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Effect of NT-pro-BNP Assay on Accuracy and Confidence of General Practitioners in Diagnosing Heart Failure or Respiratory Disease in Cats with Respiratory Signs

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Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) can distinguish congestive heart failure (CHF) from primary respiratory disease in cats with respiratory signs with approximately 90% diagnostic accuracy, but the additive benefit of NT-proBNP to improve the diagnosis obtained from conventional testing in individual cases remains unknown.

Hypothesis: NT-proBNP will improve the diagnostic accuracy and confidence of general practice veterinarians in assessing cats with respiratory signs.

Animals: Ten cats with respiratory signs.

Methods: History, physical examination, thoracic radiographs, electrocardiogram (ECG), and biochemical analysis of 10 cats presented to the University of Pennsylvania or Tufts University with a history of respiratory signs were evaluated by 50 general practice veterinarians using an online survey tool. Participants were asked to provide (1) diagnosis of CHF or primary respiratory disease, and (2) level of confidence in their diagnosis (1, lowest to 10, highest) before and after disclosure of NT-proBNP results. Diagnoses (CHF, n = 5; primary respiratory, n = 5) were compared to the gold standard defined as consensus opinion of 3 board-certified cardiologists blinded to the NT-proBNP results.

Results: Overall correctness of the practitioners was 69.2%, and significantly increased after practitioners were provided NT-proBNP results (87.0%, $P = .0039$). Median practitioner confidence before NT-proBNP disclosure was 6 (IQR, 5–8) and significantly increased after disclosure (8; IQR, 6–10; $P = .0039$).

Conclusions: These data indicate a relatively low accuracy and level of confidence in the diagnosis of feline respiratory signs. Use of NT-proBNP assay in conjunction with conventional evaluation by general practitioners significantly improved their diagnostic accuracy and confidence.

Key words: Cardiomyopathy; Congestive heart failure; Natriuretic peptides.

Differentiating congestive heart failure (CHF) from noncardiac disease in cats with respiratory signs is challenging. Results of history, physical examination, thoracic radiography, and serum biochemistry often are insensitive. Echocardiography, which frequently is used to diagnose structural cardiac disease in cats, requires specialized equipment and trained personnel not often available to general practitioners. Blood-based biomarker assays are simple and easy to perform, and have been shown in humans[1–4] and animals[5,6] to provide reliable information that helps distinguish between cardiac and noncardiac causes of dyspnea.

Abbreviations:

BNP	B-type natriuretic peptide
CHF	congestive heart failure
ECG	electrocardiogram
IQR	interquartile range
NT-proBNP	N-terminal pro-B-type natriuretic peptide

B-type natriuretic peptide (BNP) is released from the myocardium in response to increased wall stress, hypoxia, and neuroendocrine activation, and counterbalances the actions of the renin-angiotensin-aldosterone system, resulting in natriuresis and vasodilatation.[7] The inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP) is produced in a 1 : 1 ratio with BNP, has a longer half-life in circulation, and can be measured using a feline-specific NT-proBNP assay.[a] NT-proBNP is increased in cats with clinically relevant structural heart disease and increased most in cats with CHF.[6,8,9]

NT-proBNP reliably distinguishes CHF from primary respiratory disease in symptomatic cats[5,6] with a sensitivity of 90.2% and specificity of 87.9% when using a cutoff value of 265 pmol/L.[6] The additional value of the NT-proBNP assay as compared to traditional diagnostic tests such as physical examination, thoracic radiography, and serum biochemistry in individual cases has not been evaluated. In the emergency room setting in human medicine, information from BNP measurement combined with that obtained from clinical judgment increased diagnostic accuracy and decreased diagnostic uncertainty when evaluating

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dyspneic patients.[10] Thus, we hypothesized that combining the NT-proBNP assay with traditional diagnostic assessments (ie, history, physical examination, ECG, and thoracic radiography) would improve the accuracy and confidence of diagnoses made by general practitioners to discriminate between cardiac and noncardiac cause of respiratory distress in cats.

Materials and Methods

Study Population and Data Collection

Data were collected prospectively from 15 cats that were presented to the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania or Cummings School of Veterinary Medicine at Tufts University for evaluation of respiratory signs from September 2008 to October 2009. Cats were excluded if they were azotemic or had previously diagnosed clinically relevant noncardiovascular disease (e.g., hyperthyroidism, renal insufficiency) reported to affect NT-proBNP concentrations.[11] Physical examination, serum biochemistry (CBC with either a serum biochemistry panel or lactate, urea nitrogen, creatinine, glucose, sodium, potassium, chloride, ionized calcium, magnesium, pH, and bicarbonate measured by a NOVA analyzer[b]), thoracic radiographs, electrocardiogram (ECG), and echocardiogram (standard 2D, M-mode and Doppler) were performed. During initial evaluation, approximately 2 mLs of venous blood was collected in EDTA tubes. Samples were centrifuged within 1 hour of collection and plasma frozen in protease inhibitor tubes provided by the manufacturer.[c] Samples were frozen at −20°C and batched for analysis. Samples were shipped overnight on ice to a reference laboratory for NT-proBNP analysis.[a] The measurable range of the assay was 24 to >270 pmol/L. Clinical data, including echocardiography results, were independently reviewed by 3 board-certified cardiologists (MAO, JER, PRF) to achieve a consensus diagnosis of CHF or primary respiratory disease while remaining blinded to the NT-proBNP results. Ten cases (5 with CHF and 5 with primary respiratory disease) then were selected such that agreement between the interpretive criteria associated with specific NT-proBNP concentrations (Clinical Guidance on Cardiac Disease[d]) and etiology of disease was consistent with previously reported results.[5,6] Based on previously reported values for the sensitivity and specificity of the NT-proBNP assay,[5,6] 9 of the 10 selected cases had NT-proBNP concentrations in agreement with their eventual diagnoses, whereas the NT-proBNP concentration for 1 cat with primary respiratory disease fell within an intermediate range of the manufacturer's interpretive criteria. Clinical information for each of the 10 cases, excluding echocardiography findings, was compiled using an online survey site,[e] which was linked through the University of Wisconsin's Center for Continuing Education.[f] This arrangement allowed general practice veterinarians the option to receive continuing education credits for participating in the study. Demographic data were collected from survey participants including type of veterinary practice (small animal, large animal, mixed practice, academia, industry, or other), number of years actively practicing veterinary medicine (0–2 years, 2–5 years, 5–10 years, 10–20 years, 20–30 years, >30 years), percentage of feline patients believed to have cardiac disease (<20%, 20–40%, 40–60%, 60–80%, >80%), confidence in diagnosing heart failure in cats (low, moderately low, moderate, moderately high, and high), and familiarity and experience with the NT-proBNP assay (no familiarity or experience, some familiarity or experience, much familiarity or experience). Participants then reviewed each of the 10 survey cases during which they were presented with data considered readily available to general practices including signalment, history, physical examination findings, complete blood count, serum biochemistry, thoracic radiographs,[14] and ECG. They then were asked to make a diagnosis of either CHF or primary respiratory disease and to rate their level of diagnostic confidence on a scale from 1 (low) to 10 (high). NT-proBNP results then were disclosed along with a copy of the manufacturer's interpretive criteria.[d] After provision of NT-proBNP results, participants were asked to reassess each case and once again to record their diagnoses and corresponding diagnostic confidence level.

Statistical Analysis

Demographic and descriptive variables were tabulated. The mean accuracy and median level of confidence of diagnosis before and after disclosure of NT-proBNP results were compared using a paired student *t*-test and Wilcoxon matched paired test, respectively. Mean accuracy and median level of confidence between cats with CHF and cats with primary respiratory disease were compared using an unpaired student *t*-test and Mann-Whiney test. The change in mean accuracy and median level of confidence was correlated to baseline accuracy and confidence using linear regression and calculation of the Pearson correlation coefficient and by Spearman rank correlation and calculation of rho, respectively. Statistical analysis was performed using PC-based software.[g] A P value of <.05 was considered statistically significant.

Results

Of the 10 cats used in the online survey, 5 were diagnosed with CHF because of hypertrophic (n = 3), restrictive (n = 1) or unclassified (n = 1) cardiomyopathy and all 5 had plasma NT-proBNP concentrations >270 pmol/L. Five cats were diagnosed with primary pulmonary disease and all had diagnoses of asthma or other lower airway diseases. Plasma NT-proBNP concentrations in the cats with respiratory disease were <24, <24, 46, <24, and 196 pmol/L.

Fifty-seven veterinarians registered to take the survey and 50 of these individuals completed all 10 cases. Data from these 50 participants were used for further analysis. Forty-five participants (90%) worked in small animal general practice whereas 2 participants (4%) worked in mixed general practice, 2 (4%) worked in academia, and 1 (2%) worked in industry. When asked to indicate the number of years worked in practice, 6 (12%), 11 (22%), 11 (22%), 10 (20%), 9 (18%), and 3 (6%) indicated working for 0–2 years, 2–5 years, 5–10 years, 10–20 years, 20–30 years, and >30 years, respectively. When asked what percentage of their feline patients they suspected of having underlying heart disease, 32 (64%) respondents indicated <20% whereas 16 (32%), 1 (2%), and 1 (2%) indicated 20–40%, 40–60%, and 60–80%, respectively. When asked to rate their level of confidence in diagnosing heart failure in cats (1-low, 5-high), 4 (8%), 16 (32%), 15 (30%), 13 (26%), and 2 (4%) responded 1, 2, 3, 4, and 5, respectively. Thus, 35 participants (70%) indicated a moderate to low confidence level. Twenty-three (46%) participants had some familiarity with the NT-proBNP assay, 26 (52%) had no familiarity with the NT-proBNP assay, and 1 (2%) respondent indicated much familiarity with the assay.

The practitioners' accuracy in distinguishing the etiology of respiratory signs was relatively low at 69.2%. There was no statistically significant difference ($P = .51$) in the accuracy between CHF cases (72.4%) and respiratory disease cases (66.0%). After disclosure of the NT-proBNP results, practitioners' accuracy of diagnosis significantly increased from 69.2% to 87.0% ($P = .004$; Fig 1). There was no significant difference ($P = .27$) in the accuracy of diagnosis in cats with CHF (90.8%) versus those with respiratory disease (83.2%) after disclosure of the NT-proBNP results. Change in practitioners' accuracy after disclosure of NT-proBNP results was significantly correlated with accuracy of diagnosis with traditional diagnostics alone ($r = 0.80$; $P = .006$), suggesting that inclusion of NT-proBNP assay was most useful in cases where the initial accuracy was the lowest (Fig 2).

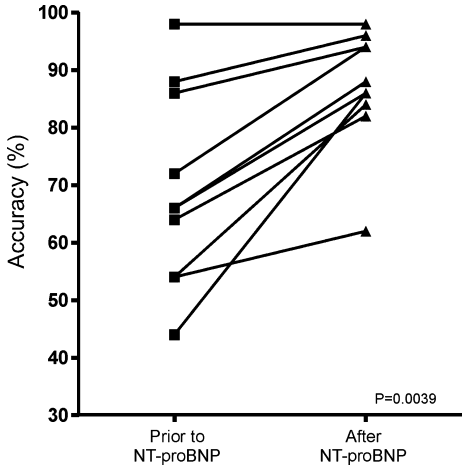

Fig 1. Accuracy of general practitioners' diagnosis in 10 cats with respiratory signs and a confirmed diagnosis of congestive heart failure or primary respiratory disease before and after disclosure of N-terminal pro-B-type natriuretic peptide results.

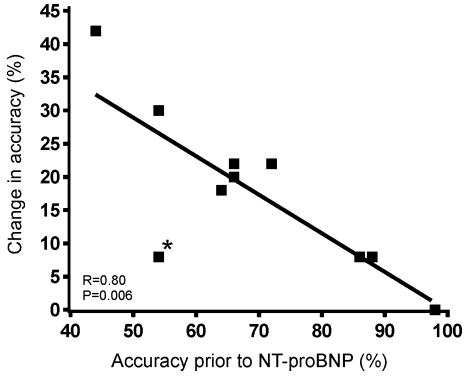

Fig 2. Accuracy of general practitioners' diagnosis in 10 cats with respiratory signs and a confirmed diagnosis of congestive heart failure or primary respiratory disease before N-terminal pro-B-type natriuretic peptide (NT-proBNP) results versus change in accuracy after disclosure of NT-proBNP results. The point denoted with (*) represents the case in which the NT-proBNP result was discrepant from the diagnosis.

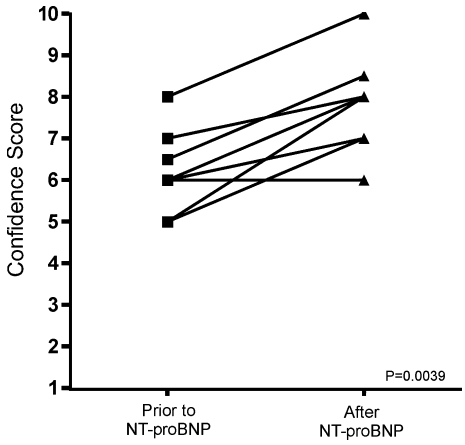

Fig 3. Confidence in general practitioners' diagnosis in 10 cats with respiratory signs and a confirmed diagnosis of congestive heart failure or primary respiratory disease before and after disclosure of N-terminal pro-B-type natriuretic peptide results. Eight lines appear owing to the fact that, in 3 cases, confidence score increased from 6 to 8.

Median practitioner confidence before divulging the NT-proBNP results was relatively low (6.0, IQR, 5.0–8.0). After disclosure of the NT-proBNP results, the median confidence significantly increased (8.0, IQR 6–10; $P = .004$; Fig 3). There was no difference between practitioner confidence when evaluating respiratory cases versus CHF cases either before or after disclosure of NT-proBNP results. Before NT-proBNP results, CHF case median was 6.0 (IQR, 5.5–7.25) as compared to respiratory case median of 6.0 (IQR, 5.5–6.5) ($P = .69$). After NT-proBNP results, CHF case median was 8.0 (IQR, 8–9.25) as compared to a respiratory case median of 7.0 (IQR, 6.5–8.0) ($P = .056$). Change in practitioners' confidence was not correlated to baseline confidence ($P = .33$).

Discussion

The present study demonstrates that NT-proBNP measurement significantly contributes to diagnostic accuracy and confidence when used by general practice veterinarians to discriminate cardiac from noncardiac causes of respiratory signs in cats. Previously, the utility of NT-proBNP in distinguishing between populations of cats with CHF versus respiratory disease had been well established,[5,6] but the effect of including NT-proBNP measurement on actual decision making has not been evaluated. The veterinarians' accuracy and confidence using traditional diagnostic tests (eg, history, physical examination findings, thoracic radiographs, serum biochemistry results and ECG) was relatively low. These findings are similar to those reported in human medicine where diagnostic accuracy by family doctors can be as low as 50%.[12] In another study, only 34% of patients referred for specialist evaluation actually had CHF.[13] In both humans and cats, diagnostic

uncertainty results from similarities in clinical signs and physical examination findings, and low sensitivities of methods utilized to differentiate CHF from primary pulmonary disease. For example, thoracic radiographs can be difficult to interpret owing to similarities in the pulmonary parenchymal pattern between cardiac and pulmonary conditions, relative insensitivity of radiographs for assessing feline cardiac size and function, and potential lack of confidence by veterinarians in interpreting thoracic radiographs of cats.

The additive value of NT-proBNP to traditional diagnostic evaluation has been established in numerous studies in outpatient and emergency room medicine in humans.[1,3,10,15–17] Specifically, an increased NT-proBNP concentration was a stronger predictor of CHF than other variables evaluated including radiographic findings and clinical signs.[3] In another study,[10] the addition of BNP assay significantly increased diagnostic accuracy (from 53% to 71%) along with increased certainty (from 34% to 82%) in the assessment of people presenting to the emergency department for possible CHF. The additive value of NT-proBNP testing to traditional diagnostic testing appears to be highest in cases in which diagnostic uncertainty is greatest.[18] Thus, in patients in whom history, ECG, radiographs, physical examination findings, or some combination of these unequivocally demonstrate CHF or primary respiratory disease, there is little advantage in performing the NT-proBNP assay. Guidelines in human medicine acknowledge this fact by stating that NT-proBNP testing should only be performed in cases that "present with signs and symptoms that are ambiguous".[18] In the present study, NT-proBNP improved diagnostic accuracy to the greatest extent in cases in which initial accuracy was lowest (Fig 2). This result suggests that NT-proBNP is most helpful in aiding veterinarians in challenging cases and provides incremental value when combined with clinical judgment.

This study has several limitations that warrant discussion. The gold standard diagnosis for this study was clinical evaluation by specialists. Despite consensus opinion of 3 veterinary cardiologists, misclassification is possible. The study population consisted entirely of cases from specialty teaching hospitals but this population is likely to include cases for which the diagnosis of signs by the general veterinarian was most uncertain. The applicability of study results to practice recommendations is only as valid as how well the cases and participants reflect the general population in which the NT-proBNP assay will be used. In this regard, the number of cases and general practice veterinarians participating in the study were relatively small which might have led to over- or under-estimation of the veterinarians' accuracy and confidence. Cases were selected based on their agreement with previously reported case accuracy, and further studies to confirm the overall accuracy of the test would be helpful. When selecting cases to be included in the study, a truly discordant BNP result (eg, a false negative result) could not be identified in the population of cats diagnosed with CHF, thus a cat with respiratory disease and a result in the manufacturer's diagnostic intermediate range was selected to achieve an overall case accuracy of 90%. This finding is consistent with data in humans indicating that owing to the very low incidence of false negative results, NT-proBNP assay is well-suited to rule out a diagnosis of CHF.[18] Finally, to achieve what the authors consider the maximal clinical impact of the NT-proBNP assay, future studies should investigate whether the increase in veterinarians' diagnostic accuracy and confidence leads to improved patient outcomes. Most,[1,16,17] but not all,[19] studies indicate improved outcome in human patients. Use of BNP assay decreased hospital admissions and hospitalization time as well as decreased 60-day rehospitalization by 35%.[16,17] In another study, decreasing physicians' diagnostic uncertainty was shown to significantly decrease hospitalization time as well as a patient's 1-year morbidity and mortality, presumably by preventing a delay in appropriate treatment.[1] In contrast to these studies, 1 report[19] indicated that despite reductions in hospital stay and readmissions, mortality rates were not improved.

In conclusion, the NT-proBNP assay, in combination with traditional diagnostic tests, significantly improved the accuracy and confidence of general practice veterinarians for diagnosing the etiology of respiratory signs in cats. These results indicate that the NT-proBNP assay is a useful ancillary diagnostic test for distinguishing cardiac from noncardiac dyspnea in cats, and affords the greatest improvement in diagnostic accuracy in the most challenging cases. These results can help veterinarians more confidently select appropriate treatment and monitoring options in cats with respiratory signs.

Conflict of Interest

Drs Oyama, Fox, Rush, and Stepien serve on a veterinary advisory board and have received speaker honoraria and reimbursement for associated travel costs from IDEXX Laboratories, Westbrook, ME. Drs Oyama, Fox, and Rush have received payment for development of educational materials. IDEXX Laboratories had no participation in the design, analysis, or manuscript preparation of this study.

Footnotes

[a] Feline CardioPet NT-proBNP, IDEXX Laboratories, Westbrook, ME
[b] NOVA, Nova Biomedical Corp., Waltham, MA
[c] NT-proBNP collection tube, IDEXX Laboratories
[d] www.idexx.com/pubwebresources/pdf/en_us/smallanimal/reference-laboratories/clinical-guidance-cardiac-disease.pdf, accessed June 1, 2010.
[e] www.surveymonkey.com, accessed March 31, 2010.
[f] ce.vetmed.wisc.edu, accessed March 31, 2010.
[g] Prism 4.0, GraphPad Software, La Jolla, CA

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