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Abstract

Objective –To assess the accuracy of focused cardiac ultrasound (FOCUS) and point-of-care NT-proBNP assay (POC-BNP) in the emergency setting for differentiation of cardiac from non-cardiac causes of respiratory distress in cats.

Design –Prospective diagnostic accuracy study between 2014-2016

Setting –Emergency room at urban university teaching hospital

Animals –Prospective cohort study of 41 cats presenting for evaluation to the Matthew J. Ryan veterinary hospital for respiratory distress

Interventions –Emergency clinicians made an initial diagnosis of non-cardiac or cardiac cause of respiratory distress based on PE findings and history. The diagnoses were updated after performing FOCUS and POC-BNP. Reference standard diagnosis was determined by agreement of a board-certified cardiologist and criticalist with access to subsequent radiographs and echocardiograms.

Measurements and Main Results –Forty-one cats were enrolled. Three cats with incomplete data and 1 cat with an uncertain reference standard diagnosis were excluded. The remaining 37 cats were used for analysis: 21 cardiac and 16 non-cardiac cases. The ratio of left atrial to aortic root diameter (LA:Ao) measured by FOCUS was significantly correlated with LA:Ao measured by echocardiography ($R=0.646$, $P<0.0001$). Emergency clinicians correctly diagnosed 27/37 (73.0%) yielding a physical examination positive percent agreement =76.2% (95% CI, 52.8, 91.8), and negative percent agreement=68.8% (41.3, 89.0). Five non-cardiac and 5 cardiac cats were misdiagnosed. Post FOCUS, overall percent agreement improved to 34/37 (91.9%) with positive percent agreement =95.2% (76.2, 99.9), and negative percent agreement=87.5% (61.7, 98.5). The POC-BNP yielded an overall percent agreement =32/34 (94.1%), positive percent

agreement =100% (82.4, 100.0), and negative percent agreement=86.7% (59.5, 98.3) in differentiating cardiac versus non-cardiac cases.

Conclusions –FOCUS evaluation of basic cardiac structure and LA:Ao by trained emergency clinicians improved accuracy of diagnosis compared to physical examination in cats with respiratory distress. FOCUS and POC-BNP are useful diagnostics in the emergent setting.

Abbreviations

C	Cardiac
CI	Confidence Interval
ECC	Emergency and critical care
FOCUS	Focused cardiac ultrasound
LA:Ao	Ratio of left atrial to aortic root diameter
NC	Non-cardiac
PE	Physical examination
POC-BNP	Point-of-care N-terminal B-type natriuretic peptide
SBP	Systolic blood pressure
TFAST	Thoracic focused assessment with sonography for trauma
VHS	Vertebral heart size

Introduction

Respiratory distress is a common complaint in cats that present for emergency room visits and may be due to either primary cardiac or respiratory diseases.[1,2] Thoracic radiography is the initial standard diagnostic test for determining the underlying etiology of the respiratory signs; whereas echocardiography is the standard diagnostic test to identify and diagnose primary cardiac disease in cases of congestive heart failure. However, severe respiratory distress may preclude safely performing these diagnostic tests. Additionally, availability and time of day may limit access to a cardiologist. Therefore, minimally invasive, readily available, and rapid diagnostics, such as focused cardiac ultrasound examination (FOCUS) and the feline point-of-care N-terminal B-type natriuretic peptide (POC-BNP)[a] assay are of great interest. FOCUS is defined by the American Society of Echocardiography as a "focused examination of the cardiovascular system performed by a physician by using ultrasound as an adjunct to the physical examination (PE) to recognize specific ultrasonic signs that represent a narrow list of potential diagnosis in specific clinical settings."[3] In human patients with respiratory distress, FOCUS performed by emergency personnel has become the standard of care in the identification of heart disease in the emergency room. [4, 5, 6] Cardiac abnormalities that have been accurately detected in human patients include: presence of pericardial effusion, reduced systolic function, left atrial and ventricular enlargement, left ventricular hypertrophy and right ventricular enlargement, as well as to guide pericardiocentesis and identify pulseless electrical activity.[3,6] In two previous veterinary studies, emergency clinicians at academic teaching hospitals that completed a prescribed training course in FOCUS were comfortable and competent using FOCUS to evaluate for presence of pericardial effusion and increased ratio of left atrial to aortic diameter (LA:Ao) and to assess left ventricular systolic function in dogs and cats.[7, b] Thus, FOCUS may help distinguish cardiac (C) vs. non-cardiac (NC) cause of respiratory distress and help guide initial

stabilization measures. However, the accuracy of FOCUS in cats with respiratory distress has not been evaluated.

B-type natriuretic peptide (BNP) and its inactive by-product, N-terminal fragment of proBNP (NT-proBNP), are markers of cardiac volume loading.[8] Quantitative measurement of circulating NT-proBNP concentrations performed by a reference laboratory helped distinguish cardiac from respiratory causes of severe respiratory distress cats with a sensitivity of 90-95% and specificity of 84.6-87.9%. [9,10,c] NT-proBNP can also be semi-quantitatively measured by a lateral flow POC-BNP colormetric assay[a] specifically developed to detect cats with moderate or severe occult (i.e., preclinical) heart disease.[11,12] The ability of the POC-BNP assay to generate "cage-side" result makes its potential use in cats with respiratory symptoms attractive and this test has been previously investigated in cats with pleural effusion.[13] In this study, the POC-BNP was able to accurate distinguish between cats with cardiac causes versus non-cardiac causes when it was run on blood but not on pleural fluid. To our knowledge, the use of the POC-BNP test on plasma in a population of cats with and without pleural effusion has not been previously investigated.[13]

The purpose of this study was to investigate whether FOCUS by trained emergency and critical care (ECC) clinicians or POC-BNP improved the accuracy in distinguishing cardiac versus non-cardiac causes of respiratory signs in cats presenting to the emergency room. It was hypothesized that both FOCUS and POC-BNP would improve the accuracy of the diagnosis of cardiac versus non-cardiac disease as compared to the medical history and PE alone.

Methods

The study protocol was approved by the University of Pennsylvania animal care and use committee. ECC faculty, residents, and specialty intern, participated in a previously described

FOCUS training program[7/b] that concentrated on assessment of left atrial and aortic root size, left ventricular systolic function and thickness, right heart size, and detection of pericardial and pleural effusion.

Cats that were presented to the University of Pennsylvania emergency service with a primary complaint of respiratory signs that were deemed in need of supplemental oxygen therapy by the ECC clinician were prospectively enrolled between June 2014 and February 2016. Client consent for study inclusion was obtained. Cats were excluded from the study if they had received intravenous fluids during the previous 72 hours, had a history of acute trauma, had thoracic imaging results from a referring veterinarian that was seen by the ECC clinician prior to completion of the study procedures, or were presented when a FOCUS trained clinician was not available.

On presentation, the ECC clinician recorded a brief history and triage PE on a standardized form. The information recorded included heart rate, pulse quality, lung auscultation abnormalities, respiratory rate and effort, presence and intensity of any heart murmur, presence or absence of a gallop, or muffled heart and lung sounds. Based on the initial triage examination and history, the ECC clinician made a preliminary (Pre-FOCUS) diagnosis as to whether the respiratory signs were primarily due to either cardiac or non-cardiac disease.

After making the Pre-FOCUS diagnosis and within 1 hour of hospital presentation, FOCUS examination was performed by the ECC clinician using a general-purpose ultrasound unit[d] housed in the emergency room. ECC clinicians measured left atrial to aortic root diameter ratio (LA:Ao-FOCUS) from the right parasternal short axis 2D view and indicated the qualitative presence or absence of right and left ventricular enlargement and pericardial and pleural effusion. If the clinician was unable to measure the LA:Ao, they recorded a subjective impression of the

ratio (e.g., increased, normal, or decreased). After completing the FOCUS, the ECC clinician made a second (Post-FOCUS) diagnosis as to whether the respiratory distress was primarily due to C or NC disease and whether or not FOCUS changed their initial therapeutic plan.

Venipuncture was performed for POC-BNP assay[a] after FOCUS examination. The POC-BNP was performed according to manufacturer instructions. Results were read out by both the veterinary technician and enrolling clinician as either normal or abnormal. A diagnosis of NC versus C was recorded by the enrolling clinician. The investigator performing the FOCUS examination was not blinded to the results of the POC-BNP.

In addition to FOCUS, all cats enrolled in the study received thoracic radiography and echocardiographic evaluation by a cardiologist or cardiology resident within 3 and 24 hours of presentation, respectively. Recorded echocardiographic parameters included 2-dimensional LA:Ao (Echo-LA:Ao) and 2D or M-mode LV wall and chamber measurements performed from the right parasternal short axis views.[14,15] All thoracic radiographs were evaluated for vertebral heart size (VHS) when cardiac margins were clearly visible as previously described.[16] All VHS measurements were performed by a single investigator (MJH).

The accuracy of the ECC clinician diagnoses was calculated against a "reference standard" diagnosis as determined by mutual agreement of a board-certified cardiologist (MAO) and criticalist (ELR) who had access to all case history and diagnostic findings, including thoracic radiography, echocardiography and POC-BNP assay.[17]

Statistics

Descriptive statistics of the patient population are presented as mean (SD) for normally distributed data, as median (interquartile range, IQR) for non-normally distributed data, and as proportion (percentage) for data involving counts. Comparisons between patient groups were

performed using unpaired t-tests, Mann-Whitney tests, Fisher's exact tests, or chi-square tests as appropriate. Agreement between the FOCUS and reference-based diagnosis was determined by construction of 2x2 tables and calculating the positive, and negative, and overall percent agreement.[18] Specifically, positive percent agreement was the proportion of cases categorized as C by both the FOCUS-based and reference-based methods over the number of C cases diagnosed by the reference method. Negative percent agreement was the proportion of cases diagnosed as NC by both the FOCUS-based and reference-based methods over the number of R cases diagnosed by the reference method. Overall percent agreement was the total number of concordant cases over the number of total cases. The proportions of pre- vs. post-FOCUS diagnoses that were agreement with the reference diagnosis were compared using McNemar's test. Receiver operating characteristic (ROC) curves were constructed to describe the positive and negative percent agreement and positive and negative likelihood ratios of cutoff points for the variables of interest. Overall percent agreement was calculated as the percentage of correctly categorized cases compared to the total number of cases. The correlation between LA:Ao-FOCUS and ECHO-LA:Ao was calculated as Pearson correlation coefficient. Analysis was performed by statistical software[e] and a P value of <0.05 was defined as significant.

Results

Forty-one cats with respiratory distress were enrolled into the study. Three cats were excluded from data analysis due to incomplete medical records (lack of complete echocardiogram report (1), missing data collection sheet (1), and failure to fully complete the data collection sheet (1). One cat was excluded due to failure to reach a consensus on the final diagnosis. Therefore, 37 cats were included in statistical analysis. Sixteen cats (16/37; 43.2%) were diagnosed as having a non-cardiac cause (group NC), and 21 cats (21/37; 56.8%) were diagnosed as having a cardiac

cause (group C) as the primary reason for their respiratory distress. Non-cardiac causes included 5 cats (5/16; 31.3%) with suspected metastatic neoplasia, 2 cats (2/16; 12.5%) with feline infectious peritonitis, 2 cats (2/16; 12.5%) with chronic lower airway disease, 2 cats (2/16; 12.5%) with suspected bronchopneumonia, and 1 cat each with non-specific pleural effusion with concurrent non-identified intracranial disease and chronic kidney disease, mediastinal mass, carcinoma, and smoke inhalation. The cat diagnosed with smoke inhalation was included in the study as it was unclear initially whether this cat's respiratory signs were secondary to smoke inhalation or due to congestive heart failure. This cat was in an apartment near to a fire and he had a heart murmur on cardiac auscultation. Cardiac cases included 16 cats with either hypertrophic cardiomyopathy or hypertrophic obstructive cardiomyopathy (16/21; 76%), 3 cats with unclassified cardiomyopathy (3/21; 14%), and 2 cats with restrictive cardiomyopathy (2/21; 10%). There was one protocol deviation in which 1 cat had POC-BNP performed prior to FOCUS exam.

Table 1 is a summary of admission characteristics, POC-BNP, VHS, and FOCUS findings of 2 groups. There were no significant differences in age, sex, weight, initial heart rate, respiratory rate, or systolic blood pressure. Thoracic radiographic findings demonstrated that patients with cardiac disease had a significantly higher VHS (median 9.0; range: 8.5-9.8), as compared to cats with non-cardiac disease (8.2 (7.5-8.6) (P=0.012). Pleural effusion was appreciated on radiographs is 31/37 (83.8%) of cats.

FOCUS examinations were performed by emergency clinicians of 3 different statuses, namely 27 by ECC residents, 1 by an ECC specialty intern, and 9 by ECC faculty. A total of 3 boarded criticalists, 8 ECC residents, and 1 ECC specialty intern participated. The status of the veterinarian performing the FOCUS examination was not recorded in 1 cat. Quantitative

measurement of LA:Ao-FOCUS was successful in 36/37 (97.3%) cats. An LA:Ao measurement was not recorded in one cat due to a failure to save the image for data capture later. A qualitative measurement of left atrial enlargement was recorded for this cat. Qualitative assessment of atrial and ventricular morphology and for the presence or absence of pleural or pericardial effusion was successful in all 37 cats. Pleural effusion was noted in 23/37 (62.2%) of cats on FOCUS. LA:Ao-FOCUS was significantly greater in cats diagnosed as having a cardiac cause of signs as compared to cats with signs due to non-cardiac disease (P=<0.0001)(Table 1).

The Pre-FOCUS diagnosis by the emergency clinician was in agreement with the reference standard diagnosis in 27 of 37 cats yielding an overall percent agreement of 73.0%, a positive percent agreement of 76.2% (95% CI =52.8% to 91.8%) and a negative percent agreement of 68.8% (95% CI =41.3% to 89.0%) (Table 2). Five cats in group C were initially misdiagnosed as having non-cardiac etiologies and 5 cats in Group NC were misdiagnosed as having cardiac etiologies. The proportion of cats in group C with a heart murmur (12/20; 60.0%) was significantly greater than in Group NC (4/16 (25.0%) (P=0.049). A gallop sound was auscultated in 8 cats (8/20; 40.0%) in group C and only 1 cat in group NC (1/16; 6.3%). The presence of either a heart murmur or gallop sound was not recorded in 1 cat with cardiac disease due to the heart sounds being muffled. Table 2 shows a summary of positive, negative and overall percent agreement and positive and negative likelihood ratios of physical exam variables. Physical examination findings varied in their positive and negative percent agreement for the diagnosis of heart disease with a gallop sound having a positive percent agreement of 40% and negative percent agreement of 93.8% and heart murmur having a positive percent agreement of 60% and negative percent agreement of 75% (Table 2).

Post-FOCUS diagnosis by the emergency clinician was in agreement with the reference standard diagnosis in 34 of 37 cats yielding an overall percent agreement of 91.9% a positive percent agreement of 95.2% (95% CI 76.2-99.9%), and a negative percent agreement of 87.5% (95% CI =61.7-98.5%). The proportion of cats with a post-FOCUS diagnosis in agreement with the reference standard was significantly higher as compared with the pre-FOCUS diagnosis (P=0.039). One cat in group C and 2 cats in group NC were misdiagnosed on the basis of post-FOCUS diagnosis. The 1 cat in group C had a correct pre-FOCUS diagnosis but was incorrectly reclassified to group NC and the 2 cats in group NC both had an incorrect pre-FOCUS diagnosis of cardiac etiology that did not change on post-FOCUS evaluation (Figure 1).

LA:Ao-FOCUS had moderate correlation with LA:Ao-ECHO (R=0.646; P<0.0001) (Figure 2). LA:Ao-FOCUS was strongly predictive of a cardiac etiology of the respiratory signs. FOCUS LA:Ao ≥ 1.5 had a positive percent agreement of of 95.0% (95% CI, 75.1-99.9%), negative percent agreement of 87.5% (95% CI, 61.7-98.5%), a positive likelihood ratio of 7.6 (95% CI, 2.1-27.9), and negative likelihood ratio of 0.057 (95% CI, 0.008-0.39) for cardiac etiologies of respiratory signs. The area under the ROC curve was 0.934 (95% CI, 0.842-1.000) (Figure 3). The diagnostic performance of LA:Ao-FOCUS was similar to that of LA:Ao-Echo and POC-BNP (see below), and superior to use of heart or respiratory rate, presence or absence of a heart murmur, gallop, or pulmonary crackles (Table 2).

POC-BNP was successfully performed in 34 cats. Three cats did not tolerate venipuncture for POC-BNP. POC- BNP results were positive in 19/19 (100.0%) cats in group C and in 2/15 (13.3%) cats in group NC with an overall percent agreement of 94.1% (32/34 cats). A positive POC-BNP test had a positive percent agreement of 100% (95% CI = 82.4% to 100.0%) and a negative percent agreement of 86.7% (95% CI = 59.5% to 98.3%) to detect a

cardiac etiology of respiratory signs. The two cats with a positive POC-BNP in the NC group had evidence of heart disease on echocardiography but not congestive heart failure; 1 cat diagnosed with smoke inhalation had hypertrophic cardiomyopathy and the other cat diagnosed with metastatic pulmonary disease had cardiac changes secondary to either hyperthyroidism or hypertrophic obstructive cardiomyopathy.

Discussion

The results of this study demonstrate that the FOCUS examination was a non-invasive diagnostic test that was able to differentiate between cardiac and non-cardiac etiologies at the cage-side in cats with respiratory distress. FOCUS was found to be superior to PE characteristics alone, and when used in conjunction with the PE, can help guide initial patient stabilization and diagnostic testing. A focused cardiac ultrasound in the emergency service may be particularly useful in cats that may require stabilization treatments in order to tolerate the manual restraint required for radiography or echocardiography or when there is a significant delay (i.e a cardiologist is not readily available) in obtaining these diagnostic tests.

The specific PE characteristics of a heart murmur or gallop sound were relatively poor for differentiating between cardiac and non-cardiac etiologies of respiratory distress in this study (Table 2). Studies in normal cats have found that the overall prevalence of heart murmurs is quite high (40-60%) suggesting that a heart murmur as a marker for heart disease or congestive heart failure is poor.[19] Gallop heart sounds are thought to be more indicative of underlying heart disease, but cannot be relied upon alone. In our study, 60% of cats with congestive heart failure had a heart murmur and 40% of cats had a gallop sound. In a previous retrospective study of cats with congestive heart failure, 56% of cats had a heart murmur and a gallop sound was only heard

in 62% of cats.[20]. Another recent study (RAPID CAT study) evaluated the use of physical examination in dyspneic cats to differentiate heart failure from other causes of feline dyspnea.[21] Overall, findings indicated that the presence of a heart murmur was not reliable for the diagnosis of heart disease or failure as half of normal cats and a quarter of cats with respiratory disease were found to have a heart murmur compared to 65% of cats with heart failure. Similar to our study, a gallop sound was only noted in patients with heart disease or failure, with a gallop sound detected in 48% of cats with congestive heart failure. Thus, a gallop sound is specific for heart disease, but the absence of a gallop sound does not rule out heart disease.

A focused cardiac ultrasound was easily and successfully implemented in this patient population and resulted in good correlation between FOCUS LA/Ao and Echo LA/Ao. A previous study[22] in healthy cats using a similar 2D measurement technique showed that the upper 97.5% reference value for LA:Ao was 1.4. Our findings indicated that FOCUS LA:Ao $\geq$ 1.5 had high utility for diagnosing congestive heart failure. These findings are similar to studies in people in which FOCUS examination findings by emergency residents were similar to that of echocardiographic findings by cardiologists.[23] In people, FOCUS along with other point-of care ultrasound techniques have become an integral part of ECC medicine.[3,24] Some studies evaluating the use of FOCUS for differentiating between causes of dyspnea support only an increase in confidence of the diagnosis not accuracy; whereas, other studies show that FOCUS has a similar accuracy compared to the reference standard diagnosis with faster results.[25] Currently, the use of FOCUS in people is recommended in many patient populations including in unstable or triage situations where formal echocardiography is not available, during patient management with serial examinations, and as a supplement to PE in at risk or symptomatic patients.[3,24]

Despite its high overall level of agreement and feasibility of FOCUS, there are limitations. FOCUS is susceptible to individual interpretation and error, which could result in a misdiagnosis. In addition, differences in the patient positioning and patient tolerance for FOCUS examination, as well as the experience of the emergency clinician with FOCUS, could increase the likelihood of a misdiagnosis. In this study, there was only a single instance of a cat that had been correctly diagnosed with congestive heart failure following the triage PE that was then incorrectly re-diagnosed as having primary respiratory disease following FOCUS. Because of the risk of misdiagnosis, FOCUS should not be used as a routine replacement for thoracic radiography or a comprehensive echocardiogram by a cardiologist. This study was also done at a busy academic teaching hospital where FOCUS was being routinely performed prior to the formal FOCUS training and study commencement. Therefore, these study results may not be applicable to all emergency departments.

The median vertebral heart scale was significantly different between cardiac and non-cardiac causes of heart failure in this study. In a previous study, VHS > 9.3 vertebrae was highly specific for the presence of heart disease.[26] However, measurements between 8.0-9.3 vertebrae were found to be equivocal, and echocardiography was recommended for these cats. Interestingly, in the current study, the VHS median and range in cats with cardiac disease all fell within the previously published equivocal range (median 9.0 [8.5-9.0] vertebrae). Cats with non-cardiogenic causes of respiratory distress did have lower VHS (median 8.2, [7.5-8.6]), however there was still overlap into the equivocal range. Thus, VHS can be a useful tool, but may not be definitive for congestive heart failure in cats that fall in the equivocal range. In these cases, FOCUS may help to provide additional information until formal echocardiography is available. More importantly, as was the goal in this study, FOCUS can help guide initial stabilization

therapies, such as initiation of diuretic therapy, in cats with severe respiratory distress in which thoracic radiography may not initially be possible. Additionally, VHS measurement is not possible in all cats as the presence of pleural effusion may obscure the cardiac silhouette preventing accurate measurement as seen with 5 cats in the current study.

In cases where radiographs are not diagnostic or definitive for the underlying disease process, FOCUS may provide supportive information to aid in diagnosis regardless of patient stability. Additionally, the use of FOCUS in conjunction with thoracic focused assessment with sonography for trauma (TFAST) prior to radiography may be most beneficial for those patients with pleural or pericardial effusion. Focused assessment with sonography for trauma (FAST) is an abbreviated thoracic (TFAST) or abdominal (AFAST) ultrasound used to assess for free fluid or pneumothorax in traumatic or critical patients.[27, 28] In these cases, thoracocentesis may be beneficial in providing a more diagnostic radiograph and improving patient stability. In our study, a relatively high proportion of patients had pleural effusion noted on FOCUS examination or echocardiogram. The use of AFAST/TFAST in non-traumatized patients presenting to the emergency room has been supported in previous studies particularly in unstable patients for the detection of free fluid.[27] Thus FOCUS, potentially in conjunction with other point-of-care ultrasound examinations, may be beneficial in all cats presenting with respiratory distress on triage.

The POC-BNP test showed comparable levels of agreement to that of the FOCUS examination. Similar to FOCUS, POC-BNP may be useful in the emergency room setting to aid in differentiation between non-cardiac and cardiac causes of respiratory distress. Previous studies have shown that the serum POC-BNP test was an accurate, sensitive and specific test for differentiating cardiac from respiratory causes of distress in cats with pleural effusion.[13]

However, it is important to note that an abnormal POC-BNP only indicates the presence of possible cardiac disease and this test is not specific for congestive heart failure. It is possible that cats with non-cardiac causes for their respiratory distress, such as asthma or neoplasia, could also have concurrent occult heart disease and an abnormal POC-BNP test result. In this study, there were 2 cats that were initially misdiagnosed as having cardiac disease based on the triage examination and an abnormal POC-BNP. However, both of these cats were correctly diagnosed as having primary non-cardiac disease after FOCUS. Similar to FOCUS, the results of the POC-BNP test should be evaluated in conjunction with the PE, medical history, and results of all diagnostic testing and it should not be used a stand-alone test. In general, in cats with an abnormal POC-BNP, a formal echocardiogram is always recommended to determine the significance of this finding as two cats in our study were found to have heart disease but NC causes of respiratory distress. It is important to note, that NT-proBNP may also be measured in pleural effusion when available using both quantitative and POC-BNP methods.[13] Quantitative ELISA has been shown to have both high sensitivity and specificity for heart disease. In comparison, POC-BNP on pleural effusion was found to be highly sensitive (100%) but had poor specificity (64.7%) which limits its use in the emergency setting. Although not as accurate as blood samples, it may provide an option when there is limited blood available for laboratory testing or if the patient cannot tolerate phlebotomy.

As compared with FOCUS, no training or expensive equipment is needed to run a POC-BNP, making the POC-BNP test attractive in the emergency setting. However, not all cats with respiratory distress will tolerate venipuncture or an adequate blood sample may be unable to be obtained due to cardiovascular collapse as was the case in 3 of the study cats. Although POC-BNP is a rapid diagnostic test, time allotted for patient phlebotomy and test preparation (30

minutes until equilibration of components to room temperature, centrifugation and serum preparation), and 10 minute incubation time is longer than that of the FOCUS examination or even thoracic radiography. Generally, the FOCUS examination should take less than 10 minutes to perform. However, in this study we did not record the time to perform the FOCUS examination because the goal was an accurate FOCUS examination rather than speed. Thus, although POC-BNP is a very useful test, it may not be as well-suited for use during patient triage as compared with the FOCUS examination.

FOCUS is one of several different ultrasound-based studies that could be used in the emergency setting. Future studies incorporating point of care lung ultrasound techniques along with the FOCUS examination may provide additional information and further improve the ability of a cage side ultrasound exam to aid in differentiating respiratory from cardiac causes of respiratory distress. A recent veterinary study describes the use of point-of-care lung ultrasound (an evaluation for increased numbers of B-lines or lung rockets) to evaluate for pulmonary edema in cats with left sided congestive heart failure compared to normal cats.[29] In this small study, all 7 cats with congestive heart failure had B-lines present on lung ultrasound compared to 12% of cats with radiographically normal lungs. Animals with pleural effusion were excluded as this could lead to false positive results (increased B-lines) and therefore decreases the utility of this test. Another study strongly supports the use of lung ultrasound for the diagnosis of cardiogenic pulmonary edema in both dogs and cats.[30] Although animals with significant (>1cm) pleural effusion were also excluded, lung ultrasound had a high sensitivity (84% and 74%) for cardiogenic pulmonary edema similar to thoracic radiography. In our study, a large proportion of patients had pleural effusion noted on FOCUS examination or echocardiogram potentially making the presence of B-lines difficult to interpret. Additionally, false positive POC

lung ultrasound results may be seen in animals with non-cardiogenic edema, pulmonary hemorrhage, neoplasia and acute respiratory distress syndrome further limiting the diagnostic accuracy of this test when used alone.[28] Future studies evaluating FOCUS with POC lung ultrasound are needed to determine whether their combined use in cats with respiratory distress results in improved diagnostic accuracy.

In conclusion, both POC-BNP and FOCUS are diagnostics that can be performed rapidly by emergency clinicians to improve early differentiation of cardiac versus non-cardiac causes of respiratory distress in cats allowing for early institution of therapy. Both FOCUS and POC-BNP increased the overall percent agreement between ECC doctors and the diagnosis made by a board certified cardiologist and ECC specialist as compared to a diagnosis based on the PE and medical history. Further studies incorporating other point of care ultrasound techniques, including lung ultrasound are warranted.

Footnotes

a. IDEXX SNAP® Feline proBNP Test, IDEXX Laboratories, Westbrook, ME

b. Wiley L, Oyama MA, Ostroski C, Reineke EA. Effect of a Basic Training Program On Emergency Clinician Accuracy To Semi-Quantitatively Assess Thoracic And Cardiac Structures Using Focused Cardiac Ultrasound (Focus). In: Research Communications of the 24th ECVIM-CA; 2015: Lisbon, Portugal. pp 423-483.

c. Wess G, Daisenberger P, Hirschberger J. The utility of NT-proBNP to differentiate cardiac and respiratory causes of dyspnea in cats (abstr). J Vet Intern Med. 2008;22:707–708.

d. LOGIQ eVET ultrasound (GE healthcare). 8 MHz curvilinear probe. GE Healthcare, Little Chalfont, United Kingdom.

e. STATA 14.2 Stata Corp., College Station TX; Prism 7.0c, GraphPad Software, La Jolla, CA.

References

1. Rozanski E, Chan DL. Approach to the patient with respiratory distress. Vet Clin North Am Small Anim Pract 2005;35:307-317.
2. Mandell DC. Respiratory distress in cats. In: King LG editors. Textbook of Respiratory Disease in Dogs and Cats. Philadelphia: 1st ed. Saunders; 2003, pp *12-17*.
3. Spencer KT1, Kimura BJ, Korcarz CE, Pellikka PA, Rahko PS, et al. Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2013:26:567-81.
4. Horowitz RS, Morganroth J, Parrotto C, Chen CC, et al. Immediate diagnosis of acute myocardial infarction by two-dimensional echocardiography. Circulation 1982; 65:323-329.
5. Kontos MC, Arrowood JA, Paulsen WHJ, Nixon JV. Early echocardiography can predict cardiac events in emergency department patients with chest pain. Ann of Emerg Med 1998; 31(5):550- 557.
6. Labovitz AJ, Noble VE, Bierig M, Goldstein SA, Jones R, Kort A, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. J Am Soc Echocardiog 2010; 23(12): 1225-1230.

7. Tse YC, Rush JE, Cunningham SM, Bulmer BJ, Freeman LM, Rozanski EA. Evaluation of a training course in focused echocardiography for noncardiology house officers. J Vet Emerg Crit Car 2013; 23(3): 268-273.
8. Oyama MA, Singletary GE. The use of f NT-proBNP assay in the management of canine patients with heart disease. Vet Clin Small Anim 2010; 40:55–558.
9. Connolly DJ, Soares Magalhaes RJ, Fuentes VL, Boswood A, Cole G, Boag A, et al. Assessment of the diagnostic accuracy of circulating natriuretic peptide concentrations to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. J Vet Card 2009; 11(Suppl 1): S41- S50.
10. Fox PR, Oyama MA, Reynolds C, Rush JE, DeFrancesco TC, Keene BW, et al. Utility of plasma N-terminal pro-brain natriuretic peptide (NT-pro BNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. J Vet Card 2009; 11(Suppl 1): S51-S61.
11. Machen MC, Oyama MA, Gordon SG, Rush JE, Achen SE, Stepien RL, et al. Multi-centered investigation of a point-of-care NT-proBNP ELISA assay to detect moderate to severe occult (pre-clinical) feline heart disease in cats referred for cardiac evaluation. J Vet Cardiol 2014;16:245–55.
12. Harris AN, Beatty SS, Estrada AHM, Winter B, Bohannon M, Sosa I, et al. Investigation of an N-terminal prohormone of brain natriuretic peptide point-of-care ELISA in clinically normal cats and cats with cardiac disease. J Vet Intern Med 2017;31:994-999.
13. Hezzell MJ, Rush JE, Humm K, Rozanski EA, Sargent J, Connolly DJ, Boswood A, Oyama MA. Differentiation of cardiac from noncardiac pleural effusions in cats using

second-generation quantitative and point-of-care NT-proBNP measurements. J Vet Intern Med. 2016;30(2):536-42

14. Hansson K, Haggstrom J, Kvart C, et al. Left atrial to aortic root indices using two-dimensional and M-mode echo-cardiography in Cavalier King Charles Spaniels with and without left atrial enlargement. Vet Radiol Ultrasound 2002;43:568–575.
15. Thomas WP, Gaber CE, Jacobs GJ, Kaplan PM, Lombard CW, Moise NS, 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.
16. Buchanan JW, Vertebral scale system to measure heart size in radiographs. In: Vet Clin North Am Small Anim Pract. BJ Watrous (ed) 2000; 30:379-393.
17. Martindale et al. Diagnosing acute heart failure in the emergency department: a systemic review and meta-analysis. Acad Emerg Med 2016;23223-242)
18. U.S. Department of Health and Human Services, Food and Drug Administration. Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests. http://www.fda.gov/cdrh/osb/guidance/1620.pdf; Issued March 13, 2007. Accessed Jun 2018
19. Payne JR, Brodbelt DC, Fuentes VL. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). J Vet Cardiol, 17 (Suppl 1) (2015), pp. S244-S257/.
20. Goutal CM, Keir I, Kenney S, Rush JE, Freeman LM. Evaluation of acute congestive heart failure in dogs and cats: 145 cases (2007-2008). J Vet Emerg Crit Care 2010; 20(3):330-7.

21. Dickson D, Little CJL, Harris J, Rishniw M. Rapid assessment with physical examination in dyspnoeic cats: the RAPID CAT study. J of Small Anim Pract. 59(2), 75–84.

22. Abbott JA, MacLean H. Two-dimensional echocardiographic assessment of the feline left atrium. J Vet Intern Med 2006;20:111-119.

23. Farsi D, Hajsadeghi S, Hajighanbari MJ, Mofidi M, Hafezimoghadam P, Rezai M, et al. Focused cardiac ultrasound (FOCUS) by emergency medicine residents in patients with suspected cardiovascular diseases. J Ultrasound. 2017;20(2):133-138

24. Perera P, Lobo V, Williams SR, Gharahbaghian L. Critical care clinics cardiac echocardiography. Critical Care Clinics 2014; 30(1):47-92.

25. Papanagnou D, Secko M, Gullett J, Stone M, Zehtabchi S. Clinician-performed bedside ultrasound in improving diagnostic accuracy in patients presenting to the ED with acute dyspnea. West J Emerg Med 2017;18(3):382-389

26. Sleeper MM, Roland R, Drobatz KJ. Use of the vertebral heart scale for differentiation of cardiac and noncardiac causes of respiratory distress in cats: 67 cases (2002-2003). Am Vet Med Assoc. 2013 Feb 1;242(3):366-71.

27. Lisciandro GR, Lagutchik MS, Mann KA, Voges AK, Fosgate GT, et al. Evaluation of a thoracic focused assessment with sonography for trauma (TFAST) protocol to detect pneumothorax and concurrent thoracic injury in 145 traumatized dogs. J Vet Emerg Crit Care 2008; 18(3); 258-269.

28. McMurray J, Boysen S, Chalhoub S. Focused assessment with sonography in nontraumatized dogs and cats in the emergency and critical care setting. J Vet Emerg Crit Care 2016; (1):64-73.

29. Lisciandro GR, Fulton RM, Fosgate GT, Mann KA. Frequency and number of B-lines using a regionally based lung ultrasound examination in cats with radiographically normal lungs compared to cats with left-sided congestive heart failure. J Vet Emerg Crit Care 2017; 27(5):499-505.

30. Ward JL, Lisciandro GR, Keene BW, Tou SP, DeFrancesco TC. Accuracy of point-of-care lung ultrasonography for the diagnosis of cardiogenic pulmonary edema in dogs and cats with acute dyspnea. J Am Vet Med Assoc. 2017 Mar 15;250(6):666-675.

Variable	Non-Cardiac (N=16)	Cardiac (N=21)	P value
Sex (F/M)	9/7	6/15	0.089
Age (yrs)	9.3 (4.6)	9.7 (4.5)	0.81
Wt (kg)	4.6 (1.3)	4.8 (1.3)	0.60
Murmur (yes/no)	4/12	12/8	0.049
Gallop (yes/no)	1/15	8/12	0.026
Crackles (yes/no)	2/14	4/17	0.68
RR (breaths/min)	65 (17)	62 (11)	0.43
HR (bpm)	191 (25)	191 (42; n=20)	0.99
SBP (mmHg)	120 (21; n=13)	110 (30; n=15)	0.29
VHS	8.2 (0.7; n=12)	9.1 (1.0; n=20)	0.012
FOCUS LA:Ao	1.00 [0.99-1.12]	2.05 [1.56-3.00; n=20]	<0.0001
NT-proBNP (+/-)	2/13	19/0	<0.0001

Table 1: Characteristics of the cardiac and non-cardiac groups. Frequency data is shown as counts. Continuous data is shown as mean (standard deviation; n) or median [interquartile range, n].

Variable	**Positive percent agreement (95% CI)**	**Negative percent agreement (95% CI)**	**Positive likelihood ratio (95% CI)**	**Negative likelihood ratio (95% CI)**	**Overall percent agreement (%)**
Pre-FOCUS diagnosis	76.2% (52.8% to 91.8%)	68.8% (41.3%-90.0%)	2.4 (1.1-5.2)	0.35 (0.15-0.80)	73.0% (27/37)
Post-FOCUS diagnosis	95.2% (76.2%-99.9%)	87.5% (61.7%-98.5%)	7.6 (2.1-28.0)	0.05 (0.08-0.37)	91.9% (34/37)
Heart rate ≥ 190	65.0% (40.8%-84.6%)	56.3% (29.9%-80.3%)	1.5 (0.78-2.8)	0.62 (0.30-1.3)	61.1% (22/36)_
Murmur (Yes)	60.0% (36.1%-80.9%)	75.0% (47.6% - 92.7%)	2.4 (0.96-6.0)	0.53 (0.29-0.98)	66.7% (24/36)
Respiratory Rate ≥61	52.4% (29.8% -	31.3% (11.0% -	0.76	1.5 (0.65-3.6)	43.2% (16/37)

	74.3%)	58.7%)	(0.45-1.3)		
Gallop (Yes)	40.0% (19.1% - 64.0%)	93.8% (69.8%- 99.8%)	6.4 (0.89-46.0)	0.64 (0.44-0.94)	63.9% (23/36)
Pulmonary Crackles (Yes)	19.0% (5.5% - 41.9%)	87.5% (61.7% - 98.5%)	1.5 (0.32-7.3)	0.93 (0.70-1.2)	48.6% (18/37)
VHS ≥8.4	80.0% (56.3-94.3%)	58.3% (27.7-84.8%)	1.9 (0.95-3.8)	0.34 (0.13-0.93)	71.9% (23/32)
ECC FOCUS LA/Ao ≥1.5 (n=36)	95.0% (75.1% - 99.9%)	87.5% (61.7%- 98.5%)	7.6 (2.1-27.9)	0.058 (0.0084-0.39)	91.7% (33/36)
POC-BNP (Positive) (n=34)	100.0% (82.4%-100.0%)	86.7% (59.5%- 98.3%)	7.5 (2.1-27.3)	NA	94.1% (32/34)

Table 2: Positive, negative and overall percent agreement and positive and negative likelihood ratios of physical exam variables and diagnostics for the differentiation of cardiac vs. non-cardiac etiology of respiratory distress in cats.

Figure 1: Agreement between ECC doctor and reference standard diagnosis before and after performance of focused cardiac ultrasound exam (FOCUS) in cats with respiratory signs due to cardiac disease (Group C) and non-cardiac disease (Group NC). The number of cats that had a change in their diagnosis after the FOCUS exam are indicated. FOCUS exam significantly increased the overall proportion of cats with an agreed upon diagnosis from 27 of 37 (73.0%) cats to 34 of 37 (91.9%) cats (P=0.039).

Figure 2: Scatter plot of left atrial to aortic root ratio (LA:Ao) measured on echocardiography (LA:Ao-ECHO) vs LA:Ao measured on the FOCUS examination (LA:Ao-FOCUS). R = 0.646, P < 0.0001, n=36).

Figure 3: Receiver operating characteristic curve showing the diagnostic utility of left atrial to aortic root dimension ratio as measured using focused cardiac ultrasound performed by ECC doctors to differentiate cardiac vs. non-cardiac etiologies of respiratory distress in cats. Area under the curve=0.934 (95% CI, 0.842-1.000).