified sonographically that could have resulted in lung atelectasis causing B lines independent of the true pulmonary disease. Patients were stabilized by provision of oxygen and sedation at the discretion of the emergency clinician.

Basic data for each dog and cat were collected immediately on hospital admission (age, sex, breed, body weight, rectal temperature, heart rate, respiratory rate, and body condition score). The time of LUS examination was also recorded. Thoracic radiography was performed within 6 hours before or after LUS, and radiographs were later reviewed in DICOM format by board-certified veterinary radiologists, who were blinded to LUS findings. After LUS had been performed, any necessary diagnostic tests and treatments were performed as determined by the emergency clinician.

LUS examination

Participating Vet BLUE examiners were cardiology and emergency clinicians who had completed a 2-hour training session with an experienced lung ultrasonographer (GRL) and had demonstrated proficiency during 3 to 5 supervised examinations. All LUS examinations were performed by use of a single portable ultrasonographic machine[a] with a curvilinear probe[b] with standardized settings (ultrasound frequency, 8 MHz; depth, 4 cm).

The Vet BLUE protocol for LUS has been described elsewhere.[24] Briefly, patients were standing or positioned in sternal recumbency for LUS evaluation. Images were acquired at 4 acoustic windows on each side of the thorax at standardized anatomic sites (caudal, perihilar, middle, and cranial), for a total of 8 sites/patient[12,24] **(Figure 1)**. For each site, hair was parted (not shaved) and alcohol was applied to facilitate probe contact. The ultrasound probe was held horizontal at each site and moved slightly (cranially and caudally 1 to 2 intercostal spaces; angled dorsally and ventrally) to optimize the view that provided the maximum number of B lines per intercostal space for that window. The ultrasound probe was then held stationary in each of the 8 windows for image acquisition. A 3-second cine loop from each site was saved and archived for later analysis.

Analysis of LUS images

Post hoc analysis of LUS images was performed independently by 2 examiners (JLW and GRL), both of whom were blinded to the thoracic radiography findings and final diagnosis of each patient. One of these examiners was experienced with LUS, and the other was a novice. Images were assessed for the presence and number of B lines, as defined and described elswhere[24] (Figure 1). The maximum number of B lines visible within a single intercostal space at each of the 4 anatomic sites in each hemithorax was recorded as follows: 0, 1, 2, 3, > 3, or infinite (confluent and no longer discernable as individual B lines[24]; **Figure 2**).

A site in which either > 3 or infinite B lines were recorded was scored as positive; therefore, these 2 score categories were not discriminated from each other in the statistical analyses.[3,10,24] In accordance with the Volpicelli method (endorsed in a human LUS consensus statement),[3] LUS examinations resulting in at least 2 positive sites on each hemithorax were
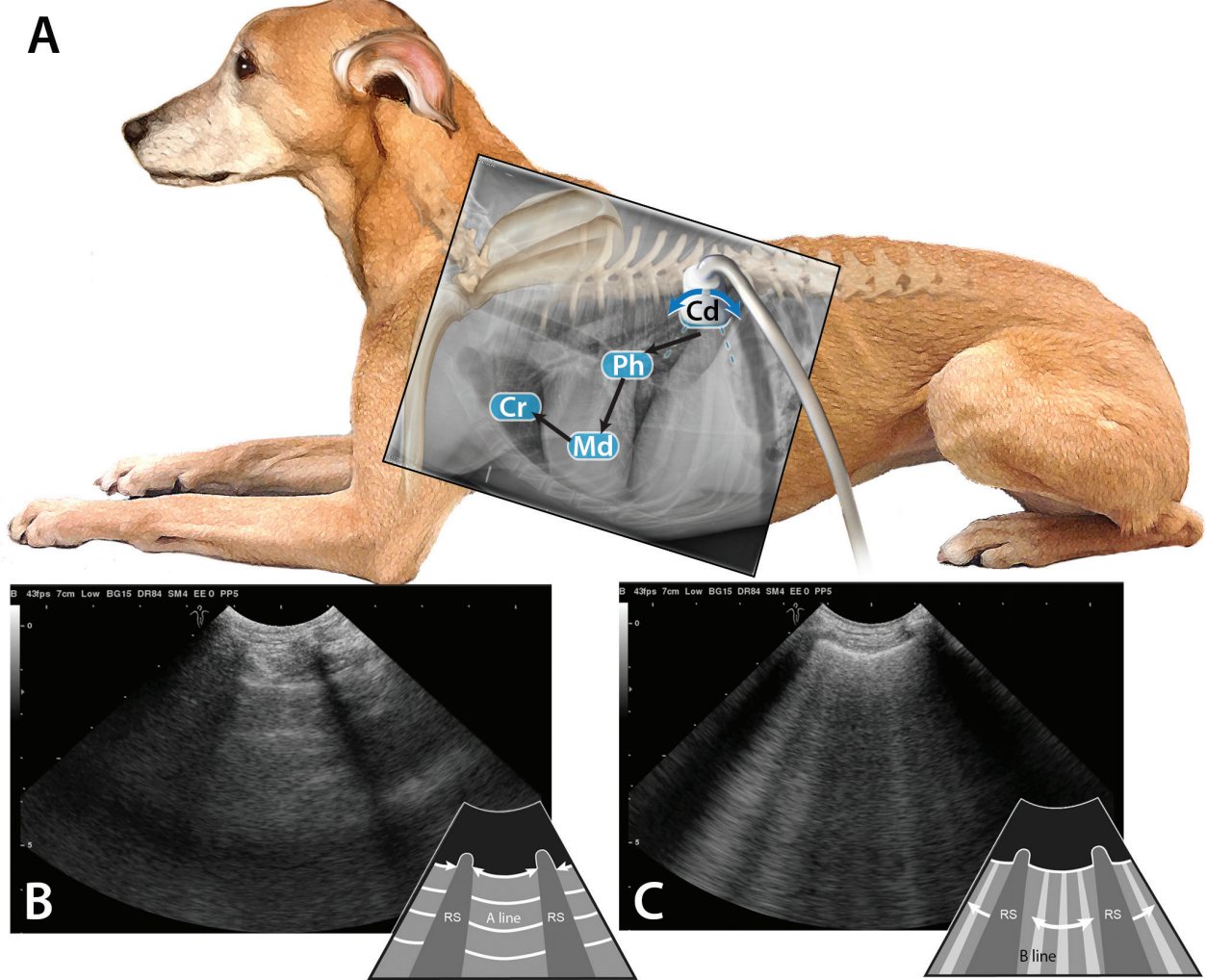
Figure 1—Stylized photographic depiction of the Vet BLUE technique for LUS (A) and representative LUS images (B and C). A—The ultrasound probe is held horizontally at 4 sites on each hemithorax to record images. Corresponding lung locations as viewed on a lateral thoracic radiographic image are also shown. Cd = Caudal. Cr = Cranial. Md = Middle. Ph = Perihilar. B—Still B-mode image and corresponding line drawing of LUS findings in a healthy dog, showing proper orientation of rib shadows and presence of A lines. C—Still B-mode image and corresponding line drawing of LUS dog in which B lines are present. The B lines are visible as multiple linear hyperechoic artifacts extending from the pleural-pulmonary interface to the far edge of the screen. Illustrations by Alice MacGregor Harvey; permission to print courtesy of North Carolina State University.
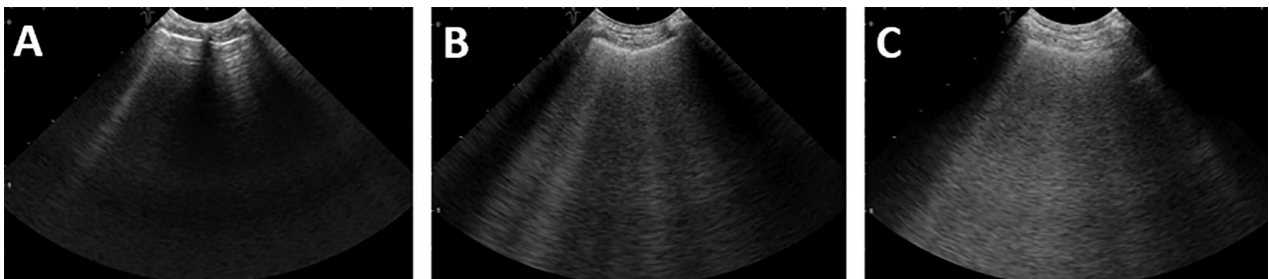

Figure 2—Representative still B-mode LUS images of dogs with respiratory distress showing a single B line (A), > 3 B lines that can still be recognized individually (B), and so-called infinity B lines, where the artifacts coalesce and individual B lines can no longer be discerned (C).

defined as being consistent with CPE. Lung ultraso-nographic examinations yielding < 2 positive sites on each hemithorax were defined as being consistent with a noncardiac cause of dyspnea.

Additional methods of defining LUS findings as indicating CPE versus noncardiac were also investi-gated to determine whether a protocol other than the Volpicelli method might result in higher diagnostic

accuracy for the evaluated dogs and cats. Specifically, the following additional definitions of CPE were considered: LUS findings that revealed at least 2, 3, or 4 total positive sites, regardless of distribution; and LUS findings that revealed at least 2, 3, or 4 total positive sites, requiring that at least 2 positive sites be perihilar or caudodorsal.

Determination of diagnosis

Medical records of each dog and cat were analyzed by a single investigator (TCD), who was blinded to the LUS findings. The radiographic diagnosis (CPE, noncardiac, or undetermined) was recorded as that documented by the board-certified radiologist in the finalized radiology report, which was generated typically within 12 to 14 hours after the images had been received, without the knowledge of the LUS findings or final diagnosis. The final clinical diagnosis (CPE or noncardiac) was determined by the same investigator (TCD), who used the entire medical record and any imaging studies (echocardiography, thoracic radiography, fluoroscopy, or bronchoscopy) for analysis. The final diagnosis was based on review of historical, physical examination, and laboratory test findings; response to treatment; echocardiographic and postmortem findings; and the investigator's personal interpretation of the radiographic findings.

Specifically, to receive a diagnosis of CPE (which was considered the reference [gold] standard for comparisons with results of LUS and thoracic radiography), patients were required to have radiographic findings of cardiomegaly and interstitial to alveolar pulmonary opacities with a perihilar to caudodorsal distribution in dogs or with a localized or diffuse distribution in cats. When the radiographic diagnosis was uncertain, patients with echocardiographic findings compatible with acutely decompensated heart failure (acute chordal rupture or infectious endocarditis vegetative lesions associated with severe valvular regurgitation), a positive clinical response to heart failure treatment, a markedly high blood NT-proBNP concentration (> 1,500 pg/mL for cats), or postmortem findings of CPE would also meet the criteria for a final diagnosis of CPE. Patients that did not meet the criteria for a CPE diagnosis were determined to have a noncardiac cause of dyspnea.

Statistical analysis

Statistical analyses were performed by use of statistical software.[c] An a priori sample size calculation revealed that 98 total patients would be required to estimate accuracy of LUS for the diagnosis of CPE within 10% with 95% confidence. Categorical data were summarized as frequencies and proportions; quantitative data were summarized as mean ± SD. Sensitivity, specificity, and positive and negative likelihood ratios were calculated for the association of LUS findings with a final diagnosis of CPE. Separate subanalyses were performed for dogs and cats. The nonparametric Wilcoxon 2-sample test was used to compare the number and distribution of positive LUS sites between the 2 possible final diagnoses (CPE vs noncardiac).

Logistical regression models and receiver operating characteristic curves were used to assess the impact of additional variables (ie, heart rate, rectal temperature, and heart murmur intensity) on the sensitivity and specificity of LUS for the diagnosis of CPE. Interobserver agreement was determined by calculation of a weighted κ statistic, both for scoring of individual sites as well as for scoring overall LUS findings as CPE versus noncardiac.

Results

Animals

One hundred patients (76 dogs and 24 cats) were enrolled in the study. Mean ± SD age was 9.7 ± 3.6 years. Thirty-one dogs were spayed females, 4 were sexually intact females, 35 were castrated males, and 6 were sexually intact males; 18 cats were castrated males, and 6 were spayed females. Mean body weight for cats was 5.7 ± 1.5 kg (12.5 ± 3.3 lb) and for dogs was 14.8 ± 14.7 kg (32.6 ± 32.3 lb). The most commonly represented cat breeds were domestic shorthair (n = 15) and domestic longhair (4). Many dog breeds were represented, the most common of which were Dachshund (n = 7), Cavalier King Charles Spaniel (7), and Chihuahua (6). Twenty-eight additional dog breeds were represented by ≤ 4 dogs each.

LUS examination

Performance of LUS was technically feasible (all images obtained at all 4 anatomic sites in each hemithorax) for all patients. The mean ± SD interval between performance of LUS and thoracic radiography was 1.63 ± 2.3 hours. Most patients (82%) were received at the hospital through the Emergency and Critical Care Service, whereas the minority (18%) were received through the Cardiology Service. Most LUS examinations (68%) were performed by a single examiner (JLW), with 7 cardiology and emergency clinicians completing the remaining examinations.

Overall, 61 (61%) patients had a final diagnosis of CPE, whereas 39 (39%) had noncardiac disease. The proportion of patients with CPE did not differ between cats (15/24 [62%]) and dogs (46/76 [61%]). Causes of CPE in dogs were degenerative mitral valve disease (n = 35), dilated cardiomyopathy (8), and aortic valve insufficiency secondary to endocarditis (3). Causes of CPE in cats were hypertrophic (with or without obstructive) cardiomyopathy (n = 13) and unclassified cardiomyopathy (2). Causes of noncardiac respiratory distress in dogs included pulmonary hypertension or thromboembolism (n = 10), airway disease (5), pneumonia (4), ARDS (3), pulmonary neoplasia (2), heartworm pneumonitis (2), neurologic disease (2), and right-to-left cardiac shunt (1); in 1 dog, the cause was unknown. Causes of noncardiac respiratory distress in cats included asthma (n = 2), diffuse pulmonary disease of unknown etiology (2), upper airway obstruc-

tion (1), heartworm pneumonitis (1), aspiration pneumonia (1), and pain caused by aortic thromboembolism (1); in 1 cat, the cause was unknown.

Lung ultrasonography resulted in identification of at least 1 positive site (> 3 B lines/site) in 55 of the 61 (90%) patients with a CPE diagnosis, with a mean of 5.3 ± 2.5 positive sites/patient. In contrast, LUS resulted in identification of positive sites in only 26 of the 39 (67%) patients with noncardiac disease, with a mean of 2.7 ± 2.8 positive sites/patient. Patients with CPE had a significantly ($P < 0.001$) higher number of positive LUS sites than did patients with noncardiac disease.

Overall, positive LUS scores were more common at all sites in patients (dogs and cats combined) with CPE than in those with noncardiac disease, and the overall distribution of positive sites differed significantly ($P < 0.001$) between these 2 groups **(Figure 3)**. For patients with CPE, the most common positive sites were the right and left middle sites, whereas for patients with noncardiac disease, the right middle site alone was most likely to be scored as positive. For both groups, the right and left caudal sites were least likely to be scored as positive.

Accuracy of LUS for the diagnosis of CPE

Overall sensitivity and specificity of LUS with the cutoff used (at least 2/4 anatomic sites deemed positive for each hemithorax) for the diagnosis of CPE in dogs and cats with acute dyspnea were 84% and 74%, respectively. The LUS result was a highly significant ($P < 0.001$) predictor of final diagnosis. For cats specifically, sensitivity and specificity of LUS were 87% and 89%, respectively; for dogs specifically, these numbers were 83% and 70%, respectively. In comparison, overall sensitivity and specificity of thoracic radiography for the diagnosis of CPE were 85% and 87%, respectively. Diagnostic accuracy of LUS versus thoracic radiography was summarized **(Table 1)**.

Use of LUS led to the incorrect classification of 10 cases of noncardiac disease as CPE (ie, false-positive results). False-positive results were obtained for all 3 dogs with ARDS, 3 of the 10 dogs with pulmonary hypertension or thromboembolism, 1 of the 2 dogs with pulmonary embolism, 1 of the 2 dogs with heartworm pneumonitis, 1 of the 4 dogs with pneumonia, and 1 of the 2 cats with diffuse pulmonary disease of unknown etiology. No false-positive results were obtained for patients with other types of noncardiac disease.

Additional patient characteristics at the initial evaluation (heart rate, respiratory rate, rectal temperature, and presence and severity of heart murmur) were investigated for the potential to augment the diagnostic accuracy of LUS. Specificity of LUS for dogs (but not cats) improved when heart rate at initial evaluation was considered. When all patients with an initial heart rate < 150 beats/min were reclassified as having noncardiac disease, specificity of LUS for dogs (but not cats) improved to 87%, although sensitivity decreased to 52%. However, addition of heart rate to the logistical regression model failed to significantly ($P = 0.08$) improve the accuracy of LUS for the diagnosis of CPE. Respiratory rate, rectal temperature, and murmur characteristics had no significant effect on diagnostic accuracy of LUS.

Interobserver agreement on LUS results

Interobserver agreement between the experienced and inexperienced examiner on results of LUS was excellent. With respect to scoring of the presence and number of B lines within the 4 individual LUS sites on each hemithorax, the κ statistic was > 0.85 for each site, indicating high agreement. Interobserver agreement for scoring individual LUS sites as positive versus negative was also excellent, with κ values ranging from 0.84 to 1.00 for individual sites. For 6 of 8 sites, the κ value was > 0.90, indicating almost perfect agreement. Final LUS diagnosis (CPE vs noncardiac) differed between observers for only 6 of the 100 patients (κ = 0.86).
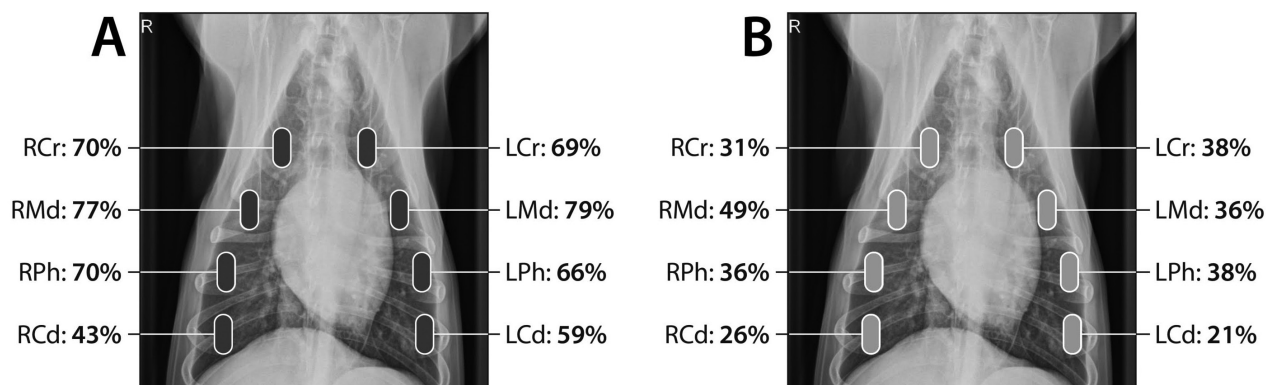

Figure 3—Frequency (%) of positive results (> 3 B lines/site) at each of 8 anatomic sites evaluated via LUS in dogs (n = 76) and cats (24) that received a diagnosis of CPE (A) or a noncardiac cause of dyspnea (B). LCd = Left caudal. LCr = Left cranial. LMd = Left middle. LPh = Left perihilar. RCd = Right caudal. RCr = Right cranial. RMd = Right middle. RPh = Right perihilar. Positive sites were significantly ($P < 0.001$) more numerous in dogs and cats with CPE than in dogs with noncardiac disease.

Table 1—Diagnostic accuracy of LUS* and thoracic radiography for the diagnosis of CPE in 76 dogs and 24 cats with acute dyspnea.

Diagnostic test	Species	Sensitivity (%)	Specificity (%)	Positive likelihood ratio†	Negative likelihood ratio†
LUS	Both	84	74	3.23	0.22
	Dogs	83	70	2.77	0.24
	Cats	87	89	7.91	0.15
Thoracic radiography	Both	85	87	6.54	0.17
	Dogs	85	87	6.54	0.17
	Cats	87	89	7.91	0.15

*A positive result of LUS was defined as at least 2 of the 4 anatomic sites deemed positive (> 3 B lines/site) for each hemithorax. †A ratio > 1 indicates an increased probability that CPE truly exists, and a ratio < 1 indicates a decreased probability that CPE truly exists.

The diagnosis of CPE (considered the reference standard for these calculations) was made through a review for each patient of historical, physical examination, and laboratory test findings; response to treatment; echocardiographic and postmortem findings; and the investigator's personal interpretation of the radiographic findings. To receive a diagnosis of CPE, patients were required to have radiographic findings of cardiomegaly and interstitial to alveolar pulmonary opacities with a perihilar to caudodorsal distribution in dogs or a localized or diffuse distribution in cats.

Discussion

In the present study, the overall sensitivity of LUS for the diagnosis of CPE in the dogs and cats with acute dyspnea was good (84%) and similar to that of thoracic radiography (85%). For cats in particular, the sensitivity of LUS was even higher (87%). Previous studies[23,24] of LUS in dogs have identified high numbers of B lines and positive LUS sites in every dog with CPE in which LUS was performed, which would suggest 100% sensitivity. However, in those studies, LUS was performed on a select small group of dogs in which a diagnosis of CPE had already been made via thoracic radiography; therefore, the studies were not designed to prospectively evaluate diagnostic accuracy.

Sensitivity of LUS for the diagnosis of CPE in the present study was slightly lower than in human studies of the diagnostic accuracy of LUS for the same purpose, in which sensitivity ranged from 81.3% to 98.3% (mean sensitivity, 94.1%)[10] and absence of B lines in all quadrants effectively ruled out CPE.[25] In the present study, 6 patients (5 dogs and 1 cat) with a final diagnosis of CPE had no positive sites identified via LUS (ie, had false-negative results). The CPE diagnosis in these patients had been made on the basis of thoracic radiographic evidence of a very mild or focal interstitial pattern or echocardiographic evidence of severe heart disease and a positive response to diuretic treatment. This lower sensitivity in veterinary patients versus humans could have reflected differences in pathophysiologic distribution of pulmonary edema or differences in technical performance of LUS attributable to chest wall conformation or other physical factors. For example, LUS may be more likely to fail to detect pulmonary lesions in an obese or barrel-chested dog than in a thin or narrow-chested dog, simply because of attenuation of the ultrasound beam.

The overall specificity of LUS for ruling out CPE in patients with noncardiac disease was also good (74%). For cats in particular, specificity of LUS was excellent (89%). Previous studies[23,24] of LUS in dogs have identified very low numbers of B lines or positive LUS sites in clinically normal dogs, which would suggest 100% specificity in differentiating clinically normal dogs from dogs with CPE. Again, however, because these studies only involved comparison of clinically normal dogs with dogs that already had a definitive diagnosis of CPE, they were not designed to prospectively evaluate the diagnostic accuracy of LUS. All patients in the present study were dyspneic and therefore had a high likelihood of having pulmonary disease that could potentially cause artifacts (such as B lines) on LUS images. Indeed, the mean number of positive sites (> 3 B lines/site) for dogs with noncardiac disease (2.7) was higher than the mean total number of B lines (sum of all sites) reported for clinically normal dogs (0.9).[23]

Certain types of noncardiac disease were more likely to result in false-positive LUS results in the present study, whereas other types were consistently categorized correctly. For both dogs and cats, LUS resulted in correct categorization of all patients with upper or lower airway disease, neurologic disease, and unknown causes of dyspnea as having noncardiac disease. False-positive LUS results were most likely to occur for patients with diffuse interstitial or alveolar disease, including ARDS, pulmonary neoplasia, pneumonitis, pulmonary hypertension (suspected pulmonary fibrosis), and pulmonary thromboembolism. Because patients with known history of trauma were excluded from the study (our goal being to enroll patients in which the cause of dyspnea was unknown and in which CPE was a plausible differential diagnosis), none of the cats and dogs had a diagnosis of pulmonary contusions or hemorrhage or noncardiogenic pulmonary edema secondary to drowning or electrocution. However, given the pathophysiologic nature of these conditions and the resulting diffuse alveolar disease, we would also have expected LUS to result in the misclassification of pulmonary hem-

orrhage or noncardiogenic pulmonary edema as CPE (ie, a false-positive result).

By including most patients with respiratory distress (excluding only pleural effusion and trauma), we attempted to include a group of patients that would accurately reflect the true prevalence of CPE and other respiratory diseases in our referral hospital. In general, we observed that use of LUS led to the correct identification of B lines and positive sites in locations in which interstitial or alveolar disease was confirmed radiographically, similar to findings in a previous study.[23] However, LUS could not be used to differentiate among the types of interstitial or alveolar infiltrate (ie, cardiogenic edema vs inflammation, neoplasia, noncardiogenic edema, or hemorrhage).

The specificity of LUS was lower in dogs (70%) in the present study than in cats (89%) and was also lower in dogs than in humans (84.2% to 96.4%; mean, 92.4%).[10] We suspect that this disparity reflected species differences in common noncardiac causes of dyspnea. In humans, the most common differential diagnoses for acute dyspnea include CPE and chronic obstructive pulmonary disease.[4,6-8,26] People with chronic obstructive pulmonary disease have restrictive airway disease and lack interstitial or alveolar infiltrates, so B lines are absent. Similarly, a common noncardiac cause of dyspnea in cats is inflammatory airway disease (also known as feline asthma), another disease in which B lines are absent. Therefore, the most common noncardiac causes of dyspnea in humans and cats do not result in diffuse interstitial or alveolar disease, and so are more likely to be correctly categorized as noncardiac by use of LUS.

In contrast, noncardiac causes of dyspnea in dogs often result in diffuse interstitial or alveolar disease (eg, ARDS, pulmonary fibrosis, heartworm disease, fungal disease, pulmonary thromboemboli, pulmonary neoplasia, and pulmonary hemorrhage). The diagnostic usefulness (particularly specificity) of LUS therefore depends on the most likely differential diagnoses for dyspnea in a given patient. The B lines can be used to accurately differentiate CPE from airway disease or nonrespiratory disease, but they cannot be used to distinguish CPE from noncardiogenic edema, ARDS, or diffuse pulmonary hemorrhage. Additional veterinary studies are needed to determine whether additional LUS artifacts or patterns of LUS findings exist that can help in the distinction of diffuse interstitial or alveolar disease from CPE or differentiate among certain noncardiac causes of dyspnea.

In the dogs of the present study, the specificity of LUS (70%) was lower than that of thoracic radiography (87%), although these values were equivalent in cats (89%). One reason for higher specificity of thoracic radiography was that a radiographic diagnosis of undetermined was allowed, whereas for LUS, an absolute diagnosis of CPE versus noncardiac was required (with no category to represent undetermined). The undetermined thoracic radiographic diagnoses did not factor into the specificity results,

and therefore decreased the number of false-positive results for that modality.

We also investigated whether consideration of initial physical examination findings could improve the diagnostic accuracy of LUS. Because of the pathophysiologic nature of the disease, congestive heart failure might be expected to cause dogs and cats to have higher heart rates, lower rectal temperatures, and louder heart murmurs than those with noncardiac disease. Adding heart rate to the analysis slightly improved the specificity of LUS for dogs only, but the difference in diagnostic accuracy was not significant. Rectal temperature and presence or severity of heart murmur had no effect on the diagnostic performance of LUS. These findings may have been attributable to the spectrum of CPE severity in the included patients (with only a subset of having overt evidence of low cardiac output), the high prevalence of heart murmurs in older dogs, or the occurrence of shock and vasoconstriction in some critically ill dogs with noncardiac disease. Other point-of-care diagnostic tests that may be used in series with LUS in the diagnosis of CPE include measurement of circulating amounts of cardiac biomarkers (eg, NT-proBNP)[8] and the ratio of left atrial dimension to aortic diameter on focused echocardiographic examination. Additional studies are warranted to maximize the diagnostic accuracy of LUS when combined with other modalities for use in dogs and cats.

The Volpicelli criterion used to define a positive LUS result in the present study requires a bilateral distribution of CPE (ie, at least 2 positive sites on each hemithorax). Previous veterinary studies have shown that the anatomic distribution of CPE differs by species and underlying structural heart disease. Cats are more likely to have a diffuse or multifocal distribution of CPE.[27] Dogs with mitral valve disease and an eccentric jet of mitral regurgitation are more likely to have focal CPE affecting the right or left caudal lung lobes or both, and dogs with dilated cardiomyopathy and a central jet of mitral regurgitation are more likely to have a symmetric perihilar or caudal distribution of CPE.[28] Given this differential distribution, it is possible that use of the Volpicelli criterion could result in false-negative LUS results being more common in dogs than in cats, and specifically in the subset of dogs with mitral valve disease. However, we investigated alternative definitions of a positive LUS result that would more closely reflect the expected distribution of CPE in dogs (for example, requiring only 2 total positive sites and allowing them to be ipsilateral, as might be expected with mitral valve disease, or requiring that at least 2 of the positive sites be perihilar or caudal, as would be expected in dilated cardiomyopathy). None of these alternative definitions resulted in better accuracy of LUS for the diagnosis of CPE, even when considering patient subgroups by species or type of structural heart disease. Therefore, despite the different distribution of CPE expected with the various disease types represented

by the included patients, diagnosis of CPE was best predicted by the Volpicelli criterion requiring bilateral distribution and ≥ 50% of total lung sites affected.

The distributions of positive LUS sites in the present study suggested that the middle lung quadrants were most commonly affected, regardless of whether patients had CPE or noncardiac disease. This differs from findings of a previous study[24] of LUS in dogs that showed the perihilar and caudodorsal quadrants were more commonly positive in a small number of dogs with CPE, and also differs from findings of the aforementioned study[28] of radiographic distribution of CPE in dogs. A possible explanation for these differences is that the cranial and caudodorsal sites might be more technically challenging sites to image, and image quality might be lower at those sites. Particularly in a dyspneic patient with poor aeration, it is possible to inadvertently acquire images cranial to the thoracic inlet or caudal to the diaphragm. In contrast, the middle sites are often the easiest to image given the landmark of the beating heart. Another possible cause may be that LUS only allows detection of lesions that extend to the periphery of the lung. Potentially, B lines were not visible in the perihilar or caudodorsal sites in a study dog with mild cardiogenic edema because the edema did not extend to the periphery in these lung lobes. A final possibility is that the study sample consisted of both dogs and cats with multiple types of underlying structural heart disease, which may have led to different patterns of CPE distribution. All image sites used when following the Vet BLUE protocol are approximate, and variability exists in probe positioning even among human LUS protocols.[7,20] Additional studies are required to more specifically correlate site-by-site LUS findings with location of pulmonary lesions on thoracic radiographs.

Lung ultrasonography was feasible in all cats and dogs in the present study, and we observed minimal signs of additional stress to these dyspneic patients. In many situations, patients were imaged through a small portal in an oxygen cage to minimize handling. Adequate images were obtained with only the use of alcohol to facilitate probe contact, without shaving of hair or use of coupling gel. Before patients were enrolled, examiners underwent a short instructional session on LUS technique, similar to instructional protocols described for LUS in humans.[8,17] Interobserver agreement between the 2 examiners (1 experienced with LUS and 1 inexperienced with LUS) was excellent and similar to that reported for humans,[8,14,16] suggesting that this technique is reliable and repeatable.

The present study had several limitations. First, the number of patients was limited (n = 100), although similar to numbers used in studies of LUS in humans.[8,13,14,16] In particular, the number of cats used was relatively low (n = 24), and therefore conclusions regarding this particular species are limited. Second, because some patients were received through the Cardiology Service rather than through the Emergency Service, and because North Carolina State University has a large cardiology referral center, our patient population may have been biased to include more patients with CPE (61%) versus noncardiac disease. Third, in determining the diagnostic accuracy of LUS, we used as our reference standard the final clinical diagnosis made by a board-certified cardiologist, who examined all available clinical data. The optimal reference standard for differentiation of CPE from noncardiogenic pulmonary edema would have been assessment of pulmonary capillary wedge pressure.[21,29,30] However, invasive hemodynamic monitoring is not routine practice in veterinary cardiology, particularly for unstable patients with respiratory compromise; therefore, we chose medical record review as a surrogate reference standard, similar to the situation in many human studies[8,13] of LUS. It is possible that the diagnostic accuracy of LUS obtained in the present study would have been different if pulmonary capillary wedge pressure were used instead.

Additional limitations of the present study were the 6-hour maximum interval allowed between LUS and thoracic radiography and the possibility that the nature of the pulmonary lesions could have changed during that period (particularly if diuretics were administered). For 17 patients, results were discordant between LUS and thoracic radiography. In 7 of these patients, results of LUS suggested CPE and those of thoracic radiography suggested noncardiac disease, and in the other 10, results of thoracic radiography suggested CPE whereas those of LUS suggested noncardiac disease. If these discordant results were attributable to a prolonged interval between the 2 examinations or to diuretic administration, one would expect LUS-positive, radiography-negative results to occur before thoracic radiography (with diuretics administered in between), and LUS-negative, radiography-positive results to occur after thoracic radiography (with diuretics administered in between). However, no such pattern was identified for patients with discordant results; mean interval between LUS and thoracic radiography was not longer for these patients, the order of examinations did not fit the aforementioned pattern, and none of the patients received diuretics between imaging modalities. Therefore, although of theoretical concern, the delay between examinations and diuretic administration did not appear to influence our results. A possible explanation for the LUS-negative, radiography-positive results may have been that several of the associated dogs had slight interstitial pulmonary edema, suggesting that LUS may not have been sensitive enough to identify very early and mild congestive heart failure. The radiographic diagnosis of left-sided heart failure in these dogs was further supported by the presence of pulmonary venous distention and left atrial enlargement.

A general limitation to the LUS technique reported here is the requirement for a point-of-care ultrasonography machine, which may not be widely available in clinical practice. Findings in human medicine

suggest that performance of LUS may be dependent on several equipment-related factors, including ultrasound model, probe, software, and quality of LUS training.[25] The ultrasonographic machine used in the present study was a moderately priced, small, portable laptop model. Given that LUS examination relies on identifying artifacts rather than specific structures with high resolution, this technique was useful even with less expensive equipment.

In the study reported here, point-of-care LUS was a feasible diagnostic test for dyspneic cats and dogs, causing minimal additional distress to the patients. High interobserver agreement was obtained for LUS results, and accuracy of the technique for the diagnosis of CPE as the cause of dyspnea was fairly high, particularly in cats, with sensitivity similar to that of thoracic radiography. Specificity was higher in cats than in dogs, likely because of species variation in types of noncardiac diseases causing dyspnea.

Acknowledgments

Footnotes

a.   Model UF-760AG, version 02, Fukuda Denshi, Tokyo, Japan.
b.   Model FUT-CA144-9P, Fukuda Denshi, Tokyo, Japan.
c.   SAS, version 9.4, SAS Institute Inc, Cary, NC.

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From this month's *AJVR*

Pharmacokinetics of meloxicam after intramuscular and oral administration of a single dose to American flamingos (*Phoenicopertus ruber*)

Jennifer L. Boonstra et al

March 2017

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OBJECTIVE
To determine pharmacokinetics after IM and oral administration of a single dose of meloxicam to American flamingos (*Phoenicopertus ruber*).
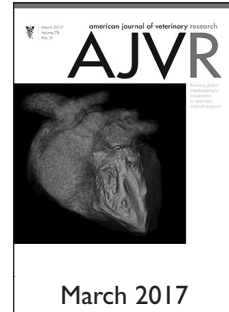
ANIMALS
14 adult flamingos.

PROCEDURES
Flamingos were allocated to 2 groups. Each group received a dose of meloxicam (1 mg/kg) by the IM or oral route. After a 4-week washout period, groups received meloxicam via the other route of administration. Plasma meloxicam concentrations were measured with high-performance liquid chromatography. Data for each bird were analyzed. Estimated values of selected pharmacokinetic parameters were compared by use of a linear mixed-effects ANOVA. Pooled concentration-time profiles for each route of administration were analyzed to examine the influence of body weight on pharmacokinetics.

RESULTS
Mean ± SD maximum plasma concentration was 1.00 ± 0.88 µg/mL after oral administration. This was approximately 15% of the mean maximum plasma concentration of 5.50 ± 2.86 µg/mL after IM administration. Mean time to maximum plasma concentration was 1.33 ± 1.32 hours after oral administration and 0.28 ± 0.17 hours after IM administration. Mean half-life of the terminal phase after oral administration (3.83 ± 2.64 hours) was approximately twice that after IM administration (1.83 ± 1.22 hours).

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that the extent and rate of meloxicam absorption were less after oral administration than after IM administration. Intramuscular administration resulted in a short period during which mean plasma concentrations met or exceeded reported efficacious analgesic concentrations in other species, whereas oral administration did not. These results suggested that higher doses may be required for oral administration. (*Am J Vet Res* 2017;78:267–273)