Clinical study into prognostic value of NT-proBNP in feline heart disease

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Martin Atkinson discusses an in-practice investigation into the importance of this test in the prediction and progression of heart disease in cats

N-TERMINAL pro-brain natriuretic peptide (NT-proBNP) is an example of a biomarker, a substance used as an indicator of a biologic state.

Brain natriuretic peptide (BNP) was originally isolated from pig brain tissue, but is now more commonly referred to as B-type natriuretic peptide as it was realised that the principal source of the circulating peptide is the cardiac ventricles. Physiologically, BNP acts as a natural antagonist of the renin-angiotensin system and decreases blood volume and vascular resistance through vasodilatory, natriuretic, and diuretic properties. In cats, BNP is synthesised as a 132-amino acid peptide, principally within ventricular myocytes. BNP is involved in the regulation of blood volume and vascular resistance by promoting sodium and fluid excretion when the venous compartment is distended, as sensed by the distended ventricles. As such, circulating BNP levels act as a chemical barometer for congestion and hypertrophy.

The major stimulus for production and release of BNP from ventricular myocytes, and the reason it is of interest as a cardiac biomarker, is mechanical stress due to distension of the heart. In cats, this is principally secondary to hypertrophic cardiomyopathy (HCM), although larger amounts of BNP would appear to be released in dilative cardiomyopathy.

As cardiac disease progresses, and congestion worsens, larger amounts of BNP are secreted in an

attempt to return blood volume and pressure towards normal. Levels of BNP correlate with the degree of cardiac distension and, thus, provide a valuable test for the severity of heart disease.

BNP only exists in the blood for a matter of seconds, making it extremely difficult to measure. It is stored in an inactive form, known as a pro-hormone, and the final step in conversion to the active form is to cleave the molecule. The redundant portion, NT-proBNP, is less labile, making it easier to measure, which is why this is used as an indication of BNP levels.

The author believes the primary indications for measurement of NT-proBNP in cats are: to determine which individuals with cardiac murmurs are likely to progress to heart failure; which non-specific symptoms, such as coughs and effusions, may be cardiogenic; and as a measure of severity of cardiac disease and response to therapy. In dogs, the primary indication for BNP in practice is presently to differentiate cardiogenic causes of coughs and dyspnoea and non-cardiogenic causes, although it is also of value in predicting the onset and monitoring progression of cardiac disease in this species.

Signalment

Measurement of NT-proBNP is indicated as an adjunct to other diagnostic procedures for the presenting signs shown in Table 1. Given that a significant number of cats present with sudden death due to cardiac failure – apparently sudden onset cardiogenic pleural effusion or catastrophic thromboembolic disease with no previous related symptoms (including murmurs) – there may be, in addition, a case for including NT-proBNP as a screening test in lines and breeds known to be predisposed to cardiac disease (notably, ragdolls, Maine coons, British shorthairs, Siamese and Burmese), in all cats older than four years of age or even as part of a routine wellness profile.

Domestic shorthair (DSH) cats are over-represented in this survey, but, although HCM is thought to be hereditary in certain lines of DSH cats, this may be just the result of the demographics of the local pet cat population.

Cardiac murmurs are a frequent finding during routine examinations in cats of all ages. In young cats, a high proportion of these murmurs are innocent and may disappear with age. Others may be diagnosable as hereditary cardiac problems, which may, or may not, self-correct with maturity or be correctable by surgery.

However, in the author’s experience, a high proportion of young cats at less than three years of age with cardiac murmurs of grade two and greater will progress to cardiac failure within three to four years. A murmur in older cats without previous history of a detectable murmur is probably always significant and may be due to the progression of existing cardiac disease with age or other disease processes – especially hyperthyroidism. Echocardiography has been the gold standard for the diagnosis of cardiac disease but can be inconvenient, expensive and time consuming, especially if repeated serially.

Cardiopet BNP[1] is an inexpensive assay system for NTproBNP using a simple blood sample. The author has, therefore, been evaluating NTproBNP as an alternative to more expensive and inconvenient techniques to diagnose heart disease in cats, and to try to reliably identify cats with heart murmurs, yet presently asymptomatic, that are likely to progress to cardiac failure and which he believes would benefit from selective pre-emptive treatment. Other clinicians[3] have found little correlation between NT-proBNP levels in cats and the prediction or diagnosis of cardiac disease. However, the author believes circumstances indicate that this was due to a combination of previously poor understanding of correct preparation and transport of samples, and lack of standardisation of testing protocol by some laboratories.

Interpreting the results

Changes in collection, transport and testing protocols have been made – using ethylenediamine tetra-acetic acid (EDTA) plasma in special transportation tubes followed by the necessary re-evaluation of the interpretation of ranges. At the time of writing, laboratory interpretation of results suggests that a NT-proBNP below 100pmol/L indicates clinically significant cardiomyopathy is unlikely; cats with levels of 100-270 may have occult cardiac disease, which could progress to cardiac failure later in life, whereas levels above 270 are indicative of current heart disease (previously these ranges were below 40, 40-100 and more than 100 respectively)[1].

Results collected prior to this change of protocol will, in all likelihood, have returned lower values than they would with the new techniques and these have to be interpreted in this light. However, results seem to indicate that cats with cardiac disease returned high values and cats unlikely to develop cardiac disease returned low values, regardless of which protocol was used, and only those in the equivocal ranges may lead to confusion when attempting to compare results.

One caveat is that some of the samples tested have returned results of zero, which is theoretically impossible. This suggests that some degradation of the sample has occurred during collection or transport, despite complying with strict sampling and transport recommendation, but some failure in analysis procedures cannot be excluded.

Subsequent retesting suggests these were cats that would have returned a low result anyway and it is unlikely we would miss those with genuinely high concentrations unless samples were allowed to degrade seriously. The major factor in the degradation of samples is the high levels of antiproBNP proteases in cats' blood. These levels vary considerably from cat to cat, which complicates the interpretation of results. With the new collection and transportation protocol using tubes containing antiproteases, these suspiciously low results should become rarer, but the fact that they still occur probably continues to reflect some breakdown in technique or unavoidable degradation of already very low titres. In dogs, rapidly increasing NT-proBNP levels on serial tests over a six-month period indicate the patient is likely to suffer from cardiac failure within a short period of time. However, although this link has not yet been proven in cats, rising levels on serial tests would be wisely interpreted as a progression of potential heart disease and further monitoring

advised. Equally, falling NT-proBNP levels may be associated with the stabilisation and improvement of cardiac function with treatment. Raised NT-proBNP levels have been demonstrated in cats with kidney disease. However, work has shown that this relates to hypertension, secondary to renal failure, and that no significant increase occurs in cats with mild to moderate normotensive kidney disease[2].

The results of the author's clinical trial have, thus far, consistently indicated that cats with cardiac disease – diagnosed either symptomatically, from radiography, ECG and/or echocardiography – have returned a range of values of 357pmol/L to more than 1,500 (this being the maximum measurable at the time of test), with all those showing symptoms of severe cardiac failure returning results above a value of 476. A summary and interpretation of results are shown in Table 2.

Conclusion

NT-proBNP has previously been recognised as a useful adjunct to the diagnosis and evaluation of the severity of cardiac disease in cats. The author believes that, from the data gathered, he is now in a position to predict, with confidence, from this test alone, which cats have cardiac disease and are likely to develop cardiac failure, and advise either further investigation or pre-emptive treatment.

Given that a distressingly high proportion of cats with heart disease present with catastrophic heart failure and fatal thromboembolic disease, although no research data currently exists to support pre-emptive therapy, the author believes that cats with NT-proBNP levels of greater than 350pmol/L nonetheless qualify for treatment with ace inhibitors and low-dose aspirin. However, additional investigation with ECG, radiography and echocardiography would always be advised where possible.

He further intends to serially monitor cats with levels of NT-proBNP of more than 270pmol/L (100 on the previous protocol) and retest the cats with values in the equivocal range between 100 and 270, (40-100 on the previous protocol) to evaluate how they develop, whether they progress to overt cardiac disease and how the levels of NT-proBNP relate to this.

It is less likely that cats returning results in the equivocal intermediate ranges will develop heart failure if they are elderly than if they were younger, but it is not presently possible to give a cut-off age. Cats in the equivocal ranges with significant increases of NT-proBNP within a six to 12-month period will be added to those to be serially monitored, and those with no increase will be removed from the trial. This, however, will obviously take some time and may be the subject of a further paper.

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Key to annotation in Table 2 and further information

All breeds domestic shorthair or crossbreeds unless stated.

Cardiac murmurs rated out of six as normal convention.

Cases where diagnosis of cardiac disease confirmed all hypertrophic cardiomyopathy unless stated.

NF = neutered female, **NM** = neutered male, **RA** = right atrium, **LV** = left ventricle, **RV** = right ventricle.

ACEi = ace inhibitor.

CHF = congestive heart failure.

CKD = chronic kidney disease.

DCM = dilative cardiomyopathy.

DLVOTO/D(R) VOTO = dynamic left (right) ventricular outflow obstruction.

DM = diabetes mellitus.

HCM = hypertrophic cardiomyopathy.

VHS = lateral vertebral heart score, 7.5-8 considered normal (dorsoventral vertebral heart score not tabulated but was proportional to lateral in all cases).

VPC = ventricular premature complex on ECG.

*Reference range: 100 probability of cardiac disease (for samples taken prior to April 2010, IDEXX Laboratories).

**Reference range: 270 probability of cardiac disease (for samples taken subsequent to April 2010, IDEXX Laboratories).

Where > symbol appears before a value this indicates that this was the highest level available at

the time of test.

1. Dynamic ventricular outflow obstruction.

2. Lateral vertebral heart score, 7.5-8 considered normal.

3. Change in 12 months.

4. ProBNP may be elevated in cases of hypertensive renal failure, but all cats in this study with CKD were normotensive.

5. Measured after thromboembolic episode.

References

- 1. IDEXX Laboratories UK.
- 2. Stephanie M Lalor, David J Connolly, Jonathon Eliot and Harriot M Syme. Department of veterinary clinical sciences, Royal Veterinary College.
- 3. Further references available upon request.