New studies show uses for NT-proBNP

The biomarker can help assess patients with cardiac, respiratory disease

Cardiac biomarkers play an important role in human medicine by helping to improve the diagnosis of cardiac disease, as well as allowing the formulation of a more accurate prognosis. And while various biomarkers have been examined in veterinary medicine, to date only N-terminal pro-brain natriuretic peptide (NT-proBNP) has become a commercially available test.

This biomarker increases as myocardial stretch increases. An increase also can occur with renal disease. The role this assay will play in small animals is still being investigated. Several research abstracts presented at the 2011 American College of Veterinary Internal Medicine (ACVIM) Forum in Denver dealt with this topic.

Evaluating cats with respiratory difficulties

NT-proBNP concentrations have been found to be useful in differentiating cardiac disease from respiratory tract disease in cats evaluated at referral institutions. Using a cutoff of 265 pmol/L, the assay was 90 percent sensitive and 88 percent specific for differentiating between cats with congestive heart failure (CHF) and those with dyspnea and respiratory disease. These results are good, since it means that with a value of

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Early intervention: The cardiac biomarker NT-proBNP has promising value in early disease diagnosis in both cats and dogs.
more than 265 pmol/L, only one out of 10 cats with CHF would be missed, and only one out of 10 cats with this value is going to have respiratory disease as the underlying cause for dyspnea.

It’s assumed this assay’s greatest value is for practicing veterinarians. Specialists can use various advanced diagnostic tests and their experience to guide a diagnosis, so the NT-proBNP assay will play less of a role in diagnosis. A multicenter study evaluated this issue by having 47 general practice veterinarians look at cases using an online survey. The veterinarians, who had been in practice between five and 10 years, were asked to diagnose either CHF or primary respiratory disease and rank how confident (1 = lowest, 10 = highest) they were of their diagnosis. Information provided included history, physical examination findings, radiographic and electrocardiographic examinations and routine blood work. Half the cats had CHF and half had primary respiratory disease. Initially, a correct diagnosis was made in 67.4 percent of the cases with a confidence level of 6. After the initial input, the veterinarians were given the NT-proBNP result, which increased their diagnostic accuracy to 85.5 percent and their confidence level to 8.

This study is similar to others that have shown the use of NT-proBNP can increase diagnostic accuracy when trying to assess patients with respiratory distress. However, unlike other studies, it looks at a more real-life scenario in that general practitioners were doing the evaluations in conjunction with routine testing (e.g., history, physical examination, radiography, electrocardiography).

Certainly this study shows the blood test can aid in accurate diagnosis in cats with respiratory distress, as well as increase veterinarians’ confidence levels when making a diagnosis. The only downside at this time is that the NT-proBNP assay is a send-out test, so in the true emergency patient, it’s of limited value. Hopefully, this assay will become available for in-house use in the near future, in which case it will allow veterinarians to make more accurate diagnoses and feel more confident in their ability to differentiate respiratory disease from cardiac disease as a cause of respiratory distress.

**Dogs with mitral valve disease**

Cardiac disease in many dogs remains asymptomatic for long periods, often years. This is especially true in dogs with mitral valve endocardiosis. Previously, little benefit has been shown in starting treatment in these dogs before CHF onset. If it were possible to predict that CHF would occur in the near future, owners could be more vigilant for the typical signs, and treatment would be started. A multicenter study presented at the ACVIM Forum looked at the ability of NT-proBNP to predict the onset of CHF. Sixty-six dogs that had mitral valve endocardiosis and an enlarged left atrium were included in the study. The dogs underwent a complete cardiac workup every two to nine months. The dogs were followed, on average, for 276 days, with some being monitored for more than four years.

During the study period, almost half the dogs developed overt CHF with radiographic evidence of pulmonary edema. The researchers looked at the data from the visit immediately before CHF developed to see what parameters would be predictive of impending CHF in comparison with those visits in which CHF did not develop. NT-proBNP concentrations were significantly different, with a median concentration of 3,001 pmol/L and an interquartile range (IQR; middle 50 percent of results) of 2,255 to 3,001 prior to CHF, and a median of 1,600 IQR of 984 to 2,863.

Not surprisingly, it was also discovered that heart size was predictive of CHF development. Dogs that developed CHF had, on average, a bigger left atrium, higher vertebral heart score and higher ratio of left ventricular internal diameter to diastolic to aortic diameter. Using a cutoff of > 2,150 pmol/L for NT-proBNP, sensitivity for detecting impending CHF was 77.4 percent and specificity was 68.6 percent. Within six months, 36 percent of dogs that had a concentration greater than 3,000 pmol/L went on to develop CHF.

The results of this study are, in a way, not surprising. With mitral valve endocardiosis, there’s a progressive increase in heart size until failure occurs, often after many years. As the heart enlarges, stretch occurs, which results in increased release of NT-proBNP by the myocytes. The more the heart is stretched, the higher the BNP and, of course, the bigger the heart on imaging studies. The ability to measure some of the parameters is dependent on a high-quality and reproducible echocardiogram. Vertebral heart score is a relatively crude method to assess the heart and, as such, would be difficult to use as a predictive test in individual patients.

This study suggests that NT-proBNP can be useful in practice to assess the likelihood that CHF will develop in the near future. In dogs with very high concentrations or a steep increase in NT-proBNP concentrations between visits, owners may be much more likely to develop in the near future. This means owners need to be reminded to monitor closely for signs of CHF, such as weakness, exercise intolerance and especially cough. If these signs develop, it’s vital the owner present the pet to a veterinarian as soon as possible for evaluation, since it’s likely these signs are indicators that the heart is beginning to fail and treatment should be instituted. However, given that even with the highest concentrations, only one-third of the dogs went on to develop CHF within six months, high NT-proBNP concentrations are not sufficient reason alone to start treating mitral valve endocardiosis.

**Noncardiac factors impact results**

NT-proBNP is a biomarker that’s increased by progressive cardiac disease. In people, hydration status can have an impact on measured values. One possible cause of increased concentrations could be physical activity.

Researchers from the University of Pennsylvania looked at this issue in 14 healthy dogs older than 1 year. The dogs were subjected to five minutes of submaximal exercise. NT-proBNP concentrations before, immediately after and one hour after exercise were evaluated. The normal reference range for the assay was < 900 pmol/L. There was no statistical difference between any of the time points. A single dog had its concentration go from 790 to 1,054 pmol/L immediately after exercise.

This study demonstrates that in healthy dogs, submaximal exercise won’t impact the NT-proBNP significantly, and only in rare cases will this result in a false positive result. But it’s also unlikely that veterinarians would be sampling dogs immediately after exercise, so the chance of a false positive result seems slim. Of course, this study doesn’t address what submaximal exercise does to dogs with underlying cardiac disease.

Other factors also may impact measured NT-proBNP results, such as how the sample is shipped to the laboratory for testing. A group of researchers from the California Animal Hospital Veterinary Specialty Group, Los Angeles, addressed this issue. Blood samples were drawn from 18 cats with cardiac disease and six control cats and placed in plastic EDTA tubes. The samples were centrifuged, and plasma was collected. Some of the plasma was placed in tubes containing a protease inhibitor and stored at 39.2 °F (4 °C), some was frozen at -4 °F (-20 °C) and some was frozen at -112 °F (-80 °C). The samples were then shipped to the laboratory for assay.

Both frozen methods resulted in similar results; however, the protease inhibitor method resulted in significantly higher values. This study is important in that it shows consistency in how a sample is shipped to the laboratory for assay of NT-proBNP is vital. Results between freezing and protease inhibitor tubes aren’t comparable and could result in misinterpretation of the results. Given that it’s easier to keep a sample cooled rather than frozen, preference should be given to shipping samples for assay using the suggested protease inhibitor tubes. This should result in more consistent and accurate results.

**Summary**

NT-proBNP has the potential to become a valuable tool in veterinary practice, especially if an in-house version becomes available. NT-proBNP has been shown to be able to differentiate between cardiac and respiratory dyspnea in cats. The research presented at the ACVIM Forum in Denver demonstrates it increases diagnostic accuracy of general practitioners and can help them feel more confident in the diagnoses they make. It also can play a role in predicting progression to CHF in dogs.

Our understanding of this biomarker is still incomplete; however, this should improve in the future as more research is generated and presented. dvm

**References**


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*The NT-proBNP assay can aid in the diagnosis in cats with respiratory distress, as well as increase veterinarians’ confidence levels when making a diagnosis.*

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