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NT-proBNP Testing in the Dog

1. WHAT IS N-TERMINAL PRO-B TYPE NATRIURETIC PEPTIDE (NT-PROBNP)?

B-type natriuretic peptide (BNP) is a hormone that causes renal sodium and water loss, as well as vasodilation. BNP is produced and secreted into the blood by the muscle cells of the heart. Low concentrations of BNP circulate at all times, but the heart increases production and secretion in response to excessive stretching of heart muscle cells. Excessive stretching of heart muscle cells is common in many forms of heart disease and in the setting of heart failure. The magnitude of the increase in circulating BNP is correlated to the severity of the underlying heart disease. BNP pro-hormone is secreted into the circulation during periods of cardiac stress and is cleaved into the carboxy-terminus (C-BNP) and the amino-terminus (NT-proBNP); thus, the concentration of either can be used to assess the magnitude of cardiac muscle stretching and commensurate increased wall and stress. NT-proBNP is more stable than proBNP or C-BNP and has a longer half-life, making it a more desirable analyte. A commercially available assay for canine NT-proBNP (Cardiopet[®] proBNP) has been available for more than five years and clinical studies have been published that support its clinical utility in the dog. A clinical test for BNP (Cardio-BNP canine), rather than NT-proBNP, is also available but less information is published regarding clinical use of this test. This article refers to clinical use of NT-proBNP, since this is a more commonly used and more clinically studied test.

2. HOW CAN I USE THE NT-PROBNP TEST IN MY PRACTICE?

Many dogs with respiratory or cardiac disease have similar clinical signs, including cough, tachypnea and dyspnea. The diagnosis of the cause of clinical signs, whether cardiac or respiratory, may be uncertain even after thoracic radiographs are reviewed. NT-proBNP assessment has proven useful in discriminating between dogs with respiratory causes of clinical signs (NT-proBNP is low) or cardiac causes of clinical signs (NT-proBNP is elevated). NT-proBNP is not a stand-alone test and results should be interpreted in the context of other appropriate information e.g., history, signalment, thoracic radiographs and an echocardiogram (if available). Results of NT-proBNP testing may not be available prior to initiation of therapy in critical patients.



Clinical Tip: *Thoracic radiographs should be obtained as soon as possible in dogs with respiratory signs. If the findings are ambiguous, the NT-proBNP test may add helpful information regarding likely etiology of signs. In addition, a second opinion regarding the radiographic interpretation may be useful. Congestive heart failure (CHF) is a more likely cause of dyspnea in dogs with evidence of cardiomegaly (i.e. VHS>10.7 and left atrial enlargement) and in small breed dogs when a prominent heart murmur is evident.*

NT-proBNP can be used in the chronic monitoring of dogs with myxomatous mitral valve disease (MMVD). Results of NT-proBNP in combination with thoracic radiography (especially VHS) and in-home monitoring of resting respiratory rate can help to detect worsening of cardiac disease and predict the risk of CHF development. In dogs, a VHS > 12.0 or an NT-proBNP >1500 pmol/L are associated with an increased risk of CHF in the next 3-6 months¹. Serial evaluation of NT-proBNP concentrations in chronic cardiac patients may provide additional information about the risk of CHF. Increasing NT-proBNP values (increases of > 60% since last visit) or increasing VHS (\geq 0.07 per month since last visit) are associated with an increased risk of CHF in the next 3-6 months. This information can be used to enhance owner education regarding signs to watch for and lead to an increased frequency of rechecks (for example, recheck every 4-6 months instead of yearly).

Doberman pinschers have a very high risk of developing cardiomyopathy over their lifetime. The recommended gold-

standard screening tests include annual echocardiogram and Holter (24 hour) ECG exams starting at 3 to 4 years of age. The expense and inconvenience of this recommendation limits the number of Dobermans that undergo serial testing. NT-proBNP testing can help identify Dobermans at highest risk for having Stage B2 cardiomyopathy; these dogs can then be strongly encouraged to undergo an echocardiogram and a Holter exam. Therapy based on NT-proBNP values alone is not recommended. Use of NT-proBNP for this indication requires the use of the most current breed-specific reference ranges.

Clinical Tip: *NT-proBNP cannot be used for population based screening of apparently healthy dogs for heart disease because the false positive rate is very high in this group. Dobermans represent the only canine exception to this rule at this time, and this test may be used when other recommended tests are unavailable or declined.*

3. HOW DO I INTERPRET THE RESULTS OF THE NT-PROBNP TEST?

Clinical Tip: *Objective evidence of structural heart disease based on auscultation (presence of a murmur, gallop heart sound or arrhythmia), and thoracic/cardiac imaging must be considered when interpreting the results of the NT-proBNP test.*

In dogs with current respiratory signs, an NT-proBNP concentration < 900 pmol/L suggests that CHF is unlikely and other conditions causing respiratory signs should be considered. If the NT-proBNP is > 2,500 pmol/L, CHF is the most likely cause of the clinical signs, but concurrent airway disease cannot be ruled out.² Values between 900 and 2,500 are difficult to interpret because they do not discriminate between CHF and other causes of respiratory signs. Thus for results in the range of 900 to 2,500 pmol/L, other tests should be evaluated or re-evaluated, or a second opinion or referral sought.

In dogs with Stage B2 MMVD, NT-proBNP > 1,500 pmol/L¹ is indicative of an increased risk of developing CHF over the next 3-6 months. These dogs will benefit from more diligent monitoring including evaluation of home resting respiratory rate and more frequent follow-up examinations (q 4-6 months). NT-proBNP concentrations have also been correlated to survival in dogs with MMVD and DCM, but the reported cut-off values for these predictions are currently ambiguous because different generations of the assay were used in different studies.

Clinical Tip: *NT-proBNP concentration \geq 1500 pmol/l, VHS > 12.0 and the ratio of the left ventricular lumen size in diastole to the aortic diameter >3.0, as determined by an echocardiogram, are all predictive of CHF in the next 3-6 months in dogs with Stage B2 MMVD. The risk is highest in dogs with more than one of these findings.¹*

► Dobermans with an NT-proBNP above the breed-specific reference range (this range is currently being finalized) should be considered at an increased risk for having occult DCM (Stage B2). Owners of this type of patient should be strongly encouraged to have the dog undergo echocardiographic examination. The sensitivity and specificity of NT-proBNP to identify both the arrhythmogenic and structural forms of DCM can be optimized when combined with a Holter study looking for ventricular ectopy. If Holter studies are not available, a 3-5 minute ECG can be performed to screen for frequent ectopy.

Clinical Tip: *NT-proBNP does not replace the gold-standard screening recommendations for Dobermans (annual echocardiogram and Holter ECG) but can be used as a scaled down alternative with informed owner consent. However, this test does not definitively diagnose the disease entity and thus cannot be used as the sole indication to initiate therapy.*

4. WHAT ARE THE LIMITATIONS OF NT-PROBNP TESTING IN THE DOG?

► General considerations

The main mistake that limits the utility of NT-proBNP testing is related to testing the wrong dog. The test should not be used as a stand-alone test or in most apparently healthy (e.g. asymptomatic) canine patients (Doberman pinschers are the exception, see above). Elevations in NT-proBNP are not disease specific and cannot be used alone to establish a diagnosis; thus, NT-proBNP does not tell you when to start treatment or what medication to use. NT-proBNP does not replace other appropriate diagnostic tests; rather, it provides additional information that when interpreted in conjunction with a thorough history, physical examination and other appropriate tests may improve the accuracy of diagnosis. The value of NT-PROBNP testing may be particularly high when the results of other tests are ambiguous. NT-PROBNP concentrations are highest in dogs with active heart failure.

Apparent false positives: there are a number of conditions that can lead to elevations in NT-proBNP that are not associated with an abnormal echocardiogram. NT-proBNP is cleared primarily by the kidney and thus significant renal insufficiency or pre-renal azotemia may lead to increased concentrations. Thus, elevated NT-proBNP should be interpreted in light of renal function when possible. NT-proBNP may increase with severe arrhythmias, pulmonary hypertension and systemic hypertension even if structural heart disease is not apparent based on an echocardiogram.

► **Test considerations**

The most current sample handling and submission recommendations from IDEXX must be followed closely to prevent artificially decreased values. Currently, submission of 1mL of EDTA plasma is recommended for canine submissions. The commercially available canine assay has gone through a

number of revisions and thus the suggested cut-offs of studies published before can be difficult to apply clinically. Day-to-day variation may be as high as 60% and should be taken into consideration with interpreting serial samples in an individual dog.

6. SUMMARY TABLE

Who should I run an NT-proBNP test on	NT-proBNP result (pmol/L)	Interpretation of test result
Dog with respiratory signs in which the cause of the signs is not obvious despite other appropriate diagnostic tests	< 900	Does NOT support at diagnosis of CHF
	900-2,500	CHF is possible; review the balance of evidence from the other tests
	> 2,500	Supports a diagnosis of CHF
Single evaluation of Stage B2 MMVD	>1500	Increased risk of developing CHF in next 6-12 months
Serial evaluation of Stage B2 MMVD	Increase of >750 or 60%	Increased risk of CHF in the next 6 months, particularly if the absolute value is > 1500
Asymptomatic Doberman who is >5 years of age and declined an echocardiogram (especially if there is physical exam evidence suggestive of occult DCM)	> 450*	Identifies this Doberman to be at increased risk for occult DCM and more specific testing such as an echocardiogram should be strongly recommended or referral to a cardiologist

* This range is currently being finalized

References

1. Reynolds CA1 to Reynolds CA, Rush JE et.al. Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: the PREDICT cohort study. J Vet Cardiol. 2012 Mar;14(1):193-202. doi: 10.1016/j.jvc.2012.01.008. Epub 2012 Feb 25.
2. Fox PR, Oyama MA, Hezzell MJ, Rush JE, et.al. Relationship of Plasma N-terminal Pro-brain Natriuretic Peptide Concentrations to Heart Failure Classification and Cause of Respiratory Distress in Dogs Using a 2nd Generation ELISA Assay. J Vet Intern Med. 2014 Oct 10. doi: 10.1111/jvim.12472. [Epub ahead of print]

Suggested Reading

- Oyama MA, Boswood A, Connolly DJ, et. Al. Clinical usefulness of an assay for measurement of circulating N-terminal pro-B-type natriuretic peptide concentration in dogs and cats with heart disease. JAVMA. 2013;243(1):71-82.



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The CEG is sponsored by an educational grant from Boehringer Ingelheim Vetmedica, Inc., and IDEXX Laboratories.

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