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CIRCULATIONS
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NT-proBNP Testing in Cats

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 stress. NT-proBNP is more stable than proBNP or C-BNP and has a longer half-life, making it a more desirable analyte. A commercial assay for feline NT-proBNP (Cardiopet® proBNP) has been available for more than five years and many clinical studies have been published that support its clinical utility in the cat. Recently, a qualitative cageside ELISA (SNAP® Feline proBNP) was introduced, which allows rapid determination of feline NT-proBNP concentrations.

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

Cats with respiratory clinical signs

The presence of respiratory signs (dyspnea, tachypnea, cough) in cats may be associated with underlying heart disease (e.g. cardiomyopathy) and congestive heart failure (CHF) or as a consequence of primary respiratory disease (e.g. bronchitis/asthma, pneumonia, neoplasia, pleural space disease, etc). At times it is unclear if clinical respiratory signs are related to cardiac or pulmonary disease, particularly if the physical exam and thoracic radiograph results are ambiguous. In such cases, evaluation of NT-proBNP may help guide further diagnostic testing and therapy. The Cardiopet proBNP test provides a quantitative, NT-proBNP concentration. Several published studies have established a cutoff for cats that helps to differentiate respiratory and cardiac causes of dyspnea. However, the time required to obtain the result from the reference laboratory limits its utility for the acutely distressed patient. The new pet side ELISA can provide rapid, qualitative NT-proBNP results to help assess the likelihood that heart disease is present in a cat with cardiac risk factors (e.g. heart murmur) and may be a useful option to rapidly assess the likelihood that heart disease is present in a cat with respiratory signs. However the new cageside SNAP® Feline proBNP assay has to date not been clinically evaluated in cats with respiratory clinical signs. NT-proBNP is not a stand-alone test and should be interpreted in the context of other appropriate information, e.g. history, signalment, thoracic radiographs and an echocardiogram (if available).

Clinical Tip: *Radiographs must be obtained in cats with respiratory signs that are stable enough to tolerate radiography and, if the findings are ambiguous, a second opinion on the radiographic interpretation may prove useful.*

Apparently healthy (asymptomatic) cats

When evaluating an apparently healthy cat that would be considered to have an increased risk of having occult cardiomyopathy (e.g. a cat with a heart murmur), an echocardiogram should be recommended. If an echocardiogram is declined, an NT-proBNP may be useful to help further assess the likelihood that the cat has underlying heart disease. An abnormal test (>100 pmol/l or SNAP abnormal) in this case could be used to encourage owners to have their cat undergo definitive testing with an echocardiogram, or acquire minimum baseline radiographs. Cats considered to be at increased risk of having occult cardiomyopathy are

those with one or more of the following characteristics: a heart murmur, gallop heart sound, arrhythmia, radiographic cardiomegaly, left axis shift on an ECG (or any other conduction abnormality) or a familial history (directly related to a cat known to have cardiomyopathy). In addition, some breeds of cats are recognized to have a higher prevalence of cardiomyopathy and are thus considered to be at increased risk.

Note: *High-risk cat breeds include-Persian, Maine Coon, Rag Doll, Birman, American Short Hair, Himalayan, Siamese, Sphinx, Burmese, Rex*

Clinical Tip: *Indiscriminate NT-proBNP testing of all apparently healthy cats should be avoided as the rate of false positive results, and thus normal echocardiograms, is increased in populations with a low prevalence of cardiac disease. However, in this group of cats an abnormal test (>100 pmol/L or SNAP abnormal) could be used to rule out heart disease with a high degree of accuracy. Targeting testing of cats with an increased likelihood of disease, based upon criteria outlined above, improves the utility of the test by reducing the rate of false positives. However, due to the fact that at least some cats with clinically significant heart disease have no recognized risk factors, screening all apparently healthy cats who are scheduled to undergo general anesthesia may be reasonable for risk aversive clients as long as the veterinarian and owner can accept the increased rate of false positives (i.e. cats with normal echocardiograms).*

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

Cats with respiratory clinical signs

Clinical Tip: *In general, objective evidence suggestive of structural heart disease must be considered when interpreting the results of the NT-proBNP test and this evidence may be based on auscultation (presence of a murmur, gallop heart sound or arrhythmia), thoracic radiography, or an echocardiogram.*

In cats with current respiratory signs, an NT-proBNP (Cardiopet proBNP) < 100 pmol/L or a normal cageside SNAP® Feline proBNP suggests that CHF is unlikely and other conditions should be more strongly considered. If the NT-proBNP is > 270 pmol/L, CHF is the most likely cause of the clinical signs although concurrent respiratory disease cannot be ruled out. Values between 100 and 270 and an abnormal cageside SNAP® Feline proBNP test are less useful but indicate that CHF is at least possible and other tests should be evaluated or re-evaluated (2nd opinion). However the new cageside SNAP® Feline proBNP assay has to date not been clinically evaluated in cats with respiratory signs.

Apparently healthy (asymptomatic) cats

In apparently healthy cats at increased risk of having heart disease (as outlined above) an NT-proBNP > 100 or an abnormal SNAP test is consistent with an additional increase in the likelihood that the cat has heart disease. Owners of these cats should be strongly encouraged to have an echocardiogram performed or, minimally, have baseline thoracic radiographs taken. Not all cats with NT-proBNP >100 or an abnormal SNAP test will have an abnormal echocardiogram, but many will. In cats with NT-proBNP < 100 or a normal SNAP test, significant structural heart disease is highly unlikely. In this case, significant structural heart disease is taken to mean that any echocardiographic abnormalities (if present) are mild and thus unlikely to cause CHF. However, because heart disease will progress in some cats, an NT-proBNP < 100 or a normal SNAP test does not imply the cat will always be normal. Optimally, at-risk cats should be re-evaluated annually.

Clinical Tip: *NT-proBNP does not replace gold-standard screening recommendation (annual echocardiogram) for cats considered to have an increased likelihood of having heart disease but can be considered as a less costly alternative with informed owner consent. In addition it may be used to "screen" apparently healthy cats with heart murmurs prior to anesthesia. In preanesthesia screens, an abnormal NT-proBNP result should lead to more definitive testing prior to anesthesia. In any case, an abnormal NT-proBNP test does not definitively diagnose heart disease or stage its severity and thus cannot be used as the sole indication to initiate therapy.*

4. IS THERE A DOWNSIDE TO USING NT-PROBNP TESTING IN THE CAT?

The prevalence of occult cardiomyopathy is likely to be lower in apparently healthy cats with no risk factors. As such, the rate of false positive test results is likely to be higher if indiscriminate population based testing is performed. However, definitive data on the rate of false positives, and thus the true performance of the test is unknown as the true prevalence of feline cardiomyopathy in the broader feline population is not currently known.

Abnormal NT-proBNP test results are not specific for any cardiac disease and cannot be used as a stand-alone test to establish a diagnosis. Additionally, abnormal NT-proBNP test results cannot advise the veterinarian on when to start treatment or what medication to use. NT-proBNP testing does not replace other appropriate diagnostic tests. It provides additional information that, when interpreted in light of a thorough history, physical examination and other appropriate tests, has been shown to

improve the accuracy of diagnosis. Its value may be particularly high when the results of other tests are ambiguous.

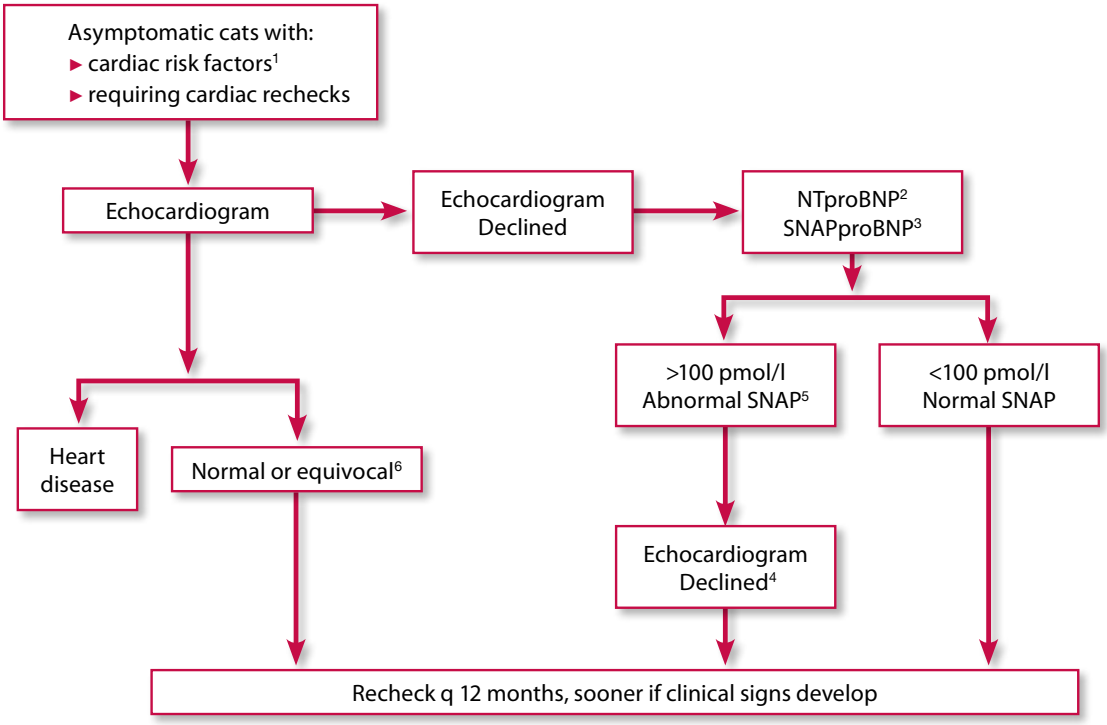
NT proBNP may decrease following the use of cardiac medications but will not normalize. It is highest in cats with active congestive heart failure. There are, unfortunately, a number of conditions that can lead to elevations in NT-proBNP that are not always associated with an abnormal echocardiogram. NT-proBNP may increase with severe arrhythmias, pulmonary hypertension (apparently rare in cats), systemic hypertension, and hyperthyroidism even if structural heart disease is not apparent on an echocardiogram. Thus, these conditions should be considered/ruled-out in cats with elevated NT-proBNP concentrations and a normal echocardiogram. NT-proBNP is cleared by the kidney and concentrations may be increased in cats with renal insufficiency or pre-renal azotemia leading to false positive tests (creatinine > 2.8). Therefore, test results should be interpreted in light of renal function tests, when possible. NT-proBNP concentration can be artificially reduced due to sample degradation, leading to false negative tests, if samples are not submitted as directed by the manufacturer.

5. HOW RELIABLE IS THE TEST?

The most current sample handling and submission recommendations from the manufacturer of the test must be followed to avoid artificially low results (false negatives). The feline assay has undergone few significant revisions and previously published studies provide robust and useful guidelines. There is some day-to-day variation in individual cat measures, but in general day-to-day variation is typically < 10 pmol/L. However, some cats (about 30%) can have concentrations that vary by as much as 100 or more pmol/L.

The new cageside SNAP® Feline proBNP test is qualitative and thus does not precisely quantify the degree of elevation in NT-proBNP levels; however, the colormetric assay does allow a semi-quantitative evaluation. As such, cats can be determined to be normal, abnormal or strongly abnormal. A normal SNAP test result can be considered to rule out structural heart disease in cats with cardiac risk factors with a high degree of accuracy. If indiscriminate population-based testing is done a normal SNAP test result can still be used to rule out structural heart disease with a high degree of accuracy. However, an abnormal test result in cats with risk factors does not establish a diagnosis of

6. FELINE NT-PROBNP TESTING ALGORITHM



Legend

1 Cardiac risk factors: murmur, gallop, rrhythmia or conduction

2 Cardiopet®proBNP

3 SNAP® Feline proBNP

4 If echocardiogram declined in cat with NTproBNP >100 or an Abnormal SNAP consider baseline thoracic radiographs

5 Consider an NTproBNP in cats with an abnormal SNAPproBNP for potential future comparison especially if an echocardiogram is declined at this time

6 Consider a baseline NTproBNP test for future comparison in cats where the recommended follow-up echocardiogram is declined

heart disease but rather should be used as tool to encourage owner to undergo definitive testing. In this population false positives (normal echocardiograms) are still expected with some frequency. If indiscriminate population-based testing is done, an abnormal SNAP test result and subsequent definitive testing (echocardiogram) will yield a higher false positive rate due to the expected reduced prevalence of heart disease in cats without cardiac risk factors, such as a murmur.

7. SUMMARY TABLE

Who should I run an NT-proBNP test on	Cardiopet® proBNP (pmol/L)	SNAP® Feline proBNP	Interpretation of test result
Cat with respiratory signs in which the cause of the signs in not obvious despite other appropriate diagnostic tests	< 100	normal	Does NOT support at diagnosis of CHF
	100-270	abnormal	CHF is possible; review the balance of evidence from the other tests
	> 270		Supports a diagnosis of CHF
Asymptomatic cat with cardiac risk factors (e.g. murmur, arrhythmia, gallop heart sound)	<100	normal	Significant heart disease can be ruled out with a high degree of accuracy
	Increase of >100	abnormal	Increased risk of having significant heart disease; recommend an echocardiogram

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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